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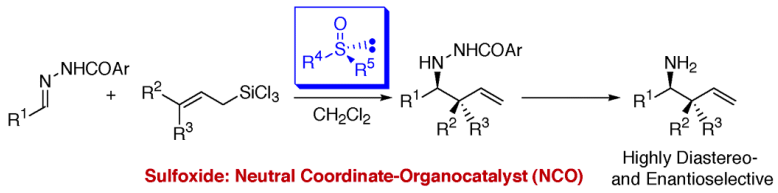

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Chiral Sulfoxides as Neutral Coordinate-Organocatalysts in Asymmetric Allylation of *N*-Acylhydrazones Using Allyltrichlorosilanes

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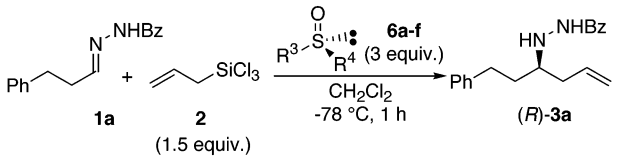
Addition of allylmetals to imines or related electrophiles is generally recognized as one of the most efficient methods for the preparation of homoallylic amine derivatives. However, the diastereospecific allylation with γ-substituted allylmetals such as crotylation and the enantioselective allylation of these electrophiles have been little explored.[1] Among various allylating agents, while allylsilanes are preferable due to their low toxicity, they often suffer from low reactivity in the allylation. To address this issue, a Lewis or Brønsted acid which activates imines has been employed.[1] It is also reported that the fluoride anions in CsF, ammonium fluorides, and tetrabutylammonium difluorotriphenylsilicate (TBAT) or alkoxides activate the C−Si bond of trimethyl-, fluoro-, or alkoxyallylsilanes by coordinating to the silicon atom.[2] Meanwhile, we have found that allyltrichlorosilanes are activated by neutral (uncharged) organic molecules such as *N*,*N*-dimethylformamide (DMF) and hexamethylphosphoramide (HMPA), to undergo allylation of aldehydes[3] or *N*-acylhydrazones[4] without the use of any metal catalyst. These organic molecules are proven to coordinate to allyltrichlorosilanes to form hypervalent silicon compounds[5] that react with electrophiles in a stereospecific manner; thus, they can be called neutral coordinate-organocatalysts (NCOs). As for enantioselective allylation of aldehydes with allyltrichlorosilanes, effective chiral NCOs such as chiral *N*-formamides, phosphoramides, and pyridine *N*-oxides have been developed.[6] On the other hand, enantioselective allylation of imines or their equivalents with allyltrichlorosilanes has been an unsolved subject.[7] Herein, we report the first example of a highly enantioselective allylation of *N*-acylhydrazones utilizing chiral sulfoxides as NCOs.

To reveal the effective functional groups in NCOs for the reaction of *N*-acylhydrazones with allyltrichlorosilanes, we first investigated the allylation of 3-phenylpropanal-derived hydrazone **1a** with allyltrichlorosilane (**2**) in the presence of an achiral NCO at −78 °C in dichloromethane. While the reaction scarcely proceeded in the absence of any NCOs, 1 equiv of DMF promoted the reaction. 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.[8] Thus, R_2-NC═O, P═O, N^+-O^-, and S═O functional groups proved to activate allyltrichlorosilane. However, these NCOs in catalytic amounts were not effective enough to promote the reaction under the employed reaction conditions. The fact that sulfoxides have not been utilized for the reactions of trichlorosilylated reagents[9] and that a variety of chiral, even *S*-chiral, sulfoxides are available[10] led us to further investigations of the catalysis using sulfoxides. Allylation of **1a** with achiral or racemic sulfoxides revealed that sulfoxides with electron-donating substituents tend to provide higher activities.[8] The amount of the sulfoxide was also critical in attaining high yields. When 3 equiv of DMSO relative to **1a** was used, the highest yield was obtained (99%). Larger or smaller amounts of DMSO decreased the yield (<86%). Using 3 equiv of DMSO, we found that the allylation of various aliphatic or aromatic hydrazones proceeded smoothly to give homoallylic hydrazides **3** in high yields.[8] Moreover, stereospecific crotylation was achieved; that is, high syn- and anti-selectivities were obtained via the reaction of **1a** with (*E*)- and (*Z*)-crotyltrichlorosilanes (**4**), respectively.[8]

Table 1. Asymmetric Allylation of **1a** Using Various Chiral Sulfoxides[a]



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

[a] Method A:[8] **2** (1.5 equiv) was added to a solution of **1** (0.3 mmol), **6** (3.0 equiv), and 2-methyl-2-butene (0.5 equiv) in dichloromethane (2 mL) at −78 °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*).

Knowing the effectiveness of sulfoxides in the reactions, we next investigated enantioselective allylation using chiral sulfoxides. At first, (*R*)-methyl *p*-tolyl sulfoxide (**6a**) was employed in the reaction of **1a** with **2** (Table 1). 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 **6a**, and the best result was obtained when 3 equiv of **6a** was employed. Addition of 2-methyl-2-butene was also found to be a key to suppress undesired racemization of **6a**. After the usual workup, **6a** could be recovered in >90% with >97% ee. Under the optimal conditions for **6a**, other chiral sulfoxides **6b**−**f** were examined. The bulkier R^3 became (R^4 = *p*-tolyl), the lower was the enantioselectivity obtained (entries 2 and 3). The steric hindrance on the R^3 substituent (R^4 = Me) also decreased the enantioselectivity, although the *ortho*-methoxy group of **6e** might coordinate to silane **2** (entries 4 and 5). Sulfoxide **6f** with an electron-donating *p*-methoxyphenyl group increased the yield (entry 6).

The substrate scope of the asymmetric allylation of *N*-acylhydrazones **1** using **6a** was next investigated (Table 2). Both several aliphatic and aromatic hydrazones provided high enantioselectivity (entries 1−7). In addition, hydrazone **1h** with a 1-alkynyl group provided the desired adduct **3h** in high yield with good selectivity (entry 8).[11] In some cases, precomplexation of **6a** 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.

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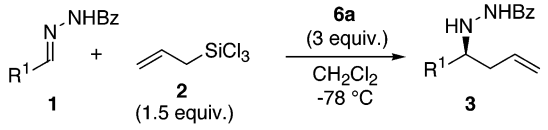
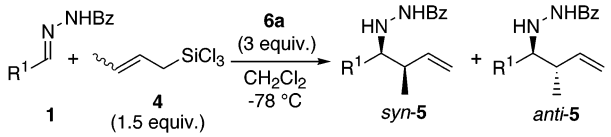
Table 2. Asymmetric Allylation of *N*-Benzoylhydrazones



entry	**1** (R^1)	time/h	**3** (% yield)	% ee (config.)
1[a,c]	**1b** (Me)	17	**3b** (78)	90 (*R*)
2[a]	**1c** (*n*-C_7H_{15})	1	**3c** (81)	88 (*R*)
3[b]	**1c**	1	**3c** (61)	92 (*R*)
4[a]	**1d** (*i*-Pr)	1	**3d** (80)	98 (*R*)
5[b]	**1e** (*c*-Hex)	1	**3e** (77)	91 (*R*)
6[a]	**1f** (*p*-$MeOC_6H_4$)	18	**3h** (82)	81 (*S*)
7[a,c]	**1g** (*p*-ClC_6H_4)	5	**3g** (69)	89 (*S*)
8[a]	**1h** (PhC≡C)	8	**3h** (95)	70 (*S*)

[a] Method A (see Table 1). [b] Method B:[8] a solution of **1** (0.3 mmol) in dichloromethane (1.2 mL) was added to a solution of **2** (1.5 equiv), **6a** (3.0 equiv), and 2-methyl-2-butene (0.5 equiv) in dichloromethane (0.8 mL) at −78 °C. [c] At a higher concentration (0.3 M).

Table 3. Asymmetric Crotylation of *N*-Benzoylhydrazones



entry	**1**	**4**[a]	time/h	**5** (% yield)	syn (% ee)	/	anti (% ee)
1[b]	**1a**	*Z*	4	**5a** (60)	<1 (−)	/	>99 (91)
2[b]	**1a**	*E*	4	**5a** (58)	99 (89)	/	1 (−)
3[c]	**1b**	*Z*	17	**5b** (99)	<1 (−)	/	>99 (73)
4[c]	**1b**	*E*	17	**5b** (99)	98 (82)	/	2 (−)
5[b]	**1c**	*Z*	3	**5c** (83)	<1 (−)	/	>99 (86)
6[b]	**1c**	*E*	3	**5c** (82)	95 (91)	/	5 (84)
7[c]	**1f**	*Z*	24	**5f** (16)	<1 (−)	/	>99 (92)

[a] (*Z*)-**4** (>99% *Z*) or (*E*)-**4** (98% *E*) was used. [b] Method B (see Table 2) at a higher concentration of **1** (0.3 M). [c] Method A (see Table 1) at a higher concentration of **1** (0.3 M).

Finally, asymmetric crotylations with (*Z*)- and (*E*)-crotyltrichlorosilanes (**4**) were investigated under the conditions using chiral sulfoxide **6a** (Table 3). It was found that the reaction of hydrazones **1a**−**c** 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, hydrazone **1f** reacted with (*Z*)-**4** slowly under the same conditions, and high diastereo- and enantioselectivity were obtained (entry 7).[12]

In summary, we have introduced sulfoxides to the reactions of *N*-acylhydrazones with allyltrichlorosilanes as highly effective neutral coordinate-organocatalysts (NCOs). Both high diastereo- and enantioselectivity were obtained when optically active *S*-chiral sulfoxides were used. According to these reactions, optically active homoallylic amine derivatives were prepared from both achiral hydrazones and silanes. Reduction of the amount of the chiral NCO as well as application to other related reactions are now under investigation.

Acknowledgment. This work was partially supported by CREST and SORT, Japan Science Technology Coporation (JST), and a Grant-in-Aid for Scientific Research from the Japan Society of the Promotion of Sciences.

Supporting Information Available: Experimental details and physical data of all compounds; the preliminary investigations on the effect of achiral or racemic NCOs and the N−N bond cleavage of products as well as assignment of absolute configurations (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Details are shown in the Supporting Information.

(9) It was reported that DMSO was incompatible with allyltrichlorosilane (**2**) in a reaction with benzaldehyde (see ref 6b). Meanwhile, DMSO was employed as a solvent for aldol-type or Michael-type additions of ketene trimethylsilyl acetals or allylation of an aldehyde with allyltrimethylstannane where interaction of DMSO with these nucleophiles was suggested: (a) Génisson, Y.; Gorrichon, L. *Tetrahedron Lett.* **2000**, *41*, 4881. (b) Cokley, T. M.; Harvey, P. J.; Marshall, R. L.; McCluskey, A.; Young, D. J. *J. Org. Chem.* **1997**, *62*, 1961.

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(11) Allylations of *N*-acylhydrazones derived from cinnamaldehyde, 2-thiophenecarboxaldehyde, 3-pyridinecarboxaldehyde, and acetophenone resulted in low yields under the present reaction conditions.

(12) Hydrazone **1f** reacted with (*E*)-**4** sluggishly under the conditions.

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