ORGANIC LETTERS

2005
Vol. 7, No. 24
5429−5431

Room Temperature Intramolecular Hydro-O-alkylation of Aldehydes: sp^3 C–H Functionalization via a Lewis Acid Catalyzed Tandem 1,5-Hydride Transfer/Cyclization

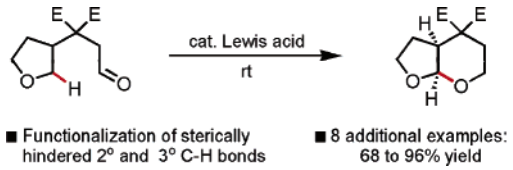
Stefan J. Pastine and Dalibor Sames*

Department of Chemistry, Columbia University, 3000 Broadway, New York, New York 10027

sames@chem.columbia.edu

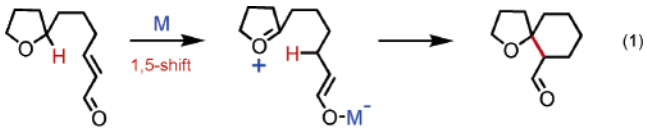
Received September 14, 2005

ABSTRACT



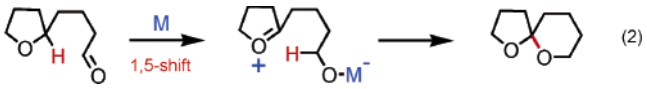
The scope and limitations of intramolecular hydro-O-alkylation of aldehyde substrates leading to spiroketals and bicyclic ketals and aminals is reported. The direct transformation of tertiary and sterically hindered secondary sp^3 C–H bonds into C–O bonds under the action of a catalytic amount of a variety of Lewis acids is described. The mechanism of these transformations is proposed to involve a tandem hydride transfer/cyclization sequence.

We recently disclosed an electrophilic approach to the problem of alkene hydroalkylation whereby the direct transformation of C−H bonds into C−C bonds occurred via a Lewis acid catalyzed intramolecular redox event. The key step in the mechanism was proposed to involve activation of the unsaturation point (electron-deficient olefin) by an electrophilic metal and subsequent C−H bond cleavage via a hydride shift (eq 1).[1] Importantly, since the initiating interaction



(1)

between the substrate and the metal catalyst occurred distant from the targeted C−H bond, functionalization could be achieved at sterically hindered positions. We considered that an analogous mechanism could be utilized for direct C−H to C−O transformations (eq 2). Although no clear thermodynamic driving force exists for the hydro-O-alkylation of aldehydes, we rationalized that spiroketal formation would be favorable as a result of the anomeric effect.[2] A survey of the literature revealed that Woodward et al. proposed and confirmed that an internal redox mechanism was responsible for the acid-catalyzed epimerization of the "normal" and "iso" sapogenins at C-25.[3] This suggests that the spiroketal structure is lower in energy than its corresponding acyclic



(2)

(1) Pastine, S. J.; McQuaid, K. M.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 12180−12181.

(2) Delongchamps, P. *Organic Chemistry Series; Vol. 1: Steroelectronic Effects in Organic Chemistry*; Baldwin, J. E., Ed.; Pergamon Press: Oxford, 1983; pp 5−20.

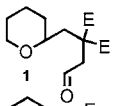
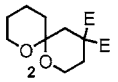
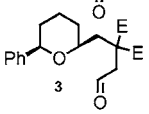
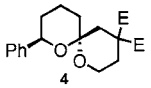
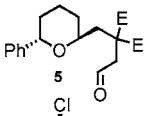
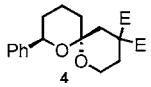
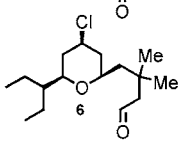
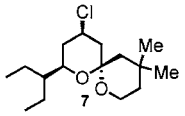
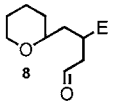
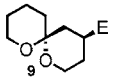
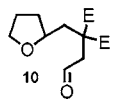
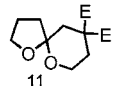
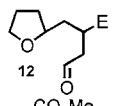
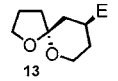
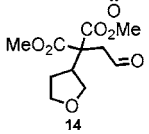
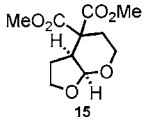
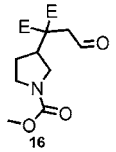
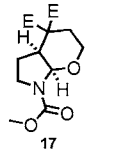
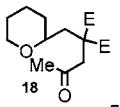
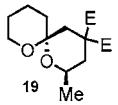
(3) Woodward, R. B.; Sondheimer, F.; Mazur, Y. *J. Am. Chem. Soc.* **1958**, *80*, 6693−6694.

10.1021/ol0522283 CCC: $30.25
Published on Web 11/04/2005

aldehyde isomer. As a result of the prevalence of the spiroketal moiety in natural products,[4] it is surprising that a tandem hydride transfer/cyclization mechanism has not been explored as a potential general method for the preparation of spiroketals. Additionally, since Woodward's account in 1958, only a few reports have appeared in the literature that utilize an internal redox mechanism for direct C−H to C−Y (Y = O, NR) transformations,[5,6] and no general catalytic method has been established. Herein, we report the scope and limitations of a Lewis acid catalyzed intramolecular hydro-O-alkylation of aldehyde substrates leading to spiroketal and bicyclic acetal products.

We initiated our studies by subjecting tetrahydropyran substrate **1** to 30 mol % $BF_3{\cdot}Et_2O$ in methylene chloride. In less than 3 h, aldehyde **1** was cleanly converted to the spiroketal **2** at ambient temperature in 91% isolated yield, with **2** being the only identifiable product via ^1H NMR analysis of the crude reaction mixture (Table 1). Clean transformation of **1** to **2** could also be accomplished with Lewis acids such as $Sc(OTf)_3$, $GaCl_3$, and TiF_4; $Sn(OTf)_2$ and $Zn(OTf)_2$ proved less effective, and $B(C_6F_5)_3$ and trifluoroacetic acid were incompetent. Because of its ease of handling and its low cost, we proceeded to examine the scope of this transformation with $BF_3{\cdot}Et_2O$ (Table 1). Both diastereomeric substrates **3** and **5** produced the same spiroketal diastereomer **4** in good yield. The trisubstituted tetrahydropyran substrate **6**, containing a chloride substituent, was smoothly converted to the spiroketal **7** in 90% yield. Geminal substitution along the aldehyde tether was not required for efficient cyclization (entries 5 and 7, Table 1). In addition to 6,6 scaffolds, 5,6 spiroketals could also be obtained in excellent yields (Table 1, entries 6 and 7), and notably in the case of substrate **10**, as little as 5 mol % $BF_3{\cdot}Et_2O$ could be used. This transformation was not limited to spiroketalization, as demonstrated by the conversion of **14** into the cis-fused bicyclic acetal **15** as a single diastereomer (Table 1). In this case $BF_3{\cdot}Et_2O$ was unreactive, and only the strong Lewis acid TiF_4 catalyzed the transformation. Similarly, TiF_4 converted the N-protected pyrrolidine substrate **16** into the cis-fused bicyclic aminal **17** as a single diastereomer; however, 1.3 equiv of TiF_4 and elevated temperature were required (Table 1). In addition to aldehyde substrates, methyl ketone **18** was converted into the spiroketal **19** under the action of TiF_4 in 30% yield (Table 1, entry 10). $BF_3{\cdot}Et_2O$ was unable to promote hydroalkylation of the less electrophilic ketone, and stronger Lewis acids were required for the transformation.[7] The production of **19** was accompanied by the formation of unidentified byproducts, and thus more selective catalysts will have to be discovered for ketone substrates.

Table 1. Lewis Acid Catalyzed Hydride Transfer/Cyclization of Aldehyde Substrates

entry	substrate	product	time (h)	yield(%)[a]
1			3	91
2			5	85 dr = >50 : 1
3			5	68 dr = >50 : 1
4			3	90 dr = >50 : 1
5			<8	93 dr = >15 : 1
6			3	96[b]
7			3	94 dr = >20 : 1
8			24	90[c] dr = >50 : 1
9			48	68[d] dr = >50 : 1
10			3	30[e] dr = >50 : 1

E = CO_2Et

[a] All reactions were preformed on a 0.5 or 0.25 mmol scale in CH_2Cl_2 (0.025 M substrate) at room temperature with 30 mol % $BF_3{\cdot}Et_2O$. Isolated yields after flash chromatography. [b] 5 mol % $BF_3.Et_2O$ used. [c] 20 mol % TiF_4 used. [d] 1.3 equiv of TiF_4, 50 °C. [e] 100 mol % TiF_4 used.

Convincing evidence for the postulated intramolecular hydride transfer mechanism was obtained by the subjection of the deuterated substrate **6-D** to the standard conditions to form **7-D** (Scheme 1). ^1H NMR analysis of the product **7-D** showed that no loss of deuterium occurred during the course of the hydride transfer, with approximately 60% and 40% of the deuterium residing on the axial and equatorial positions, respectively.[8] Additionally, subjection of a 1:1 mixture of **1** and **6-D** to 30 mol % $BF_3{\cdot}Et_2O$ resulted only in the production of **2** and **7-D** with no crossover of deuterium.

(4) For reviews on the synthesis of spiroketals including spirioketal natural products, see: (a) Mead, K. T.; Brewer, B. N. *Curr. Org. Chem.* **2003**, *7*, 227−256. (b) Perron, F.; Albizati, K. F. *Chem. Rev.* **1989**, *89*, 1617−1661. (c) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309−3362.

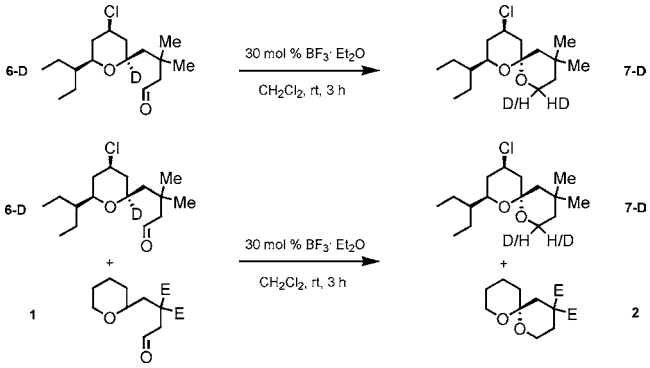
(5) C−H to C−O: Schulz, J. G. D.; Onopchenko, A. *J. Org. Chem.* **1978**, *43*, 339−340. Only two examples are provided in this report.

(6) C−H to C−N: (a) Wölfling, J.; Frank, É.; Schneider, G.; Tietze, L. F. *Angew. Chem., Int. Ed.* **1998**, *38*, 200−201. (b) Wölfling, J.; Frank, É.; Schneider, G.; Tietze, L. F. *Eur. J. Org. Chem.* **2004**, 90−100.

(7) $GaCl_3$ performed similarly to TiF_4.

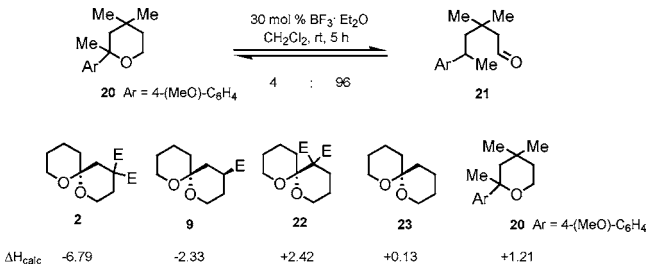
(8) For deuterium studies regarding the epimerization of spirostanols, see: Seo, S.; Uomori, A.; Takeda, K. *J. Org. Chem.* **1986**, *51*, 3823−3827.

Scheme 1



The role of the Lewis acid in this transformation apparently is to catalyze the equilibration of the aldehyde starting materials into the spiroketal products. To support this notion we synthesized the tetrasubstituted-pyran **20** and subjected it to the reaction protocol. Indeed, $BF_3{\cdot}Et_2O$ catalyzed the ring opening equilibration of **20** into its acyclic aldehyde isomer **21** (Scheme 2). The 4:96 ratio obtained of **20**:**21** (^{1}H NMR) is in acceptable agreement with DFT calculations,[9] which suggested that pyran **20** is 1.21 kcal/mol uphill from the acyclic aldehyde isomer **21**.[10,11] In the case of spiroketalization of the aldehyde substrates, the anomeric effect is assumed to be responsible for making spiroketal formation favorable. However, the substitution pattern on the pyran nucleus is also critical. The conversion of **1** to **2** and **8** to **9** was calculated to be favorable by 6.8 and 2.3 kcal/mol, respectively (Scheme 2). Spiroketal **22**, with the diester group adjacent to the ketal linkage, was calculated to be 2.42 kcal/mol uphill from its corresponding aldehyde isomer (Scheme 2). Furthermore, the unsubstituted spiroketal **23** was found to be essentially thermonetural with respect to the aldehyde, being disfavored by 0.13 kcal/mol (Scheme 2).[12] In accord with these calculations, **2** and **9** were obtained in excellent yield, **22** was not obtained, and **23** could only be obtained in low yield.[13]

Scheme 2



In summary, we have shown that hydro-O-alkylation of aldehyde substrates provides spiroketals and bicyclic acetals in good to excellent yields. The preparation of the ester containing ketal products described herein would be difficult via traditional routes (i.e., lactonization of dihydroxy ketone precursor). The metal catalyst serves to promote the equilibration of the substrates via a proposed tandem hydride transfer/cyclization mechanism. As a result, simple DFT calculations can be used to predict the plausibility of product formation. The reversibility of the transformation allows for excellent diastereoselectivity with the most thermodynamically favored products being formed. This is in contrast to the analogous alkene hydroalkylation reaction,[1] where product formation is likely irreversible under the reaction conditions and diastereoslectivity is kinetically determined. This intramolecular ketalization process is formally an annulation reaction, which results from the room temperature functionalization of sterically hindered C−H bonds, highlighting the electrophilic approach as an attractive alternative to processes initiated by metalation of C−H bonds.

Acknowledgment. This work was supported by the NIGMS, GlaxoSmithKline, Johnson & Johnson Focused Giving Program, and Merck Research Laboratories. D.S. is a recipient of the Astrazeneca Excellence in Chemistry Award, the Pfizer Award for Creativity in Organic Synthesis, and the Bristol-Myers Squibb unrestricted research grant. We thank Mike Holman for performing computational experiments.

Supporting Information Available: Experimental procedures and spectroscopic data for starting materials and products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) DFT calculations were preformed using Jaguar 4.1. See Supporting Information for details.

(10) Subjection of **21** to the reaction conditions yields the same ratio of **20**:**21**.

(11) The formation of **21** from **20** is essentially the reverse of the reactions in ref 4.

(12) The opening of a spiroketal without substitution along the tether has been reported: Deslongchamps, P.; Rowan, D. D.; Potheir, N. *Heterocycles* **1981**, *15*, 1093−1096.

(13) Aldol products were found to be the major products of these reactions.