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## Imino-ene reaction of *N*-tosyl arylaldimines with $\alpha$ -methylstyrene: application in the synthesis of important amines

Manoj K. Pandey, Alakesh Bisai, Ankur Pandey and Vinod K. Singh\*

Department of Chemistry, Indian Institute of Technology Kanpur, Kanpur 208 016, India

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Abstract—Copper(II) or tin(II) trifluoromethanesulfonate in combination with TMSCl effectively activates a C–H bond for the imino-ene reaction of *N*-tosylarylaldimines with  $\alpha$ -methylstyrene. A wide variety of *N*-tosylarylaldimines were used to give homo-allylamines in good to excellent yields under mild conditions. The imino-ene adduct was converted into a  $\beta$ -amino ketone. The synthesis of a 2,4-substituted pyrrolidine and a piperidine was also achieved from the imino-ene product via a Mitsunobu reaction and a Grubbs cyclization, respectively.

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The development of new methods for the preparation of homoallylamines is important for the synthesis of nitrogen-containing compounds. Moreover, these are also useful building blocks for the synthesis of many natural products. The obvious procedure for the synthesis of homoallylic amines is via nucleophilic addition of allyl metal reagents to imines.<sup>1</sup> Alternatively, they can be obtained from imino-ene reactions, which involve addition of an olefin bearing an allylic hydrogen (ene) to an imine (enophile).<sup>2</sup> The reaction is easy only when the imines are activated ( $\alpha$ -imino esters)<sup>3</sup> or the reaction is intramolecular.<sup>2,4</sup> Even for these cases, the presence of Lewis

Table 1. Imino-ene reaction of N-tosylbenzaldimine and  $\alpha$ -methylstyrene at rt<sup>a</sup>

	Ph N <sup>-Ts</sup> + Ph	M(OTf) <sub>2</sub> , TMSCI, solvent,	$\xrightarrow{\text{rt}} Ph \xrightarrow{\text{Is-NH}} Ph$	
Entry	M(OTf) <sub>2</sub>	Solvent	Time	Isolated yield (%)
1	$Cu(OTf)_2$ (10 mol%)	THF	10 h	85
2	$Cu(OTf)_2$ (5 mol %)	THF	10 h	80
3	$Cu(OTf)_2$ (5 mol %)	CHCl <sub>3</sub>	15 h	63
4	$Cu(OTf)_2$ (5 mol %)	$CH_2Cl_2$	12 h	73
5	$Cu(OTf)_2$ (5 mol %)	MeNO <sub>2</sub>	2 h	80
6	$Cu(OTf)_2$ (5 mol %)	Benzene	2.5 h	83
7	$Cu(OTf)_2$ (5 mol %)	Toluene	30 min	89
8	$Cu(OTf)_2$ (5 mol %)	THF/CH <sub>2</sub> Cl <sub>2</sub> <sup>b</sup>	1.5 h	91
9	Sn(OTf) <sub>2</sub> (5 mol %)	Toluene	45 min	85
10	Sn(OTf) <sub>2</sub> (5 mol %)	THF/CH <sub>2</sub> Cl <sub>2</sub> <sup>b</sup>	4 h	75
11	$Zn(OTf)_2$ (5 mol %)	Toluene	10 h	44
12	Zn(OTf) <sub>2</sub> (10 mol%)	Toluene	10 h	62

<sup>a</sup> The amount of TMSCl used was the same as the amount of the Lewis acid.

<sup>b</sup> The ratio was 1:4.

Keywords: Imino-ene reaction; Lewis acids; Homoallylic amines.

<sup>\*</sup> Corresponding author. Tel.: +91 512 2597291; fax: +91 512 2597436; e-mail: vinodks@iitk.ac.in

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	$ \begin{array}{c} & & & \\ & & \\ & & \\ & X \\ & 1b - 1j \end{array} + Ph \\ \end{array} \begin{array}{c} & & \\ & M(OTf)_2, TMSCI, toluene, rt \\ & & & \\ & & \\ & & & \\ & & \\ & & & \\ & & & \\ & & & \\$					
Entry	Arylaldimine	Homoallylic amine	% Isolated yield (time)			
			Cu(OTf) <sub>2</sub>	Sn(OTf) <sub>2</sub>		
1	<b>1b</b> (X = $p$ -F)	2b	80 (20 min)	62 (30 min)		
2	1c (X = $p$ -Cl)	2c	70 (35 min)	65 (75 min)		
3	1d (X = p - iPr)	2d	57 (30 min)	76 (90 min)		
4	1e (X = $m$ -Cl, $p$ -F)	2e	91 (15 min)	88 (90 min)		
5	1f(X = m - Br)	2f	58 (30 min)	56 (40 min)		
6	1g (X = m - Cl)	2g	73 (15 min)	60 (45 min)		
7	1h (X = m - OMe)	2h	78 (30 min)	57 (90 min)		
8	1i (X = o, p - di - F)	2i	68 (35 min)	63 (60 min)		
9	$1\mathbf{j} (\mathbf{X} = o - \mathbf{Cl})$	2j	60 (60 min)	65 (90 min)		

Table 2. Imino-ene reaction of a variety of N-tosylarylaldimines and  $\alpha$ -methylstyrene at rt<sup>a</sup>

 $^a\,5\,mol\,\%$  of TMSCl was used in combination with 5 mol % of the Lewis acid.

acids such as BF<sub>3</sub>·OEt<sub>2</sub>, SnCl<sub>4</sub>, AlCl<sub>3</sub> and TiCl<sub>4</sub> are required. Whereas these traditional Lewis acids failed to activate other imines for intermolecular imino-ene reactions, lanthanoid metals have proved to be very effective.<sup>5</sup> In this letter, we report that the imino-ene reaction of *N*-tosylarylaldimines and  $\alpha$ -methylstyrene can be catalyzed using Cu(OTf)<sub>2</sub> or Sn(OTf)<sub>2</sub> in combination with TMSCl in an efficient way. We have further shown the importance of the reaction by the synthesis of several important amines.

A systematic study was carried out for the reaction of *N*-tosylbenzaldimine **1a** and  $\alpha$ -methylstyrene under various conditions. It was observed that there was no reaction in the presence of 10 mol % of Cu(OTf)<sub>2</sub> (reaction time 15 h). However, on addition of TMSCl, the expected

homoallylic amine 2a was isolated in high yield. This was not surprising as the TMSCl might be preventing coordination of the amine formed to the Lewis acid, thus providing high yields of products. The reaction is hardly affected when the amount of Cu(OTf)<sub>2</sub> was reduced to 5 mol % (Table 1; entry 2). Based on a solvent study, toluene was selected for further study (Table 1). In order to see whether TMSCl is essential with Sn(OTf)<sub>2</sub>, the iminoene reaction was carried out in its absence and the adduct 2a was isolated in 55% yield (reaction time 15 h). This indicated a different behaviour for these two Lewis acids. The addition of TMSCl to the Sn(OTf)<sub>2</sub>-catalyzed reaction improved the yield and reduced the reaction time (Table 1, entry 9). Zn(OTf)<sub>2</sub> was also assessed, but it proved to be inferior (Table 1, entries 11 and 12). Under the optimized conditions (Table 1, entry 7), other silvl

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Scheme 1. Conversion of an imino-ene adduct into various synthetic intermediates.

reagents such as TIPSOTf (2 h, 60% yield), TBDMSCl (12 h, 10% yield), TBDPSCl (12 h, 28% yield) and 1,2-

so, it was concluded that TMSCl is optimal. In order to explore the generality of the reaction, it was extended to a variety of aldimines 1 using a general procedure: a solution of a *N*-tosylimine 1 (0.5 mmol) and metal triflate (5 mol %) in toluene (2 mL) was treated with 1.5 equiv of  $\alpha$ -methylstyrene solution in toluene (1 mL) followed by TMSCl (5 mol % from a stock solution) at rt. The reaction mixture was stirred for an appropriate period of time. It was worked up by partitioning the reaction mixture between EtOAc and water. The organic layer was washed with brine and dried. Solvent removal and purification over silica gel (10% EtOAc in hexane) provided homoallylic amines 2 (Table 2). As shown in Table 2, copper and tin triflate

bis (chlorodimethylsilyl)ethane (10 h, 71%) were tested,

were both used but consistently, the latter required a little longer time for completion of the reaction. Having established a protocol for the synthesis of homoallylic amines, we turned our attention to applications of these imino-ene adducts. The adduct 2a could be converted into a  $\beta$ -amino ketone **3** by osmylation of the double bond followed by cleavage of the resulting diol. We also extended the methodology for synthesis of a substituted pyrrolidine and a piperidine. Such compounds are potentially useful intermediates for the synthesis of biologically active natural products.<sup>6,7</sup> The construction of the pyrrolidine ring was accomplished in two steps. Hydroboration of 2a followed by treatment of the resulting alcohol 4 with Ph<sub>3</sub>P/DIAD<sup>8</sup> provided 2,5-diphenyl *N*-tosylpyrrolidine 5. The tosyl group could be cleaved using Mg in MeOH<sup>9</sup> and the free amine was protected with a Cbz group, thus giving 6. For the substi-

tuted piperidine, *N*-allylation of the homoallylamine **2a** using allyl bromide in the presence of sodium hydride gave **7** and then ring closing metathesis, using Grubbs' 1st generation catalyst produced **8** in high yield. The tosyl group in **8** could be removed by using Mg/MeOH<sup>9</sup> at reflux and after protection of the free amine with a Cbz group, **9** was obtained in 90% yield (Scheme 1).

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