Phosphomolybdic Acid-Catalyzed Efficient Three-Component Reaction: A Facile Synthesis of Protected Homoallylic Amines

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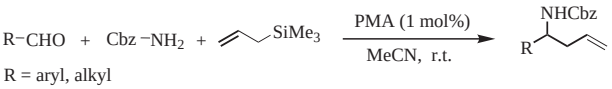
Abstract: A new and efficient phosphomolybdic acid ($H_3PMo_{12}O_{40}$)-catalyzed three-component reaction of aldehydes, carbamate and allyltrimethylsilane to yield the corresponding protected homoallylic amines in good yields is described.

Key words: phosphomolybdic acid, three-component reaction, homoallylic amines, heteropolyacid

Homoallylamines are useful synthetic intermediates in natural product synthesis and also precursors to β-amino acids and β-lactams.[1] They are commonly prepared by the allylation of aldimines prepared from aldehydes and amines in advance using allylic nucleophiles such as allyl silanes, allyl stannanes, and allylic organometallics.[2,3] To avoid the prior synthesis of aldimines a direct three-component reaction has been reported for the preparation of homoallylamines.[4,5] These three-component reactions are useful, not only because two bonds are formed in one step, but also because the methods are useful for preparing a broad variety of compound libraries. The catalysts employed for these three-component reactions are $BF_3{\cdot}OEt_2$,[4a] triphenyl methyl perchlorate,[4b] $Bi(OTf_3)$,[4d] I_2,[4e] etc.[4c] However, these methods while offering some advantages, also suffer from drawbacks such as the requirement of stoichiometric amounts of Lewis acid ($BF_3{\cdot}OEt_2$), prior silylation of the carbamate, use of a presynthesized organometallic agent, use of expensive catalysts and long reaction times. Furthermore, the protected homoallyl amines can easily undergo further conversions using well-established protective group chemistry without effecting the double bond.[6] Therefore, there is an important need to develop new methods for the synthesis of protected homoallylic amines using commercially available, pollution preventing green catalysts.

The application of solid acids as efficient heterogeneous catalysts continues to gain importance in organic synthesis.[7] Heteropolyacids (HPAs) are environment-friendly and economically feasible solid acids owing to their high catalytic activities and reactivities, ease of handling, allow cleaner reactions in comparison to conventional catalysts (less waste production), non toxicity and experimental simplicity.[8] Among the heteropolyacids, phosphomolybdic acid (PMA) is one of the less expensive commercially available catalysts that has not been utilized for the synthesis of protected homoallylic amines.[9]

In continuation of our interest in one-pot synthesis of amines from carbonyl compounds,[10] here we wish to report a facile and efficient synthesis of protected homoallylic amines using phosphomolybdic acid (PMA) as a catalyst. Accordingly, a three-component reaction of aldehydes, carbamate and allyltrimethylsilane in the presence of PMA ($H_3PMo_{12}O_{40}$) resulted in the formation of corresponding homoallylic amines in good yields (Scheme 1).

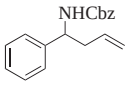
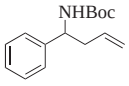
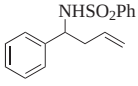


Scheme 1

First we examined the reaction of benzaldehyde and allyltrimethylsilane with benzyl, *tert*-butyl carbamate and benzene sulfonamide in the presence of 1 mol% PMA catalyst. The results are summarized in Table 1. The reaction with benzyl carbamate went to completion in ten minutes to provide the Cbz-protected homoallyl amine in 92% yield. Whereas, *tert*-butyl carbamate and benzene sulfonamide reactions are slower with relatively lower yields.

Based on the above results, we next examined the reaction of various aldehydes with benzyl carbamate and allyltrimethylsilane using 1 mol% of PMA catalyst in acetonitrile. The results are summarized in Table 2. Various

Table 1 Synthesis of N-Protected Homoallyl Amines from Benzaldehyde[a]

Entry	Amide	Time (min)	Amine	Yield (%)[b]
1	Cbz-NH_2	10		92
2	Boc-NH_2	45		64
3	$PhSO_2NH_2$	30		81

[a] Reaction condition: PMA (1 mol%), MeCN, r.t.
[b] Isolated yield after purification.

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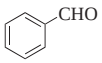
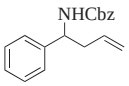
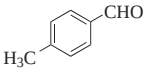
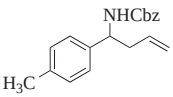
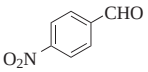
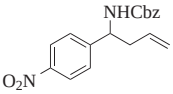
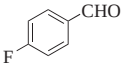
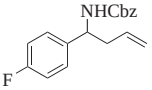
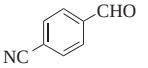
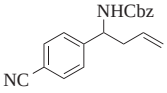
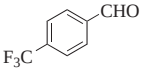
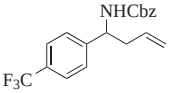
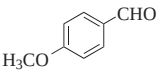
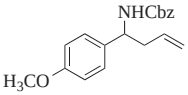
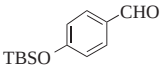
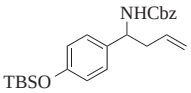
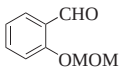
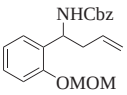
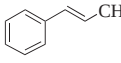
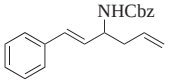
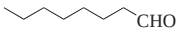
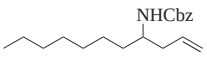
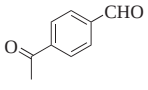
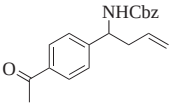
aromatic aldehydes having methyl, nitro, halo, cyano and trifluoro methyl groups at the *para*-position were employed for the production of the corresponding protected homoallylic amines in good yields (entries 2–6, Table 2). Application of the present methodology was also examined using aldehydes processing acid sensitive ethers (protecting groups) such as methyl, *tert*-butyl dimethylsilyl (TBS) and methoxy methyl (MOM). These correspond to entries 7–9 in Table 2. Similarly, the present protocol also behaved well with cinnamaldehyde and octanaldehyde to yield the corresponding Cbz-protected homoallylamines. The chemoselectivity of the present reaction was demonstrated by the conversion of the aldehyde to the homoallylamines in the presence of a keto group for the first time, as shown in entry 12.

Table 2 Synthesis of Cbz-Protected Homoallyl Amines

Entry	Aldehyde	Time (min)	Amine[a]	Yield (%)[b]
1		10		92
2		10		90
3		20		82
4		20		78
5		25		79
6		15		80
7		15		90
8		20		78
9		20		80
10		10		95
11		30		78
12		30		89

[a] All the products characterized by ^{1}H NMR, IR and mass spectroscopy.
[b] Isolated yields after purification.

In conclusion, an efficient and selective three-component reaction has been developed to produce the protected homoallylic amines in the presence of a catalytic amount (1 mol%) of PMA. The advantages of this protocol include mild reaction conditions, cleaner reaction profiles, and simple experimental procedure that all together make this method efficient.

General Experimental Procedure

To a stirred solution of aldehyde (1 mmol) in MeCN (10 mL), benzyl carbamate (0.151 g, 1 mmol) and allyltrimethylsilane (0.125 g, 1.1 mmol), PMA (18 mg, 1 mol% and commercially available) was added and the reaction mixture was stirred at r.t. for the given time (see Table 2). The solvent was evaporated in vacuo and the crude product was purified by column chromatography to yield the corresponding homoallylic amine.[11]

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(11) Spectroscopic data for the selected products:
Table 1, Entry 3: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 7.6 Hz, 2 H), 7.45 (t, *J* = 7.6 Hz, 1 H), 7.34 (t, *J* = 7.6 Hz, 2 H), 7.18–7.14 (m, 3 H), 7.07–7.04 (m, 2 H), 5.55–5.47 (m, 1 H), 5.08–5.04 (m, 2 H), 4.93 (br s, 1 H), 4.42–4.40 (m, 1 H), 2.46 (t, *J* = 5.2 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.6, 140.3, 133.2, 132.2, 128.7 (2 C), 128.3 (2 C), 127.4, 127.0 (2 C), 126.6 (2 C), 118.9, 57.6, 41.8. IR (neat): 3276, 2949, 2331, 1319, 1161, 753 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $C_{16}H_{17}NO_2S$: 310.0877 $[M + Na]^+$; found: 310.0870.
Table 2, Entry 8: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35–7.26 (m, 5 H), 7.18 (d, *J* = 7.5 Hz, 2 H), 6.85 (d, *J* = 8.5 Hz, 2 H), 5.67–5.61 (m, 1 H), 5.30–5.10 (m, 5 H), 4.85 (br s, 1 H), 2.56 (br s, 1 H), 1.05 (s, 9 H), 0.26 (s, 6 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.6, 154.6, 136.5, 134.7, 133.9, 128.4 (2 C), 128.0 (2 C), 127.3 (2 C), 119.9 (3 C), 118.1, 66.9, 54.5, 41.3, 26.1 (3 C), 18.6, –3.8 (2 C). IR (neat): 3325, 2929, 1698, 1509, 1256, 914 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $C_{24}H_{33}NO_3Si$: 434.2127 $[M + Na]^+$; found: 434.2120.
Table 2, Entry 9: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.41–7.34 (m, 5 H), 7.24 (dd, *J* = 2.0, 6.0 Hz, 2 H), 7.16 (d, *J* = 8.0 Hz, 1 H), 7.01 (t, *J* = 7.5 Hz, 1 H), 5.80–5.70 (m, 2 H), 5.30 (s, 2 H), 5.17–5.08 (m, 5 H), 3.52 (s, 3 H), 2.64 (t, *J* = 6.0 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.5, 154.2, 136.6, 134.5, 130.2, 128.4, 128.3, 128.1, 128.0, 127.9, 121.7 (3 C), 117.7, 114.2, 94.3, 66.8, 56.4, 52.2, 40.3. IR (neat): 3342, 2954, 1716, 1492, 1233, 995 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $C_{20}H_{23}NO_4$: 364.1524 $[M + Na]^+$; found: 364.1517.
Table 2, Entry 12: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (d, *J* = 8.0 Hz, 2 H,), 7.43–7.34 (m, 7 H), 5.66–5.58 (m, 1 H), 5.14–5.02 (m, 4 H), 4.85 (br s, 1 H), 2.58 (s, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.8, 155.9, 136.2, 133.4, 128.7 (3 C), 128.5 (2 C), 128.1 (2 C), 128.0 (2 C), 126.5 (2 C), 118.7, 116.5, 66.8, 40.8, 26.5. IR (neat): 3329, 3065, 1708, 1681, 1530, 1219, 698 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $C_{20}H_{21}NO_3$: 346.1417 $[M + Na]^+$; found: 346.1409.