



Rare earth triflates/chlorotrimethylsilane induced activation of triethylamine as a latent acetaldehyde anion: a new synthesis of α,β -unsaturated aldehydes

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ABSTRACT

A synthetic methodology for α,β -unsaturated aldehydes employing rare earth triflate is reported. Activated triethylamine reacts with aldehydes to form two carbon extended aldehydes, which is promoted by a catalytic amount of Yb, Sc, Y, and In(OTf)₃, in the presence of chlorotrimethylsilane. We investigated the conditions applicable to aromatic aldehydes as well as heterocyclic compounds as substrates. A deuterium labeling experiment supported our proposed reaction mechanism.

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Triethylamine (TEA) is a cheap and versatile reagent for organic synthesis. In addition, TEA has received much attention as a base due to the nitrogen-free lone pair, which may act as a Brønsted base and accept a proton in an acidic reaction vessel¹ or attach into electrophiles as a Lewis base.²

Herein we describe a one-pot method to transform aldehydes into α,β -unsaturated aldehydes with a two-carbon homologation. Although α,β -unsaturated aldehydes have potent activities for many transformations in organic synthesis,³ there are difficulties in synthesizing cinnamaldehydes from benzaldehydes in a one-step procedure.⁴ To our best knowledge, this is the first example of synthesizing α,β -unsaturated aldehydes using TEA with catalytic metal salts.

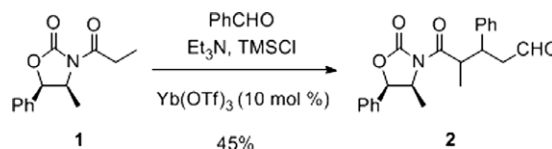
Our group has previously reported an unusual reaction promoted by 10 mol % Yb(OTf)₃ for a cross-aldol condition with oxazolidinone **1** (Scheme 1).⁵

In this discovery, we predicted the in situ formation of a cinnamaldehyde equivalent from benzaldehyde by activated TEA.⁶ To confirm the intermediate for this reaction, we roughly applied this condition to benzaldehyde as a substrate, and obtained a mixture of *cis*- and *trans*-cinnamaldehyde when a stoichiometric amount of Yb(OTf)₃ and an excess amount of chlorotrimethylsilane (TMSCl) were employed. The result prompted us to survey the details of this reaction.

We initially examined Lewis acids for the desired reaction using benzaldehyde **3a** as a representative substrate (Table 1).⁷ The reaction proceeded smoothly in 24 h using 1 equiv Yb(OTf)₃ with 5 equiv TMSCl in CH₂Cl₂ at rt and TEA to generate cinnamaldehyde **4a** in 53% yield. Product formation was further optimized by increasing both the amount of reagents and reaction time (20 equiv TMSCl, 30 h) to give 86% yield.⁸ Hence, we decided to

use a standard protocol [20 equiv TMSCl and 40 equiv TEA] to determine the effects of Lewis acids on this potentially useful reaction. A two-carbon homologation occurred using numerous types of Lewis acids, except for Yb(NTf)₃ (Table 1, entry 9). Both 100 mol % of Y(OTf)₃ and 100 mol % of In(OTf)₃ resulted in over 60% yields (Table 1, entries 2 and 4). Interestingly, TEA can be sufficiently activated by GaCl₃ or FeCl₃ to afford the product (Table 1, entries 7 and 8). Catalytic trials for the present reaction by selecting different Lewis acids revealed that Sc(OTf)₃ can remain effective longer than the others under these conditions (Table 1, entries 1–8).

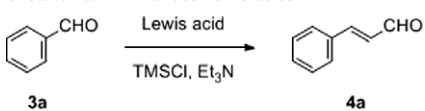
Table 2 summarizes the scope of the substrates for this phenomenon. With *p*-fluorobenzaldehyde **3b**, product **4b** was obtained in a reasonable yield using Yb(OTf)₃, Y(OTf)₃, and Sc(OTf)₃ (Table 2, entry 1). A methoxy substituent on the benzaldehyde did not negatively affect the reaction (Table 2, entries 2–4), although only *m*-tolualdehyde **3f** afforded the product in an acceptable yield (entry 5). When the reaction proceeded with 2-naphthaldehyde **3g**, favorable conditions for the catalytic use of Lewis acids were not established, but the product was obtained in moderate yields (Table 2, entries 6 and 7). The homologation process gave 2-furaldehyde **3h** using Yb(OTf)₃, Sc(OTf)₃, In(OTf)₃, and Y(OTf)₃. Hence, these results suggest that 2-furaldehyde is the most reactive and a suitable substrate for this reaction (Table 2, entries 8–11). An excellent yield was observed for **3h** with 30 mol %



Scheme 1. Unique reaction of oxazolidinone **1** with benzaldehyde under cross-aldol reaction conditions.

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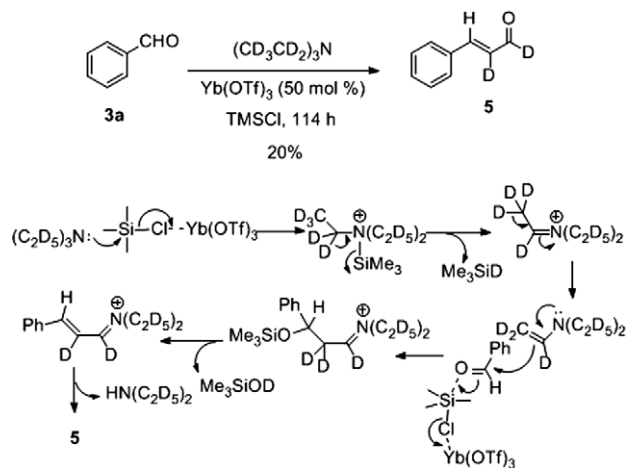
Table 1
Transformation of **3a** to **4a** with various Lewis acids^a


Entry	Lewis acid	Yield ^b (%)			
		10 mol %	30 mol %	50 mol %	100 mol %
1	Yb(OTf) ₃	7	35	59	86 ^c
2	Y(OTf) ₃	8	—	33	60
3	Sc(OTf) ₃	15	—	27	37
4	In(OTf) ₃	7	34	45	65
5	Bi(OTf) ₃	—	—	—	27
6	Sm(OTf) ₃	—	—	—	12
7	GaCl ₃	0	—	21	44
8	FeCl ₃	0	—	2	14
9	Yb(Nf) ₂	—	—	—	0

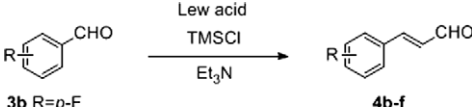
^a Reactions were carried out in CH₂Cl₂ at rt for 24 h.^b Isolated yields.^c 30 h.

of Sc(OTf)₃ (Table 2, entry 9). Bicyclic heterocyclic compounds such as 2-benzofuran-2-carboxaldehyde **3i** and 1-methylindole-3-carboxaldehyde **3j** gave products in relatively good yields (Table 2, entries 12–15).⁹

In addition, we performed a deuterium labeling experiment to gather evidence about the reaction mechanism (Scheme 2). Deuterated-cinnamaldehyde **5**, in which two hydrogens were replaced with deuterium imported from (CD₃CD₂)₃N in plausible positions was formed in 20% yield. Product formation was very sluggish due to the primary isotope effect. Additionally, both the quartet and the triplet NMR-peaks for diethylamine disappeared.

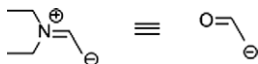
**Scheme 2.** Deuterium labeling experiment and plausible reaction mechanism.

We realized that TEA could be doubly activated by various Lewis acids and TMSCl under our conditions to become a protected acetaldehyde anion equivalent in the reaction (Scheme 3). Enamine Et₂N-CH=CH₂ has been previously reported in both the photo-oxidation of TEA¹⁰ and the chemical oxidation of TEA.¹¹ Goodman and Whitten implicated the formation of the iminium ion, Et₂N⁺=CHCH₂ in the photoreaction, but it was not detected directly via NMR. Periasamy and co-workers have reported a useful transformation of benzophenone derivatives by excess TiCl₄ using TEA, and reported an example of 46% of cinnamaldehyde as a product.¹² When we attempted to transform benzophenone by our protocol, a reaction was not observed.

Table 2
Scope of substrates for ethylene part insertion


Entry	Substrate	Product	Catalyst	mol %	Yield ^a (%)
1	3b	4b	Yb(QTf) ₃	100	68
2	3c	4c	Sc(OTf) ₃	100	67
3	3d	4d	In(OTf) ₃	50	70
4	3e	4e	Yb(OTf) ₃	50	64
5	3f	4f	In(OTf) ₃	50	69
6	3g	4g	Yb(OTf) ₃	50	40
7	3g	4g	In(OTf) ₃	100	61
8	3h	4h	Yb(OTf) ₃	50	63
9	3h	4h	Sc(OTf) ₃	30	93
10	3h	4h	In(OTf) ₃	50	78
11	3h	4h	Y(QTf) ₃	10	31
12	3i	4i	Yb(OTf) ₃	50	55
13	3i	4i	Y(OTf) ₃	50	23
14	3j	4j	In(OTf) ₃	50	61
15	3j	4j	Sc(OTf) ₃	50	41

^a Isolated yields.



Scheme 3. Design of synthon for acetaldehyde anion.

In summary, we have developed a one-pot method to transform aldehydes into α,β -unsaturated aldehydes with a two-carbon homologation. This method can be applied to aromatic aldehydes to produce α,β -unsaturated aldehydes. Various Lewis acids, including $\text{Yb}(\text{OTf})_3$, $\text{In}(\text{OTf})_3$, $\text{Y}(\text{OTf})_3$, and $\text{Sc}(\text{OTf})_3$, serve as catalysts to promote this reaction.

The scope, mechanism, and synthetic application of this reaction are under investigation.

Acknowledgment

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- Isolated yields for trans- α,β -unsaturated aldehydes were described.
- Typical procedure:** To a suspension of $\text{Yb}(\text{OTf})_3$ (302.4 mg, 0.49 mmol) and TMSCl (1.25 mL, 9.78 mmol) in CH_2Cl_2 (4 mL) was added dropwise a solution of benzaldehyde (0.05 mL, 0.49 mmol) and Et_3N (2.75 mL, 19.7 mmol) in CH_2Cl_2 (1 mL) under Ar. The solution was stirred for 24 h at rt. Saturated aqueous NaHCO_3 (4 mL) was added, and the resulting mixture was stirred for 30 min. The layers were separated and the aqueous layer was further extracted with EtOAc . The combined organic extracts were washed with brine, and dried over anhydrous MgSO_4 . The solvent was removed. Purification of the crude product by flash chromatography (5:1 hexane/ EtOAc) provided cinnamaldehyde (49.1 mg, 76%) as a yellow oil. This structure was confirmed by comparison with the reported spectral data. ^1H NMR (400 MHz, CDCl_3) δ 6.73 (dd, $J = 15.8$ and 7.6 Hz, 1H), 7.42–7.49 (m, 2H), 7.49 (d, $J = 15.8$ Hz, 1H), 7.55–7.60 (m, 2H), 9.72 (d, $J = 7.6$ Hz, 1H); see: Battistuzzi, G.; Cacchi, S.; Fabrizi, G. *Org. Lett.* **2003**, *5*, 777. (*E*)-3-(2-Benzofuranyl)propenal (**4i**): IR (neat): 1664 cm^{-1} ^1H NMR (500 MHz, CDCl_3) δ 6.82 (dd, $J = 15.6$ and 7.8 Hz, 1H), 7.09 (s, 1H), 7.25–7.29 (m, 1H), 7.35 (d, $J = 15.6$ Hz, 1H), 7.39–7.43 (m, 1H), 7.50–7.53 (m, 1H), 7.62 (d, $J = 7.8$ Hz, 1H), 9.72 (d, $J = 7.8$ Hz, 1H) ^{13}C NMR (400 MHz, CDCl_3) δ 111.7, 112.9, 122.0, 123.6, 127.2, 128.2, 128.4, 137.8, 151.9, 155.9, 192.7 LRMS m/z : 172 (M^+). HRMS m/z : calcd for $\text{C}_{11}\text{H}_8\text{O}_2$: 172.0547. Found: 172.0544.
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