Neutral Coordinate-Organocatalysts in Organic Synthesis: Allylation of Acylhydrazones with Allyltrichlorosilanes

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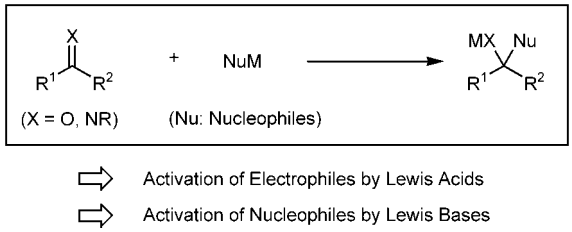
Abstract: *N,N*-Dimethylformamide (DMF), sulfoxides, and phosphine oxides, etc., which are neutral, uncharged molecules and coordinate to silicon atoms of organosilicon reagents to activate nucleophilic addition, are defined as *neutral coordinate-organocatalysts (NCOs)*. In the presence of *NCOs*, allylation reactions of acylhydrazones, useful imine surrogates, using allyltrichlorosilanes proceed smoothly to afford the synthetically useful racemic and non-racemic homoallylic amine derivatives in high yields with high diastereoselectivities.

Keywords: allylation; amides; C–C bond formation; hydrazones; organic catalysis; phosphane oxides; sulfoxides

1 Introduction

Addition of carbon nucleophiles to carbonyl and related compounds is one of the most important carbon-carbon bond-forming reactions in organic chemistry.[1] While carbanions such as lithium enolates[2] and Grignard reagents[3] react with electrophiles without the aid of any promoters in many cases, other nucleophiles were recently desired because the addition occurs under milder conditions without losing other functional groups.[4] These nucleophiles are inherently inert to the electrophiles without external promoters. There are two types of external promoter (Scheme 1). The first one, probably the most popular promoter, is a Lewis acid, which activates aldehydes, ketones, and imines, etc. under mild conditions.[5] While various Lewis acid catalysis processes including asymmetric variants using chiral Lewis acids have been investigated, drawbacks are that most Lewis acids are hygroscopic and are sensitive to nitrogen and other heteroatoms. The second one is a Lewis base, which activates nucleophiles. While anionic compounds such as fluoride anions and alkoxides have been used for this purpose,[6] drawbacks in this case are that these anionic compounds are sometimes too basic in the reaction mixture, inducing epimerization of enantiomerically enriched compounds. In addition, these compounds are incompatible with Lewis acids in many cases.

In 1993, it was found in our group that the allylation of aldehydes using allyltrichlorosilanes proceeded smoothly to afford the corresponding homoallylic alcohols in high yields in DMF or hexamethylphosphoramide (HMPA) as a solvent without any additional promoters.[7] In this reaction, it was confirmed by NMR analysis that DMF (or HMPA) coordinated to the silicon atoms of the allyltrichlorosilanes to form reactive hypervalent silicon intermediates.[8] After this report,



Scheme 1. Modes of activation for the nucleophilic addition to carbonyl and related compounds.

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Shū Kobayashi was born in Tokyo in 1959. He received his Ph. D. in 1988 under the direction of Professor T. Mukaiyama (The University of Tokyo). After spending eleven years at the Science University of Tokyo, he moved to the Graduate School of Pharmaceutical Sciences of the University of Tokyo in 1998. His research interests include the development of new synthetic methods and novel catalysts, organic reactions in water, solid-phase synthesis, total synthesis of biologically interesting compounds, and organometallic chemistry. He has received the Springer Award in Organometallic Chemistry (1997), the IBM Science Award (2001), and the Organic Reactions Lecturer Award (2002).

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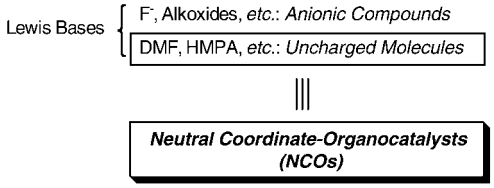


Scheme 2. Neutral coordinate-organocatalysts.

several groups have disclosed that not only DMF[9] and HMPA[10] derivatives but also *N*-oxides[11] and other organic compounds,[12] including their optically active derivatives for asymmetric catalysis, promoted the allylation of aldehydes.[13,14] These molecules work as Lewis bases to activate nucleophiles, but they are uncharged and neutral, thus the reactions proceed under neutral conditions. We thought that these molecules should be distinguished from the former anionic Lewis bases such as fluoride anions and alkoxides (Scheme 2). Hence, we defined these molecules as *neutral coordinate-organocatalysts* (*NCOs*).[15] In this paper, we describe the allylations of acylhydrazones using allyltrichlorosilanes, which are promoted by several *NCOs* to afford synthetically useful homoallylic amine derivatives.[16]

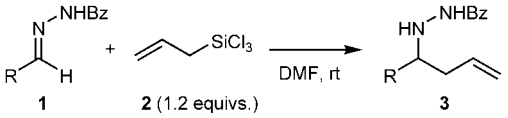
2 *N,N*-Dimethylformamide as an *NCO*[17]

2.1 Allylation of Aldehyde-Derived Acylhydrazones

We have previously reported that allyltrichlorosilanes reacted with aldehydes in DMF or HMPA to afford the corresponding homoallylic alcohols in high yields with high regio- and stereoselectivies.[7] This reaction system was quite attractive for us, because the reactions realized high yields and diastereoselectivities in a simple procedure under mild conditions. In view of the utility of these reactions, we undertook a study to apply them to the stereoselective synthesis of homoallylic amines by employing nitrogen analogues of aldehydes.

We first examined the reaction of allyltrichlorosilane with imines prepared from benzaldehyde and benzhydrylamine, but no addition occurred in DMF. An attempt to increase the electrophilicity of imines by using those derived from *p*-chloroaniline also failed to give the desired adduct. Assuming that the activation of allyltrichlorosilane by DMF might not be sufficient to react with imines, other Lewis bases such as HMPA, tributylphosphine, 4-(dimethylamino)pyridine, and ureas were added to the reaction mixture. However, they did not catalyze the addition. We judged on the basis of these results that imines were inert or very sluggish toward allyltrichlorosilane.[18] Thus, our attention was turned to using other nitrogen-containing electrophiles as imine equivalents.

Table 1. Allylation in DMF.

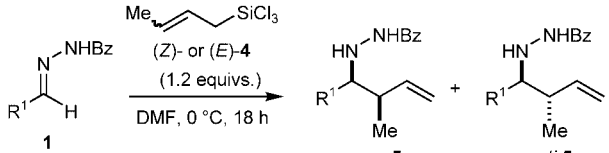


1 2 (1.2 equivs.) 3

Entry	1 (R)	Time [h]	Product	Yield [%]
1[a]	**1a** (Ph)	2	**3a**	95
2[b]	**1a**	2	**3a**	91
3	**1a**	1	**3a**	96
4	**1b** ((*E*)-PhCH=CH)	1	**3b**	90
5	**1c** ($Ph(CH_2)_2$)	15	**3c**	77
6	**1d** ($CH_3(CH_2)_4$)	13	**3d**	76
7	**1e** (*i*-Bu)	1	**3e**	73
8	**1f** (*c*-C_6H_{11})	15	**3f**	74
9	**1g** (*t*-Bu)	7	**3g**	77

[a] At 0 °C
[b] Carried out in HMPA at 0 °C.

Table 2. Crotylation in DMF.



1 *syn*-**5** *anti*-**5**

Entry	1 (R)	4[a]	Product	Yield [%]	*syn*/*anti*
1	**1a** (Ph)	*Z*	**5a**	79	1/99
2	**1a**	*E*	**5a**	59	78/22
3	**1b** ((*E*)-PhCH=CH)	*Z*	**5b**	80	3/97
4	**1b**	*E*	**5b**	82	95/5
5[b]	**1c** ($Ph(CH_2)_2$)	*Z*	**5c**	65	9/91
6[b]	**1c**	*E*	**5c**	66	92/8
7[b]	**1d** ($CH_3(CH_2)_4$)	*Z*	**5d**	65	7/93
8[b]	**1d**	*E*	**5d**	67	93/7
9[b]	**1e** (*i*-Bu)	*Z*	**5e**	65	7/93
10[b]	**1e**	*E*	**5e**	68	94/6
11[b,c]	**1f** (*c*-C_6H_{11})	*Z*	**5f**	61	5/95
12[b,c]	**1f**	*E*	**5f**	48	55/45
13	**1g** (*t*-Bu)	*Z*	**5g**	16	77/23
14[d]	**1g**	*Z*	**5g**	60	81/19
15[d]	**1g**	*E*	**5g**	49	3/97

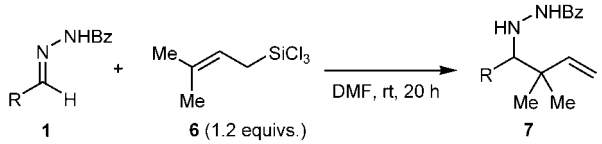
[a] Z-isomer (>99% *Z*) or *E*-isomer (97% *E*) was used.
[b] In the presence of *N,N*-diisopropylethylamine (0.1 equiv.).
[c] For 20 h.
[d] At room temperature.

Acylhydrazones, which are readily prepared from the corresponding aldehydes, have been shown in our laboratory to serve as electrophiles in Mannich-type, allylation, and cyanation reactions in the presence of a catalytic amount of a Lewis acid.[19] The resulting hydrazides can be converted to the corresponding primary amines.[20] To our delight, when the benzaldehyde-derived acylhydrazone (**1a**) was treated with allyltrichlorosilane (**2**) in DMF at 0 °C, the reaction proceeded smoothly to give the corresponding homoallylic hydrazide **3a** in excellent yield (Table 1, entry 1). The addition also proceeded cleanly in HMPA as solvent (entry 2), but only moderately in *N,N*-dimethylacetamide (DMA), THF, CH_3CN, and CH_2Cl_2 (44–29%). We then applied the allylation reaction with a range of acylhydrazones in DMF. The reaction was found to be tolerant not only to the aromatic acylhydrazone but also to α,β-unsaturated and aliphatic acylhydrazones **1b–g** including bulky ones to give the desired products **3b–g** in good yields (entries 3–9).

2.2 Crotylation of Aldehyde-Derived Acylhydrazones

Next, crotylation reactions were examined (Table 2). In the reaction of the benzaldehyde-derived acylhydrazone **1a** with (*Z*)-crotyltrichlorosilane (**4**), high *anti*-selectivity up to 99/1 was obtained (entry 1). In contrast, the reaction of (*E*)-crotyltrichlorosilane (**4**) gave the *syn*-adduct **5a** predominantly at 0 °C (entry 2). Similarly, the reaction of the cinnamaldehyde-derived acylhydrazone **1b** with (*Z*)- and (*E*)-**4** afforded *anti*- and *syn*-adducts **5b**, respectively, with exclusive 1,2-addition selectivity (entries 3 and 4). Meanwhile, initial attempts at crotylation of the 3-phenylpropanal-derived acylhydrazone **1c** gave a mixture of γ- and α-adducts unexpectedly. It was speculated that an acid inevitably produced from the reaction of crotyltrichlorosilane and water, despite careful manipulation, promoted the isomerization from the γ-adduct to the α-adduct.[21] Indeed, exclusive formation of the γ-adduct was achieved when 0.1 equiv. of *N,N*-diisopropylethylamine was added as a neutralizing agent, although the mechanism of the isomerization is still unclear (entries 5 and 6). Under these improved conditions, aliphatic acylhydrazones **1d–e** reacted with (*Z*)- and (*E*)-**4** to afford stereoselectively *anti*- and *syn*-adducts **5d–e**, respectively (entries 7–10). The stereoselectivity was extremely high in both cases. Interestingly, however, it was also observed that (*E*)-crotylation of a bulkier aliphatic acylhydrazone **1f** showed an eroded *syn*-selectivity, whereas (*Z*)-crotylation of **1f** provided high *anti*-selectivity (entries 11 and 12). More markedly, reversal of the stereochemistry was observed in (*E*)- and (*Z*)-crotylation of pivalaldehyde-derived acylhydrazone **1 g** (entries 13–15). This assignment was made on the basis of the observed tendency that a higher temperature gave a better diastereomeric ratio (entry 13 *vs.* 14) and that (*E*)-crotylsilane was more diastereoselective (entry 13 *vs.* 15), and was also supported by the similarity of the ^1H and ^{13}C NMR spectra of the related products. We discuss the origin of stereochemistry in Section 2.5.

Table 3. Prenylation in DMF.



1 **6** (1.2 equivs.) **7**

Entry	**1** (R)	Product	Yield [%]
1	**1a** (Ph)	**7a**	44
2	**1b** ((*E*)-PhCH=CH)	**7b**	48
3	**1c** ($Ph(CH_2)_2$)	**7c**	55

2.3 Prenylation of Aldehyde-Derived Acylhydrazones

It is noteworthy that the sterically more encumbered prenylation proceeded to afford the desired products in moderate yields, though the reaction rate was slower (Table 3).

2.4 Allylation and Crotylation of Ketone-Derived Acylhydrazones

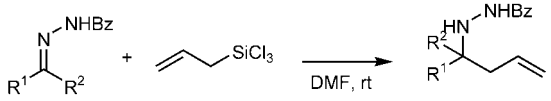
Although the addition of allylmetals to ketimines and their equivalents provides an efficient route to α,α-disubstituted homoallylic amines, it has been little investigated, since it often suffers from low reactivity due to steric hindrance and competing enolization.[1b,3b] In addition, the stereospecific addition of γ-substituted allylic metals has been unprecedented. In this context, we examined the allylation of ketone-derived acylhydrazones by means of the DMF-promoted addition of allyltrichlorosilanes (Table 4). We were delighted to find that the reaction of both aromatic and aliphatic ketone-derived hydrazones **1h–o** occurred smoothly to afford the corresponding adducts **3h–o** in high yields (entries 1–8).

More significantly, the sterically more demanding crotylation of aromatic ketone-derived acylhydrazones proceeded well by using 2.5 equivalents of crotylsilanes **4** at a high concentration (0.3 M) to show high levels of stereospecificity (from *Z* to *anti* and from *E* to *syn*) and high tolerance of electron-withdrawing and -donating substituents on the aromatic ring (Table 5). It can be concluded from the above results that the present allylation reactions tolerate well the steric hindrance of both acylhydrazones and allyltrichlorosilanes.

2.5 Transition State Models

Coordination of DMF to the silicon atom would enhance the nucleophilicity of the allyl group of allyltrichlorosilanes and, at the same time, the Lewis acidity of the silicon atom by dissociation of a chloride anion.

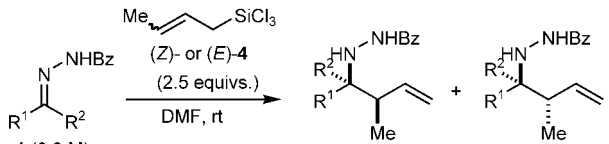
Table 4. Allylation of ketone-derived acylhydrazones in DMF.



1 **2** (1.2 equivs.) **3**

Entry	**1** (R^1, R^2)	Time [h]	Product	Yield [%]
1	**1h** (Ph, Me)	3	**3h**	95
2	**1i** (p-$MeOC_6H_4$, Me)	3	**3i**	95
3	**1j** (m-$NO_2C_6H_4$, Me)	3	**3j**	90
4	**1k** (2-naphthyl, Me)	3	**3k**	96
5	**1l** (Me, Me)	2	**3l**	60
6	**1m** ($Ph(CH_2)_2$, Me)	0.3	**3m**	81
7	**1n** ($-(CH_2)_5-$)	2	**3n**	62
8	**1o** (Ph, *n*-Pr)	3	**3o**	87

Table 5. Crotylation of ketone-derived acylhydrazones in DMF.



Entry	**1** (R^1, R^2)	**4**[a]	Time [h]	Product	Yield [%]	*syn*/*anti*
1	**1h** (Ph, Me)	*Z*	24	**5h**	52	2/98
2	**1h**	*E*	24	**5h**	46	92/8
3	**1p** (Ph, Et)	*Z*	24	**5p**	65	<1/>99
4	**1p**	*E*	24	**5p**	61	86/14
5	**1o** (Ph, *n*-Pr)	*Z*	12	**5o**	88	3/97
6	**1o**	*E*	24	**5o**	78	87/13
7	**1q** (p-ClC_6H_4, *n*-Pr)	*Z*	36	**5q**	77	<1/>99
8	**1q**	*E*	36	**5q**	68	91/9
9	**1r** (p-MeC_6H_4, *n*-Pr)	*Z*	29	**5r**	74	<1/>99
10	**1r**	*E*	29	**5r**	58	93/7
11	**1j** (m-$NO_2C_6H_4$, Me)	*Z*	24	**5j**	49	7/93
12	**1j**	*E*	24	**5j**	47	93/7
13	**1k** (2-naphthyl, Me)	*Z*	24	**5k**	37	2/98
14	**1k**	*E*	24	**5k**	49	93/7

[a] *Z*-isomer (>99% *Z*) or *E*-isomer (97% *E*) was used.

Two DMF molecules might also be involved according to the related allylation of aldehydes.[10] Meanwhile, coordination of the imino nitrogen and the benzoyl carbonyl group of acylhydrazones to the silicon atom is likely to serve for increasing the electrophilicity of the imino carbon and for stabilization of the transition structures. Accordingly, the stereochemistry of the reaction is most likely accounted for by assuming a chair-like transition state in which the imino nitrogen atom, the benzoyl carbonyl group, and DMF coordinate to the silicon atom (Figure 1).[22] The *trans*-geometry of acylhydrazone

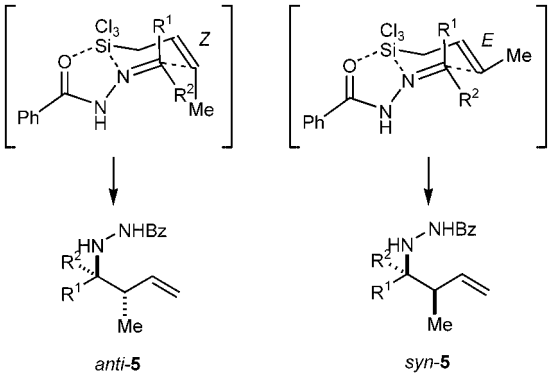


Figure 1. Assumed chair-like transition states.

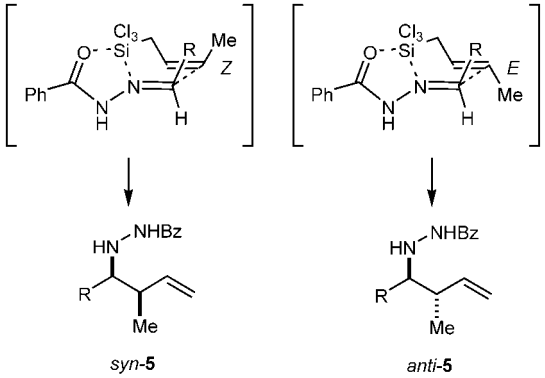


Figure 2. Assumed boat-like transition states.

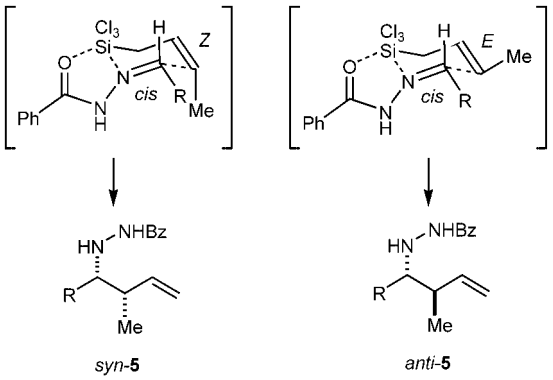


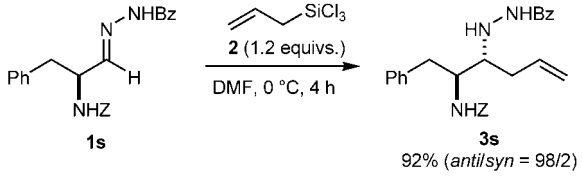
Figure 3. Assumed chair-like transition states with *cis*-acylhydrazones.

puts the R^1 group at an axial direction; consequently, *syn*- and *anti*-homoallylic hydrazines are stereospecifically obtained from (*E*)- and (*Z*)-crotyltrichlorosilanes, respectively.[16] It should be pointed out that the stereochemistries of these reactions are the reverse of those observed in type I crotylation of aldehydes.[14,16]

Meanwhile, erosion or reversal of diastereoselectivity was observed in the crotylation of bulky aliphatic acylhydrazones **1f** and **1 g**. In these cases, a boat-like transition structure (Figure 2)[23] or a chair-like structure with the R group at an equatorial position after geometrical isomerization of the acylhydrazone (Figure 3) could be considered.

2.6 Allylation of α-Chiral Acylhydrazones

The allylation of α-chiral, heteroatom-substituted acylhydrazones exhibited high levels of *anti*-diastereofacial selectivity (Scheme 3 and Table 6). A Felkin–Anh transition model with the electron-withdrawing heteroatom group as the large substituent could account for the stereochemistry (Figure 4).[24]



Scheme 3. Allylation of an α-amino acylhydrazone.

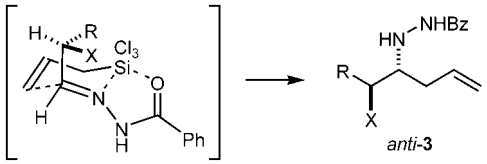
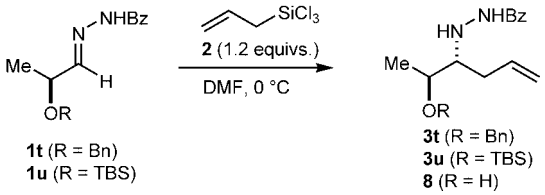


Figure 4. Assumed transition states.

Table 6. Allylation of α-oxy acylhydrazones.



1	Additive	Time [h]	Yield [%]	*anti*/*syn*[a]
1t	none	3	9 (**3t**), 56 (**8**)	92/8
1u	none	4	32 (**3u**), 35 (**8**)	97/3
1u	$(Me_3SiOCH_2)_2$ (0.2 equivs.)	12	66 (**3u**), 8 (**8**)	97/3

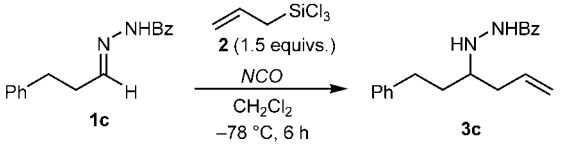
[a] The diastereomeric ratios of **3** and **8** were the same in each case.

3 Sulfoxides as *NCOs*[25]

3.1 Dimethyl Sulfoxide as an *NCO*

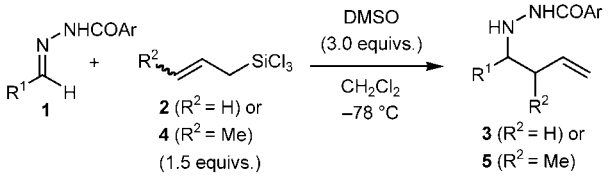
Since our finding of DMF- or HMPA-promoted allylation of aldehydes with allyltrichlorosilanes, an enantioselective version of this reaction has been achieved by

Table 7. Survey of *NCOs* in the allylation of **1c**.



Entry	NCO (equivs.)	Yield [%]
1	– (–)	9
2	DMF (1.0)	47
3	NMP (1.0)	49
4	$Me_2NCONMe_2$ (1.0)	38
5	Pyridine *N*-oxide (1.0)	36
6	Pyridine *N*-oxide (0.2)	30
7	HMPA (1.0)	64
8	HMPA (0.2)	16
9	$Ph_3P{=}O$ (1.0)	70
10	DMSO (1.0)	65
11	Tetramethylene sulfone (1.0)	9
12	Diphenyl sulfoxide (1.0)	40
13	Dibenzyl sulfoxide (1.0)	73
14	Tetramethylene sulfoxide (1.0)	57
15	(±)-Methyl phenyl sulfoxide (1.0)	57
16	DMSO (0.2)	24
17	DMSO (2.0)	85
18	DMSO (3.0)	99
19	DMSO (5.0)	86
20	DMSO (10.0)	33

Table 8. Allylation Using DMSO as an *NCO*.



Entry	**1** (R^1, Ar)	**2** or **4**	Time [h]	**3** or **5** (% yield, selectivity)
1	**1c** ($Ph(CH_2)_2$, Ph)	**2**	6	**3c** (99)
2	**1v** (Me, Ph)	**2**	15	**3v** (78)
3	**1w** (n-C_7H_{15}, Ph)	**2**	1	**3w** (86)
4	**1x** (*i*-Pr, Ph)	**2**	6	**3x** (89)
5	**1f** (c-C_6H_{11}, Ph)	**2**	6	**3f** (88)
6	**1y** (p-$MeOC_6H_4$, Ph)	**2**	6	**3y** (70)
7	**1z** (p-ClC_6H_4, Ph)	**2**	6	**3z** (33)
8	**1aa** (PhC≡C, Ph)	**2**	8	**3aa** (93)
9	**1ab** (Ph, p-$MeOC_6H_4$)	**2**	6	**3ab** (87)
10	**1ac** (p-MeC_6H_4, Ph)	**2**	6	**3ac** (72)
11[a]	**1c**	(*E*)-**4**[b]	6	**5c** (71, 98% *syn*)[d]
12[a]	**1c**	(*Z*)-**4**[c]	6	**5c** (69, >99% *anti*)[d]

[a] *i*-Pr_2EtN (0.1 equiv.) was added.
[b] 98% *E*.
[c] >99% *Z*.
[d] No α-adduct was obtained.

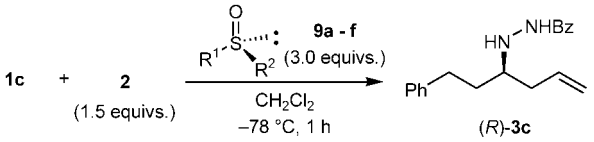
the development of effective chiral *NCOs* such as chiral *N*-formamides, phosphoramides, and pyridine *N*-oxides.[7,9–12,14] On the other hand, the enantioselective allylation of aza-equivalents has not been reported.[26] As already mentioned, it has been revealed that acylhydrazones serve as effective imine equivalents and react stereoselectively with allyltrichlorosilanes in the presence of DMF or HMPA as a solvent. Therefore, to address this issue, we first attempted to reduce the amount of *NCOs* employed. Several kinds of *NCOs* having different functional groups (0.2–10 equivs.) were tested for the reaction of the 3-phenylpropanal-derived acylhydrazone **1c** with allyltrichlorosilanes at $-78\,^{\circ}C$ in dichloromethane (Table 7). While the reaction scarcely proceeded in the absence of any *NCOs* (entry 1), 1 equiv. of DMF promoted the reaction (entry 2). Likewise, *N*-methyl-2-pyrrolidinone (NMP), 1,1,3,3-tetramethylurea, HMPA, triphenylphosphine oxide, pyridine *N*-oxide, and dimethyl sulfoxide (DMSO) were found to be effective (entries 3–5, 7, 9 and 10). Thus, $R_2NC{=}O$, $P{=}O$, $N^+{-}O^-$, and $S{=}O$ functional groups proved to activate allyltrichlorosilane. However, these *NCOs* in catalytic amounts were insufficient to promote the reaction under the employed reaction conditions (entries 6, 8, and 16). The fact that sulfoxides have not been utilized for the reactions of trichlorosilylated reagents[27] and that a variety of chiral, even *S*-chirogenic, sulfoxides are available[28] led us to a further investigation of the catalysis using sulfoxides. Allylation of **1c** with achiral or racemic sulfoxides revealed that sulfoxides with electron-donating substituents tended to provide higher activities (entries 10–15). The amount of the sulfoxide was also critical for obtaining high yields (entries 10 and 16–20). When 3 equivalents of DMSO relative to **1c** were used, the highest yield was obtained (99%). Larger or smaller amounts of DMSO decreased the yield (<86%).

Using 3 equivalents of DMSO, we found that the allylation of various aliphatic or aromatic acylhydrazones proceeded smoothly to give homoallylic hydrazides **3** in high yields (Table 8, entries 1–10). Moreover, stereospecific crotylation was achieved; that is, high *syn*- and *anti*-selectivities were obtained *via* the reaction of **1c** with (*E*)- and (*Z*)-crotyltrichlorosilanes (**4**), respectively (entries 11 and 12).

3.2 Asymmetric Allylation Using Chiral Sulfoxides

Knowing the effectiveness of sulfoxides in the reactions, we next investigated enantioselective allylation using chiral sulfoxides. At first, (*R*)-methyl *p*-tolyl sulfoxide (**9a**) was employed in the reaction of **1c** with **2** (Table 9). To our surprise, this simple sulfoxide was found to be effective, and high enantioselectivity was obtained after optimization of the reaction conditions (entry 1). The selectivity depended on the amount of **9a**, and the best

Table 9. Asymmetric allylation of **1c** using various chiral sulfoxides.



Entry	**9** (R^1, R^2)	Yield [%]	% ee (config.)
1	(*R*)-**9a** (Me, *p*-tolyl)[b]	73	93 (*R*)
2	(*R*)-**9b** (Et, *p*-tolyl)[c]	77	50 (*R*)
3	(*R*)-**9c** (*i*-Pr, *p*-tolyl)[d]	74	1 (*S*)
4	(*S*)-**9d** (*o*-tolyl, Me)[e]	75	30 (*S*)
5	(*S*)-**9e** (*o*-$MeOC_6H_4$, Me)[f]	79	42 (*S*)
6	(*S*)-**9f** (*p*-$MeOC_6H_4$, Me)[g]	91	69 (*S*)

[a] Method A: **2** (1.5 equivs.) was added to a solution of **1c** (0.3 mmol), **9** (3.0 equivs.), and 2-methyl-2-butene (0.5 equivs.) in dichloromethane (2 mL) at $-78\,^{\circ}C$.
[b] >99% ee (*R*).
[c] 98% ee (*R*).
[d] 91% ee (*R*).
[e] 90% ee (*S*).
[f] >99% ee (*S*).
[g] 88% ee (*S*).

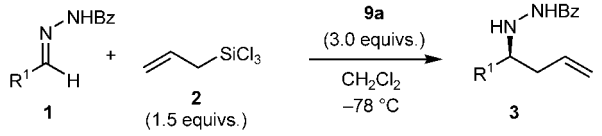
result was obtained when 3 equivalents of **9a** were employed. Addition of 2-methyl-2-butene was also found to be a key to suppress undesired racemization of **9a**. After a usual work-up, **9a** could be recovered in >90% with >97% ee. Under the optimal conditions for **9a**, other chiral sulfoxides **9b–f** were examined. The bulkier R^2 (R^2 = *p*-tolyl) became, the lower was the enantioselectivity obtained (entries 2 and 3). The steric hindrance on the R^1 substituent (R^2 = Me) also decreased the enantioselectivity, although the *ortho*-methoxy group of **9e** might coordinate to silane **2** (entries 4 and 5). Sulfoxide **9f** with an electron-donating *p*-methoxyphenyl group increased the yield (entry 6).

The substrate scope of the asymmetric allylation of acylhydrazones **1** using **9a** was next investigated (Table 10). Both aliphatic and aromatic acylhydrazones provided high enantioselectivity (entries 1–7). In addition, acylhydrazone **1aa** with a 1-alkynyl group provided the desired adduct **3aa** in high yield with good selectivity (entry 8). In some cases, precomplexation of **9a** with allyltrichlorosilane (**2**) before addition of **1** as well as a higher concentration improved the selectivity. This might be ascribed to the favorable formation of more enantioselective allylating species under the conditions.

3.3 Asymmetric Crotylation Using a Chiral Sulfoxide

Next, asymmetric crotylations with (*Z*)- and (*E*)-crotyltrichlorosilanes (**4**) were investigated under the conditions using chiral sulfoxide **9a** (Table 11). It was found that the reaction of aliphatic acylhydrazones proceeded well at a higher concentration exhibiting high stereospecificity (entries 1–6). (*E*)-**4** afforded *syn*-adducts **5**, while *anti*-adducts **5** were obtained from (*Z*)-**4** with excellent diastereoselectivity and good to high enantioselectivity. Meanwhile, acylhydrazone **1y** reacted with (*Z*)-**4** slowly under the same conditions, and high diastereo- and enantioselectivities were obtained (entry 7). Allylations of acylhydrazones derived from cinnamaldehyde, 2-thiophenecarboxaldehyde, 3-pyridinecarboxaldehyde, and acetophenone resulted in low yields under the present reaction conditions. In addition, acylhydrazone **1y** reacted with (*E*)-**4** sluggishly under the conditions.

Table 10. Asymmetric allylation of acylhydrazones.



Entry	**1** (R1)	Time [h]	**3** (% yield)	% ee (config.)
1[a,c]	**1v** (Me)	17	**3v** (78)	90 (*R*)
2[a]	**1w** (*n*-C_7H_{15})	1	**3w** (81)	88 (*R*)
3[b]	**1w**	1	**3w** (61)	92 (*R*)
4[a]	**1x** (*i*-Pr)	1	**3x** (80)	98 (*R*)
5[b]	**1f** (*c*-C_6H_{11})	1	**3f** (77)	91 (*R*)
6[a]	**1y** (*p*-$MeOC_6H_4$)	18	**3y** (82)	81 (*S*)
7[a,c]	**1z** (*p*-ClC_6H_4)	5	**3z** (69)	89 (*S*)
8[a]	**1aa** (PhC≡C)	8	**3aa** (95)	70 (*S*)

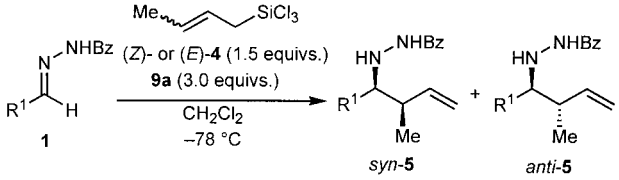
[a] Method A (see Table 9).
[b] Method B: a solution of **1** (0.3 mmol) in dichloromethane (1.2 mL) was added to a solution of **2** (1.5 equivs.), **9a** (3.0 equivs.), and 2-methyl-2-butene (0.5 equivs.) in dichloromethane (0.8 mL) at $-78\,^{\circ}C$.
[c] At a higher concentration (0.3 M).

4 Phosphine Oxides as *NCOs*[29]

4.1 Monophosphine Oxides as *NCOs*

As seen above, sulfoxides were found to be one of the most effective *NCOs* in the allylation of acylhydrazones with allyltrichlorosilanes, and enantioselective allylations have been achieved utilizing chiral sulfoxides. However, three equivalents of sulfoxides were required to obtain high reactivity and selectivity, and 2-methyl-2-butene was used as an acid scavenger due to the instability of sulfoxides under acidic conditions.[30] Therefore, our attention was turned to phosphine oxides, which were anticipated to be promising *NCOs* (see Table 7, entry 9) and more stable under acidic or oxidative conditions than sulfoxides.

Table 11. Asymmetric crotylation of acylhydrazones.



Entry	1	4[a]	Time [h]	5 (%yield)	*syn* (% ee) / *anti* (% ee)
1[b]	**1c**	*Z*	4	**5c** (60)	<1 (-) / >99 (91)
2[b]	**1c**	*E*	4	**5c** (58)	99 (89) / 1 (-)
3[c]	**1v**	*Z*	17	**5v** (99)	<1 (-) / >99 (73)
4[c]	**1v**	*E*	17	**5v** (99)	99 (82) / 1 (-)
5[b]	**1w**	*Z*	3	**5w** (83)	<1 (-) / >99 (86)
6[b]	**1w**	*E*	3	**5w** (82)	95 (91) / 5 (84)
7[c]	**1y**	*Z*	24	**5y** (16)	<1 (-) / >99 (92)

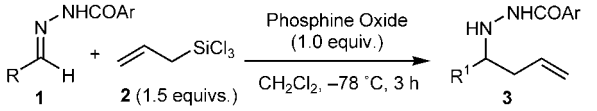
[a] (*Z*)-4 (>99% *Z*) or (*E*)-4 (98% *E*) was used.
[b] Method B (see Table 10) at a higher concentration of **1** (0.3 M).
[c] Method A (see Table 9) at a higher concentration of **1** (0.3 M).

To get more information on the activity of phosphine oxides as *NCOs*, their structural elucidation was investigated in the allylation of typical aromatic and aliphatic acylhydrazones with allyltrichlorosilane (1.5 equivs.) in the presence of a phosphine oxide (1.0 equiv.) (Table 12). Of phosphine oxides tested, triphenylphosphine oxide proved to be the most effective for allylation of 3-phenylpropanal-derived acylhydrazones (entries 3, 5 and 6), while benzaldehyde-derived acylhydrazones gave lower yields (entries 7–9).[31]

4.2 Bisphosphine Dioxides as *NCOs*

We then conducted a kinetic study at the initial stage of allylation of **1c** using different equivalents of triphenylphosphine oxide ranging from 50 mol % to 300 mol %, and the results are shown in Figure 5. With increasing equivalents of the *NCO* up to 200 mol %, the yield improved significantly. However, the use of 300 mol % phosphine oxide did not improve the yield any more. It was suggested that two *NCO* molecules coordinated to allyltrichlorosilane to facilitate the reaction. Meanwhile, Denmark and his co-workers investigated the mechanism of the allylation of aldehydes with allyltrichlorosilanes using phosphoramides as *NCOs*.[10] They concluded that the allylation was promoted *via* activation of the silane by two phosphoramide molecules. Based on these results, we next decided to examine the effect of methylene-tethered bisphosphine dioxides on the allylation of the less reactive aromatic hydrazone **1a** (Table 13). It was found that by changing the length of the tether, the yield was dramatically improved. When one equivalent of 1,3-bis(diphenylphosphino)-

Table 12. Effect of the structure of phosphine oxides.



Entry	1 (R, Ar)	Phosphine Oxide	3	Yield [%]
1	**1c** (Ph(CH_2)$_2$, Ph)	Ph_3P=O	**3c**	72
2	**1c**	*n*-Bu_3P=O	**3c**	57
3	**1c**	(*c*-C_6H_{11})$_3P$=O	**3c**	4
4	**1c**	(*o*-Tol)$_3P$=O	**3c**	5
5	**1ad** (Ph(CH_2)$_2$, *p*-ClC_6H_4)	Ph_3P=O	**3ad**	79
6	**1ae**(Ph(CH_2)$_2$, *p*-$CF_3C_6H_4$)	Ph_3P=O	**3ae**	67
7	**1a** (Ph, Ph)	Ph_3P=O	**3a**	3
8	**1a**	*n*-Bu_3P=O	**3a**	12
9	**1ab** (Ph, *p*-MeOC_6H_4)	Ph_3P=O	**3ab**	24

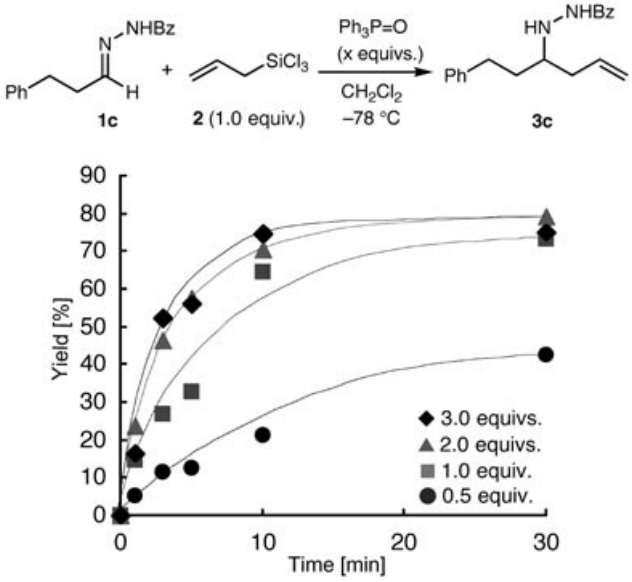
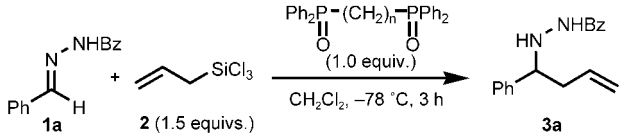


Figure 5. Effect of the amount of Ph_3P=O.

propane dioxide (n = 3, dppp dioxide) was used, the best yield was obtained, while in the case of n = 4, the reaction scarcely proceeded, possibly because of poor solubility of the *NCO*.

We then examined substrate generality using dppp dioxide as an *NCO* (Table 14). Aliphatic, aromatic, and α,β-unsaturated acylhydrazones underwent allylation and stereospecific crotylation in the presence of dppp dioxide. While *syn*-adducts were obtained stereoselectively from (*E*)-crotyltrichlorosilane, *anti*-adducts were formed preferentially from (*Z*)-crotyltrichlorosilane. A higher concentration (0.3 M relative to an acylhydrazone) improved the yield significantly (entry 1 *vs.* 2). Although the yields were still unsatisfactory in some cases (entries 6, 7, 10 and 13), it should be noted that yields were further improved by using dppp dioxide instead

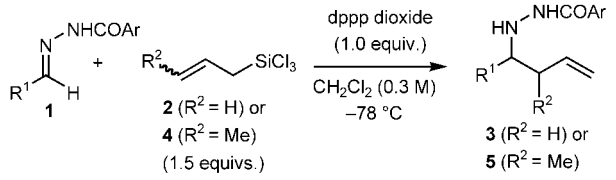
Table 13. Effect of methylene-tethered bisphosphine oxides.



n	1	2	3[a]	4	5	6	3[b]
Yield [%]	6	15	71	3	23	24	45

[a] 1,3-Bis(diphenylphosphino)propane dioxide = dppp dioxide.
[b] 50 mol % of phosphine oxide was used.

Table 14. Allylation and crotylation of acylhydrazones using dppp dioxide.



Entry	1 (R^1, Ar)	2 or 4[a]	Time [h]	3 or 5	Yield [%]	*syn*/*anti*
1[b]	**1c** ($Ph(CH_2)_2$, Ph)	**2**	1	**3c**	46	–
2	**1c**	**2**	1	**3c**	quant	–
3	**1c**	(*E*)-**4**	6	**5c**	88	98/2
4	**1c**	(*Z*)-**4**	6	**5c**	quant	<1/>99
5	**1ab** (Ph, *p*-$MeOC_6H_4$)	**2**	6	**3ab**	87	–
6	**1ab**	(*E*)-**4**	6	**5ab**	16	80/20
7	**1ab**	(*Z*)-**4**	6	**5ab**	60	<1/>99
8	**1b** ((*E*)-PhCH=CH, Ph)	**2**	6	**3b**	90	–
9	**1b**	(*E*)-**4**	6	**5b**	85	99/1
10	**1b**	(*Z*)-**4**	6	**5b**	23	15/85
11	**1aa** (PhC≡C, Ph)	**2**	6	**3aa**	92	–
12	**1aa**	(*E*)-**4**	6	**5aa**	83	99/1
13	**1aa**	(*Z*)-**4**	6	**5aa**	55	<1/>99

[a] *Z*-isomer (>99% *Z*) or *E*-isomer (98% *E*) was used.
[b] At 0.15 M.

of DMSO which we previously utilized as an *NCO*. For example, with 3 equivalents of DMSO as an *NCO*, aromatic acylhydrazone **1ab** hardly afforded the desired products [(*Z*)-crotylation: 9%, (*E*)-crotylation: 3%]. More strikingly, the α,β-unsaturated substrate **1b** did not undergo allylation using DMSO.

5 Polymer-Supported *NCOs*[32]

Metal-free organocatalysts have been intensively studied from the viewpoint of their environmentally benign nature.[33] Compared with metal-catalyzed reactions, while there is no concern of contamination, waste, and disposal of metals in reactions using organocatalysts, problems have been incurred in the separation of the catalysts from the products. Polymer-supported organocatalysts may address this issue; however, only a limited number of examples have been reported.[34] This is in remarkable contrast to the versatile metal-containing polymer-supported catalysts reported, in the use of which, however, leaching of metals from polymer supports is still a serious problem in many cases.[35]

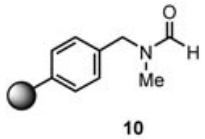
We decided to develop polymer-supported *NCOs*, and at first polymer-supported (PS) formamide **10** (Figure 6) was prepared from chloromethylated resins[36] by treatment of *N*-methylformamide and NaH in DMF. The structure of **10** was confirmed by ^{13}C swollen resin magic angle spinning (SR-MAS) NMR[37] and IR analyses, and the loadings of **10** were determined by chlorine titrations.

We then performed the allylation of 3-phenylpropanal with allyltrichlorosilane using PS-formamides **10**. Acetonitrile was chosen as an appropriate solvent, in which no reaction occurred in a control experiment without catalyst. Several reaction conditions were examined, and the results are summarized in Table 15. It was found that the polymers with higher loadings showed higher activity (entries 1–3). The yield of the desired homoallylic alcohol was further improved when the amounts of **10** and allyltrichlorosilane were increased (entry 4). It is also noted that even a catalytic amount of **10** was shown to be effective at a higher concentration (entry 5).

The allylation of other aldehydes was tested under the optimized conditions (Table 16). In all cases, the desired homoallylic alcohols were obtained in good to excellent yields, although 300 mol % of PS-formamide **10** and longer reaction times were required to complete the reactions in some cases.

One advantage of polymer-supported catalysts is that the catalysts can be readily recovered and reused, even when excess amounts of catalysts are used as promoters in the reactions. Thus, we investigated the reusability of PS-formamide **10**. It was found that when an automatic shaker was used, the activity of **10** was retained through several uses to afford the desired homoallylic alcohols in high yields (Table 17). Recovery of the formamide was quantitative in all three runs, and a significant loss of activity of the formamide was not observed. In addition, the recovered PS-formamide **10** showed exactly the same ^{13}C NMR spectra as the freshly prepared **10**.

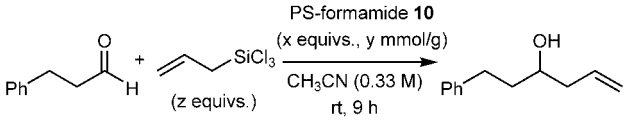
As seen above, PS-formamide **10** worked well in the allylation of aldehydes with allyltrichlorosilane, while it showed lower activity in the allylation of acylhydrazones. We therefore investigated immobilization of a



10

Figure 6. Polymer-supported formamide.

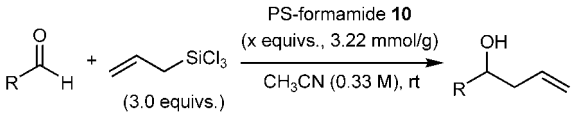
Table 15. Allylation of 3-phenylpropanal.



Entry	x	y	z	Yield [%]
1	0.5	0.62	1.5	43
2	0.5	3.22	1.5	58
3	0.5	4.66	1.5	58
4	1.0	3.22	3.0	91
5[a]	0.1	3.22	3.0	79

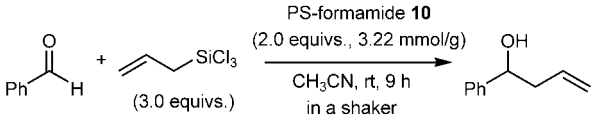
[a] At 0.66 M.

Table 16. Allylation of aldehydes using PS-formamide **10**.



Entry	R	x	Time [h]	Yield [%]
1	Ph	2.0	9	90
2	*p*-MeC_6H_4	3.0	40	87
3	*p*-$NO_2C_6H_4$	3.0	12	95
4	1-Naphthyl	3.0	34	92
5	(*E*)-PhCH=CH	3.0	12	66

Table 17. Recovery and reuse of PS-formamide **10**.



Run	1st	2nd	1st
yield [%][a]	90 (90)	86 (85)	86 (43)
Recovery [%]	quant.	quant.	quant.

[a] Yields obtained using a magnetic stirrer are given in parentheses.

phosphine oxide on a polymer-support. It turned out that PS-phosphine oxide **11** (Figure 7), which was readily prepared from the oxidation of commercially available PS-phosphine, served as an effective immobilized *NCO*. Thus, allylation of **1c** using **11** (2.0 equivs.) afforded the desired product quantitatively (Scheme 4).

6 Perspectives

Allylation reactions of acylhydrazones with allyltrichlorosilanes have been surveyed. The reactions proceed smoothly in the presence of neutral coordinate-

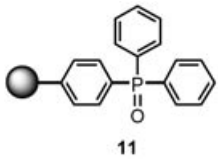
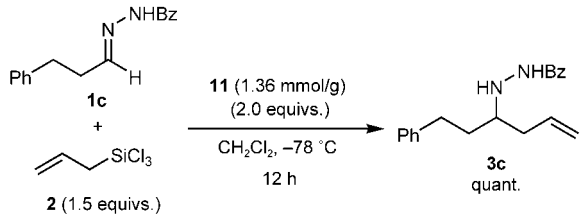


Figure 7. Polymer-supported phosphine oxide.



Scheme 4. Allylation of an acylhydrazone using PS-phosphine oxide **11**.

organocatalysts (*NCOs*) such as DMF, sulfoxides, and phosphine oxides. The high stereospecificity of these reactions is remarkable; *syn*- and *anti*-adducts are obtained from (*E*)- and (*Z*)-crotyltrichlorosilanes, respectively. Moreover, chiral *NCOs* enable enantioselective synthesis of homoallylic amine derivatives starting from both achiral hydrazones and allyltrichlorosilanes with high diastereo- and enantioselectivities.

On the other hand, most of these reactions require more than stoichiometric amounts of *NCOs*. More mechanistic studies will be needed to reduce the amount of *NCO*, leading to truly catalytic processes. In the allylation reactions of aldehydes with allyltrichlorosilanes, catalytic amounts of *NCOs* work well in some cases in the presence of excess amounts of amines. In the reactions with hydrazones, however, amines themselves often promote the allylation reactions. Development of some Lewis bases other than amines may lead to truly efficient catalytic allylation reactions of hydrazones. For asymmetric catalysis, many other chiral *NCOs* are candidates to achieve excellent chiral inductions.

Although this article covers the allylation of acylhydrazones with allyltrichlorosilanes in the presence of *NCOs*, *NCOs* should promote many other reactions. The reaction should proceed under mild conditions without losing other functional groups. *NCOs*, new types of organocatalysts, will be a key to attain truly efficient and powerful organic synthesis.

References and Notes

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