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

Shū Kobayashi* and Ryoji Hirabayashi

Graduate School of Pharmaceutical Sciences
The University of Tokyo
CREST, Japan Science and Technology Corporation (JST)
Hongo, Bunkyo-ku, Tokyo, 113-0033

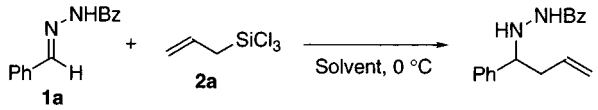
Received February 16, 1999

Homoallylic amines are useful intermediates for the synthesis of versatile nitrogen-containing compounds which are biologically important.[1] Although addition of allylmetals to imines or their analogues potentially provides a direct and efficient way to these compounds, the reactivity and selectivity are not satisfactory in most cases. This is in contrast to the addition of allylmetals to aldehydes which proceeds in high yields with high stereoselectivities in some cases.[2] Several major problems are pointed out in the addition of allylmetals to imines for synthesis of homoallylic amines:[3] first, basic allylmetal reagents sometimes cause competitive α-deprotonation of imines; second, regioisomers, which correspond to different positions of the allyl units, are formed; third, there is no crotylmetal that provides both *syn* and *anti* diastereomers stereoselectively, to the best of our knowledge; and finally, the secondary amines produced cannot routinely be deprotected to give the corresponding primary amines.

On the other hand, we have recently reported that allyltrichlorosilanes react with aldehydes in *N*,*N*-dimethylformamide (DMF) without a catalyst to afford the corresponding homoallylic alcohols in a highly regio- and stereoselective manner.[4] In these reactions, (*Z*)- and (*E*)-crotyltrichlorosilanes give *syn*- and *anti*-homoallylic alcohols, respectively, under neutral conditions. In view of the utility of these reactions, we undertook a study to apply them to the synthesis of homoallylic amines by employing nitrogen analogues of aldehydes. Herein we describe the first examples of the addition of allyltrichlorosilanes to imine analogues where the stereo- and regioselectivities are successfully controlled, leading to the preparation of both *syn*- and *anti*-homoallylic amines.

In our initial investigations, the reactions of allyltrichlorosilane (**2a**) with several imines were studied. While the reaction did not proceed at all in DMF, none of the donor additives such as HMPA, tributylphosphine, urea, and 4-(dimethylamino)pyridine, and so forth, catalyzed the addition. After searching for alternative nitrogen-containing electrophiles, it was found that benzaldehyde benzoylhydrazone[5] (**1a**) reacted with **2a** in DMF (without using any catalyst) to afford the corresponding adduct in an excellent yield. It should be noted that benzoylhydrazones have several advantages over imines as substrates. They are readily prepared from benzoylhydrazine and aldehydes including aliphatic and α,*β*-unsaturated ones, and they are all stable and can be stored at room temperature. Moreover, the adducts are easily converted to primary amines (vide infra). The significant effect of solvents in the reaction of **1a** with **2a** at 0 °C is shown in Table 1. Among the solvents we examined, DMF and HMPA gave better yields, and lower yield was obtained when *N*,*N*-dimethylacetamide (DMA) was used. In CH_3CN, CH_2Cl_2, and THF, yields were around 30%. Addition proceeded sluggishly in MeOH, presumably because **2a** was decomposed.[6,7] According to these results, we decided on the following standard reaction conditions: to a solution of **1** (0.3 mmol) in DMF (2.4 mL) was added allyltrichlorosilane (0.36 mmol) at room temperature or 0 °C. After 1−20 h (checked by TLC), diluted aqueous sodium hydroxide (∼0.2 N) was added to the reaction mixture until the pH value indicated ∼9. After filtration, the aqueous solution was extracted with dichloromethane. The combined organic phase was dried (Na_2SO_4) and filtered, and the solvents were removed under reduced pressure. The residue was purified by preparative TLC (hexane/ethyl acetate = 3/2) to yield the target adduct.

Table 1. Effect of Solvents



run	solvent	time, h	yield, %
1	DMF	2	95
2	HMPA	2	91
3	DMA[a]	18	44
4	THF	18	32
5	CH_3CN	18	31
6	CH_2Cl_2	18	29
7	MeOH	18	<1

[a] *N*,*N*-Dimethylacetamide.

We then undertook to carry out the addition reactions over a range of benzoylhydrazones and allyltrichlorosilanes. The results are summarized in Table 2. It was proved that allylation of benzoylhydrazones derived from aromatic, α,*β*-unsaturated, and aliphatic aldehydes also proceeded smoothly. Only 1,2-addition of **2a** to α,*β*-unsaturated hydrazone **1b** occurred exclusively, and no 1,4-addition adduct was obtained (run 4). Crotylation of **1a** or **1b** with (*Z*)-crotyltrichlorosilane (**2b**)[8] proceeded with excellent *anti*-selectivity at 0 °C (runs 2 and 5), while the *syn*-adduct was obtained predominantly from the (*E*)-isomer (**2c**) (runs 3 and 6).[9] In crotylation of **1c**, an initial experiment gave a mixture of the desired adduct (branched adduct) and an unexpected linear adduct (Scheme 1). Although the branched/linear formation mechanism is not clear at this stage, exclusive formation of the branched adduct was achieved when *i*-Pr_2NEt (0.1 equiv) was added to

(1) (a) Kleinmann, E. F.; Volkmann, R. A. In *Comprehensive Organic Synthesis*; Heathcock, C. H., Ed.; Pergamon: 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) Keck, G. E.; Enholm, E. J. *J. Org. Chem.* **1985**, *50*, 146. (b) Yamamoto, Y.; Komatsu, T.; Maruyama, K. *J. Org. Chem.* **1985**, *50*, 3115. (c) Hoffmann, R. W.; Endesfelder, A. *Liebigs. Ann. Chem.* **1987**, 215. (d) Yamamoto, Y.; Ito, W. *Tetrahedron* **1988**, *44*, 5415. (e) Kira, M.; Hino, T.; Sakurai, H. *Chem. Lett.* **1991**, 277.

(4) (a) Kobayashi, S.; Nishio, K. *Tetrahedron Lett.* **1993**, *34*, 5453. (b) Kobayashi, S.; Nishio, K. *J. Org. Chem.* **1994**, *59*, 6620. See also, (c) Marshall, J. A. *Chemtracts: Org. Chem.* **1998**, *11*, 697. (d) Denmark, S. E.; Coe, D. M.; Pratt, N. E.; Griedel, B. D. *J. Org. Chem.* **1994**, *59*, 6161. (e) Kobayashi, S.; Nishio, K. *J. Am. Chem. Soc.* **1995**, *117*, 6392. (f) Iseki, K.; Kuroki, Y.; Takahashi, M.; Kobayashi, Y. *Tetrahedron Lett.* **1996**, *37*, 5149. (g) Short, J. D.; Attenoux, S.; Berrisford, D. J. *Tetrahedron Lett.* **1997**, *38*, 2351. (h) Nakajima, M.; Saito, M.; Shiro, M.; Hashimoto, S. *J. Am. Chem. Soc.* **1998**, *120*, 6419.

(5) (a) Oyamada, H.; Kobayashi, S. *Synlett* **1998**, 249. (b) Kobayashi, S.; Furuta, T.; Sugita, K.; Oyamada, H. *Synlett* **1998**, 1019. Cf. (c) Burk, M. J.; Feaster, J. E. *J. Am. Chem. Soc.* **1992**, *114*, 6266.

(6) The addition of allyltrichlorosilane to benzoylhydrazone proceeded in DMA, CH_3CN, CH_2Cl_2, and THF, whereas no addition to aldehydes occurred in these solvents. See refs 4a and b.

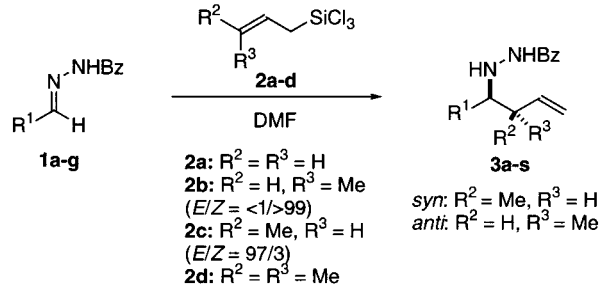
(7) It is noted that solubility in solvents other than DMF, HMPA, and DMA was inadequate.

(8) Synthesis of (*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. (*E*)-isomer, see: (c) Furuya, N.; Sukawa, T. *J. Organomet. Chem.* **1975**, *96*, C1.

(9) *syn* and *anti* configuration was determined after converting to the corresponding amine. See Supporting Information.

10.1021/ja990497g CCC: $18.00
Published on Web 07/07/1999

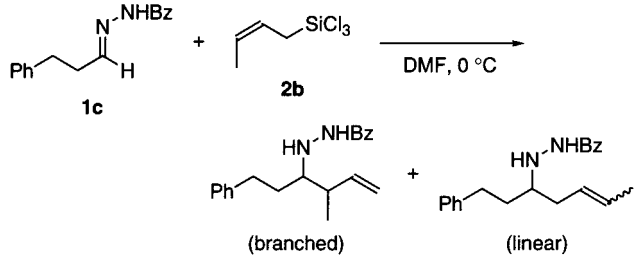
Table 2. Stereoselective Reactions of Benzoylhydrazones with Allyltrichlorosilanes



run	R^1	allyl-silanes	temp, °C	time, h	product	yield, %	*syn*/*anti*[b]
1	Ph	**2a**	rt	1	**3a**	96	
2	(**1a**)	**2b**	0	18	**3b**	79	1/99
3		**2c**	0	18	**3c**	59[c]	78/22
4	(*E*)-PhCH=CH	**2a**	rt	1	**3d**	90	
5	(**1b**)	**2b**	0	18	**3e**	80	3/97
6		**2c**	0	18	**3f**	82	95/5
7		**2d**	rt	20	**3g**	48	
8	$Ph(CH_2)_2$	**2a**	rt	15	**3h**	77	
9[a]	(**1c**)	**2b**	0	18	**3i**	68	9/91
10[a]		**2c**	0	18	**3j**	66	92/8
11		**2d**	rt	20	**3k**	55	
12	$CH_3(CH_2)_4$	**2a**	rt	13	**3l**	76	
13[a]	(**1d**)	**2b**	0	18	**3m**	65	7/93
14[a]		**2c**	0	18	**3n**	67	93/7
15	*i*-Bu	**2a**	rt	1	**3o**	73	
16[a]	(**1e**)	**2b**	0	18	**3p**	65	7/93
17[a]		**2c**	0	18	**3q**	68	94/6
18	*c*-C_6H_{11} (**1f**)	**2a**	rt	15	**3r**	74	
19	*t*-Bu (**1g**)	**2a**	rt	7	**3s**	77	

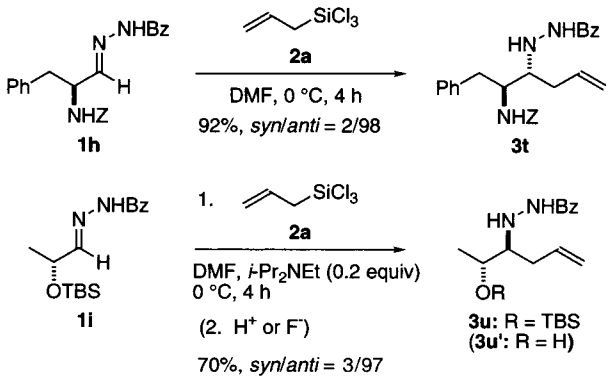
[a] *i*-Pr_2NEt (0.1 equiv) was added. [b] Determined by ^1H NMR analysis. [c] 37% of the starting material was recovered.

Scheme 1

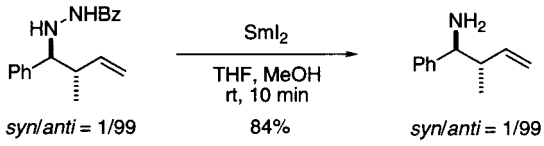


the reaction mixture.[10] A similar phenomenon was observed in crotylation of **1e**, and also in this case, the *syn*-adduct was obtained from **2c**, while the *anti*-adduct was produced from **2b** with high selectivity. Furthermore, bulky benzoylhydrazones such as those derived from cyclohexanecarboxaldehyde (**1f**) and pivalaldehyde (**1g**) reacted smoothly. In the reactions using chiral benzoylhydrazones (**1h** and **1i**), the expected Cram (Felkin) adducts were obtained in excellent selectivities (Scheme 2).[11] Using SmI_2, the homoallylic hydrazine produced was converted to the corresponding homoallylic amine in high yield without epimerization (Scheme 3).[5c]

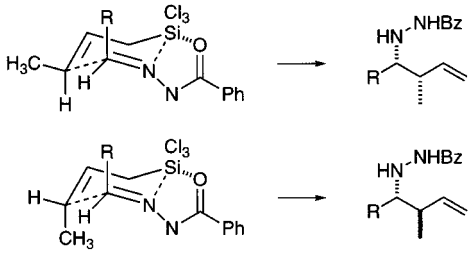
Scheme 2



Scheme 3



The high diastereoselectivities obtained in these reactions (from *E* to *syn*; from *Z* to *anti*) are remarkable, because stereoselective crotylation of aldehydes and oximes previously reported proceeded with reverse selectivities (from *E* to *anti*; from *Z* to *syn*).[2,3c] Although the precise transition states are not clear, these unique selectivities would be explained by assuming the following chairlike models[13] in which bidentate coordination of benzoylhydrazones to silicon atoms of allyltrichlorosilanes is a key to form the structures.



In summary, we have demonstrated that benzoylhydrazones reacted with allyltrichlorosilanes in DMF to afford the corresponding adducts, homoallylic hydrazines in good to high yields. The reactions proceeded without using any catalyst under neutral conditions, and *syn*- and *anti*-adducts were stereoselectively obtained from (*E*)- and (*Z*)-crotyltrichlorosilanes, respectively. This is the first example, as far as we know, to show high selectivities (both *syn*- and *anti*-adducts) in the reactions of allylmetals with imines or their analogues. Since the adducts can be readily converted to homoallylic amines in high yields without epimerization, these reactions provide novel stereoselective ways for the syntheses of homoallylic amines.

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 procedures and physical data of the products. This material is available free of charge via the Interment at http://pubs.acs.org.

JA990497G

(10) We assume that the formation of the undesired linear adduct was induced by an acid that would be formed by the reaction of **2c** with water which would exist in DMF. Since it was difficult to dehydrate DMF completely in such micromolar-scale experiments, we decided to add a small amount of *i*-Pr_2NEt to neutralize the acid.

(11) Relative configuration assignment was performed after converting to the corresponding amine. See Supporting Information.

(12) Nitrogen−nitrogen bonds can be also cleavaged under other reductive conditions. For examples, see refs 5a and b.

(13) Similar models were proposed in the addition reactions of (*E*)-crotylboranes with imines to produce *syn*-homoallylic amines.[3b]