

Scandium Trifluoromethanesulfonate, an Efficient Catalyst for the Intermolecular Carbonyl-Ene Reaction and the Intramolecular Cyclisation of Citronellal.

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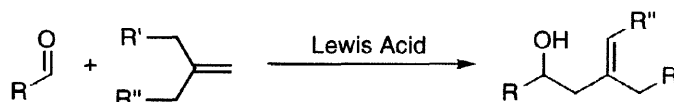
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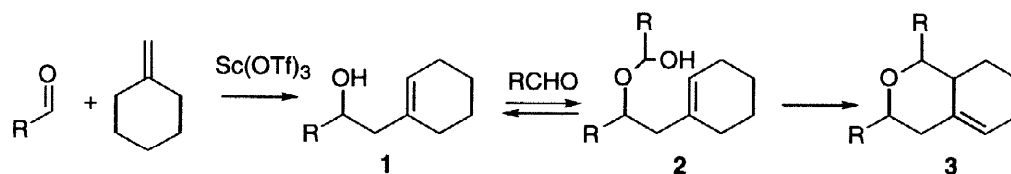
Abstract: Scandium trifluoromethanesulfonate (5–10 mol%) has been found to be an efficient catalyst for both intra and intermolecular carbonyl-ene reactions. © 1998 Elsevier Science Ltd. All rights reserved.

The carbonyl-ene reaction, whilst synthetically very useful^{1,2} is severely substrate limited: only intramolecular ene reactions^{1–4} and intermolecular reactions with either highly activated carbonyl components (e.g. glyoxylates⁵, formaldehyde⁶ or chloral⁷) or highly activated ene components (e.g. 3-methylene-2,3-dihydrofuran⁸) have been reported. Furthermore, stoichiometric amounts of powerful Lewis acids are usually required due to the low nucleophilicity of the olefin and tight binding of the product homoallylic alcohol to the catalyst. Unaware of any examples of intermolecular carbonyl-ene reactions between aromatic aldehydes and simple olefins, we sought to remedy this situation.



Scheme 1

Based on our recent finding⁹ that in the related metallo-ene reaction between allyltrimethylsilane and aldehydes, Sc(OTf)₃ was a highly efficient catalyst, we screened a range of group IIIb and lanthanide catalysts and again found that Sc(OTf)₃ provided the greatest activation. Unfortunately, our initial attempts at catalysis of the intermolecular ene reaction between methylene cyclohexane and a range of aromatic and aliphatic aldehydes produced only pyrans **3** in which two aldehyde groups had become incorporated (Scheme 2). Presumably Sc(OTf)₃, as well as catalysing the addition of the alkene to the aldehyde, also catalyses the formation of the hemiacetal **2** and oxonium ion¹⁰ prior to final cyclisation.



In order to inhibit incorporation of the second aldehyde we needed to trap the alcohol **1** in a highly efficient manner and considered doing so by acylation. $\text{Sc}(\text{OTf})_3$ is also known to catalyse the acylation of alcohols with acetic anhydride in acetonitrile extremely rapidly¹¹ and so we applied these conditions to the ene reaction (Table 1).

Table 1: The Intermolecular Carbonyl-Ene Reaction between Methylene Cyclohexane and Aromatic Aldehydes Catalysed by Scandium Triflate.¹²

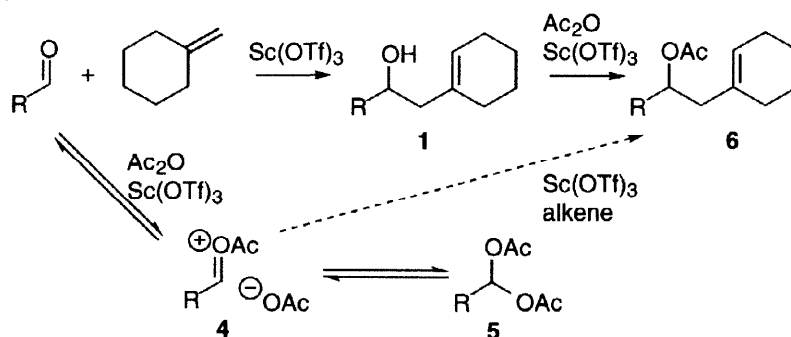
Entry	R	Method	mol% $\text{Sc}(\text{OTf})_3$	Isolated yield/%
1		A,B or C	0	0
2		A	10	68
3		B	5	73
4		B	10	75
5		C	10	40*
6		A	5	61
7		A	5	0
8		A	5	29

Methods: **A** Alkene (1.2 equiv) was added to a mixture of aldehyde (1.0 equiv), Ac_2O (1.5 equiv) and $\text{Sc}(\text{OTf})_3$ in MeCN ¹². **B** Alkene (1.0 equiv) was added to an excess of aldehyde (3.0 equiv), Ac_2O (4.5 equiv) and $\text{Sc}(\text{OTf})_3$ in MeCN . **C** Alkene (1.2 equiv) was added to aldehyde (1 equiv) and $\text{Sc}(\text{OTf})_3$ in the absence of Ac_2O , in DCM . * Product obtained as free alcohol.

We were pleased to find that a range of simple aromatic aldehydes reacted smoothly.¹² Moderately electron rich aromatic aldehydes worked well (entries 2, 3, 6 & 8) but highly electron rich aldehydes did not (entry 7). In the latter case a mixture of products were obtained presumably due to the ease of carbocation formation and subsequent rearrangements. Moderately electron deficient aldehydes worked well (entry 4) but highly electron deficient aldehydes (*p*-nitrobenzaldehyde) gave the stable geminal diacetates (acylals) **5**. In

this latter case it was possible to obtain the ene-product in moderate yield in the absence of acetic anhydride (entry 5). Aliphatic aldehydes also gave stable geminal diacetates (acylals) and so were unreactive.¹³ Indeed, acylals **5** are seen to be present in each case and in the absence of a nucleophile are the sole products.

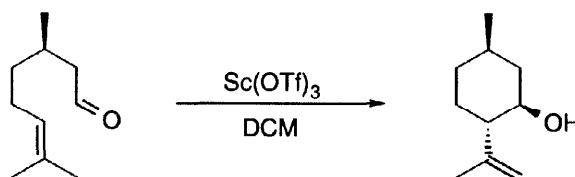
There are two possible mechanisms by which the acylated products **6** may be formed: an ene reaction followed by acylation of the alcohol or by formation of oxonium ion **4**¹⁴ followed by capture by the alkene (Scheme 3). We do not know which mechanism applies but for successful reactions acylal equilibration is required (Scheme 3).¹⁵



Scheme 3

To extend the scope of reaction our catalyst system was applied to the industrially important cyclisation of citronellal¹⁶ (Table 2). Reported procedures^{1,17} generally use stoichiometric amounts of Lewis acids and give the product in moderate yields and diastereoselectivities. Zinc bromide (1 equivalent in benzene) has been shown to be the optimum Lewis acid¹⁷ giving the product in good yield (70%) and high selectivity (94:6 isopulegol:other isomers).

Table 2: The Intramolecular Carbonyl-Ene Cyclisation of Citronellal.



Entry	mol% Sc(OTf) ₃	Temp/°C	Time/hrs	Isolated Yield/%	Isomer Ratio (isopulegol:others)
1	0	25	8	0	-
2	5	25	2	58	80:20
3	10	-40	0.5	86	88:12
4	10	-78	1	>95	94:6
5	5	-78	1.5	>95	94:6

The intramolecular carbonyl-ene reaction was studied, initially without modification. Using scandium triflate in dichloromethane (at room temperature) the product was obtained in low yield and selectivity (entry 2) (due to the reaction of isopulegol with citronellal). As the temperature was decreased (entries 3 & 4) this

intermolecular process was inhibited and complete conversion to isopulegol (>95%) was observed (entry 4). The expected increase in selectivity was also observed. We have also shown that a lower catalyst loading is practicable (entry 5), and that the catalyst could be recovered by simple extraction into aqueous phase, and reused without loss in yield or diastereoselectivity.

In summary, we have found conditions for affecting the carbonyl-ene reaction of methylene cyclohexane and aromatic aldehydes. The process requires low catalyst loadings, is carried out at ambient temperature and pressure, and provides the products in good yields. This represents the first example of the carbonyl-ene reaction of unactivated olefins and aromatic aldehydes. Additionally, the process has been extended to the intramolecular cyclisation of citronellal (a key step in the synthesis of menthol).

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- (12) *Typical Experimental Procedure*; To a stirred solution of benzaldehyde (102 μ L, 1.0 mmol) and scandium triflate (49.2 mg, 0.10 mmol) in acetonitrile (1.0 cm³) at 20°C was added acetic anhydride (142 μ L, 1.5 mmol) and methylene cyclohexane (144 μ L, 1.2 mmol). The mixture was stirred at room temperature overnight, after which the solution was poured into brine (5 cm³). The product was extracted into dichloromethane (3 x 5 cm³) and dried (MgSO₄) to give the crude product. Further purification by flash chromatography [silica gel; 2% EtOAc/Petroleum (40-60)] gave the product as a colourless oil (166 mg, 0.68 mmol, 68%).
- (13) In the absence of acetic anhydride a complex mixture of products was obtained.
- (14) For a detailed discussion of gem-diacetate hydrolysis see: Gregory, M. J. *J. Chem. Soc. (B)* **1970**, 1201.
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