Intermolecular Oxonium–Ene Reaction: a New Entry to Stereocontrolled Synthesis of Tetrahydropyrans

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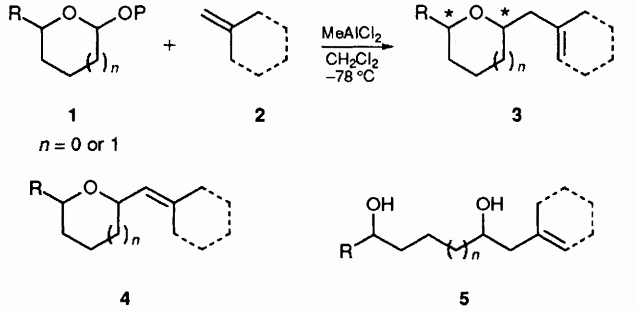
The intermolecular ene-type reaction with a lactol-derived oxonium ion intermediate as an enophile is shown to exhibit a high level of diastereofacial selectivity to afford predominantly the 2,6-*trans*-tetrahydropyrans in spite of the diastereoisomeric ratio of the starting δ-lactol derivatives.

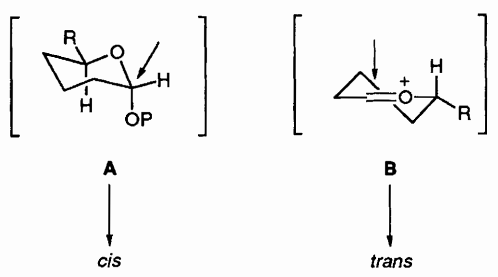
The ene reaction involving carbonyl compounds, aldehydes in particular, as enophiles (carbonyl–ene reaction) has been emerging as a new methodology for stereochemical control. However, the types of enophile explored so far have been severely limited.[1] Herein we report a new type of intermolecular ene reaction with a lactol[2]-derived oxonium ion intermediate as an enophile (oxonium–ene reaction) (Scheme 1). The ene reactions involving oxonium ion intermediates have been reported so far only for the intramolecular cases.[3]

Typical experimental procedure for the oxonium–ene reactions is as follows. To a dichloromethane solution of lactol or its derivative **1** was added $MeAlCl_2$† (1 equiv.) at −78 °C. To the mixture was then added olefin **2** (1.5 equiv.) at that temperature.‡ After several hours, the usual work-up followed by silica gel chromatography gave the oxonium–ene product **3** without any detectable amount of the regioisomeric olefin **4** and lactol–ene product **5**. Other Lewis acids such as $SnCl_4$ and $TiCl_4$, which provide the chlorinated product, afford lower yields of the oxonium–ene products **3**.



Scheme 1

Representative results of the oxonium–ene reaction are summarized in Table 1. The present reaction is characterized by the exclusive ene-regioselectivity. Particularly interesting is that the reaction of lactol derivatives give higher yields of the oxonium-ene products **3** in a high level of *trans*-diastereofacial selectivity along with their independence of the diastereoisomeric ratio of the starting δ-lactol derivatives (entries 6–8).



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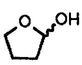
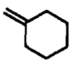
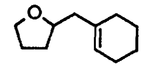
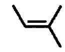
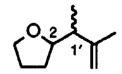
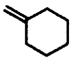
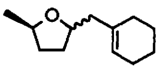
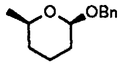
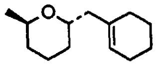
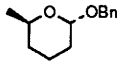
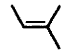
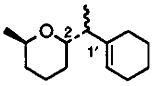
† Me_2AlCl provides a lower yield of the oxonium–ene product **3**.

‡ Above −30 °C, the lactol–ene product **5** was formed.

Table 1 Intermolecular oxonium–ene reactions[a]

Entry	Enophile 1	Ene 2	Time/h	Product 3	Yield (%)	Diastereofacial selectivity[b]
1			2		34	—
2			2		41[c]	—
3			16		50	—
4			16		38[d]	—
5			2		91	1:1
6			2		63	>10:1
7			2		60	>10:1
8			2		(—)[e]	>10:1

[a] Unless otherwise noted, all reactions were carried out as described in the text. [b] For the stereochemical assignment, see ref. 4. [c] 2.5 Equiv. each of the lactol and $MeAlCl_2$ were used. [d] 2:1 Diastereoisomeric mixture with respect to the C-2 and C-1′. [e] 3:1 Diastereoisomeric mixture with respect to the C-2 and C-1′, not isolated.

These results show clearly that the present reactions would rarely proceed in a S_N2 fashion (**A**) leading to the *cis*-product from the *trans*-lactol derivatives, but involve mainly the oxonium ion intermediate (**B**) leading eventually to the same 2,6-*trans*-tetrahydropyran[4] from either diastereoisomer of the starting δ-lactol (S_N1 fashion). However, the five-membered oxonium ion intermediate would be conformationally rather flexible[5] and hence lead to the lower diastereofacial selectivity (entry 5).[4]

In summary, we have disclosed herein the first example of the intermolecular ene reaction with an oxonium ion, which provides a simple, stereocontrolled route to tetrahydropyrans.

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References

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