Pergamon

Tetrahedron Letters 39 (1998) 9283–9286

TETRAHEDRON
LETTERS

Ytterbium Triflate Catalysed Allylation of Aldehydes: An Unusual Benzoic Acid Induced Acceleration

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Received 13 August 1998; accepted 1 October 1998

Abstract

Addition of one equivalent of benzoic acid greatly enhances the efficiency of our ytterbium triflate catalyzed allylation of aldehydes with allyltributyltin in acetonitrile. Crucial modifications to reaction conditions result in a dramatically increased rate at remarkably low catalyst loading.

Keywords: Lanthanides; Catalysis; Acidity; Tin and compounds

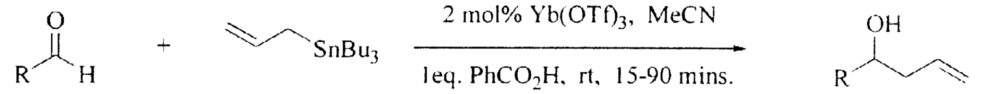
Over recent years, lanthanide triflate mediated Lewis acid catalysis has attracted tremendous interest throughout scientific communities [1,2]. Their low toxicity, ease of handling, recyclable nature and low cost make lanthanide derived species attractive alternatives to their classical competitors such as $TiCl_4$, particularly in large-scale industrial processes.

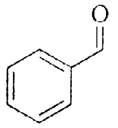
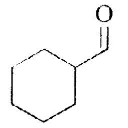
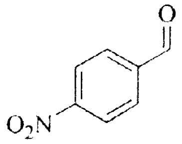
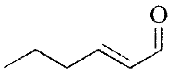
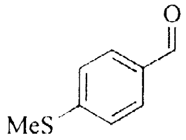
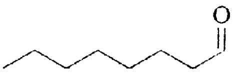
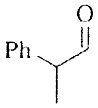
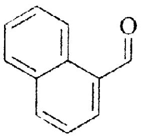
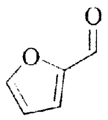
Allyltin and allylsilicon reagents have been widely used for the mild conversion of aldehydes and ketones to versatile homoallylic alcohol intermediates. Whilst numerous Lewis acids promote these reactions, there has been little precedent for catalysis by lanthanide derivatives – which can potentially be recovered and reused. Aggarwal and co-workers have demonstrated that scandium triflate is capable of catalysing the allylation of aldehydes with allyltrimethylsilane [3]. We have previously reported that $Yb(OTf)_3$ [4] and lanthanide triflate polyethethylene glycol complexes [5] catalyse analogous allylations with allyltributyltin in dichloromethane solvent. Although these novel procedures are very mild and versatile, there has been considerable scope for improvement: up to 10mol% of the catalyst is necessary, the reactions are rather sluggish, and require as long as 24 hours to reach completion.

PII: S0040-4039(98)02086-3

Studies directed towards an asymmetric variant of this reaction have demonstrated that modifications to the solvent as well as addition of 1eq of benzoic acid to the reaction mixture greatly facilitate this process. Not only do these improvements allow a reduction of catalyst loading to just 2mol%, but total conversion is achieved in as little as 15 minutes at room temperature (table 1). Good to excellent yields of homoallylic alcohol products were isolated for a broad selection of aliphatic and aromatic aldehydes.

Table 1
Scope of improved allylation conditions[a]



Aldehyde	Time / mins.	Yield / %	Aldehyde	Time / mins.	Yield / %
	15	84		90	88
	45	96		90	71
	45	77		90	89
	120 *ca.* 3:1 mixture of diastereoisomers	68		15	85
	90	83			

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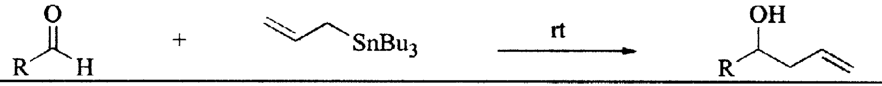
[1] In a typical procedure, Yb(OTf)$_3$ (15.2mg, 0.024mmol, 0.02eq.) was weighed into a 25mL Schlenk flask containing a magnetic stirrer, and dried under high vacuum for 2h at 160 °C. The flask was cooled to room temperature and filled with dry nitrogen, before adding solid benzoic acid (149mg, 1.22mmol, 1eq), followed by dry acetonitrile (1mL), allyltributyltin (454μl, 1.46mmol, 1.2eq) and aldehyde (1.22mmol, 1eq). Stirring was initiated and the suspended benzoic acid rapidly dissolved to give two immiscible liquid phases. The reaction was monitored by thin layer chromatography and on completion, quenched with 2M NaOH (2mL), before partitioning between DCM (20mL) and water (20mL). The aqueous phase was extracted with DCM (3 x 20mL) and the combined organic extracts were dried over MgSO$_4$. Upon filtration followed by concentration under reduced pressure, the oily residue was purified by silica-gel chromatography (initial eluent 2% diethyl ether in light petroleum ether (b.p. 40-60 °C) and then the polarity was increased to 10% diethyl ether) to yield the products which were found to be completely free of tin contamination.

The background leading to development of this improved procedure, together with some interesting mechanistic implications will now be discussed. Table 2 summarises some important findings. Our initial observation was that acetonitrile proved to be a superior reaction solvent to dichloromethane (entries 1-2). Only 2mol% Yb(OTf)$_3$ was required for the allylation of 1-naphthaldehyde, and the reaction was found to be complete after 5h. In DCM under the same conditions, the aldehyde had barely reacted after a much longer period of time. This is probably owing appreciable dissociation of lanthanide triflates in MeCN [6], much more so than in DCM. Thus electrostatic activation of the carbonyl substrate will be stronger.

Table 2
Studies leading to the benzoic acid mediated allylation



Entry	R	eq. of $Yb(OTf)_3$	eq. of $PhCO_2H$	Solvent	Time / h	% reaction[a]
1	1-Naphthyl	0.02	0	DCM	22	3
2	1-Naphthyl	0.02	0	MeCN	5	100
3	Cyclohexyl	0.02	0	MeCN	48	33[b]
4	*p*-MeS-(C_6H_4)-	0.02	0	MeCN	0.5	22
5	*p*-MeS-(C_6H_4)-	0.02	0	MeCN	48	27
6	***p*-HO_2C-(C_6H_4)-**	**0.02**	**0**	**MeCN**	**0.3**	**100**
7	*p*-MeS-(C_6H_4)-	0.02	1	MeCN	0.75	100
8	Cyclohexyl	0.02	1	MeCN	1.5	100
9	*p*-NO_2-(C_6H_4)-	0.02	1	MeCN	0.45	100
10	Ph	0.02	1	MeCN	0.25	100
11	**Ph**	**0**	**1**	**MeCN**	**48**	**0**

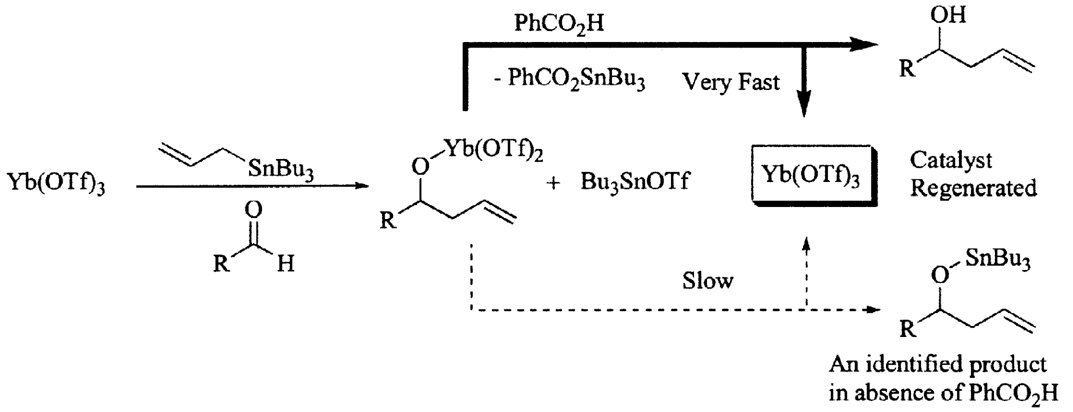
[a] The reactions were monitored by ^1H NMR.
[b] Isolated yield.

Encouraged by this result, we attempted to extend the generality of this modification to a range of other aldehydes (entries 3-6). Disappointingly we were unable to obtain high yields with most other substrates reproducibly. Most reactions were taking considerably longer, and in some cases they failed to reach completion at all. The notable exception was *p*-carboxybenzaldehyde, which only required 20 minutes at room temperature (entry 6).

We hypothesised that the inherent carboxylic acid functionality in *p*-carboxybenzaldehyde was accelerating the catalytic cycle, and attempted to capitalize on this observation by adding one equivalent of benzoic acid to the other reaction mixtures. In the absence of benzoic acid, we found that *p*-(methylmercapto)benzaldehyde had reached 22% completion after 30 minutes. But we were puzzled to find that the reaction had hardly progressed any further after an additional 2 days, and a precipitate was evident. However, on addition of 1 equivalent of benzoic acid to the same reaction flask, these residues rapidly dissolved and total conversion to the alcohol was accomplished in a further 30 minutes. Repetition of the reaction with adding one equivalent of benzoic acid at the start (entry 7), revealed that all of the aldehyde had been consumed after only 45 minutes. Similar observations were made with cyclohexanecarboxaldehyde and *p*-nitrobenzaldehyde (entries 8-9). The possibility that the Lewis acid-catalysed mechanism had been superseded by a pathway involving a Brønsted acid was explored, but no reactivity was observed in the absence of ytterbium triflate (entry 11).

Scheme 1 illustrates a proposed pathway for the reaction. We believe that at low catalyst loading, a considerable proportion of the Lewis acid gets tied up in an alkoxide intermediate (possibly the precipitate that was observed). An alkoxide ligand would be intimately associated with the lanthanide, and species of this type would exhibit greatly reduced Lewis acidity. In the absence of protic acid, the subsequent catalyst regeneration step is likely to be very slow, since it probably involves reaction of the alkoxide with tributyltin triflate - both of which are present in very low concentration. Addition of 1 equivalent of Brønsted acid would rapidly destroy the alkoxide species, thus immediately restoring the activity of the Lewis acid. This would explain why the activity of the Lewis acid diminishes with time (entries 4-5, table 2).

Scheme 1
Postulated mechanism illustrating the role of the benzoic acid



In summary we have reported an unusual benzoic acid induced acceleration of the lanthanide triflate catalysed allylation of aldehydes with allyltributyltin in acetonitrile solvent. Apart from the practical implications of this observation in its own right, we are several steps closer to understanding how these catalysts operate, which may help with the ultimate challenge to develop enantioselective variants of this reaction [7].

Acknowledgement

We would like to thank EPSRC for the financial support of this project.

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