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Re_2O_7-catalyzed three-component synthesis of protected secondary and tertiary homoallylic amines†

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Three-component synthesis of protected secondary and "for the first time" tertiary homoallylic amines is achieved from carbonyl, carbamate, and allyltrimethylsilanes using a Re_2O_7-catalyst under mild and open flask conditions. Excellent chemoselectivities and diastereoselectivities were observed.

In recent years, the synthesis of protected homoallylic amines[1] *via* a direct three-component reaction of carbonyl, carbamate, and semi-metallic allyl-reagents of silicon[2,3] or tin[4] has become an attractive strategy, because this eliminated the prior isolation of sensitive imines.[5–7] Unfortunately, these attempts are *limited to the synthesis of secondary homoallylic amines* starting from aldehydes; synthesis of the corresponding *tertiary homoallylic amines* from ketones using this strategy *still remains elusive*.[8–11] However, allylsilanes are more desirable as they are less toxic and more stable than allyltin. But, the low reactivity of allylsilanes limits their broader synthetic utility and this also involves the use of stronger Brönsted or Lewis acid-catalysts, such as $BF_3{\cdot}OEt_2$,[2a,c] triphenyl methyl perchlorate,[2b] $Bi(OTf)_3$,[2d] I_2,[2e] or phosphomolybdic acid.[2f] The strongly acidic conditions for these methods are incompatible with many functional groups. Also, they suffer from other limitations like, requirement of stoichiometric Lewis acid,[2a,c] prior silylation of the carbamate,[2b] and long reaction times.[2d] Therefore, a milder catalyst aimed towards allylsilane activation to *in situ* formed aldimines as well as ketimines is needed. Moreover, achieving the chemoselectivity of homoallylamine over allyl-alcohol formation should be an important factor, as imines are relatively less reactive than carbonyls.[7,12]

Recently, *oxo-rhenium* complexes in higher oxidation states have attracted considerable attention as catalysts for numerous organic reactions due to their mild reactivity, low toxicity, and air/moisture-tolerant nature.[13] We became interested to utilize those *oxo-rhenium* complexes as catalysts for this one-pot reaction constituted of the carbonyl, carbamate, and allyltrimethylsilane for the synthesis of the above said amines (Fig. 1).

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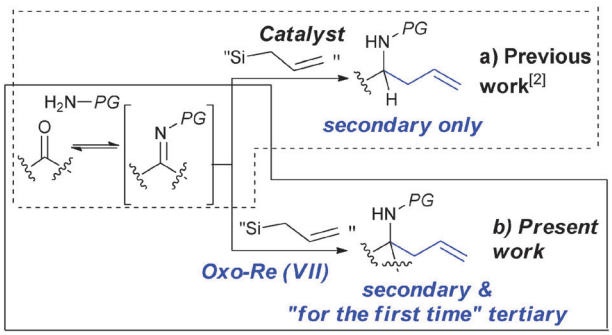
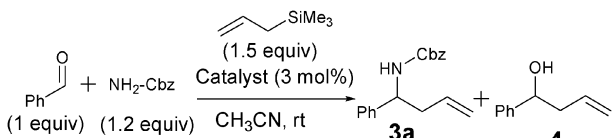


Fig. 1 Strategic representations: (a) a one-pot homoallylic amination of aldehydes, (b) a one-pot homoallylic amination of aldehydes and ketones using *oxo-rhenium(VII)* complexes.

The efficiencies of various oxo-rhenium catalysts were screened by treatment of benzaldehyde (**1a**) and allyltrimethylsilane with benzyl carbamate (**2a**) in the presence of 3 mol% of the catalyst in acetonitrile at room temperature (summarized in Table 1). Amongst the various *oxo-rhenium*(V)- and *oxo-rhenium*(VII)-catalysts, Re_2O_7 (1.5 mol%) was identified as the most efficient catalyst, with which the reaction proceeded to completion within 1 h to chemoselectively provide the desired homoallylic amine **3a** (Table 1). A further survey of the reaction conditions revealed that acetonitrile was the solvent of choice with respect to the rate as well as the chemoselective homoallylic amine formation.

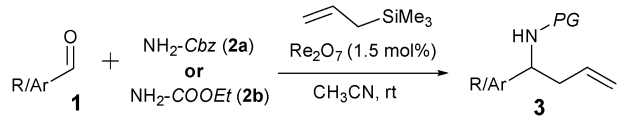
Table 1 Optimization of the reaction conditions



Entry	Catalyst	*t*/h	**3a**[a] [%]	**3a**/**4**[b]
1	None	3	0	—
2	$ReCl_3O(PPh_3)_2$	3	Trace	—
3	$ReIO_2(PPh_3)_2$	3	Trace	—
4	$ReCl_3O(SMe_2)PPh_3$	1	75	Trace
5	$MeReO_3$ (MTO)	1	40	60/40
6	Re_2O_7 (1.5 mol%)	1	90	>99/<1

[a] Yield of the isolated product after column chromatography. [b] Ratio was determined by ^1H NMR spectroscopy of the reaction mixture.

Table 2 Synthesis of secondary *N*-protected homoallylic amines



No.	R/Ar (**1**)	*PG*	*t*/h	**3**, [%][a,b]
1	*p*-MeC$_6$H$_5$-(**1b**)	*Cbz*	0.5	**3b**, 90
2	*p*-MeO–C$_6$H$_5$-(**1c**)	*Cbz*	0.75	**3c**, 84
3	*p*-Cl–C$_6$H$_5$-(**1d**)	*Cbz*	1	**3d**, 82
4	*p*-NO$_2$–C$_6$H$_5$-(**1e**)	*Cbz*	3	**3e**, 63
5	*p*-CN–C$_6$H$_5$-(**1f**)	*Cbz*	3	**3f**, 64
6	*p*-CF$_3$–C$_6$H$_5$-(**1g**)	*Cbz*	0.3	**3g**, 87
7	3-Thiophenyl-(**1h**)	*Cbz*	0.25	**3h**, 92
8	α-Naphthyl-(**1i**)	*Cbz*	1	**3i**, 93
9	Cinnamyl-(**1j**)	*Cbz*	0.25	**3j**, 85
10	Ph-C≡C-(**1k**)	*Cbz*	0.25	**3k**, 98
11	Cyclohexyl-(**1l**)	*Cbz*	0.3	**3l**, 96
12	Isobutyl-(**1m**)	*Cbz*	0.3	**3m**, 90
13	PhCH$_2$-(**1n**)	*Cbz*	0.25	**3n**, 76
14	PhCH$_2$CH$_2$-(**1o**)	*Cbz*	0.5	**3o**, 88
15	PhCHO (**1a**)	*EtOCO*	0.75	**3p**, 95
16	PhCH(OMe)$_2$ (**1p**)	*Cbz*	0.50	**3a**, 96

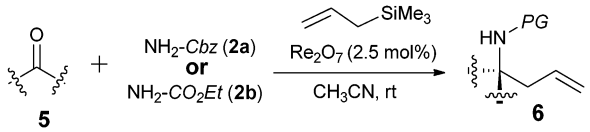
[a] Reaction conditions: **1** (1.0 mmol), **2a** or **2b** (1.2 mmol, 1.2 equiv.), Re_2O_7 (0.015 mmol, 1.5 mol%), allyltrimethylsilane (1.5 mmol, 1.5 equiv.), acetonitrile (4 mL), room temperature. [b] Yield of the isolated products after column chromatography; Cbz = carbobenzyloxy.

Encouraged by the efficiency of the Re_2O_7-catalyst for the above reaction, the scope of this methodology was examined with a variety of aldehydes (see Table 2). Various aromatic aldehydes having *–Me*, *–OMe*, *–Cl*, *–NO$_2$*, *–CN*, and *–CF$_3$* substitution at the *para*-position provided the corresponding secondary homoallylic amines in high yields (entries 1–6). Different aromatic aldehydes, like 3-thiophenyl and α-naphthyl aldehydes, were also successfully examined (entries 7 and 8 respectively).

Even unsaturated aldehydes (cinnamaldehyde **1j** and acetylenaldehyde **1k**) and aliphatic aldehydes (**1l–o**) provided the corresponding homoallylamine (entries 9–14) without any complication. Similar reactivity was observed on replacing *Cbz–* with *EtOCO–* (entry 15). Interestingly, benzaldehyde dimethylacetal also provided the corresponding homoallylic amine (**3a**) in excellent yield, as shown in entry 16.

Once the present protocol was well established for various aldehydes, we were interested to extend it towards ketones, which have been nearly unachievable so far using these reagents. Amazingly, the reaction worked smoothly even at room temperature using 2.5 mol% Re_2O_7 for cyclohexanone with *Cbz*–NH$_2$ (**2a**) and allyltrimethylsilane to provide the corresponding tertiary homoallylic amine (entry 1, Table 3). Eventually, we explored various cyclic and acyclic ketones (summarized in Table 3). Substituted cyclohexanones, like *2-Me, 4-Me, 4-HO*, and *4-tert-butyl* cyclohexanones, also were successful and the obtained yield varied from moderate to high (entries 3–7). The course of the reaction remained unaltered on replacement of *Cbz*–NH$_2$ (**2a**) by *EtOCO*–NH$_2$ (**2b**) (entries 2 and 7). Other cyclic ketones, cycloheptanone (**5f**) and adamantanone (**5g**) led to the desired products in good yield. Furthermore, we also extended the present methodology to acyclic ketones, which successfully proceeded to provide the corresponding tertiary homoallylic amines (entries 10–15).

Table 3 Synthesis of tertiary *N*-protected homoallylic amines



No.	Ketone, **5**	*t*/h	**6**, *PG*	[%][a,b]	(dr[c])
1	**5a** (X = H)	10	**6a**, *Cbz*	70	—
2		14	**6b**, *CO$_2$Et*	75	—
3	**5b** (X = 2-Me)	16	**6c**, *Cbz*	61	(20 : 80)
4	**5c** (X = 4-Me)	10	**6d**, *Cbz*	82	(10 : 90)
5	**5d** (X = 4-OH)	6	**6e**, *Cbz*	76	(23 : 77)
6	**5e** (X = 4-^{t}Bu)	8	**6f**, *Cbz*	90	(6 : 94)
7		6	**6g**, *CO$_2$Et*	86	(6 : 94)
8	**5f** (Cycloheptanone)	10	**6h**, *Cbz*	77	—
9	**5g** (2-Adamantanone)	12	**6i**, *Cbz*	68	—
10	**5h** (R = Me)	10	**6j**, *Cbz*	62	—
11	**5i** (R = Et)	12	**6k**, *Cbz*	40	—
12	**5j** (R = ^{i}Pr)	12	*Cbz*	—	—
13	**5k** (*n* = 4, R = Me)	10	**6l**, *Cbz*	54	—
14	**5l** (*n* = 10, R = Me)	12	**6m**, *Cbz*	49	—
15	**5m** (*n* = 2, R = Et)	18	**6n**, *Cbz*	78	—
16		8	**6a**, *Cbz*	76	—

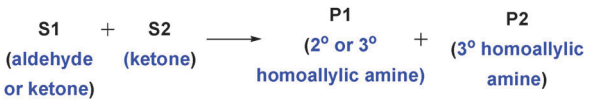
[a] Reaction conditions: **5** (1.0 mmol), **2a** or **2b** (1.5 mmol, 1.5 equiv.), Re_2O_7 (0.025 mmol, 2.5 mol%), allyltrimethylsilane (2.0 mmol, 2.0 equiv.), acetonitrile (4 mL), room temperature. [b] Isolated yield after column chromatography. [c] Diastereoselectivity (dr) was determined by ^{1}H NMR spectroscopy of the product mixture.

Interestingly, the reactivity also largely depends on the steric nature of the ketones. For example, upon changing the substitution from *Me-* to *Et-* to *^{i}Pr-*, the observed reactivity decreased significantly (entries 10 → 11 → 12). Furthermore, the corresponding dimethylketals of cyclohexanone also equally worked under the above optimized conditions (entry 16, Table 3).

Finally, we became interested to see the diastereoselectivity of the present methodology using carbonyls having a pre-existing stereocenter. This was demonstrated for the tertiary homoallylic amines obtained from *2-Me, 4-Me, 4-HO,* and *4-tert-butyl* cyclohexanones. Encouragingly, the ratio was observed up to *94 : 6* for homoallylic amines from *4-tert-butyl* cyclohexanones.

Finally, a series of competitive experiments were performed to study the chemoselectivity of the present protocol for the synthesis of secondary *vs.* tertiary and also between various tertiary homoallylic amines only (summarized in Table 4). When an equimolar mixture of aldehyde (**1o**) and corresponding methyl ketone **5h** was treated with amine **2a** and allyl-silane under the standard reaction conditions, a highly selective secondary homoallylic amine (**3o**) was obtained (entry 1) accompanied with unreactive ketone **5h**. The selectivity for the formation of secondary homoallylic amine (**3o**) increased on increasing the steric demand of ketones (*e.g.*, *Et-* and *^{i}Pr-*) (entries 1 → 2 → 3). Even excellent selectivity was observed between the formations of tertiary homoallylic amines. For example, between *Me- vs. Et-* or

Table 4 Chemoselective one-pot homoallylic amine synthesis



	S1 (1 eq.)	S2 (1 eq.)	t/h	P1[c] [%]	P1/P2[d]
1	**1o**	**5h**	2[a]	**3o**, 66	97 : 3
2	**1o**	**5i**	2[a]	**3o**, 87	>99 : 1
3	**1o**	**5j**	2[a]	**3o**, 84	>99 : 1
4	**5h**	**5i**	15[b]	**6j**, 25	>99 : 1
5	**5h**	**5j**	15[b]	**6j**, 43	>99 : 1
6	**5h**	PhCH=CHCOMe (**5o**)	15[b]	**6j**, 60	>99 : 1

[a] **S1** and **S2** (1 mmol each), **2a** (1 mmol), Re_2O_7 (1.5 mol%), allyl-TMS (1.1 mmol); [b] **S1** and **S2** (1 mmol each); **2a** (1.5 mmol), Re_2O_7 (6 mol%), allyl-TMS (2 mmol); [c] Isolated yield; [d] Determined by ^{1}H NMR spectroscopy of the product mixture.

Me- vs. ^{i}*Pr*-ketones, under similar conditions, selective formation of *Me*-substituted homoallylic amine was observed (entries 4 and 5). Finally, the selectivity between ketone (**5h**) and corresponding α,β-unsaturated ketone (**5o**) was compared; interestingly, the only obtained product (**6j**) was from ketone (**5h**) (entry 6).

In conclusion, we have developed a mild, one-pot, chemoselective, open-flask protocol using the Re_2O_7 catalyst for the synthesis of protected secondary and "for the first time" tertiary homoallylic amines from carbonyl, carbamate, and allyltrimethylsilane. This not only has offered a significant advantage over the previous reports for the synthesis of *secondary homoallylic amines,* but has also provided the unachievable synthetic protocol for *tertiary homoallylic amines* with high diastereoselectivity. The chemoselective formation of secondary as well as tertiary homoallylic amines has also been demonstrated. Further utilization of such *oxo-rhenium* complexes for catalytic reactions and developing their enantioselective variants are our current focus.

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