A Simple and Efficient Method for the Three-Component Synthesis of Homoallylic Amines Catalyzed by Indium Triflate

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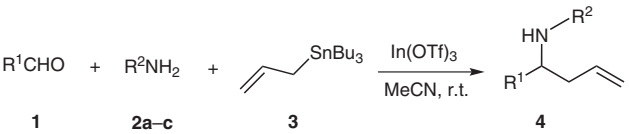
Abstract: Indium triflate catalyzes efficiently the one-pot three-component condensation of aldehydes, amines, and allyltributylstannane to afford the corresponding products of homoallylic amines in excellent yields at room temperature. All reactions were carried out using the catalyst in 10 mol%. This methodology was successfully applied to a variety of aldehydes and amines.

Key words: aldehydes, amines, allyltributylstannane, indium triflate, homoallylic amines

The reaction in which three or more reactants come together in a single reaction vessel to form a new product that contain portions of all the components is called the multicomponent condensation reaction. The multicomponent condensation strategies offer significant advantages over conventional linear type synthesis to provide products with the diversity needed for the discovery of new lead compounds or lead optimization employing combinatorial chemistry. The one-pot synthesis of homoallylic amines comes under multicomponent condensation reactions in which aldehyde, amine, and allylating agent are reacting at a time. The resulting homoallylic amines are useful intermediates in the synthesis of biologically active compounds such as statin, conine, lobeline, sedamine, SKF-100330-A, epothilone, β-lactams, β-amino acids, and many natural products.[1] In view of the synthetic importance, the homoallylic amine preparation attracts many researchers. In general, homoallylic amines are prepared either by the addition of organometallic reagents to imines or by the nucleophilic addition of allylsilane or allyltin or allylborane or allylgermane reagents, in the presence of a variety of catalysts.[2] The catalysts include different metals such as magnesium, silicon, tin, samarium, lithium, zinc, cerium, boron, molecular iodine, indium and chromium,[3] metal halides such as CuI, $TiCl_4$, $SnCl_2$, $TaCl_5$,[4] metal triflates,[5] ionic liquids,[6] metal perchlorates, $BF_3{\cdot}OEt_2$, metal oxychlorides,[7] and other catalysts.[8] However, many of the methods have some drawbacks, which involve use of strong Lewis acids, prolonged reaction times, vigorous reaction conditions, and low yields of products. Therefore, the development of an efficient one-pot synthesis of homoallylic amines is an active ongoing research area and there is scope for further improvement towards milder reaction conditions. Indium triflate is well known in the literature as an efficient catalyst for various organic transformations.[9] Herein we report a simple and efficient protocol for the synthesis of homoallylic amines using aldehyde, amine, and allyltributylstannane in the presence of a mild Lewis acid, indium triflate [$In(OTf)_3$], at room temperature.

In a typical experiment, an equimolar amount of 3,4,5-trimethoxybenzaldehyde, *p*-toluidine, and allyltributylstannane were reacted in the presence of a catalytic amount (10% mol) of indium triflate to afford the corresponding derivative of 4-methyl-*N*-[1-(3,4,5-trimethoxyphenyl)but-3-enyl]benzeneamine (**4a**) as shown in Scheme 1. The conversion was complete within three hours at room temperature and the product was obtained in 95% yield (Table 1). In a similar manner, an equimolar amount of 3-allyloxy,4-methoxybenzaldehyde, aniline, and allyltributylstannane were reacted in presence of a catalytic amount (10% mol) of indium triflate to afford the corresponding derivative of *N*-[1-(3-(allyloxy)-4-methoxyphenyl)but-3-enyl]benzeneamine (**4b**) in 90% yield. The conversion was complete within five hours at room temperature. Encouraged by the results obtained with the above reactions, this methodology was applied successfully to a variety of aldehydes such as aromatic, heteroaromatic, aliphatic and alicyclic with aniline, *p*-toluidine, and cyclohexylamine. The aldehydes containing electron-withdrawing and electron-donating groups in the aromatic ring were reacted smoothly to afford the corresponding derivatives of homoallylic amines in very good yields. The aliphatic system of butyraldehyde was reacted smoothly with aniline (Table 1, entry **h**) to afford the corresponding derivatives in very good yields. The acid sensitive aldehydes such as furfuraldehyde (entry **f**), cinnamaldehyde (entry **i**), indole aldehyde (entry **j**), and pyridine aldehyde (entry **m**) were reacted with aniline and *p*-toluidine to afford the homoallylic amine derivatives in very good yields and no decomposition or polymerization or allylic alcohol was found under these reaction conditions. Furthermore, benzalde-



2a R^2 = Ph
2b R^2 = 4-MeC_6H_4
2c R^2 = *c*-Hex

Scheme 1

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hyde and cyclohexylamine (entry **l**), cyclohexanecarboxaldehyde and aniline (entry **n**), and cyclohexanecarboxaldehyde and *p*-toluidine (entry **o**) were found to undergo efficient conversion with allylstannane in the presence of indium triflate to furnish the homoallylic amines. In general, the reactions were complete with in three to seven hours and the yields of products were in the range of 80 to 95%. All the products were isolated and purified by column chromatography and identified by their ^{1}H NMR, IR, and mass spectroscopy data.

Table 1 One-Pot Synthesis of Homoallylic Amines Catalyzed by $In(OTf)_3$

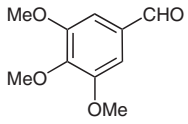
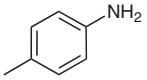
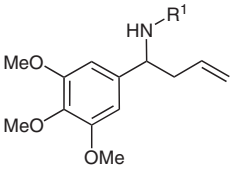
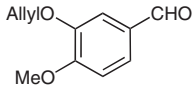
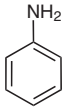
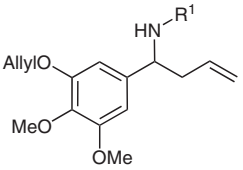
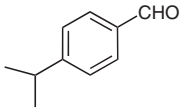
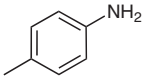
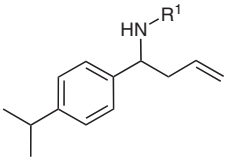
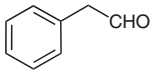
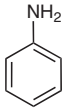
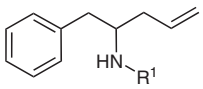
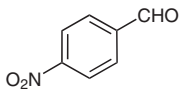
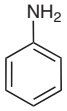
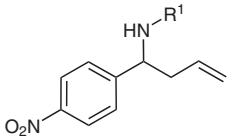
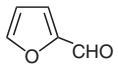
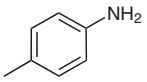
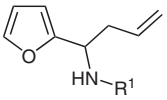
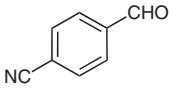
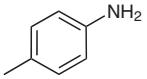
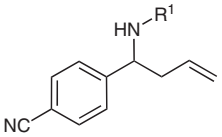
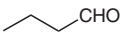
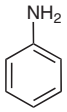
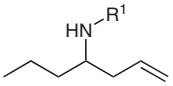
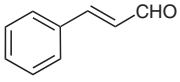
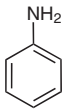
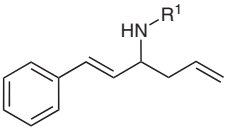
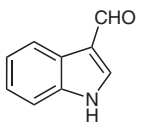
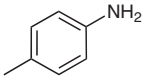
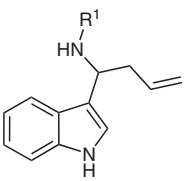
Entry	Aldehyde	Amine	Product[a] **4a–o**	Time (h)	Yield (%)[b]
a				3	95
b				5	90
c				4	89
d				6	87
e				7	84
f				3	92
g				5	91
h				6	80
i				6	84
j				7	85

Table 1 One-Pot Synthesis of Homoallylic Amines Catalyzed by In(OTf)$_3$ (continued)

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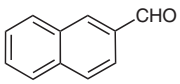
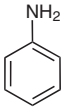
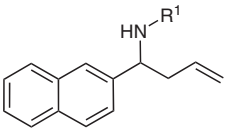
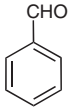
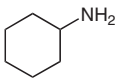
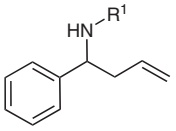
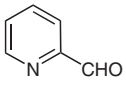
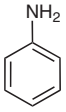
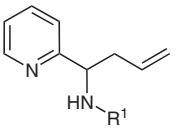
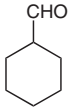
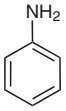
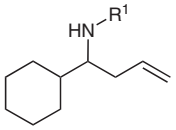
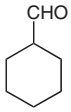
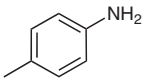
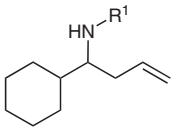
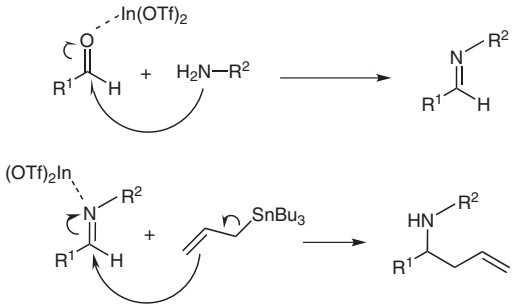
k				5	87
l				7	81
m				6	80
n				7	80
o				7	82

[a] R^1 = PhNH, R^2 = 4-MeC$_6$H$_4$NH, R^3 = *c*-C$_6$H$_{11}$NH. All products were identified by their ^{1}H NMR, IR, and mass spectra.
[b] Unoptimized yields of isolated products.

The proposed reaction mechanism (Scheme 2) shows that the aldehyde reacts first with amine to form imine. Thus formed imine undergoes nucleophilic addition by allyltributylstannane to afford the corresponding derivative of homoallylic amine. In this process the catalyst indium triflate plays a vital role in the activation of the carbonyl group to form the imine and in the activation of the imine to react with allylating agent as shown in Scheme 2.



Scheme 2 A plausible reaction mechanism for the formation of homoallylic amines

In conclusion, we have demonstrated a simple and efficient three-component condensation methodology for the synthesis of homoallylic amines in excellent yields using indium triflate as catalyst. The method is very simple, clean, and applicable to a variety of reactants such as aromatic, hetero aromatic, aliphatic, and alicyclic systems.

IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectrophotometer using KBr optics. ^{1}H NMR spectra were recorded on a Gemini-200 spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finning MAT 1020 mass spectrometer operating at 70 eV.

Homoallylic Amines; General Procedure

To a stirred mixture of aldehyde (2 mmol), amine (2 mmol) and catalyst In(OTf)$_3$ (10 mol%) in MeCN (10 mL) was added allyltributylstannane (2 mmol) at 0 °C. The resulting reaction mixture was stirred at r.t. for the specified time shown in Table 1. The progress of the reaction was monitored by TLC. After completion of the reaction as indicated by TLC, the mixture was quenched by adding crushed ice at 0 °C and extracted with EtOAc (2 × 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to afford crude products, which were purified by column chromatography using silica gel (60–120 mesh) (eluent: EtOAc–hexanes, 3:7) (Table 1). The structures of all the products were confirmed by their ^{1}H NMR, IR, and mass spectroscopy data.[7,8] Spectral data for selected products are given below.

4-Methyl-*N*-[1-(3,4,5-trimethoxyphenyl)but-3-enyl]benzeneamine (4a)

Yellow solid; mp 65–66 °C.

IR (neat): 3402, 2959, 2932, 2873, 1618, 1591, 1521, 1458, 1417, 1324, 1269, 1232, 1183, 1125, 1041, 1002, 959, 915, 835, 808, 712 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.20 (s, 3 H), 2.38–2.48 (m, 1 H), 2.51–2.61 (m, 1 H), 3.85 (s, 9 H), 4.15–4.25 (m, 1 H), 5.12–5.22 (m, 2 H), 5.70–5.90 (m, 1 H), 6.35 (d, *J* = 6.5 Hz, 2 H), 6.85 (q, *J* = 6.0 Hz, 2 H), 7.10 (dd, *J* = 7.5, 3.0 Hz, 2 H).

EIMS: *m/z* (%) = 328 (M^+ + 1, 70), 297 (10), 278 (12), 253 (10), 223 (10), 221 (100), 191 (12), 190 (20), 175 (10), 159 (10), 151 (10), 130 (10).

_N_-[1-(4-Isopropylphenyl)but-3-enyl]-4-methylbenzeneamine (4c)
Brown liquid.

IR (neat): 3405, 3015, 2962, 2926, 2869, 2730, 1702, 1611, 1577, 1518, 1461, 1421, 1305, 1265, 1213, 1171, 1108, 1054, 994, 918, 830, 727 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.20 (s, 6 H), 2.18 (s, 3 H), 2.45–2.65 (m, 2 H), 2.85–3.05 (m, 1 H), 4.25–4.35 (m, 1 H), 5.20 (t, *J* = 6.5 Hz, 2 H), 5.68–5.78 (m, 1 H), 6.35 (d, *J* = 6.5 Hz, 2 H), 6.85 (d, *J* = 6.5 Hz, 2 H), 7.10 (d, *J* = 6.5 Hz, 2 H), 7.25 (d, *J* = 6.5 Hz, 1 H), 7.40 (d, *J* = 6.5 Hz, 1 H).

EIMS: *m/z* (%) = 280 (M^+ + 1, 100), 279 (15), 262 (20), 238 (35), 223 (10), 223 (10), 174 (10), 173 (20), 158 (10), 138 (10), 109 (10).

_N_-[1-(Furan-2-yl)but-3-enyl]-4-methylbenzeneamine (4f)
Yellow syrup.

IR (neat): 3415, 2924, 2859, 1618, 1518, 1442, 1300, 1260, 1218, 1183, 1150, 1074, 1005, 920, 808, 737 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.21 (s, 3 H), 2.62 (t, *J* = 6.0 Hz, 2 H), 4.49 (t, *J* = 6.0 Hz, 1 H), 5.12 (dd, *J* = 10.5, 6.0 Hz, 2 H), 5.60–5.80 (m, 1 H), 6.08 (s, 1 H), 6.22 (s, 1 H), 6.45 (d, *J* = 6.5 Hz, 2 H), 6.89 (d, *J* = 6.5 Hz, 2 H), 7.31 (s, 1 H).

EIMS: *m/z* (%) = 228 (M^+ + 1, 60), 226 (M^+ – 1, 100), 190 (10), 158 (45), 144 (25), 102 (20).

4-[1-(*p*-Toluidino)but-3-enyl]benzonitrile (4g)
Light-colored thick syrup.

IR (neat): 3401, 2924, 2855, 2227, 1615, 1519, 1460, 1411, 1300, 1265, 1112, 993, 921, 834, 809, 772 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.20 (s, 3 H), 2.45 (q, *J* = 5.0 Hz, 1 H), 2.55–2.65 (m, 1 H), 4.33–4.41 (m, 1 H), 5.15–5.25 (m, 2 H), 5.65–5.80 (m, 1 H), 6.28 (d, *J* = 6.5 Hz, 2 H), 6.82 (d, *J* = 6.5 Hz, 2 H), 7.48 (d, *J* = 6.5 Hz, 2 H), 7.60 (d, *J* = 6.5 Hz, 2 H).

EIMS: *m/z* (%) = 263 (M^+ + 1, 100), 261 (M^+, 10) 247 (10), 225 (10), 210 (10), 182 (20), 168 (10), 149 (15), 144 (10), 108 (25).

_N_-(1-Phenylbut-3-enyl)cyclohexaneamine (4l)
Brown syrup.

IR (neat): 3423, 3069, 3029, 2925, 2854, 1642, 1492, 1455, 1376, 1261, 1195, 1048, 915, 871, 800, 757, 701, 608 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 0.78–0.98 (m, 2 H), 1.22–1.42 (m, 7 H), 1.65 (s, 1 H), 1.80 (br s, 1 H, NH), 2.05 (s, 1 H), 2.40–2.55 (m, 2 H), 4.70 (t, *J* = 6.0 Hz, 1 H), 5.15 (t, *J* = 6.0 Hz, 2 H), 5.70–5.85 (m, 1 H), 7.25–7.40 (m, 5 H).

_N_-(1-Cyclohexylbut-3-enyl)benzeneamine (4n)
Yellow thick syrup.

IR (neat): 3409, 3075, 3018, 2924, 1639, 1601, 1505, 1321, 992, 912, 747, 691 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.00–1.28 (m, 5 H), 1.40–1.56 (m, 1 H), 2.12–2.38 (m, 2 H), 3.22 (dd, *J* = 5.1, 12.9 Hz, 1 H), 3.50 (br s, 1 H), 5.00–5.08 (m, 2 H), 5.72–5.84 (m, 1 H), 6.56 (d, *J* = 8.7 Hz, 2 H), 6.62 (t, *J* = 7.2 Hz, 1 H), 7.12 (dt, *J* = 7.2, 8.7 Hz, 2 H).

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