

# Indium-Mediated One-Pot Three-Component Reaction of Aromatic Amines, Enol Ethers, and Allylic Bromides

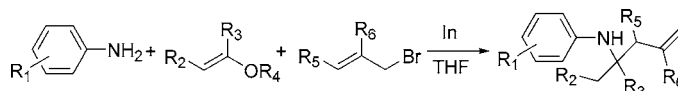
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## ABSTRACT



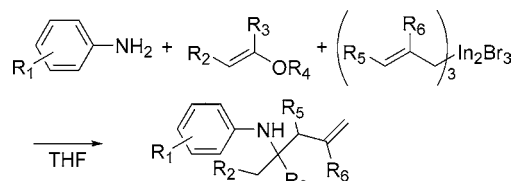
A new and efficient indium-mediated one-pot three-component reaction for the synthesis of *N*-aryl-substituted homoallylamines from aromatic amines, enol ethers, and allylic bromides in THF at room temperature is described.

Homoallylic amines are important fundamental building blocks for the synthesis of many nitrogen-containing natural products<sup>1</sup> and many biologically active compounds.<sup>2</sup> Moreover, *N*-aryl homoallylic amine compounds show potent antifungal activity.<sup>3</sup> A variety of synthetic methods have been developed for the preparation of homoallylamines.<sup>4</sup> In particular, the Lewis acid catalyzed allylation of aldimines provides a useful procedure for their synthesis, and diverse homoallylamines are rapidly accessible by a direct three-component reaction, which requires an aldehyde, an amine (or an amide), and a presynthesized allylic organometallic (Si, Sn, or Ge) reagent.<sup>5</sup> The chemistry of metallic indium is of current interest in organic synthesis due to its mediation ability for many organic transformations and its unique

property.<sup>6</sup> Recently, indium reagents have evolved as mild Lewis acids, increasing the rate of the reaction and affording high regio-, chemo-, and stereoselectivity in various chemical transformations.<sup>7</sup>

Our continuous efforts in the area of indium<sup>8</sup> led us to determine the utility of allylic indium compounds for the reaction of arylamines and enol ethers resulting in the construction of homoallylic amines (Scheme 1). This study

**Scheme 1.** Indium-Mediated Reaction of Aromatic Amines, Enol Ethers, and Allylic Bromides



demonstrated that enol ethers could be used as an aldehyde equivalent for the generation of imines in the one-pot reaction.

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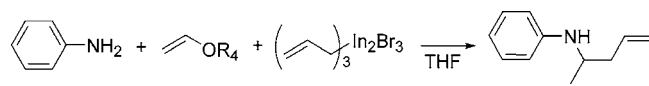
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We wish to disclose herein an efficient indium-mediated one-pot three-component reaction for the synthesis of *N*-aryl-substituted homoallyl amines from aromatic amines, enol ethers, and allylic bromides. Thus treatment of allylic indium compounds, generated in situ from allyl bromides and indium powder, with aromatic amines and enol ethers in THF at room temperature under argon for 2–24 h resulted in the formation of the corresponding homoallylic amine derivatives in moderate to good yields.

In our initial study, the reaction of various vinylic ether type compounds with aniline and allyl bromide was investigated to optimize the reaction conditions (Table 1).

**Table 1.** Indium-Mediated Reaction of Allyl Bromide, Aniline, and Various Vinylic Ether Compounds



entry	R <sub>4</sub>	isolated yield(%)
1	Et	91
2	Bu	84
3	Ac	21
4	SiMe <sub>3</sub>	59

Among them, ethyl vinyl ether was the best choice in this case, resulting in the formation of the corresponding homoallylic amine in 91% yield (entry 1).<sup>9</sup> Employing vinyl acetate led to poor result because acetanilide was formed (entry 3), and this reaction was applicable to trimethylsilyl enol ether (entry 4). No trace of aromatic allyl amines was

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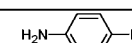
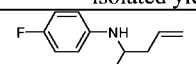
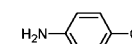
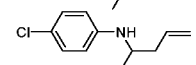
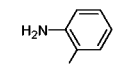
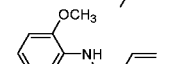
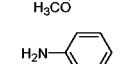
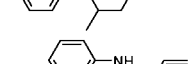
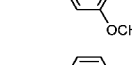
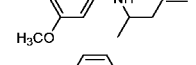
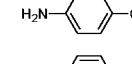
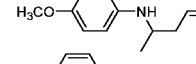
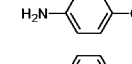
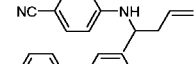
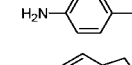
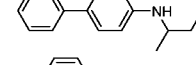
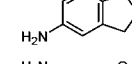
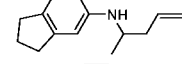
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(9) **Typical Procedure.** A mixture of indium (2 mmol) and allyl bromide (3 mmol) in THF (2 mL) was stirred for 1 h at room temperature under argon. Aniline (1 mmol) and ethyl vinyl ether (2 mmol) were added to the reaction mixture. After stirring for 2 h, the reaction was quenched with saturated aqueous ammonium chloride (5 mL). The whole mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with water (20 mL), dried over MgSO<sub>4</sub>, and evaporated. A pure product was obtained by flash column chromatography on silica gel (*n*-hexane/ethyl acetate = 20:1): <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 7.22 (t, 2H, *J* = 7.8 Hz), 6.73 (t, 1H, *J* = 7.4 Hz), 6.64 (d, 2H, *J* = 7.8 Hz), 5.95–5.81 (m, 1H), 5.18–5.13 (m, 2H), 3.60 (sxt, 1H, *J* = 6.3 Hz), 2.44–2.36 (m, 1H), 2.31–2.22 (m, 1H), 1.24 (d, 3H, *J* = 6.6 Hz); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 147.3, 134.9, 129.2, 117.5, 117.0, 113.2, 47.9, 40.8, 20.3; MS (EI, 70 eV) *m/z* (%) 161 (M<sup>+</sup>, 7.8), 120 (100), 104 (4.3), 91 (3.4), 77 (12.0).



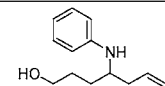


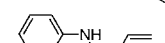

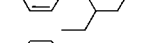


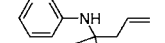


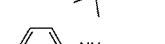

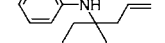
**Table 2.** Indium-Mediated Reaction of Allyl Bromide, Ethyl Vinyl Ether, and Various Amines

entry	aromatic amine	homoallylic amine	isolated yield(%)
1			88
2			82
3			81
4			85
5			94
6			5
7			94
8			92
9			88

detected in the crude reaction mixtures, whereas the reaction of aliphatic amines gave allylic amines exclusively via direct allylation reaction of amines.

The result of indium-mediated reactions of various aromatic amines with ethyl vinyl ether and allyl bromide is shown in Table 2. The reaction of anilines substituted with halogen, alkyl, or electron-donating alkoxy groups proceeded

**Table 3.** Indium-Mediated Reaction of Allyl Bromide, Aromatic Amines, and Various Enol Ether Type Compounds

entry	aromatic amine	enol ether	homoallylic amine	isolated yield(%)
1				72
2				17
3	aniline			52
4 <sup>a</sup>				34 <sup>b</sup>
5				52
6	<i>p</i> -anisidine			20

<sup>a</sup> 1-Ethoxycyclohex-1-ene was prepared from cyclohexanone and triethylorthoformate using *p*-toluenesulfonic acid by the known procedure.<sup>10</sup>

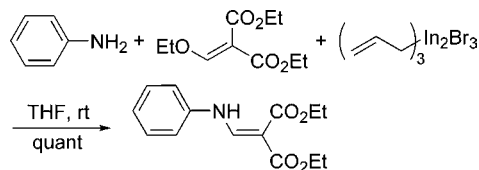
<sup>b</sup> Reaction was carried out at 60 °C (bath temperature) for 24 h.

to give the corresponding homoallylamines in high yields. In the case of 4-aminobenzonitrile, an electron-deficient aromatic amine, only a small amount of the product was obtained (entry 6).

Next, the generality of the indium-mediated reaction was examined with various enol ether type reagents, and the results are listed in Table 3. In all cases, the three-component one-pot reaction of enol ether type compounds with aromatic amines and allyl bromide proceeded smoothly to give the corresponding homoallylic amine. Under these conditions 2,3-dihydrofuran, a cyclic enol ether, undergoes ring opening to generate the homoallylic amine derivative bearing a hydroxypropyl side chain in a good yield (entry 1).

The reactions of  $\beta$ -substituted-(*E*)-vinyl ethers gave the corresponding product in lower yields. When 1-propenyl ether was treated with aniline or *p*-anisidine in the presence of allyl bromide and indium powder, the expected homoallylic amines were isolated in only less than 20% yields (entries 2 and 6). In the case of methyl *trans*-3-methoxyacrylate no reaction occurred at room temperature; however, the corresponding homoallylic amine was obtained in 52% yield at 60 °C for 24 h (entry 5). The low reactivity of methyl *trans*-3-methoxyacrylate could be explained by the generation of the stable enamine adduct through tautomerization of the imine intermediate formed by elimination of methanol. For example, under the same reaction conditions, diethyl ethoxy-methylenemalonate was converted exclusively into the corresponding enamine compound at room temperature (Scheme 2).

**Scheme 2.** Indium-Mediated Reaction of Aniline, Diethyl Ethoxymethylenemalonate, and Allyl Bromide



Further, the three-component reaction of *p*-anisidine and ethyl vinyl ether with various allylic bromides was investigated, and the results are summarized in Table 4. Starting from  $\gamma$ -substituted allylic bromides such as crotyl bromide, methyl 4-bromocrotonate, and cinnamyl bromide, the branched homoallylic amines were obtained exclusively in moderate yields as a mixture of diastereomers. Their  $\gamma$ -regioselectivities were analogous to the selectivity observed for the indium-mediated allylation of carbonyl compounds<sup>11</sup> and imines,<sup>12</sup> with  $\gamma$ -substituted allylic bromides.

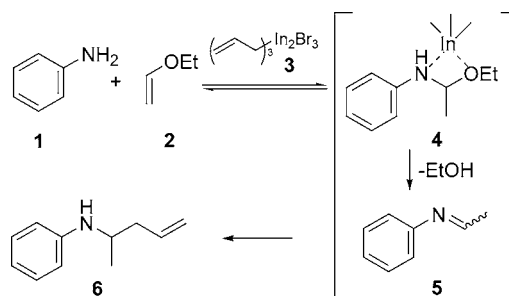
The proposed mechanism for the reaction of an aniline, an ethyl vinyl ether, and an allyl bromide in the presence of indium metal is illustrated in Figure 1. We suggest that the

**Table 4.** Indium-Mediated Reaction of *p*-Anisidine, Ethyl Vinyl Ether, and Substituted Allylic Bromides

entry	allylic bromide	homoallylic amine isolated yield(%)	dr <sup>a</sup>
1			51 62:38
2			60 -
3			64 80:20
4			54 70:30

<sup>a</sup> Diastereomeric ratio was determined by GC.

product was formed via a cascade hydroamination of an ethyl ether type compound/elimination of an alcohol/allylation of



**Figure 1.** Plausible reaction pathway.

an imine intermediate process. First of all, the *N,O*-acetal intermediate **4** is formed via  $\alpha$ -selective hydroamination of a vinyl ether **2** with an aromatic amine **1** in the presence of in situ generated allylic indium reagent **3** from allyl bromide and indium metal. Then, an imine adduct **5**<sup>13</sup> generated from **4** via subsequent elimination of an alcohol undergoes allylation reaction with the allylic indium compound **3** to give the corresponding homoallylic amine **6**. In this reaction, the allylic indium compound **3** plays a role in both the generation of an imine intermediate as a Lewis acid and the allylation reaction of imine as a nucleophile.

The generation of the imine intermediate by the hydroamination/elimination process has been confirmed by the reaction of aniline-*d*<sub>7</sub>. Thus, the one-pot three-component reaction of aniline-*d*<sub>7</sub>, ethyl vinyl ether, and allylindium bromide **3** proceeded to provide the corresponding homoallylamine compound **7** with deuterium on the carbon of the methyl group in 76% isolated yield (Scheme 3).

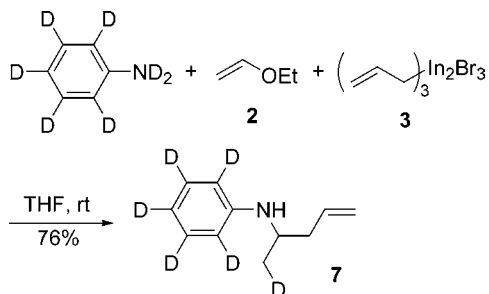
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**Scheme 3.** Indium-Mediated Reaction of Aniline-*d*<sub>7</sub>, Ethyl Vinyl Ether, and Allylindium Bromide



In conclusion, we have described a new and gentle indium-promoted one-pot three-component reaction for the preparation of *N*-aryl-substituted homoallylic amines from aromatic

amines, enol ethers, and allylic bromides. The reaction showed complete  $\gamma$ -regioselectivity and reasonable diastereoselectivity when  $\gamma$ -substituted allylic bromides were used. We were able to extend the scope of the utility of indium in organic synthesis. Further studies on the application of this protocol to organic synthesis are currently underway in our laboratory.

**Acknowledgment.** This work was fully supported by the Korea Institute of Science and Technology.

**Supporting Information Available:** General methods, characterization data, and spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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