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Stereoselective Intermolecular Oxymercurations of Allylic Ethers.

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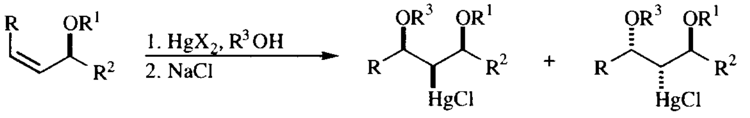
Abstract: The influence of alkene geometry and allylic substitution on the stereochemical outcome of intermolecular oxymercurations of allylic ethers is described.

We have recently reported studies on the structural features of allylic ethers which are important in order to achieve useful levels of diastereoselectivity in intramolecular oxymercurations.[1-3] We found that the combination of Z-alkene stereochemistry and a remote, allylic silyloxy substituent gave the best results. In this Letter we report on the results of a related study involving *inter*molecular oxymercurations of allylic ethers (equation 1).[4,5]



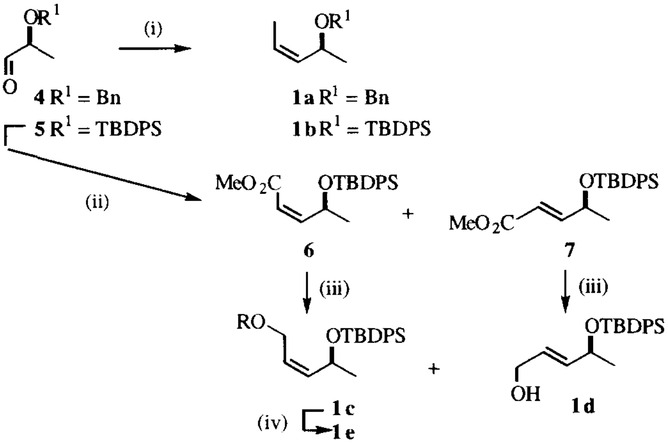
(1)

1a-g **2a-g** **3a-g**

1	R	R^1	R^2
a	Me	Bn	Me
b	Me	TBDPS	Me
c	CH_2OH	TBDPS	Me
d	(*E*)-CH_2OH	TBDPS	Me
e	$CH_2OTBDMS$	TBDPS	Me
ent-**f**	$(CH_2)_2CO_2Et$	TBDPS	$CH_2OTBDPS$
g	$(CH_2)_4NHCO_2Bn$	TBDPS	Ph

Scheme 1 outlines the preparation of alkenes **1a-g**, which are being used in a number of different projects in our group. Alkenes **1a** and **1b** were prepared by Wittig reactions of the appropriately protected lactaldehydes **4** and **5** respectively with ylid **8**.[2] Alkenes **1c** and **1d** were prepared by Wittig reaction with the stabilized ylid **9**. The resulting *Z* and *E* isomers, **6** and **7**, respectively could be separated easily by silica gel chromatography. Reduction with lithium aluminium hydride then gave the two alkenes. Silylation of **1c** provided **1e**. The preparation of alkene **1f** has been reported by us previously.[1] **1g** was prepared in a manner analogous to that for **1f**.

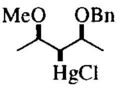
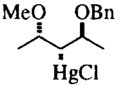
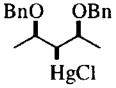
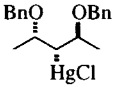
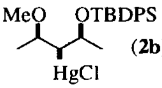
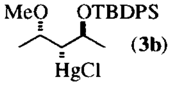
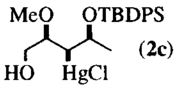
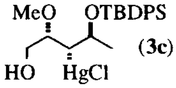
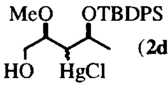
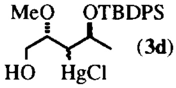
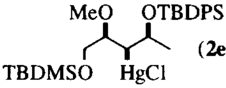
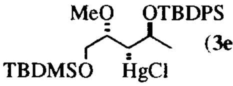
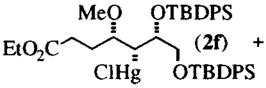
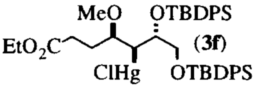
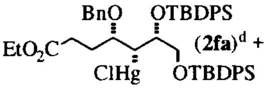
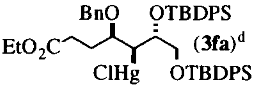
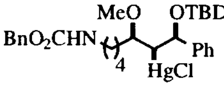
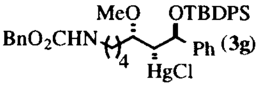
Scheme I. Synthesis of oxymercuration precursors **1a** - **e**.



(i) $Ph_3P{=}CHCH_3$ (**8**) (ii) (a) $Ph_3P{=}CHCO_2Me$ (**9**) (b) Silica gel chromatography (iii) (a) $LiAlH_4$, Et_2O, reflux, 1h (b) H_2O (iv) TBDMSCl, Im., DMF.

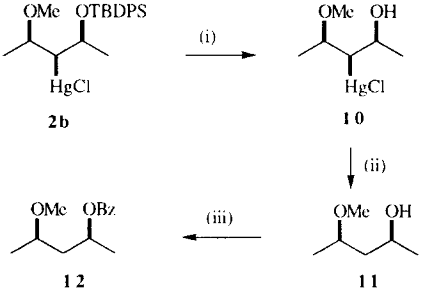
From the results in the Table several trends emerge. First, all the alkoxymercurations were completely regioselective (ie only 1,3-dioxygenated products were obtained). Second, where R is larger than methyl, diastereoselection in the methoxymercuration of Z-alkenes is $\geq$ ~3.0 : 1 in favour of the *syn*-diastereomers **2** (entries 1, 4, 6, 7 and 9). Methoxymercuration of an *E*-alkene gave excellent chemical yields but as a mixture of all four possible diastereomers (entry 5). This surprising result is currently under investigation as oxymercurations of *E* or Z-alkenes are usually stereospecific with respect to the mode of addition (*anti-*) across the double bond. Third, as steric hindrance increased the rate of reaction dropped quite dramatically (compare entry 3 with entries 6 and 7). Fourth, the use of an allylic benzyl ether protecting group gave similar diastereoselection although in much poorer chemical yield than the corresponding TBDPS ether (compare entries 1 and 3). Fifth, some *benzyl*oxymercurations were also carried out. In one case, no reaction was observed after seven days. However, switching to mercury(II)trifluoroacetate led to rapid reaction. In both cases the diastereoselectivity was diminished (although still useful, see entry 8) compared to the corresponding methoxymercuration (compare entry 1 with 2, and entry 7 with 8). Finally, when both R and R^2 were sterically demanding the diastereoselection was greatly improved (entry 7). (Lowering the temperature had no significant effect on diastereoselectivity and so all reactions were conducted at room temperature).

Table Results from Intermolecular Oxymercurations[a] of Alkenes **1a** - **g**.[f]

Entry	Alkene	Products	Yield[b] (%)	Time (h)	Ratio (2 : 3)
1	**1a**	 (**2a**) +  (**3a**)	34	5	4.4 : 1
2	**1a**	 (**2aa**)[d] +  (**3aa**)[d]	30	24	2.2 : 1
3	**1b**	 (**2b**) +  (**3b**)	100	2	5.0 : 1
4	**1c**	 (**2c**) +  (**3c**)	98	48	3.0 : 1
5	**1d**	 (**2d**) +  (**3d**)	100	72	1 : 1
6	**1e**	 (**2e**) +  (**3e**)	95	72	5.5 : 1
7	**1f**	 (**2f**) +  (**3f**)	56	168	8.0 : 1
8	**1f**	 (**2fa**)[d] +  (**3fa**)[d]	44[c]	3	3.7 : 1
9	**1g**	 (**2g**) +  (**3g**)	56	108	4.6 : 1

(a) All reactions were carried out at r.t., using 1.2 eq. of $Hg(OAc)_2$ in the appropriate alcoholic solvent; The reaction mixtures were treated with aq. NaCl to effect ligand exchange on mercury. (b) Total isolated yield. (c) 4.0 eq. of $Hg(OCOCF_3)_2$ used instead of $Hg(OAc)_2$. (d) Products of *benzyloxymercuration*. (f) All new compounds gave satisfactory spectroscopic and elemental analysis.

The diastereoselectivity of these reactions was confirmed by conversion of **2b** into benzoate **12** (whose enantiomer has been reported previously) using the sequence of reactions outlined below. Thus successive fluorodesilylation, reductive demercuration and benzoylation led to **12** whose ^{1}H nmr spectra and optical rotation ($[a]_D$ = +33.5°, *c* 2.0, $CHCl_3$; lit.[6]$[a]_D$ = -35°, *c* 3.0, $CHCl_3$) were in excellent agreement (although the latter is opposite in sign as **12** and Fujioka's compound are enantiomeric) with those quoted in the literature[6] and significantly different to those of the possible diastereomer (which would have been derived from **3b**).



(i) Bu_4NF, THF, overnight, r.t.53%; (ii) Bu_3SnH, AIBN, toluene, r.t.2h; (iii) BzCl, DMAP, pyridine/toluene (1:1) 22% (two steps).

Thus we have demonstrated that chiral allylic ethers undergo alkoxymercurations with diastereoselectivities ranging from modest to excellent. In all cases regioselectivity was complete, ie only 1,3-oxygenated products (as opposed to their 1,2-isomers[7]) were obtained. It appears that the role of the nucleophile (at least when it is used as solvent) is also important in determining the diastereoselectivity. This may have more to do with the lower polarity of benzyl alcohol as solvent compared to methanol than with any difference in the size of the nucleophiles (ie MeOH vs BnOH). We have noted a similar correlation between solvent polarity and diastereoselectivity in related *intra*molecular oxymercurations.[1] The application of these results to the synthesis of poly-oxygenated molecules will be reported shortly.

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