ORGANIC LETTERS

2000
Vol. 2, No. 20
3197−3199

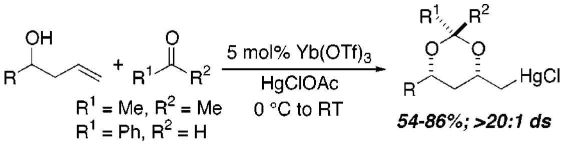
$Yb(OTf)_3$-Catalyzed Oxymercuration of Homoallylic Alcohol-Derived Hemiacetals and Hemiketals

Spencer D. Dreher, Keith R. Hornberger, Stella T. Sarraf, and James L. Leighton*

Department of Chemistry, Columbia University, New York, New York, 10027
leighton@chem.columbia.edu

Received July 27, 2000

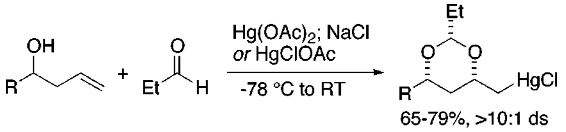
ABSTRACT



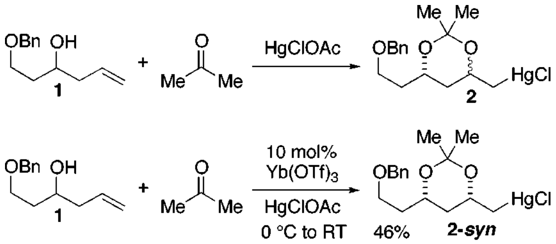
1,3-Diol synthons, protected as acetonides or benzylidene acetals, may be synthesized efficiently from homoallylic alcohols and acetone or benzaldehyde by oxymercuration of the derived hemiketals and hemiacetals with HgClOAc. The use of catalytic amounts of $Yb(OTf)_3$ is crucial to the success of the reaction, which was determined to be reversible.

As part of our laboratory's ongoing development of new methods for the synthesis of (1,3,5...)-polyols,[1] a common structural motif in biologically active natural products,[2] we recently reported a diastereoselective oxymercuration of homoallylic alcohol-derived hemiacetals (Scheme 1).[1d] In this reaction, a homoallylic alcohol is added to a mixture of a mercury (II) salt and propionaldehyde to furnish diastereoselectively the depicted organomercury chlorides. During this study a significant limitation was noted in that the reaction is not successful when acetone or benzaldehyde is used in place of propionaldehyde. Since the corresponding acetonide and benzylidene acetal products are considerably more labile to acidic hydrolysis than propylidene acetals, we decided to revisit the reaction with acetone and benzaldehyde in the expectation that success would render the reaction more generally useful.

Scheme 1



Scheme 2



Treatment of homoallylic alcohol **1** with acetone and HgClOAc[1d,3] for 2 h at room temperature (RT) resulted in only partial conversion to a ∼1:1 mixture of acetonides **2** (Scheme 2). ^{1}H NMR analysis of the unpurified reaction mixture showed significant amounts of unreacted **1** and several decomposition products. The sluggishness of this reaction relative to the reaction with propionaldehyde seemed attributable either to the presumably far lower concentration of hemiketal or the presumably slower rate of hemiketal formation, allowing other pathways to compete. This sug-

---

(1) Leighton, J. L.; O'Neil, D. N. *J. Am. Chem. Soc.* **1997**, *119*, 11118−11119. (b) Sarraf, S. T.; Leighton, J. L. *Tetrahedron Lett.* **1998**, *39*, 6423−6426. (c) Leighton, J. L.; Chapman, E. *J. Am. Chem. Soc.* **1997**, *119*, 12416−12417. (d) Sarraf, S. T.; Leighton, J. L. *Org. Lett.* **2000**, *2*, 403−405. (e) Zacuto, M. J.; Leighton, J. L. *J. Am. Chem. Soc.* **2000**, *122*, Articles ASAP, August 19, 2000.

(2) Rychnovsky, S. D. *Chem. Rev.* **1995**, *95*, 2021−2040.

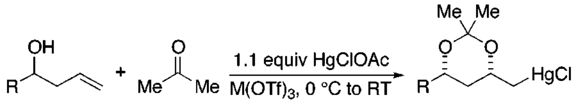
(3) Bowmaker, G. A.; Churakov, A. V.; Harris, R. K.; Oh, S.-W. *J. Organomet. Chem.* **1998**, *550*, 89−99.

10.1021/ol0063860 CCC: \$19.00

gested to us that a simple solution might be to activate the acetone with a Lewis acid, which might be expected to catalyze hemiketal formation.[4] The Lewis acid would have to be relatively mild to be compatible with the many functional groups present in the reaction mixture, and we thus chose to focus on lanthanide triflates.[5] Indeed, treatment of alcohol **1** in acetone with HgClOAc and 10 mol % of $Yb(OTf)_3$ (20 min at 0 °C, then 1.5 h at RT) provided organomercury chloride **2-*syn*** in 46% yield and >20:1 diastereoselectivity as judged by ^1H NMR analysis of the unpurified reaction mixture.

Optimization experiments with homoallylic alcohol **1** revealed that the use of HgClOAc consistently gave better results than the $Hg(OAc)_2$/salt metathesis protocol (entry 1 vs entry 2, Table 1). Concentration proved to be a critical factor as the yield of **2-*syn*** rose to 85% simply by dropping the concentration of **1** in acetone to 0.125 M (entry 3).[6] It was also discovered that the use of $Sm(OTf)_3$ and $La(OTf)_3$ as catalyst gave comparable results to the use of $Yb(OTf)_3$ (entries 3, 4, and 5). Optimization of the catalyst loading was carried out with homoallylic alcohol **3** (entries 7, 8, and 9). With 1 mol % of catalyst there was only a slight diminution in the yield of **4-*syn*** (entry 8), whereas the use of 0.1 mol % of catalyst led to a lower yield of a 1.5:1 mixture of diastereomers (entry 9). Although in many cases less than 5 mol % of catalyst may effectively be used, we settled on 5 mol % as the standard value for maximum efficiency and yield.

Table 1. Optimization of the $Yb(OTf)_3$-Catalyzed Oxymercuration of Homoallylic Alcohol/Acetone-Derived Hemiketals



1, R = $BnO(CH_2)_2$
3, R = *i*-Bu

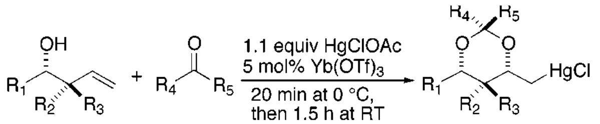
2-*syn*, R = $BnO(CH_2)_2$
4-*syn*, R = *i*-Bu

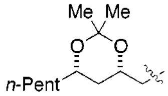
entry	substrate	M (mol%)	[alcohol] (M)	yield (%)[a]
1[b]	**1**	Yb (10)	0.5	41
2	**1**	Yb (10)	0.5	46
3	**1**	Yb (10)	0.125	85
4	**1**	Sm (10)	0.125	78
5	**1**	La (10)	0.125	85
6	**1**	Yb (5)	0.125	85
7	**3**	Yb (5)	0.125	85
8	**3**	Yb (1)	0.125	83
9	**3**	Yb (0.1)	0.125	64[c]

[a] Isolated yield of purified product. In every case the diastereoselectivity was >20:1 as judged by ^1H NMR analysis of the unpurified reaction mixtures. [b] 1.1 equiv $Hg(OAc)_2$, followed by treatment with aq. NaCl. [c] Yield of a 1.5:1 mixture of diastereomers.

With optimal conditions identified, an examination of the scope of the reaction was undertaken (Table 2). In every case except entry 4 the diastereoselectivity was found to be >20:1 as judged by ^1H NMR analysis of the unpurified reaction mixtures. Simple alkyl, benzyloxy, and silyloxy groups are well-tolerated (entries 1, 2, and 3). Both *syn*- and *anti*-disposed allylic methyl groups are tolerated (entries 4 and 5), albeit with a small drop in diastereoselectivity (11:1) and yield (72%) for the *syn* substrate. Substrates bearing an allylic double bond (entry 6) or another acetonide (entry 7) can be tolerated when the reaction is maintained at 0 °C, although the yields were moderate in these cases. The diminished yields for entries 3 and 7 may be attributed to the acidic nature of the reactions, as these substrates carry acid-labile protecting groups, whereas the low yield for entry 6 is at present not well-understood, in that there is no evidence for reaction of the allylic alkene in the ^1H NMR spectrum of the unpurified reaction mixture. Finally, we have also briefly investigated the $Yb(OTf)_3$-catalyzed formation of benzylidene acetals using benzaldehyde in place of acetone (entries 8 and 9). In these cases the best results were obtained with only 3.0 equiv of benzaldehyde. Under these conditions, a more efficient reaction takes place with the diene substrate (entry 9), giving the benzylidene acetal in an improved 68% yield (relative to entry 6).

Table 2. $Yb(OTf)_3$-Catalyzed Oxymercuration of Homoallylic Alcohol-Derived Hemiketals and Hemiacetals



entry	R_1	R_2	R_3	R_4	R_5	yield (%)[a]
1	*i*-Bu	H	H	Me	Me	85
2	$BnO(CH_2)_2$	H	H	Me	Me	85
3	*t*-$BuMe_2SiO(CH_2)_2$	H	H	Me	Me	76
4	*i*-Pr	Me	H	Me	Me	72[b]
5	*t*-$BuPh_2SiO(CH_2)_2$	H	Me	Me	Me	83[c]
6	(*E*)-*i*-PrCH=CH	H	H	Me	Me	54[d]
7		H	H	Me	Me	60[d,e]
8	*n*-Oct	H	H	Ph	H	86
9	(*E*)-*i*-PrCH=CH	H	H	Ph	H	68[c]

[a] Isolated yield of purified product. In every case, except where noted, the diastereoselectivity was >20:1 as judged by ^1H NMR analysis of the unpurified reaction mixtures. [b] 11:1 diastereoselectivity; 3 h at RT. [c] Reaction performed at -78 °C to RT. [d] Reaction run at 0 °C. [e] 10 mol% $Yb(OTf)_3$.

---

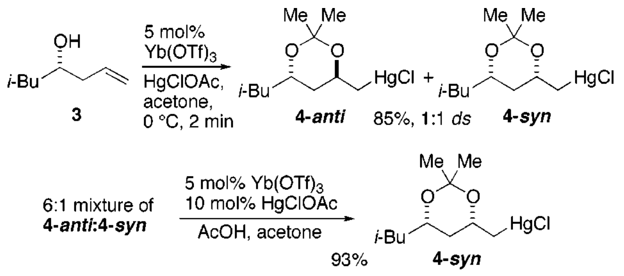
[4] Brønsted acid catalysis (usually perchloric acid) has been reported for oxymercurations with hemiacetals and hemiperacetals. See: (a) Kitching, W.; Lewis, J. A.; Fletcher, M. T.; De Voss, J. J.; Drew, R. A. I.; Moore, C. J. *J. Chem. Soc., Chem. Commun.* **1986**, 855−856. (b) Bloodworth, A. J.; Shah, A. *J. Chem. Soc., Chem. Commun.* **1991**, 947−948. (c) Bloodworth, A. J.; Tallant, N. A. *J. Chem. Soc., Chem. Commun.* **1992**, 428−429. (d) Bloodworth, A. J.; Curtis, R. J.; Spencer, M. D.; Tallant, N. A. *Tetrahedron* **1993**, *49*, 2729−2750.

[5] For an excellent review on the utility of lanthanides in organic synthesis, including their use as Lewis acids, see: Molander, G. A. *Chem. Rev.* **1992**, *92*, 29−68.

[6] This finding contrasted our previous results (ref 1d) using propionaldehyde, where higher concentrations gave better results.

We have examined more closely the reaction of homoallylic alcohol **3** and acetone under the standard conditions of Table 2. Surprisingly, the alcohol is completely consumed within 2 min at 0 °C. At this point a $\sim$1:1 mixture of the products **4-*syn*** and **4-*anti*** may be isolated in 85% yield (Scheme 3). This result indicated that the oxymercuration event is reversible,[7] and the observed *syn* diastereoselectivity is the result of equilibration to the thermodynamically more stable product after a kinetically nonselective cyclization.[8] To establish conclusively whether the reaction is reversible, a 6:1 mixture of **4-*anti***:**4-*syn*** was subjected to the conditions present at the end of a typical reaction (10 mol % of HgClOAc, 5 mol % of Yb(OTf)$_3$, and 1 equiv of AcOH in acetone). From this reaction **4-*syn*** was isolated in 93% yield. Control experiments where HgClOAc, Yb(OTf)$_3$, and AcOH were added in every possible combination to a $\sim$1:1 mixture of **4-*anti***:**4-*syn*** in acetone showed that Yb(OTf)$_3$ alone is necessary for the equilibration, although the rate of equilibration was greatly increased when AcOH was also present.[9]

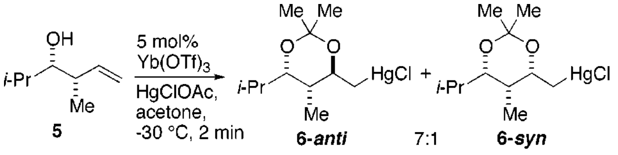
Scheme 3



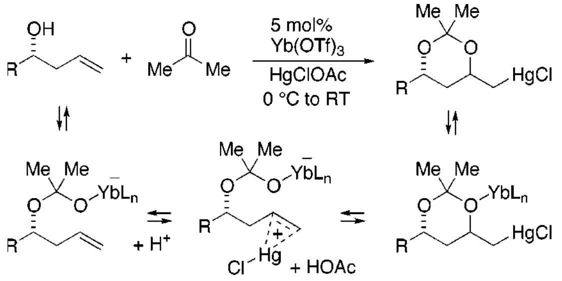
An interesting consequence of the reversibility of this reaction is the possibility that different diastereomers may be selected for based solely on reaction time. That this is feasible was demonstrated by subjection of alcohol **5** to the standard reaction conditions, except quenching after only 2 min at −30 °C (Scheme 4). This procedure produced a 7:1 mixture of **6-*anti***:**6-*syn*** whereas **6-*syn*** is the major product at longer reaction times (entry 4, Table 2).

Although the original proposal that led to these results was that the Yb(OTf)$_3$ might simply catalyze hemiketal formation, the actual role of the catalyst is almost certainly more complex. This conclusion is indicated both by the greatly increased rate of the reaction relative to the uncatalyzed propionaldehyde reaction and by the reversibility of the reaction. One possibility is that the Yb(OTf)$_3$ leads to rapid formation of the Yb-alkoxide of the hemiketal (Scheme 5). Rate-determining (and nonselective) mercurinium ion formation is then followed by fast oxymercuration of the Yb-alkoxide.[10] In this scenario, the role of the catalyst is to greatly increase the rate of, and thereby render reversible, the oxymercuration step. This is plausible in that a Yb-alkoxide might be expected to be more reactive than a hemiketal-OH.

Scheme 4



Scheme 5



Lanthanide triflates are mild and efficient catalysts for the oxymercuration of homoallylic alcohol-derived hemiacetals and hemiketals. The reactions are rapid, highly diastereoselective, and furnish good yields of protected 1,3-diol synthons. The reactions are reversible, and the diastereoselectivity results from equilibration to the thermodynamically more stable *syn* products. Further studies to expand the scope of this process and examine its applicability to synthetic endeavors are in progress.

Acknowledgment. The National Institutes of Health (National Institute of General Medical Sciences-R01 GM-58133) is acknowledged for financial support of this work. We thank Pharmacia and Upjohn for graduate fellowships to K.R.H. and S.T.S. and Merck Research Laboratories and DuPont Pharmaceuticals for generous financial support. J.L.L. is a recipient of a Sloan Research Fellowship, a Camille Dreyfus Teacher-Scholar Award, a Bristol-Myers Squibb Unrestricted Grant in Synthetic Organic Chemistry, a Cottrell Scholar Award from the Research Corporation, an Eli Lilly Grantee Award, an AstraZeneca Excellence in Chemistry Award, and a GlaxoWellcome Chemistry Scholar Award.

Supporting Information Available: Experimental procedures and characterization data for all products in Table 2. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0063860

---

[7] In several instances, oxymercurations of this type have been determined to be reversible. See ref 4d and: (a) Overman, L. E.; Campbell, C. R. *J. Org. Chem.* **1974**, *39*, 1474−1481. (b) Kocovsky, P. *Organometallics* **1993**, *12*, 1969−1971.

[8] This stands in direct contrast to our previous results with the uncatalyzed propionaldehyde cyclization, where control experiments established unambiguously that the oxymercuration was irreversible and the stereoselectivity resulted from kinetic control. See ref 1d.

[9] Acetic acid alone was insufficient to catalyze the equilibration reaction. Although previous results (ref 4) suggest that strong Brønsted acids should catalyze the reaction, we have found that 5 mol % of HClO$_4$ does not provide the desired product cleanly or diastereoselectively.

[10] The obstervation of kinetic selectivity when an allylic stereocenter is present (Scheme 4) is consistent with rate-determining mercurinium ion formation.