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Highly Stereoselective Synthesis of Homoallylic Amines Based on Addition of Allyltrichlorosilanes to Benzoylhydrazones

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Abstract: Allyltrichlorosilanes reacted with benzoylhydrazones in DMF without the use of any catalyst to afford the corresponding homoallylic benzoylhydrazines in good to high yields. The reactions proceeded at 0 °C to room temperature under mild conditions. In addition, it was found that the reactions tolerated well the steric hindrance of hydrazones and allyltrichlorosilanes. Indeed, ketone-derived benzoylhydrazones reacted with allyltrichlorosilane smoothly to afford the corresponding *N*′-*tert*-alkyl-*N*-benzoylhydrazines in high yields. In crotylation with (*E*)- and (*Z*)-crotyltrichlorosilanes, *syn*- and *anti*-adducts were stereospecifically obtained, respectively. These reactions are most likely to proceed via a cyclic chairlike transition state where the R group takes an axial position. When α-heteroatom-substituted chiral benzoylhydrazones were used, high *anti*-diastereoselectivities were observed. These adducts can be readily converted to homoallylic amines in high yields without epimerization.

Introduction

Nucleophilic addition of allylmetal reagents to imines or their analogues has been widely utilized for the syntheses of nitrogen-containing compounds, since the resulting homoallylic amines are useful intermediates for further transformations.[1,2] However, unlike in the case of aldehydes, the results of the processes have often been unsatisfactory due to the low electrophilicity of imines. With typical strong nucleophiles such as allyllithium or -magnesium, α-deprotonation takes place exclusively over the addition reactions when nonbranched "enolizable" imines are applied. Moreover, a synthetically useful level of diastereo- and regioselectivities is not achieved in crotylation using these metals. Among the allylmetals devised to address these issues, boron and tin in the presence of a Lewis acid catalyst have been shown to be effective to some extent. Although excellent diastereoselectivities have been shown in the reactions of crotyltrialkylborons with some imines, the selectivities are strongly dependent upon the imine structures, and it is not possible to obtain both *syn*- and *anti*-adducts stereoselectively from one specific imine.[3a,b] While crotyltins selectively give *syn*-homoallylic amines, as in their reactions with aldehydes, *anti*-adducts are not obtained preferentially.[3c] As for silicon nucleophiles, allyltrimethylsilane is usually weakly nucleophilic toward imines even in the presence of a Lewis acid. It was reported that crotyltrifluorosilanes react with imines in the presence of a stoichiometric amount of cesium fluoride, but that the diastereoselectivities are not high.[3d] To date, there are no crotylmetals available to give both *syn*- and *anti*-homoallylic amines stereoselectively, to the best of our knowledge. Another problem is that the secondary amines produced in the reaction with imines cannot routinely be deprotected to the corresponding primary amines.

(1) (a) Kleinmann, E. F.; Volkmann, R. A. In *Comprehensive Organic Synthesis*; Heathcock, C. H., Ed.; Pergamom: Oxford, 1990; Vol. 2, p 975. (b) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407. (c) Enders, D.; Reinhold: U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895.

(2) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207.

(3) (a) Yamamoto, Y.; Komatsu, T.; Maruyama, K. *J. Org. Chem.* **1985**, *50*, 3115. (b) Hoffmann, R. W.; Endesfelder, A. *Liebigs Ann. Chem.* **1987**, 215. (c) Keck, G. E.; Enholm, E. J. *J. Org. Chem.* **1985**, *50*, 146. (d) Kira, M.; Hino, T.; Sakurai, H. *Chem. Lett.* **1991**, 277.

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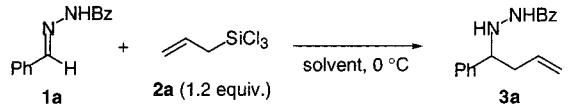
Table 1. Effect of Solvents



entry	solvent	time/h	yield/%
1	DMF	2	95
2	HMPA	2	91
2	*N*,*N*-dimethylacetamide (DMA)	18	44
4	THF	18	32
5	CH_3CN	18	31
6	CH_2Cl_2	18	29
7	MeOH	18	<1

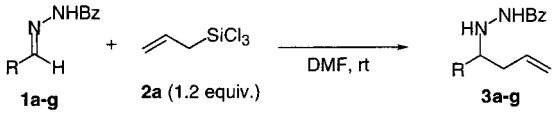
On the other hand, we have previously reported that allyltrichlorosilanes reacted with aldehydes in *N*,*N*-dimethylformamide (DMF) without a catalyst to afford the corresponding homoallylic alcohols in a highly regio- and stereoselective manner.[4−6] The strict stereospecificity of the transfer of the geometry of the silanes to the products suggested a six-membered chairlike transition state. This reaction system seemed to us to be quite attractive, because the reactions have realized high yields and diastereoselectivities in a simple procedure under mild conditions using environmentally less harmful reagents. In view of the utility of these reactions, we undertook a study to apply them to the stereoselective syntheses of homoallylic amines by employing nitrogen analogues of aldehydes. Herein we describe the full details of the studies.[7]

Results and Discussion

We first examined the reaction of allyltrichlorosilane with imines prepared from benzaldehyde and benzhydrylamine, but no addition proceeded in DMF. An attempt to increase the electrophilicity of imines by using that 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, ureas, and so forth were added to the reaction mixture. However, they did not catalyze the addition either. We judged on the basis of these results that imines were inert or very sluggish toward allyltrichlorosilane. Thus, our attention was turned to using other nitrogen-containing electrophiles as imine equivalents.

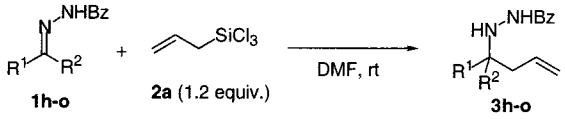
Acylhydrazones, which are readily prepared from the corresponding aldehydes, have been shown in our laboratory to serve as electrophiles in Mannich-type, allylation, and cyanation reactions in the presence of a catalytic amount of a Lewis acid.[8]

Table 2. Allylation of Aldehyde-Derived Benzoylhydrazones



entry	R	time/h	product	yield/%
1	Ph (**1a**)	1	**3a**	96
2	(*E*)-PhCH=CH (**1b**)	1	**3b**	90
3	$Ph(CH_2)_2$ (**1c**)	15	**3c**	77
4	$CH_3(CH_2)_4$ (**1d**)	13	**3d**	76
5	*i*-Bu (**1e**)	1	**3e**	73
6	c-C_6H_{11} (**1f**)	15	**3f**	74
7	*t*-Bu (**1g**)	7	**3g**	77

Table 3. Allylation of Ketone-Derived Benzoylhydrazones



entry	R^1	R^2	time/h	product	yield/%
1	Ph	CH_3 (**1h**)	3	**3h**	95
2	*p*-MeOPh	CH_3 (**1i**)	3	**3i**	95
3	*m*-NO_2Ph	CH_3 (**1j**)	3	**3j**	90
4	2-naphthyl	CH_3 (**1k**)	3	**3k**	96
5	CH_3	CH_3 (**1l**)	2	**3l**	60
6	$Ph(CH_2)_2$	CH_3 (**1m**)	0.3	**3m**	81
7	$-(CH_2)_5-$ (**1n**)		2	**3n**	62
8	Ph	C_3H_7 (**1o**)	3	**3o**	87

The resulting hydrazines can be converted to the corresponding primary amines. To our delight, when benzaldehyde benzoylhydrazone (**1a**) was treated with allyltrichlorosilane (**2a**) in DMF, the reaction proceeded without the use of any catalyst to give the corresponding adduct, homoallylic hydrazine, in excellent yield. It is noted that the reaction proceeded at room temperature under mild conditions. Moreover, benzoylhydrazones have advantages over imines. They are usually stable crystals, including those derived from aliphatic, α,β-unsaturated, and aromatic aldehydes, and the resulting adducts can be easily converted to the corresponding primary amines (vide infra).

The effect of solvents was then surveyed using **1a** as a substrate (Table 1). As illustrated in the table, a significant effect of solvents was observed in this reaction. The addition proceeded cleanly in DMF or HMPA to afford the desired adducts in high yields (entries 1 and 2), whereas the reaction mixture turned somewhat messy and lower yields were obtained in other solvents (entries 3−6). In methanol allyltrichlorosilane decomposed rapidly (entry 7). It is noteworthy that the reaction proceeded in even lower yields in other solvents than DMF and HMPA, while no reaction of aldehydes with allyltrichlorosilane occurred in these solvents.[4a,b] This result is presumably due to the coordination of the benzoyl carbonyl to allyltrichlorosilane, since allyltrichlorosilane is known to be a very weak nucleophile if not coordinated.[9] The mechanism of these reactions will be discussed later. It should be pointed out here that the solubility of **1a** in other solvents than DMF, HMPA, and DMA is

(4) (a) Kobayashi, S.; Nishio, K. *Tetrahedron Lett.* **1993**, *34*, 5453. (b) Kobayashi, S.; Nishio, K. *J. Org. Chem.* **1994**, *59*, 6620. (c) Kobayashi, S.; Nishio, K. *J. Am. Chem. Soc.* **1995**, *117*, 6392.

(5) For examples for enantioselective synthesis of homoallylic alcohols using a chiral Lewis base and related work, see: (a) Denmark, S. E.; Coe, D. M.; Pratt, N. E.; Griedel, B. D. *J. Org. Chem.* **1994**, *59*, 6161. (b) Iseki, K.; Kuroki, Y.; Takahashi, M.; Kobayashi, Y. *Tetrahedron Lett.* **1996**, *37*, 5149. (c) Iseki, K.; Mizuno, S.; Kuroki, Y.; Kobayashi, Y. *Tetrahedron* **1999**, *50*, 977. (d) Angell, R. M.; Barrett, A. G. M.; Braddock, D. C.; Swallows, S.; Vickery, B. D. *J. Chem. Soc., Chem. Commun*. **1997**, 919. (e) Nakajima, M.; Saito, M.; Shiro, M.; Hashimoto, S. *J. Am. Chem. Soc.* **1998**, *120*, 6419. (f) Chataigner, I.; Piarulli, U.; Gennari, C. *Tetrahedron Lett.* **1999**, *40*, 3633. (g) Denmark, S. E.; Fu, J. *J. Am. Chem. Soc.* **2000**, *122*, 12021. For other related works, see: (h) Short, J. D.; Attenoux, S.; Berrisford, D. J. *Tetrahedron Lett.* **1997**, *38*, 2351. (i) Fürstner, A.; Voigtlander, D. *Synthesis* **2000**, *7*, 959.

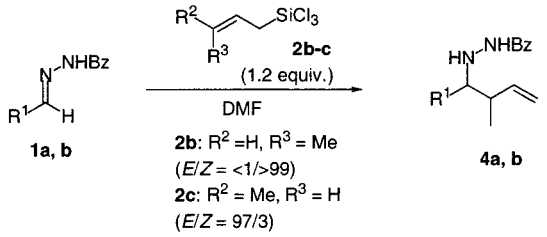
(6) For related reviews, see: (a) Nakajima, M. *J. Synth. Org. Chem. Jpn*. **2000**, *58*, 839. (b) Marshall, J. A. *Chemtracts: Org Chem.* **1998**, *11*, 697.

(7) For a preliminary communication of this work, see: Kobayashi, S.; Hirabayashi, R. *J. Am. Chem. Soc.* **1999**, *121*, 6942.

(8) (a) Oyamada, H.; Kobayashi, S. *Synlett* **1998**, 249. (b) Kobayashi, S.; Hasegawa, Y.; Ishitani, H. *Chem. Lett*. **1998**, 1131. (c) Kobayashi, S.; Furuta, T.; Sugita, K.; Oyamada, H. *Synlett* **1998**, 1019. (d) Kobayashi, S.; Sugita, K.; Oyamada, H. *Synlett* **1999**, 138. (e) Kobayashi, S.; Furuta, T.; Sugita, K.; Okitsu, O.; Oyamada, H. *Tetrahedron Lett*. **1999**, *40*, 1341. (f) Manabe, K.; Oyamada, H.; Sugita, K.; Kobayashi, S. *J. Org. Chem.* **1999**, *64*, 8054. (g) Okitsu, O.; Oyamada, H.; Furuta, T.; Kobayashi, S. *Heterocycles* **2000**, *52*, 1143.

(9) Hagen, G.; Mayr, H. *J. Am. Chem. Soc.* **1991**, *113*, 4954.

Table 4. Crotylation of Benzoylhydrazones (**1**)



entry	R^1	crotylsilane	temp/°C	time/h	yield/%	*syn*/*anti*[a]
1	Ph (**1a**)	**2b**	rt	1	68 (**4a**)	9/91
2	Ph (**1a**)	**2b**	0	18	79 (**4a**)	1/99
3	Ph (**1a**)	**2c**	0	18	59[b] (**4a**)	78/22
4	Ph (**1a**)	**2c**	rt	1	56 (**4a**)	40/60
5	Ph (**1a**)	**2c**	−10	51	41[c] (**4a**)	80/20
6	(*E*)-PhCH═CH (**1b**)	**2b**	0	18	80 (**4b**)	3/97
7	(*E*)-PhCH═CH (**1b**)	**2c**	0	18	82 (**4b**)	95/5

[a] Determined by ^{1}H NMR analyses. [b] The amount of starting material recovered was 37%. [c] A 1.5 equiv sample of **2c** was used.

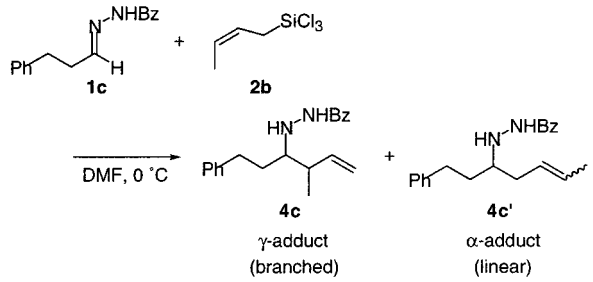
inadequate.[10] However, the solvent effect is not a mere consequence of the difference in the solubility, because the reaction of 3-phenylpropanal benzoylhydrazone (**1c**), which is soluble in dichloromethane, also gave a low yield (23%) in the solvent, while in DMF a good yield was obtained as subsequently shown.

We then applied the allylation reaction over a range of benzoylhydrazones in DMF (Table 2). A reaction of an α,*β*-unsaturated aldehyde (cinnamaldehyde) benzoylhydrazone (**1b**) proceeded to afford a 1,2-adduct exclusively over a 1,4-adduct in high yield (entry 2). Hydrazones derived from aliphatic aldehydes including bulky ones such as cyclohexanecarboxaldehyde (**1f**) and pivalaldehyde (**1g**) reacted smoothly to give the products in good yields (entries 3−7). Note that the difference in the reaction time does not signify a difference in the reactivity.[11]

In addition, it was found that hydrazones derived from ketones also reacted with allyltrichlorosilane smoothly to afford the corresponding adducts in high yields (Table 3). The adducts, *N*′-*tert*-alkyl-*N*-benzoylhydrazines, provide an interesting class of compounds, but their synthesis is known to be difficult.[1a,12] While the addition of Grignard reagents to aldimines for preparation of α-substituted secondary amines has been reported, the addition to ketimines for synthesis of α,α-disubstituted tertiary amines is not well precedented, because ketimines are sterically hindered, and competing enolization of ketimines causes serious side reactions.[13] Moreover, even aldimines are less reactive, and activation by Lewis acids is often needed to complete the reactions. It is noteworthy in the present system that ketone-derived acylhydrazones smoothly reacted with allyltrichlorosilane without the use of any catalyst under mild conditions (0 °C to room temperature) to afford the desired adducts in high yields.

Next, we examined the crotylation reactions (Table 4). In the reaction of benzaldehyde benzoylhydrazone with (*Z*)-crotyltrichlorosilane,[14a,b] high *anti*-selectivity up to 99/1 was obtained (entries 1 and 2). In contrast, the reaction of (*E*)-crotyltrichlorosilane[14c] gave *syn*-adduct predominantly at 0 °C (entry 3). These results suggest that the reactions proceed via a cyclic transition state. When the reaction with (*E*)-crotyltrichlorosilane was performed at room temperature, the course of diastereoselection changed to yield the *anti*-adduct as the slightly major product (entry 4), suggesting that other transition states, which gave the *anti*-product, competed here. A trial to obtain better *syn*-selectivity by lowering the reaction temperature to −10 °C met with lower reactivity and yield (entry 5). Similarly, in the reaction of cinnamaldehyde benzoylhydrazone with (*Z*)- and (*E*)-crotyltrichlorosilane, 1,2-addition proceeded exclusively again to afford stereoselectively *anti*- and *syn*-adducts, respectively (entries 6 and 7). It is remarkable that the correlations between the geometry of crotylsilanes and the stereochemistry of products in these cases (from *Z* to *anti*; from *E* to *syn*) are found to be the reverse of those observed in reactions of aldehydes with crotylsilanes.[4a,b]

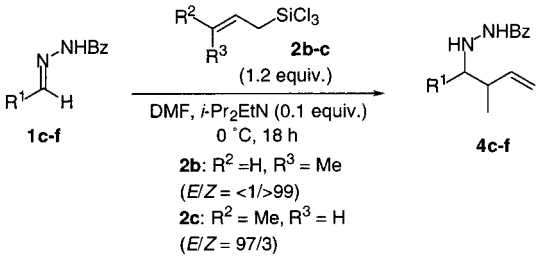
Scheme 1. Crotylation of Benzoylhydrazones Derived from 3-Phenylpropanal without a Base



In crotylation of 3-phenylpropanal benzoylhydrazone, initial experiments gave a mixture of a branched and an unexpected linear adduct (Scheme 1). The linear product was found to be a single isomer irrespective of the geometry of the starting crotylsilane, and the branched/linear ratio was not constant. That the diastereomeric ratio of the branched product was high led us to investigate the method of obtaining the branched isomer selectively. Since it is well-known that nucleophilic attack of allylsilanes occurs selectively at the *γ* positions of the silicon atoms, the linear adduct was assumed to be formed via isomerization of crotyltrichlorosilane before the addition[15] or isomerization of the product after the addition.[16] Nevertheless, the possibility of the former appeared to be low because the reactions with benzaldehyde and cinnamaldehyde benzoylhy-

(10) Product **3a** is soluble in all the solvents shown in Table 1.
(11) The reaction time of each allylation is not optimized.
(12) Spero, D. M.; Kapadia, S. R. *J. Org. Chem*. **1997**, *62*, 5537.
(13) Wang, D.-K.; Dai, L.-X.; Hou, X.-L.; Zhang, Y. *Tetrahedron Lett*. **1996**, *37*, 4187.
(14) For synthesis of the *Z*-isomer, see: (a) Kira, M.; Kobayashi, M.; Sakurai, H. *Tetrahedron Lett.* **1987**, *28*, 4081. (b) Kira, M.; Hino, T.; Sakurai, H. *Tetrahedron Lett.* **1989**, *30*, 1099. For synthesis of the *E*-isomer, see: (c) Furuya, N.; Sukawa, T. *J. Organomet. Chem*. **1975**, *96*, C1.
(15) For an example of iomerization of allylic silanes, see: Hosomi, A.; Shibahara, A.; Sakurai, H. *Chem. Lett*. **1978**, 901.

Table 5. Crotylation of Benzoylhdrazones (**2**)



entry	R^1	crotylsilane	product	yield/%	*syn*/*anti*[a]
1	$Ph(CH_2)_2$ (**1c**)	**2b**	**4c**	65	9/91
2	$Ph(CH_2)_2$ (**1c**)	**2c**	**4c**	66	92/8
3	$CH_3(CH_2)_4$ (**1d**)	**2b**	**4d**	65	7/93
4	$CH_3(CH_2)_4$ (**1d**)	**2c**	**4d**	67	93/7
5	*i*-Bu (**1e**)	**2b**	**4e**	65	7/93
6	*i*-Bu (**1e**)	**2c**	**4e**	68	94/6
7[b]	c-C_6H_{11} (**1f**)	**2b**	**4f**	61	5/95
8[b]	c-C_6H_{11} (**1f**)	**2c**	**4f**	48	55/45

[a] Determined by ^{1}H NMR analyses. [b] The reaction time was 20 h.

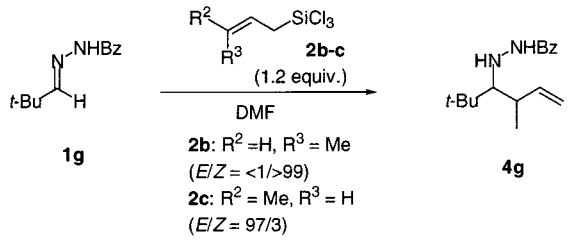
drazones gave only the branched adducts. Actually, during the course of the investigation, we found that the ratio of the linear to the branched isomer gradually increased in $CDCl_3$ after isolation of the product. On the basis of a conjecture that the isomerization was brought about by the acid originated from $CDCl_3$, we assumed that the acid produced in the reaction of crotyltrichlorosilane with water, which would inevitably be present in DMF despite careful manipulation, promoted the isomerization during the reaction. As expected, exclusive formation of the branched adduct was achieved when 0.1 equiv of *N*,*N*-diisopropylethylamine was added to the reaction mixture as a neutralizing agent, though the mechanism of the isomerization is still unclear.

Thus, crotylation of other benzoylhydrazones was performed in the presence of *N*,*N*-diisopropylethylamine, and the results are summarized in Table 5. Again in these cases *anti*-products were uniformly obtained selectively with (*Z*)-crotyltrichlorosilane (entries 1, 3, 5, and 7), while (*E*)-crotyltrichlorosilane gave *syn*-products selectively (entries 2, 4, and 6) except in the case of bulky cyclohexanecarboxaldehyde benzoylhydrazone (entry 8). Interestingly, when these reactions were carried out in the absence of a base, no linear adduct was obtained from hexanal benzoylhydrazone, while almost all the products were linear isomers in the case of isobutyraldehyde and cyclohexanecarboxaldehyde benzoylhydrazones.

In crotylation of pivalaldehyde benzoylhydrazone (**1g**), yields were acceptable at room temperature and good diastereoselectivities were shown (Table 6). Especially, when (*E*)-crotylsilane was used, excellent diastereoselectivity was obtained (entry 4). No linear adduct was formed in these reactions even without an amine. As for the relative configuration of these products, we assigned it in this case assuming that *syn*- and *anti*-adducts were preferentially obtained from (*Z*)- and (*E*)-crotylsilane, respectively. That is, the correlation of crotylsilane geometry and the product stereochemistry was the reverse of that in other substrates (**1a**−**f**). This assignment was made on the basis of the observed tendency that a higher temperature gave a better diastereomeric ratio and that (*E*)-crotylsilane was more diastereoselective. As already shown in the case of bulky benzaldehyde benzoylhydrazone (Table 4, entry 4), (*E*)-crotylsilane was

(16) Isomerization of homoallylic alcohols under Lewis acidic conditions has been reported: (a) Nokami, J.; Yoshizane, K.; Matsuura, H.; Sumida, S. *J. Am. Chem. Soc.* **1998**, *120*, 6609. (b) Sumida, S.; Ohga, M.; Mitani, J.; Nokami, J. *J. Am. Chem. Soc.* **2000**, *120*, 1310.

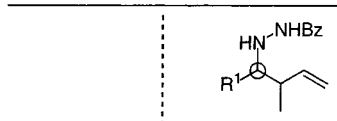
Table 6. Crotylation of a Benzoylhydrazone Derived from Pivalaldehyde



entry	crotylsilane	temp/°C	time/h	yield/%	*syn*/*anti*[a]
1	**2b**	0	18	16	77/23
2	**2b**	rt	18	60	81/19
3	**2b**	40	7	49	87/13
4	**2c**	rt	18	49	3/97

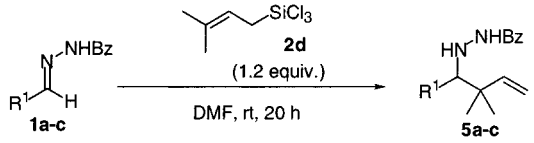
[a] Determined by ^{1}H NMR analyses.

Chart 1. Chemical Shift Values of *syn*- and *anti*-Isomers



R^1	^{1}H-NMR: δ (ppm) *syn*	*anti*	^{13}C-NMR: δ (ppm) *syn*	*anti*
Ph	4.10	3.82	15.4	17.8
(*E*)-PhCH=CH	3.61	3.42	16.2	17.4
c-C_6H_{11}	2.69	2.59	13.5	17.9
t-Bu	2.77	2.63	13.9	20.4

Table 7. Prenylation of Benzoylhydrazones



entry	R^1	product	yield/%
1	Ph (**1a**)	**5a**	44
2	(*E*)-PhCH═CH (**1b**)	**5b**	48
3	$Ph(CH_2)_2$ (**1c**)	**5c**	55

slightly *anti*-selective at room temperature, and it would be more *anti*-selective at higher temperature. This assignment was also supported by ^{1}H and ^{13}C NMR analyses (Chart 1). The chemical shift values of the α-nitrogen methyne proton of *syn*-isomers and the methyl carbon of the *anti*-isomers have invariably appeared at lower field than those of the corresponding *anti*- and *syn*-isomers, respectively.

Next, prenylation was investigated (Table 7). Although the reaction rate was slower, prenylation also proceeded to afford the desired products in moderate yields. It can be concluded from these results that the present allylation reactions tolerate well the steric hindrance of hydrazones and allyltrichlorosilanes.

The stereoselectivities in these reactions are most likely accounted for by assuming a chairlike transition structure in which the nitrogen atom and a benzoyl carbonyl group coordinate to the silicon atom (Figure 1). The *E*-geometry of hydrazone puts the R group at an axial direction; consequently, *syn*- and *anti*-homoallylic hydrazines are stereospecifically obtained from (*E*)- and (*Z*)-crotyltrichlorosilanes, respectively. Similar transition structures where the R group is located at an axial position have already been proposed in reactions of other allylmetals (Li, Mg, and B) with imines.[3a] Another possibility

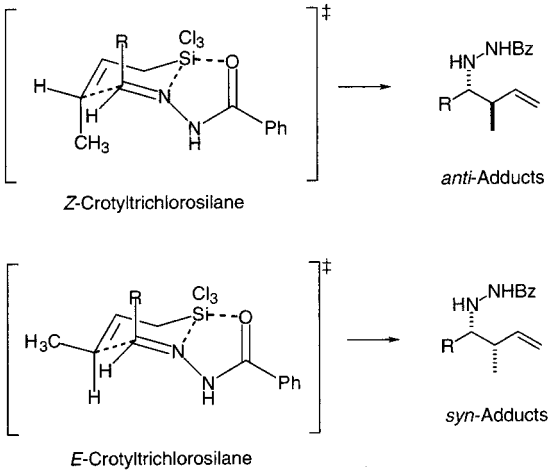


Figure 1. Assumed transition states.

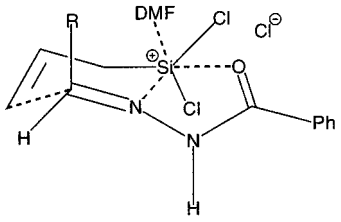


Figure 2.

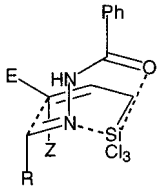


Figure 3.

is formation of a transition structure in which a cationic siliconate species is involved when a coordinating solvent such as DMF or HMPA is used (Figure 2). Similar intermediates have been suggested in the Lewis base catalyzed addition of allyltrichlrosilanes to aldehydes.[4b,5g,h] Coordination of a Lewis base to the silicon atom would enhance the nucleophilicity of allyltrichlorosilane, while the Lewis acidic silicon activates the hydrazone. Both factors would be essential for the reaction to take place. Accordingly, coordination of the benzoyl carbonyl group to the silicon atom must be essential, because benzoylhydrazones reacted with allyltrichlorosilane even in noncoordinating solvents where external coordination is absent (see Table 1). The coordination is also likely to serve for stabilization of the transition structures.

As already shown, in the crotylation of moderately bulky benzaldehyde and cyclohexanecarboxaldehyde benzoylhydrazones, the diastereoselectivities deteriorated when (*E*)-crotyltrichlorosillane was used (Table 3, entry 4, and Table 4, entry 8), while even bulkier pivalaldehyde benzoylhydrazone (**1g**) gave the reverse correlation between the crotylsilane geometry and the product stereochemistry (from *Z* to *syn*; from *E* to *anti*). Since the reactions should proceed via cyclic transition states, these results indicate the presence of another competing cyclic transition structure. It seems that a boatlike (Figure 3) or a chairlike structure with the R group at an equatorial direction after $E \rightarrow Z$ isomerization of hydrazone (Figure 4) is worth considering.[3a,b] The stereochemical outcome of the possible transition structures is summarized in Figure 5. The coordination of the benzoyl carbonyl group is omitted for clarity.

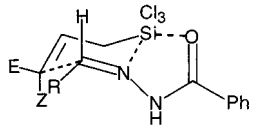


Figure 4.

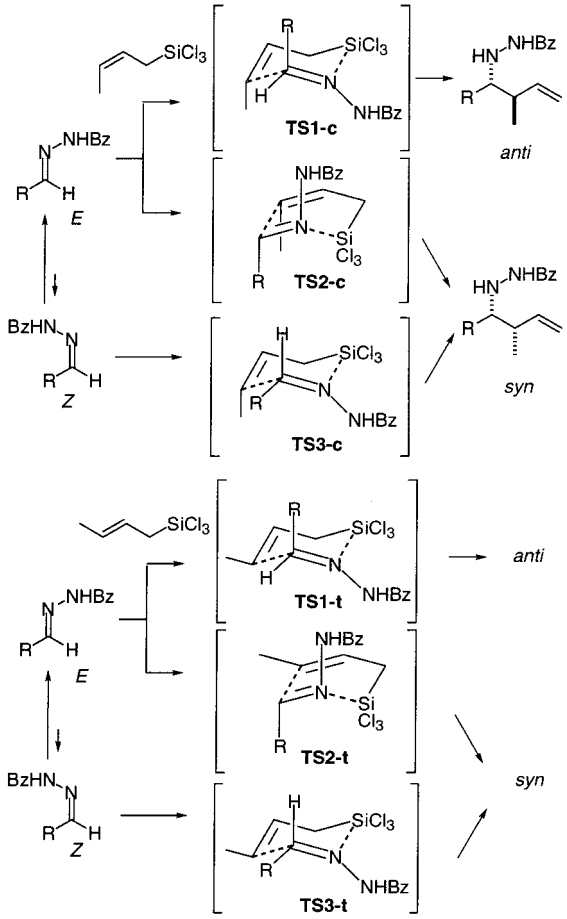


Figure 5. Possible reaction pathway.

The following reaction courses are considered to rationalize the change in diastereoselectivity in those substrates. As already illustrated in Figure 1 (or Figure 2), when R is not so bulky (R is not *t*-Bu, Ph, and c-Hex), **TS1** is the most favorable and the "normal" correlation is given as a consequence. On the other hand, since the 1,3-diaxial interaction of R with the substituents on the silicon atom increases with the steric bulk of R, **TS1** is no longer favorable when R is considerably bulky (R = *t*-Bu). Therefore, the reaction mainly proceeds via **TS2** and/or **TS3**, leading to the reverse correlation. The tendency that better diastereoselectivity was given at higher reaction temperatures would be explained by taking **TS3** into account. The contribution from **TS3** would be larger at higher temperature, because the *E*/*Z* isomerization of benzoylhydrazone should be easier.

When the bulkiness of R is moderate (R = c-Hex, Ph), a distinct difference between (*E*)-and (*Z*)-crotylsilanes arises. While large 1,3-diaxial interaction is present in both **TS1-c** and **-t**, **TS2-c** is also unfavorable due to repulsion between R and the methyl group of (*Z*)-crotylsilane. On the other hand, no such repulsion is present in **TS2-t**. As a result, the reaction proceeds selectively via **TS1-c** with (*Z*)-crotylsilane, leading to high diastereoselectivity, whereas **TS2-t** competes against **TS1-t**, resulting in low diastereoselectivity when (*E*)-crotylsilane is used. **TS3** would not be dominant in these cases.

Scheme 2. Allylation of an α-Chiral Benzoylhydrazone

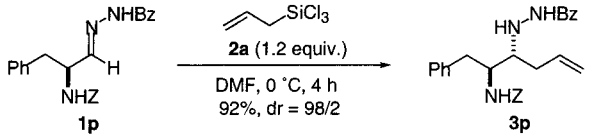
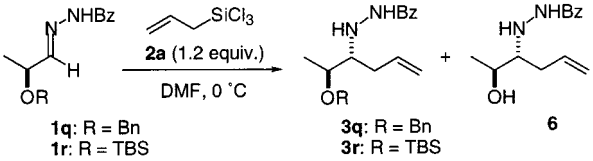


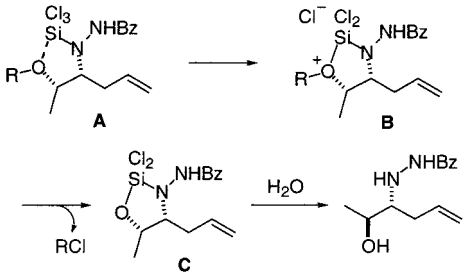
Table 8. Allylation of α-Alkoxy Benzoylhydrazones



entry	R	time/h	additive	yield/% (**3**/**6**)	*syn*/*anti*[b]
1	Bn	3	none	9/56	8/92
2[a]	TBS	4	none	32/35	3/97
3[a]	TBS	3	*i*-Pr_2EtN (0.2 equiv)	32/38	3/97
4	TBS	12	$(Me_3SiOCH_2)_2$ (2.0 equiv)	66/8	3/97
5	TBS	4	$(MeOCH_2)_2$ (2.0 equiv)	26/39	3/97

[a] The opposite enantiomer was used in the reaction. [b] Estimated by ^{13}C NMR analyses. The diastereomer ratios of **3** were identical with those of **6.**

Scheme 3. Mechanism for the Cleavage of Ether



Diastereoselective Allylation of Chiral Benzoylhydrazones. Next, we investigated allylation of α-chiral benzoylhydrazones. In the reaction of phenylalaninal derivative **1p**, an expected *anti*-adduct was obtained in 92% yield with high selectivity (*syn*/*anti* = 2/98) (Scheme 2). Although *anti*-adducts were also selectively obtained from α-alkoxy benzoylhydrazones, the reactions were accompanied by partial cleavage of the ethers (Table 8). While addition of an amine did not suppress the generation of the alcohol (entry 3), it was found that the trimethylsilyl (TMS) ether ($(Me_3SiOCH_2)_2$ as an additive) significantly reduced the alcohol product (entry 4). On the other hand, dimethoxyethane provided no such effect (entry 5). We presently assume the mechanism of the cleavage of ether as follows (Scheme 3): The silicon atom of the initial product **A** coordinates to the neighboring ether oxygen, and successive formation of the O−Si bond affords **C**. Intermediate **C** gives rise to the alcohol on quenching. Therefore, the effect of the external TMS ether should stem from its action to inhibit the intramolecular formation of the O−Si bond as shown in Scheme 4. The high *anti*-diastereoselectivity observed can be explained by considering the Cram (Felkin−Anh) transition structure (Figure 6).[17] The *anti*-Cram (*anti*-Felkin−Anh) structure is further destabilized by additional repulsion between the side chain of the hydrazone and the substituents on the silicon atom.

(17) (a) Chérest, H.; Felkin, H. *Tetrahedron Lett.* **1968**, 2205. (b) Anh, N. T. *Top. Stereochem.* **1980**, *88*, 145. High 1,2-asymmetric induction in the reaction of an allylic boron reagent with chiral imines is explained by a similar transition state. (c) Yamamoto, Y.; Nishii, S.; Maruyama, K.; Komatsu, T.; Itoh, W. *J. Am. Chem. Soc.* **1986**, *108*, 7778.

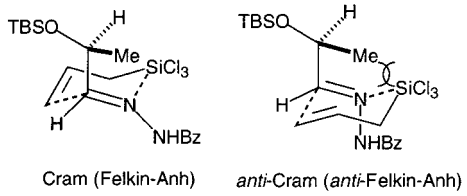


Figure 6.

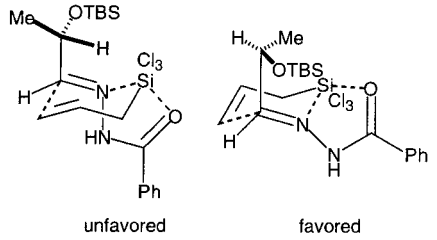
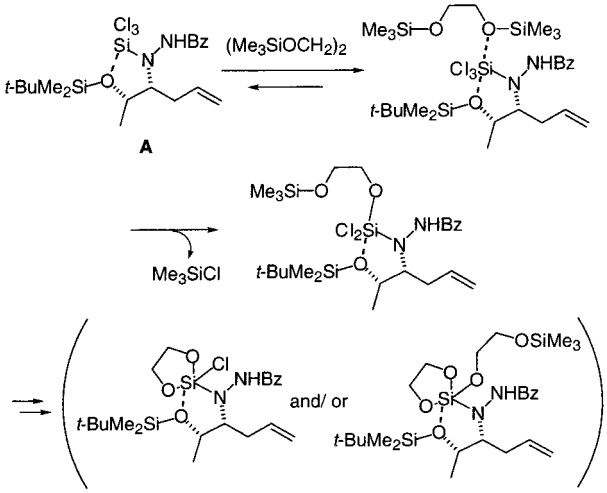
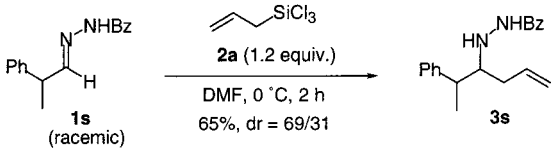


Figure 7.

Scheme 4. Effect of TMS Ether



Scheme 5. Allylation of an α-Chiral Benzoylhydrazone without a Heteroatom Substituent

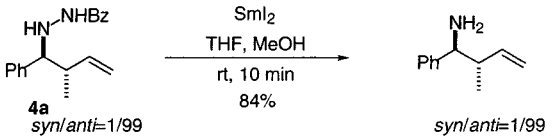


Another possibility that an electron-withdrawing effect of the heteroatom moiety is a major determinant for the stereochemistry should be taken into consideration (Figure 7), because the substrate without a heteroatom substituent furnished a lower diastereomeric ratio (Scheme 5).

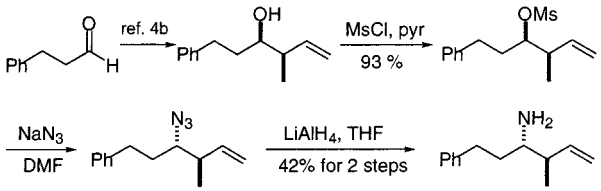
Conversion of the Products to Homoallylic Amines. Using SmI_2, the homoallylic hydrazines produced can be converted to the corresponding primary amines in high yields without epimerization as exemplified in Scheme 6.[18] Thus, the hydrazine was treated with SmI_2 in THF−MeOH at room temperature for 10 min. That the dark-blue color of SmI_2 turned yellow showed completion of the cleavage of the N−N bond, and this facile deprotection process should be noted because tedious procedures are often required for deprotection of secondary amines in many other cases. Moreover, the reductive cleavage of the N−N bond would also be possible with Raney nickel/H_2,[19] though in this case transformation of the double bond moiety beforehand may be required.

(18) Burk, M. J.; Feaster, J. E. *J. Am. Chem. Soc.* **1992**, *114*, 6266.

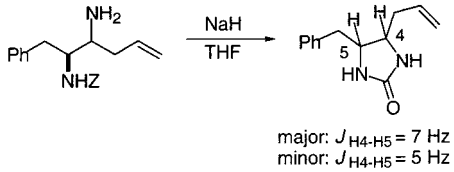
Scheme 6. Reductive Cleavage of the N−N Bond Using SmI_2



Scheme 7. Synthesis of an Authentic Sample of the *anti*-Primary Amine



Scheme 8. Relative Configuration Assignment for **3p**



Relative Configuration Assignment. Assignment of the relative configuration of the crotylation products was made after their conversion to the corresponding primary amines. The determination was actually made on the products **4a**[20] and **4c**, and the others are assigned by analogy. An authentic sample of the primary amine corresponding to *anti*-**4c** was synthesized according to the unambiguous method shown in Scheme 7. The relative configuration of the product **3r** was also determined after conversion to the corresponding primary amine,[21] and desilylation of *anti*-**3r** established the stereochemistry of **6**. Since the diastereomeric ratio of **3q** was the same as that of **6**, we judged the major isomer in **3q** was *anti*. The product from the phenylalaninal derivative (**3p**) was converted to cyclic urea via scission of the N−N bond followed by cyclization. The larger H4−H5 coupling constant in the urea derived from the major isomer suggests that the original adduct was the *anti*-isomer (Scheme 8), because it is known in an analogous oxazolidinone system that the H4−H5 coupling constant of the *cis*-isomer is larger than that of the *trans*-isomer.

Conclusion

We have developed a novel method for the stereoselective synthesis of homoallylic amines based on addition of allyltrichlorosilanes to benzoylhydrazones. The addition reactions proceeded smoothly in DMF without the use of any catalyst to afford the corresponding homoallylic benzoylhydrazines in good to high yields. While the reactions proceeded under mild conditions (0 °C to room temperature), even sterically bulky hydrazones and allyltrichlorosilanes reacted smoothly. It should be noted that benzoylhydrazones derived from ketones reacted smoothly to afford the *N*′-*tert*-alkyl-*N*-benzoylhydrazines in high yields at room temperature within 3 h. In crotylation, *syn*- and *anti*-adducts were stereospecifically obtained from (*E*)- and (*Z*)-crotyltrichlorosilanes, respectively. These reactions most likely proceed via a cyclic chairlike transition state where the R group takes an axial position. This is the first example to show high selectivities (both *syn*- and *anti*-adducts) in the reaction of crotylmetals with imines or their analogues. When α-heteroatom-substituted chiral benzoylhydrazones were used, high *anti*-diastereoselectivities were observed. The adducts can be readily converted to homoallylic amines in high yields without epimerization. Further investigations to apply the present reactions to asymmetric catalysis are in progress.

Experimental Section

A General Experimental Procedure for the Reaction of Benzoylhydrazone with Allyltrichlorosilane. Allyltrichlorosilane (0.36 mmol) was added dropwise to a solution of benzoylhydrazone (0.3 mmol) in DMF (2.4 mL) at a temperature according to the reaction conditions shown in the text. The mixture was stirred at the same temperature, and then aqueous NaOH (ca. 0.2 N) was added to the reaction mixture until the pH value of the solution was about 9. The solution was filtered through a pad of Celite (if necessary) and washed with dichloromethane, and the aqueous layer was further extracted with the same solvent. The combined organic phase was dried over Na_2SO_4 and filtered, and then solvents were removed under reduced pressure. The residue was purified by preparative TLC (hexane/ethyl acetate = ∼3/1 to ∼2/1) to yield the adduct.

A Typical Experimental Procedure for the Reductive Cleavage of the Hydrazine to the Corresponding Amine. 2-Methyl-1-phenyl-3-butenylamine.[3b] **4a** (*syn*/*anti* = 1/99) (28.2 mg, 0.10 mmol) was dissolved in MeOH (0.2 mL), and to this solution was added SmI_2 in THF (0.1 M, 3.0 mL, 0.3 mmol). Upon addition, the dark blue color of SmI_2 turned yellow. The mixture was stirred for 10 min, and then solvents were removed under reduced pressure. The residue was purified by preparative TLC (hexane/*i*-$PrNH_2$ = 10/1) to afford 2-methyl-1-phenyl-3-butenylamine (*syn*/*anti* = 1/99) (13.6 mg, 84%). ^{1}H NMR ($CDCl_3$) (*anti*): δ = 0.82 (d, 3H, J = 6.8 Hz), 1.43 (br, 2H), 2.32−2.41 (m, 1H), 3.64 (d, 1H, J = 8.5 Hz), 5.11 (dd, 1H, J = 2.0, 10.2 Hz), 5.17 (ddd, 1H, J = 0.9, 1.7, 17.1 Hz), 5.74 (ddd, 1H, J = 8.5, 10.2, 17.2 Hz), 7.22−7.35 (m, 5H).

Acknowledgment. This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan.

Supporting Information Available: Experimental details and characterization of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

JA011125M

(19) Gilchrist, T. L. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 8, pp 388−389.

(20) Both *syn*- and *anti*-isomers of the primary amine corresponding to **4a** are known compounds. See ref 3b.

(21) Cainelli, G.; Giacomini, D., Mezzina, E.; Panunzio, M.; Zarantonello, P. *Tetrahedron Lett.* **1991**, *32*, 2967.