Iodine as a Very Powerful Catalyst for Three-Component Synthesis of Protected Homoallylic Amines

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Abstract: Iodine catalyzes efficiently the three-component condensation of aldehydes, benzyl carbamate, and allyltrimethylsilane to afford the corresponding protected homoallylic amines in excellent yields.

The stereoselective addition of allylmetal reagents to aldimines has become an important reaction for carbon−carbon bond formation.[1] The resulted homoallylamines are useful intermediates in natural product synthesis.[2] Moreover, acylated homoallylic amines are important synthons for many synthetic applications.[3] Usually, allylation of aldimines is carried out using allylstannane in the presence of a Lewis acid such as $TiCl_4$, $BF_3{\cdot}OEt_2$, $PdCl_2(PPh_3)_2$, $PtCl_2(PPh_3)_2$, bis-π-allyl palladium complex, lanthanide triflates, and $LiClO_4$.[4] However, use of allyltributylstannane is not a desired reagent from the point of green chemistry as a result of its toxicity. Other allylmetal reagents such as allylgermane and allylgalium were also employed for this important synthetic protocol,[5] but the allylic metal is still the reagent of choice. The use of allylsilanes is more desirable, but because of low reactivity (as compared to allylstannane) this reagent is finding limited applications. There are only a few reports on the use of allylsilane for the synthesis of homoallylic amine.[6] The first method was a three-component reaction developed by Veenstra where a stoichiometric amount of $BF_3{\cdot}OEt_2$ was used.[6a] Yamamoto reported the use of allyl palladium complex as catalyst,[6b] but the main drawback of this method is the use of 0.5 equiv (based on reactant) of tetrabutylammonium fluoride as cocatalyst. The reaction does not proceed without the use of cocatalyst. The third method used *N*-trimethylsilylcarbamate as amine source in the presence of a catalytic amount of triphenylmethyl perchlorate.[6c] This method needs prior silylation of carbamate to carry out the reaction. In addition to the drawback of the use of expensive catalyst (and cocatalyst), these methods use stringent dry reaction condition and long reaction time. Ollevier et. al. reported very recently an one-pot method for the synthesis of Cbz-protected homoallylamines using bismuth triflate as catalyst.[6d] This method has drawback of long reaction time and use of expensive metal triflate. In recent years, iodine is emerging as a very effective Lewis acid catalyst for various organic transformations.[7] We recently reported the effectiveness of iodine in catalyzing Mukaiyama aldol reactions.[8] Herein, we wish to report the simplest, rapid and one-pot procedure for the synthesis of homoallylic amine using iodine as catalyst (Scheme 1).

SCHEME 1

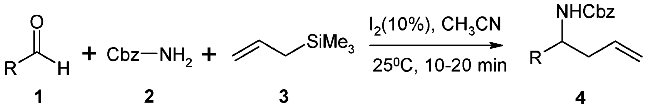

TABLE 1. Synthesis of Homoallylic Amine 4a under Different Conditions[a]

run	iodine (mol %)	solvent	time (min)	yield[b] (%)
1	5	MeCN	25	82
2	10	MeCN	10	80
3	20	MeCN	7	75
4	10	CH_2Cl_2	25	74

[a] Reaction conditions: benzaldehyde, 1 mmol; benzyl carbamate, 1.05 mmol; allyltrimethylsilane, 1 mmol; solvent, 2 mL; 25 °C. [b] Isolated yield after chromatographic purification.

Initially a systematic study was carried out for catalytic evaluation of iodine for benzaldehyde (Table 1). The reaction was carried out by adding benzyl carbamate and allyltrimethylsilane to a solution of benzaldehyde and iodine in acetonitrile at room temperature. Reaction went into completion in 10 min when 10 mol % of iodine was used as catalyst. Rate enhancement was observed when

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TABLE 2. Synthesis of Cbz-Protected Homoallylic Amine

entry	R	product	time (min)	yield[a] (%)
a	Ph	**4a**	10	80
b	4-NO_2-Ph	**4b**	20	69
c	4-Br-Ph	**4c**	10	78
d	4-MeO-Ph	**4d**	15	79
e	3-Cl-Ph	**4e**	10	82
f	2-Furyl	**4f**	10	66
g	Ph-CH_2	**4g**	15	72
h	Ph-CH_2-CH_2	**4h**	15	72
i	$CH_3(CH_2)_6$	**4i**	15	71
j	$(CH_3)_2CH$	**4j**	15	74

[a] Isolated yield after chromatographic purification.

20 mol % of iodine was used, but relatively lower yield was observed. Moreover, use of dichloromethane as solvent instead of acetonitrile led to weaker results (74%, 25 min).

Encouraged by these results, we have extended the process to a variety of aldehydes, which are summarized in Table 2. In general, excellent yields of homoallylamines were obtained with 10 mol % of iodine at room temperature in acetonitrile. No traces of the corresponding homoallylic alcohol resulting from direct addition of allyltrimethylsilane to the aldehyde were observed. Both aromatic and aliphatic aldehydes undergo homoallylation with 66−82% yield irrespective of the nature of the substrate.

Mechanistically, the reaction proceeds through the formation of bisurethane at the initial stage.[6a,c] The bisurethane was isolated by quenching the reaction at an intermediate stage. The reaction proceeds further via the formation of intermediate acylimine, which undergoes nucleophilic attack by allyltrimethylsilane in the presence of Me_3Si^+. It is well-known that iodine reacts with allyltrimethylsilane to form trimethylsilyliodide.[9] The role of Me_3Si^+ in the case of allylation of aldehyde catalyzed by Me_3SiI[10] and $TfOH_2^+B(OTf)_4^-$[11] is well documented. These facts support the involvement of Me_3Si^+ in the catalytic cycle.

In conclusion, iodine shows a very strong catalytic activity, which is much faster then any catalyst reported so far, for the synthesis of Cbz-protected homoallylamines. The merits of this method are that (a) it is a very simple, one-pot, rapid, and high yielding process; (b) iodine is very cheap and easily available as compared to any other catalyst; (c) a catalytic amount of iodine is required to promote the reaction whereas an equimolar amount of $BF_3{\cdot}OEt_2$ was used in earlier methods; (d) the method is not toxic; and (e) iodine is not moisture-sensitive and reactions are carried out in air. Moreover, this method does not require prior isolation of the imine. The present work demonstrates that iodine is extremely powerful catalyst for the synthesis of homoallylic alcohols with excellent yield.

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Supporting Information Available: Analytical data of the compounds and ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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