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Highly efficient three-component synthesis of protected homoallylic amines by bismuth triflate-catalyzed allylation of aldimines

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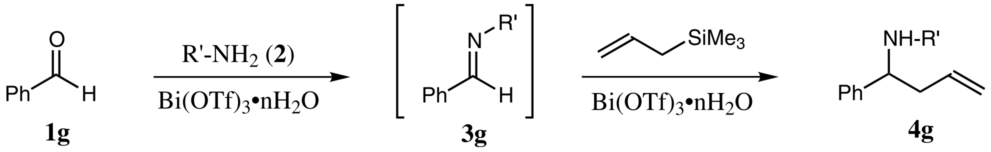
Abstract—Bismuth triflate catalyzes the allylation of a variety of in situ generated protected aldimines using aldehydes, primary carbamates, and allyltrimethylsilane in a three-component reaction. The reaction proceeds rapidly and affords the corresponding protected homoallylic amine in good yield (up to 86%). Scope and limitations of the aldehyde and carbamate components are reported.

Over the past two decades, Lewis acid catalyzed allylation of aldimines has become an important carbon–carbon bond forming reaction in organic synthesis. Allylation of aldimines provides a useful synthetic methodology for homoallylic amines, which are useful intermediates in natural product preparation,[1] and rapidly accessible by a three-component reaction recently developed by Veenstra[2] and pioneered by Panek.[3] In particular, acylated homoallylic amines are important synthons for many synthetic applications, notably for acyliminium chemistry.[4] A variety of catalysts have been introduced for the allylation of aldimines.[2,5–8] High catalytic activity, low toxicity, moisture and air tolerance make use of lanthanide triflates attractive catalysts. However, the high cost of these catalysts limits their use. Lately, synthetic methodologies involving bismuth triflate conjointly used with benzoic acid as catalyst for allylation of aldehydes or aldimines have been reported but have the major drawback of using stoichiometric quantities of allytributylstannane and benzoic acid.[9] To overcome these limitations, we report herein a mild and efficient method for the allylation of a variety of imines with allyltrimethylsilane catalyzed by bismuth(III) without any additives.

Bismuth compounds have attracted recent attention due to their low toxicity,[10] low cost, and good stability.[11,12] Bismuth salts have been reported as environmentally friendly catalysts for allylation reactions,[9,13,14] rearrangement of epoxides to aldehydes and ketones,[15] opening of epoxides,[16–18] acylation of alcohols,[19,20] formation or deprotection of acetals,[21–24] Friedel–Crafts acylations and sulfonylations,[25–28] Diels–Alder or aza-Diels–Alder reactions,[29,30] and intramolecular Sakurai cyclizations.[31,32]

$Bi(OTf)_3$ is particularly attractive because it can be easily prepared from commercially available starting materials.[33,34] In this context, we have examined $Bi(OTf)_3$ as a Lewis acid for the allylation of protected aldimines generated in situ from a protected amine and



Scheme 1.

Keywords: bismuth triflate; allylation; aldimines; allylsilane.

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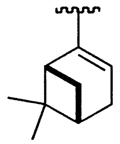
Table 1. Synthesis of *N*-protected homoallylic amines

Entry	R′	Conditions	Yield **4g** (%)[a]
1	Boc	20% Bi(OTf)$_3$, MeCN, 0.5 M, 25°C, 6 h	27
2	Cbz	10% Bi(OTf)$_3$, CH$_2$Cl$_2$, 1 M, 25°C, 24 h	51
3	Cbz	10% Bi(OTf)$_3$, MeCN, 1 M, 25°C, 3 h	59
4	Cbz	1% Bi(OTf)$_3$, MeCN, 0.5 M, 25°C, 3 h	74

[a] Refers to yield of isolated product.

Table 2. Synthesis of Cbz-protected homoallylic amines[a]

Entry	R	Product[b]	Time (h)	Yield (%)[c]
1	Me	**4a**	5	78
2	CH$_3$(CH$_2$)$_2$	**4b**	6	82
3	(CH$_3$)$_2$CH	**4c**	7	58
4	*c*-C$_6$H$_{11}$	**4d**	4	86[d]
5		**4e**	8	77
6	Ph-CH=CH	**4f**	8	73
7	Ph	**4g**	3	74
8	*p*-ClC$_6$H$_4$	**4h**	4	75
9	*p*-MeOC$_6$H$_4$	**4i**	6	81
10	*p*-CF$_3$C$_6$H$_4$	**4j**	6	75
11	*p*-NO$_2$C$_6$H$_4$	**4k**	6	27

[a] *Conditions*: substrate **1** and **2** were mixed in 1:1 ratio with 1.1 equiv. of allyltrimethylsilane.

[b] All the products (except products **4e**, **4f**, **4h**, and **4j**) have been previously reported in the literature.[2,35,36]

[c] Refers to yield of isolated product.[37]

[d] Yield based on the reaction time 23 h with substrate concentration of 0.2 M.

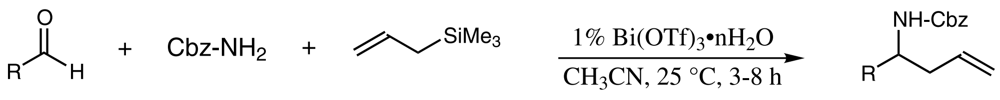
an aldehyde. We wish to present a one-pot, three-component reaction of an aldehyde, a carbamate, and allyltrimethylsilane in the presence of Bi(OTf)$_3$. The allylation was advantageously performed using an allylsilane instead of an allylstannane and the protected homoallylic amines **4** were obtained in very good yields.

The bismuth-catalyzed allylation reaction was first studied with isolated imines. Interestingly, when equimolar amounts of *N*-(benzyloxycarbonyl)benzaldimine **3g** and allyltrimethylsilane were treated with 1% Bi(OTf)$_3$ in acetonitrile for 14 h at 25°C, the protected homoallylic amine **4g** was isolated in low yield (18%). Consequently, a one-pot sequence involving the formation of the imine and its in situ allylation was investigated. We tried to generate the imine by the reaction of Cbz-NH$_2$ or BocNH$_2$ with benzaldehyde catalyzed by Bi(OTf)$_3$ (Scheme 1). The imine formed in situ was then subsequently allylated with allyltrimethylsilane to afford the desired homoallylic amine. Boc-protected homoallylic amine was obtained in poor yield using 20% Bi(OTf)$_3$ (Table 1, entry 1). When Cbz was used as the protecting group, the protected homoallylic amine **4g** could be obtained in modest yield with 10% of the catalyst. When acetonitrile was used instead of dichloromethane, a better yield was obtained (Table 1, entries 2 and 3). Moreover, a decreased quantity of Bi(OTf)$_3$ (1% versus 10%) led to a good yield of the Cbz-protected homoallylic amine (Table 1, entry 4).

Encouraged by our results in the one-pot fashion starting from aldehydes, we studied the scope and limitations of this reaction with respect to the aldehyde employed in the process. We chose to use the Cbz protecting group (Scheme 2). The results are summarized in Table 2.

Allyltrimethylsilane was used as the allylation agent in all the reactions. Generally excellent yields of homoallylic amines were obtained with 1% Bi(OTf)$_3$ at 25°C in acetonitrile. No traces of the corresponding homoallylic alcohols resulting from direct addition of allyltrimethylsilane to the aldehyde were observed. All the aromatic and aliphatic aldehydes gave very good results using benzylcarbamate. The allylation was efficient using aliphatic aldehydes and the corresponding homoallylic amines were obtained with very good yields (Table 2, entries 1, 2, 4, and 5). Isobutyraldehyde led to the product **4c** with moderate yield (Table 2, entry 3). Steric hindrance in the aldehyde component does not seem to play a significant role (Table 2, entry 5). Conjugated aldehydes were good substrates as well (Table 2, entries 5 and 6). Several aromatic aldehydes led to the desired products in good yields (Table 2, entries 8–10) except *p*-nitrobenzaldehyde leading to **4k** in poor yield (Table 2, entry 11).

In summary, we have found that allylation of in situ prepared imines proceeds smoothly with allyltrimethylsilane and a catalytic amount of Bi(OTf)$_3$. This method offers several advantages including mild reaction conditions, low quantity of the catalyst (1%), and no formation of by-products. Moreover, our protocol does not require prior isolation of the imine. The homoallylic amine is directly obtained as Cbz-protected group in a one-pot process. The application of Bi(OTf)$_3$ as a catalyst for other transformations is currently being pursued.



1a-k **2** **3** **4a-k**

Scheme 2.

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37. *Typical procedure for the bismuth triflate-catalyzed three-component reaction*: Under an inert atmosphere of argon, to a stirred solution of aldehyde (1 mmol), benzyl carbamate (1 mmol) and allyltrimethylsilane (1.1 mmol) in anhydrous acetonitrile (2 ml) at 25°C was added $Bi(OTf)_3$ (1%) in one portion. The mixture was stirred at 25°C during 3–8 h. After evaporation of the solvent under reduced pressure, the crude product was purified by column chromatography on silica gel (2% ethyl acetate–hexane).

    N-Benzyloxycarbonyl-1-(4-trifluoromethylphenyl)but-3-enylamine, ***4j***: White crystalline solid (yield 75%), mp: 77–78°C (from ether/hexane = 1:1). IR (KBr, cm^{-1}): 3283, 1718; ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 7.60$ (2H, d, $J = 7.8$ Hz), 7.31 (7H, m), 5.65 (1H, m), 5.11 (5H, m), 4.86 (1H, m), 2.53 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 155.6$, 146.1, 136.1, 132.9, 129.5 (q, $J = 32$ Hz, CF_3), 128.5, 128.2, 126.5, 125.5, 125.4, 122.7, 119.1, 66.9, 54.1, 40.8; HRMS: calcd for $C_{19}H_{19}F_3NO_2$ (MH^+): 350.1368; found: 350.1362.