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Facile and Specific Nickel-Catalyzed De-*N*-allylation

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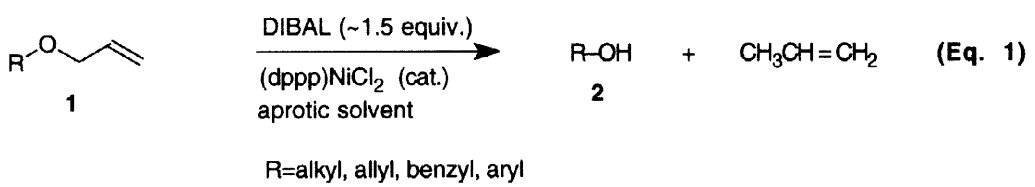
Abstract: A general procedure for a chemoselective removal of the allyl (2-propenyl) functionality on basic, neutral and acidic nitrogens by diisobutylaluminum hydride or trimethylaluminum in the presence of a catalytic amount of (dppp)$NiCl_2$ has been developed.

Keywords: Aluminum and compounds; Catalysts; Nickel and compounds; Protecting groups

Because it is not only basic as amines but also acidic as imides and neutral as amides, a nitrogen-hydrogen (-NH-) functionality requires various procedures for its protection as those for an oxygen-hydrogen (-OH) functionality. An allyl (2-propenyl) group is sometimes used for the protection of -NH- as well as for -OH functionalities, but difficulty in its removal prevents its versatile utility[1,2]. We recently discovered that a variety of allyl (2-propenyl) ethers are cleaved facilely to give the corresponding alcohols with specific removal of the allyl functionality as propene on exposure to diisobutylaluminum hydride (DIBAL) in the presence of dichlorobis(diphenylphosphino)propane nickel[4] [(dppp)$NiCl_2$] in an aprotic solvent[3] **(Eq. 1)**. In relation to this finding, we wanted to investigate its expansion to the cleavage of an allyl (2-propenyl) group on a variety of nitrogen functionalities so as to develop an efficient nitrogen-hydrogen (-NH-) protection-deprotection procedure. We wish to report herein the results that selective allyl cleavage did really occur as expected for most *N*-allyl substrates to afford the corresponding -NH- products ranging from a basic to acidic nature by use of a DIBAL in the presence of (dppp)$NiCl_2$.



1 **2** **(Eq. 1)**

R=alkyl, allyl, benzyl, aryl

Our studies began with the reaction of a series of allyl substrates on aliphatic, allylic, benzylic and aromatic amines. The reaction was carried out by treating a substrate amine in toluene with DIBAL (1.5 M in toluene: 1.5 equiv. for a tertiary amine and 2.5 equiv. for a secondary amine) at 0 °C in the presence of a catalytic amount of

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(dppp)$NiCl_2$ (4 mol % equiv.). The reaction completed after the mixture was stirred for 1 h at room temperature to give a deallylated amine[5]. The reaction proceeded without difficulty, regardless of the aliphatic, allylic, benzylic or aromatic amine substrates used, to give the corresponding secondary or primary amines in satisfactory yields with specific removal of the allyl (2-propenyl) group. When a substrate carried two different allyl functionalities on the same nitrogen, cleavage occurred specifically with the 2-propenyl functionality to give a monoallyl (prenyl) amine in high yield (Substrates: **3**f and **3**g). Selective monodeallylation of *N*,*N*-diallylamine was found to be difficult, even when using a limited amount of DIBAL (1.1 equiv.), to give a mixture of the monoallylamine (29 %) and the primary amine (26 %) accompanied with the unchanged starting material (30 %) though double deallylation occurred excellently with an excess amount of DIBAL (3.0 equiv.) (Substrate: **3** h). Most importantly, the deallylation did not occur at all in the absence of (dppp)$NiCl_2$ **(Eq. 2 and Table 1)**.

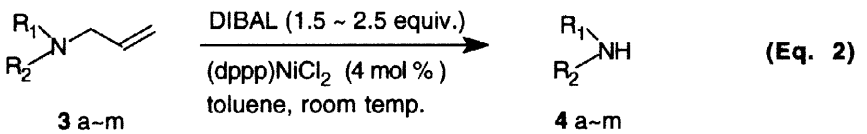


Table 1 Deallylation of Secondary and Tertiary Amines

Substrate **3**	R_1	R_2	Yield of **4** (%)[1]	Substrate **3**	R_1	R_2	Yield of **4** (%)[1]
a:	*O*-benzy-2-prolinol		a: 69	h:	$PhCH_2$	CH_2=$CHCH_2$	h: 79
b:	$PhCH_2CH_2$	$PhCH_2$	b: 87	i:	Ph	Me	i: 91
c:	$PhCH_2$	Me	c: 84	j:	Ph	$PhCH_2$	j: 80
d:	$PhCH_2$	$PhCH_2$	d: 82	k:	$PhCH_2CH_2$	H	k: 69
e:	1,2,3,4-tetrahydroisoquinoline		e: 90	l:	$PhCH_2$	H	l: 66
f:	$PhCH_2$	$(Me)_2C$=$CHCH_2$	f: 77	m:	Ph	H	m: 79
g:	Ph	$(Me)_2C$=$CHCH_2$	g: 80				

1) Isolated yield after SiO_2 column chromatography.

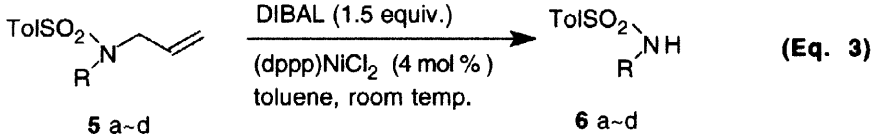
We next examined the reaction of *N*-allylated five-membered nitrogen hetero-aromatic compounds. As shown the deallylation occurred without difficulty to give the corresponding -NH- products in satisfactory yields under the same conditions using DIBAL in toluene at room temperature **(Table 2)**.

Table 2 Deallylation of Five-membered *N*-Hetero-aromatic Compounds

Substrate	Product	Yield (%)[1]	Substrate	Product	Yield (%)[1]
a: *N*-allylpyrrole	pyrrole	38[2]	d: *N*-allyltetrahydrocarbazole	tetrahydrocarbazole	81
b: *N*-allylimidazole	imidazole	81	e: *N*-allylcarbazole	carbazole	71
c: *N*-allylindole	indole	72	f: *N*-allyl-3,5-$(Me)_2$-pyrazole	3,5-$(Me)_2$-pyrazole	86

1) Isolated yield after SiO_2 column chromatography. 2) Low yield is due to its high volatility.

Similarly, facile deallylation also occurred with tertiary and secondary allylsulfonamides under the same conditions as above using DIBAL in toluene at room temperature to give the corresponding deallylated sulfonamides excellently. Generally, the cleavage of sulfonamides proceeded at much faster rate than with the amine and the hetero-aromatic counterparts **(Eq. 3 and Table 3)**.



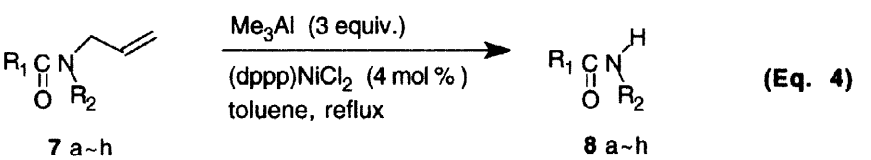
(Eq. 3)

Table 3 Deallylation of Sulfonamides

Substrate **5**	R	Yield of **6** (%)[1]
a:	$PhCH_2CH_2$	a : 93
b:	$PhCH_2$	b : 89
c:	Ph	c : 95
d:	H	d : 81

1) Isolated yield after SiO_2 column chromatography.

Disappointingly, it was found that *N*-allylamides were incompatible under these conditions where reduction of their carbonyl functionality prevailed. However, this drawback was overcome by using trimethylaluminum (3.0 equiv.) in place of DIBAL in the presence of (dppp)$NiCl_2$ (4 mol % equiv.) in toluene at boiling temperature to give the deallylated amides in good yields[6] **(Eq. 4 and Table 4)**. Without the nickel catalyst, deacylation instead of deallylation occurred to give the allylamines in poor yields. However, even under the modified conditions using trimethylaluminum, specific *N*-deallylation did not occur in the reaction of a variety of *N*-allyl carbamates which gave a complex mixture of products.



(Eq. 4)

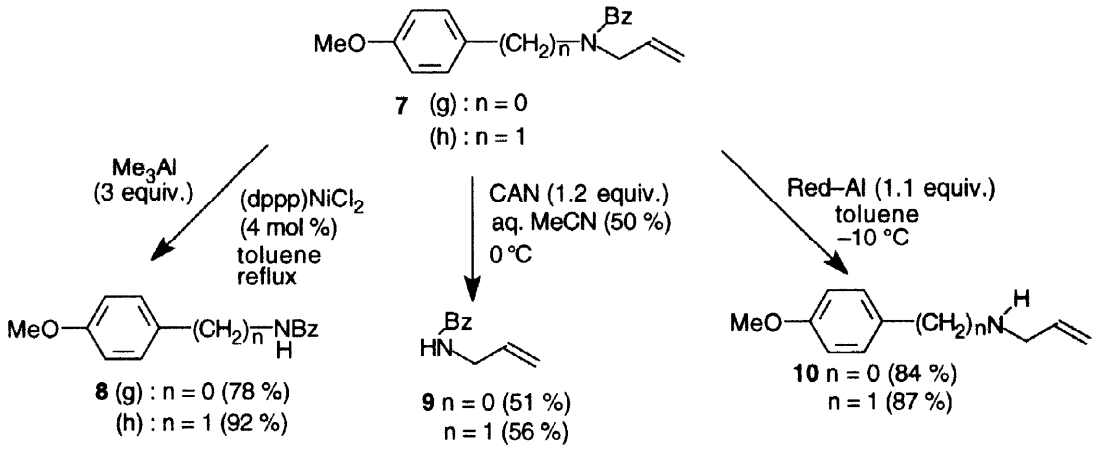
Table 4 Deallylation of Secondary and Primary Amides[1]

Substrate **7**	R_1	R_2	Yield of **8** (%)[2]	Substrate **7**	R_1	R_2	Yield of **8** (%)[2]
a:	Me	$PhCH_2CH_2$	a: 57	e:	Ph	$PhCH_2$	e: 70
b:	Me	$PhCH_2$	b: 51	f:	Ph	Ph	f: 73
c:	Me	Ph	c: 54	g:	Ph	4-$MeOPhCH_2$	g: 92
d:	Ph	$PhCH_2CH_2$	d: 78	h:	Ph	4-MeOPh	h: 78

1) The reaction did not occur at all at room temperature. 2) Isolated yield after SiO_2 column chromatography.

The controlled deprotection of two *N*-allyl benzamide derivatives, **7g** and **7h**, which may be taken as triply-protected forms of ammonia, demonstrates a potential of the present finding. Although only the mono-deprotection stage was shown, three *N*-protecting groups of **7g** and **7h** may be removed selectively without affecting one another to give ammonia in a three-step sequence by combination of the present de-*N*-allylation reaction, reductive removal of *N*-benzoyl group[7] and oxidative removal of *N*-4-methoxyphenyl[8] or *N*-4-methoxybenzyl group[9] **(Scheme 1)**.

In summary, the present study offers a convenient procedure for the removal of the *N*-allyl protecting group from a variety of nitrogen compounds.



Scheme 1

References and Notes

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5. All products were isolated and shown to possess satisfactory spectral (IR, ^{1}H NMR, MS) data.
6. Imides, however, gave ketoamides (eq. *N*-allylphthalimide gave *N*-allyl-2-acetylbenzamide) without generation of deallylation products even when using trimethylaluminum and (dppp)$NiCl_2$.
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10. Typical procedures: (a) **Use of DIBAL**— To a stirred solution of **3i** (100 mg, 680 μmol) and (dppp)$NiCl_2$ (15 mg, 27 μmol) in toluene (2 ml) was added DIBAL (1.5 M in toluene, 680 μl, 1.0 mmol) at 0 °C and the temperature raised to room temperature. After stirring at the same temperature for 1 h, the mixture was treated with 0.5 N NaOH (680 μl) and Et_2O (3 ml) for 1 h and the mixture was dried directly over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed (SiO_2 elution with Et_2O-hexane, 1:5 v/v) to give **4i** (66 mg, 91 %) (Table 1).
(b) **Use of Me_3Al**— A solution of **7f** (100 mg, 422 μmol) and (dppp)$NiCl_2$ (9 mg, 17 μmol) in toluene (2 ml) was refluxed with Me_3Al (0.98 M in hexane, 1.3 ml, 1.3 mmol) for 7 h. After cooling, the mixture was treated with 0.5 N NaOH (1.3 ml) and Et_2O (3 ml) for 1 h and the mixture was dried directly over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed (SiO_2 elution with Et_2O-hexane, 1:5 v/v) to give **8f** (61 mg, 73 %) (Table 4).