



Trifluoromethanesulfonic Acid, an Efficient Catalyst for the Hetero Diels-Alder Reaction and an Improved Synthesis of Mefrosol.

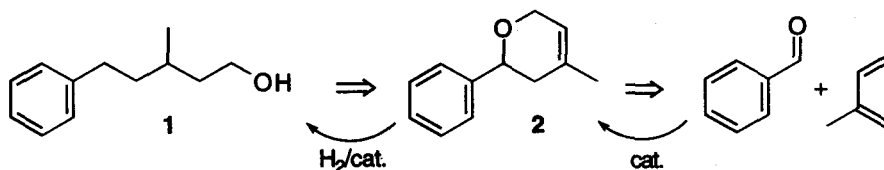
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Abstract: Trifluoromethanesulfonic (triflic) acid (1 mol%) has been found to be an efficient catalyst for the hetero Diels-Alder reaction between aromatic aldehydes and unactivated dienes. © 1997 Elsevier Science Ltd.

The hetero Diels-Alder reaction is a powerful method in the construction of heterocycles.¹⁻³ However for pyran synthesis, this method is severely limited to the reaction of either highly electron rich dienes (typically Danishefsky's diene)^{4,5} with a broad range of aldehydes or highly activated aldehydes (e.g. glyoxylates)⁶ with a broad range of dienes. There are very few examples of hetero Diels-Alder reactions between simple dienes and unactivated aldehydes,^{7,8} but a recent report involving the use of cationic Pd²⁺ catalysts⁹ prompts us to report our own research in this area. We have been interested in expanding the scope of the hetero Diels-Alder reaction as we recognised that it could be applied to a short and economic synthesis of the fragrance material mefrosol 1 (Scheme 1). Mefrosol can be obtained from the hetero Diels-Alder adduct 2 by simple hydrogenation.¹⁰



Scheme 1

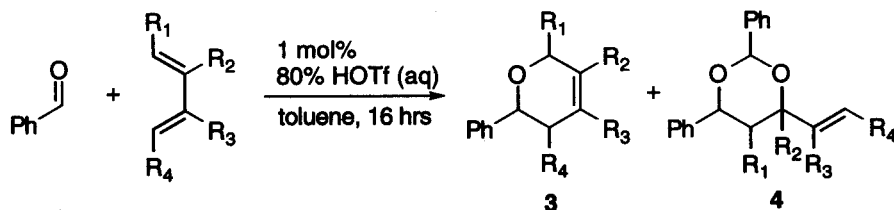
Our studies have focused on finding a suitable catalyst for the hetero Diels-Alder reaction. We screened a range of potential catalysts [Sc(OTf)₃, CeCl₃, Yb(OTf)₃, HNTf₂, HOTf] in the reaction between benzaldehyde and isoprene and found that trifluoromethanesulfonic (triflic) acid in toluene provided the greatest activation. Using as little as 1 mol% of 80% TfOH (aq) a high yield (72%) of pyran 2 was obtained.¹¹ This reaction has been carried out on 1 mol scale and the pyran 2 was obtained in similar yield (64% by distillation). To probe the generality of this procedure a range of aldehydes were tested (Table 1).

Table 1: Hetero Diels-Alder Reaction of Isoprene with Aldehydes Catalysed by Triflic Acid.

Entry	R	mol% HOTf	Isolated yield/%
1		0	0
2		1	72
3		1	68
4		1	40
5		1	65
6		5	14
7		1	45
8		1	5

We were pleased to find that isoprene underwent the desired hetero Diels-Alder reaction with complete regioselectivity with both activated and weakly deactivated aromatic aldehydes (entries 3-5). For the strongly deactivated aldehyde (*p*-anisaldehyde, entry 6) a single regioisomer was again obtained but in a lower yield. This is evidently an electronic effect as the reaction of *m*-anisaldehyde (entry 7) occurred with greater efficiency. Valeraldehyde (entry 8) reacted to give a low yield of pyran and a mixture of other high boiling products.

To further investigate the scope of the process we tested the reaction between benzaldehyde and several simple dienes (Table 2).

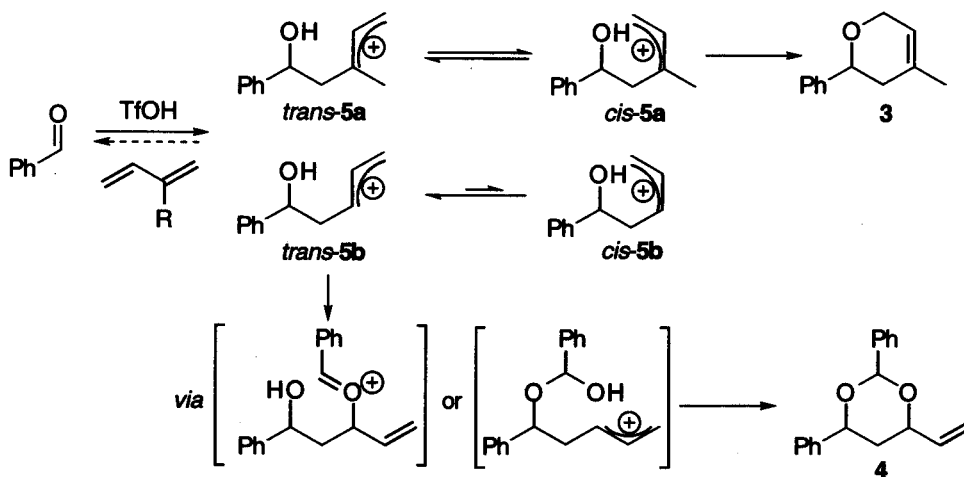
Table 2: Competition between the Hetero Diels-Alder and Prins Reactions of Benzaldehyde with Simple Unactivated Dienes Catalysed by Triflic Acid.

Entry	Diene	Isolated Yield 3 /%	Isolated Yield 4 /%
1		72	0 ^b
2		85	0 ^b
3		82 ^a	0 ^b
4		0 ^c	40 ^{a,d} (R ₄ =Me)
5		0 ^c	33 ^{d,e} (R ₃ ,R ₄ =Me)
6		0	0

^a Product obtained as a ca. 1:1 mixture of diastereomers. ^b None isolated but some Prins product detected by nmr (<5%). ^c None isolated but some hetero Diels-Alder product detected by nmr (<10%). ^d Yields obtained using procedure indicated in ref. 11. However, a slight modification of conditions gave increased yields of Prins adduct (see ref. 12). ^e Product obtained as a ca. 4:1 mixture of isomers.

Whilst dienes substituted with an alkyl group in the 2-position (entries 1-3) reacted smoothly to give the corresponding pyrans in high yields, dienes with a substituent in the 1-position (entries 4-5) gave the alternative Prins product in moderate yield and low diastereoselectivity.¹² Cyclopentadiene (entry 6) polymerised under the reaction conditions.

It is likely that both reactions (hetero Diels-Alder and Prins) occur *via* the common carbocationic intermediate 5 (Scheme 2).



Scheme 2

For carbocations derived from 2-substituted dienes the difference in energy between the *trans* and *cis* forms **5a** will be small, and rapid equilibration¹³ between the two eventually results in formation of the hetero Diels-Alder adduct. For carbocations which are derived from dienes lacking a 2-substituent, the energy difference between the *cis* and *trans* forms **5b** will be much greater and the *trans* carbocation will be favoured. This cannot undergo direct ring closure, but further reaction with benzaldehyde leads to an intermediate which can. 1,2-Disubstituted dienes (e.g. Table 2, entry 5) can react either through the 1 or 4 positions : both are similarly activated but the 4-position is less hindered, and evidently favoured. This leads to a carbocation lacking a 3-substituent and gives rise to the Prins product as the major component.

In summary, we have found conditions for affecting the hetero Diels-Alder reaction from readily available unactivated dienes and aromatic aldehydes. The process requires extremely low catalyst loadings, is carried out at ambient temperature and pressure, and provides the products as single regioisomers in good to excellent yields. Additionally, the process now represents an extremely efficient and competitive route to the fragrance material, Mefrosol.

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References and notes.

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- (11) General procedure; To a stirred solution of benzaldehyde (1.0 cm³, 10.0 mmol) and 80% triflic acid (aq) (18.8 mg, 0.10 mmol) in toluene (1.5 cm³) was added isoprene (1.5 cm³, 15.0 mmol) over 10 mins, with cooling (ambient temperature water bath). The mixture was stirred at room temperature overnight, after which time the reaction was quenched using sat. sodium carbonate (aq) (3 cm³). The product was extracted into dichloromethane (3 x 3 cm³), washed with brine (3 cm³) and dried over magnesium sulfate. Purification by flash chromatography (silica gel, 2% EtOAc/Petroleum (b.p. 40-60)) gave the pure pyran (883 mg, 5.07 mmol, 72 % based on recovered aldehyde) as a colourless oil, and benzaldehyde (320 mg, 3.01 mmol).
- (12) Increasing the amount of aldehyde in the reaction to three equivalents resulted in increased yields (60-85%) and diastereoselectivities (>90:10) of the Prins products.
- (13) Equilibration of the *cis/trans* carbocations can occur either by formation of oxetane intermediates or by reversion to starting materials.