

## A Chiral Formamide: Design and Application to Catalytic Asymmetric Synthesis

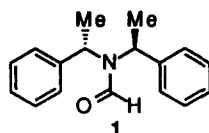
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**Abstract:** (*S,S*)-*N,N*-bis(- $\alpha$ -methylbenzyl)formamide is the first example of chiral formamides that function as Lewis base catalysts to effectively serve catalytic asymmetric synthesis. The chiral formamide in combination with an additive, HMPA, catalyzes allylations of aliphatic aldehydes with allyl- and crotyltrichlorosilanes with high enantioselectivity (up to 98% ee). In the crotylations with (*E*)-crotyltrichlorosilane, cyclohexanecarboxaldehyde and hydrocinnamaldehyde gave the corresponding *anti* homoallylic alcohols exclusively with 98 and 94% ee's, respectively. © 1998 Elsevier Science Ltd. All rights reserved.

*N,N*-Dimethylformamide (DMF) has been proven an effective Lewis base that catalyzes some important reactions such as allylation<sup>1,2</sup> and hydrosilylation<sup>3</sup> of carbonyl compounds.<sup>4</sup> However, asymmetric catalysis using chiral DMF analogs is not known. We became very interested in the development of chiral formamides as asymmetric catalysts for enantioselective synthesis. The present paper discloses herein the design of chiral formamides as Lewis base catalysts and the first successful application to catalytic asymmetric synthesis. This application consists of the highly enantioselective allylation of aliphatic aldehydes with allylic trichlorosilanes using a newly prepared chiral formamide: (*S,S*)-*N,N*-bis(- $\alpha$ -methylbenzyl)formamide (**1**).<sup>5</sup>



Denmark *et al.* and we have previously succeeded in the asymmetric allylation and crotylation of *aromatic aldehydes* with allylic trichlorosilanes using chiral phosphoramides.<sup>6</sup> While chiral Lewis acid catalysis provides optically active *syn* homoallylic alcohols with high diastereoselectivity from either stereoisomer of crotylsilanes and -stannanes,<sup>7,8</sup> the reactions catalyzed by chiral Lewis bases<sup>9</sup> including the phosphoramides have the advantage of stereoselectively affording the *syn* and *anti* homoallylic alcohols from (*Z*)- and (*E*)-crotylsilanes or -stannanes, respectively. However, these phosphoramides are not effective for *aliphatic aldehydes*, giving only a trace of the corresponding homoallylic alcohols.<sup>6</sup> We decided to evaluate the ability of chiral formamides to promote the allylation of *aliphatic aldehydes*.

Among the *C*<sub>2</sub>-symmetric formamides designed and prepared, formamide **1** was found to be one of the best candidates for the asymmetric allylation. Treatment of cyclohexanecarboxaldehyde (**2**), chosen as a model substrate, with allyltrichlorosilane (**3**)<sup>10</sup> (10 equiv to **2**) in the presence of a stoichiometric amount of **1** in dichloromethane at -78°C for 7 d produced (*R*)-enriched homoallylic alcohol **4** in 81% yield with 68% ee (Table 1, entry 1).<sup>11a</sup> However, a decrease in the amount of catalyst **1** dramatically suppressed the chemical yield and enantioselectivity (entries 2–4). Interestingly, use of 10 and 25 mol% caused the reversal of enantioselection to give the (*S*)-enriched alcohol **4** with 30 and 32% ee's, respectively (entries 3 and 4). The last drawback has been mostly overcome by the finding of hexamethylphosphoramide (HMPA) as an

additive. Noteworthy was the fact that addition of HMPA (100 mol%) effectively improved the enantioselectivity significantly at all concentrations of catalyst **1** (entries 5-8).<sup>12</sup> After extensive optimization the best molar ratio of **1** to HMPA was found to be 1:5 for the enantioselectivity and chemical yield. Even in the presence of 10 mol% of **1** and 50 mol% of HMPA, the reaction of **2** with **3** (1.5 equiv to **2**) in propionitrile at -78°C for 7 d afforded the (*R*)-enriched alcohol **4** of 94% ee in 38% chemical yield (entry 9). Use of 20 mol% of **1**, 100 mol% of HMPA and 1.5 equiv of **3** in propionitrile at -78°C provided the highest enantiomeric excess (98% ee, entry 10). However, elevating reaction temperature dramatically decreased the enantioselectivity (entries 11 and 12).

**Table 1.** Asymmetric Allylation of Cyclohexanecarboxaldehyde (**2**) with Allyltrichlorosilane (**3**) Catalyzed by Formamide **1**

$\text{Cyclohexanecarboxaldehyde (2)} + \text{Allyltrichlorosilane (3)} \xrightarrow[\text{solvent}]{\text{1, HMPA}}$

$(S)\text{-4 } R^1 = \text{OH}, R^2 = \text{H}$   
 $(R)\text{-4 } R^1 = \text{H}, R^2 = \text{OH}$

Entry	Catalyst <b>1</b> (mol%)	HMPA (mol%)	<b>3</b> (equiv)	Solvent	Temp (°C)	Time (d)	Yield <sup>a</sup> (%)	( <i>S</i> )- <b>4</b> / ( <i>R</i> )- <b>4</b> <sup>b</sup>
1	100	0	10	CH <sub>2</sub> Cl <sub>2</sub>	-78	7	81	16/84
2	50	0	10	CH <sub>2</sub> Cl <sub>2</sub>	-78	7	45	28/72
3	25	0	10	CH <sub>2</sub> Cl <sub>2</sub>	-78	7	20	65/35
4	10	0	10	CH <sub>2</sub> Cl <sub>2</sub>	-78	7	12	66/34
5	100	100	10	CH <sub>2</sub> Cl <sub>2</sub>	-78	7	89	2/98
6	50	100	10	CH <sub>2</sub> Cl <sub>2</sub>	-78	7	79	3/97
7	25	100	10	CH <sub>2</sub> Cl <sub>2</sub>	-78	7	33	3/97
8	10	100	10	CH <sub>2</sub> Cl <sub>2</sub>	-78	7	8	15/85
9	10	50	1.5	C <sub>2</sub> H <sub>5</sub> CN	-78	7	38	3/97
10	20	100	1.5	C <sub>2</sub> H <sub>5</sub> CN	-78	14	80	1/99
11	20	100	1.5	C <sub>2</sub> H <sub>5</sub> CN	-60	7	59	13/87
12	20	100	1.5	C <sub>2</sub> H <sub>5</sub> CN	-20	2	62	48/52

a) Isolated yield; b) Determined by HPLC analysis of the corresponding 3,5-dinitrobenzoate (Chiralcel OD-H, Daicel Chemical Industries, Ltd.).

Table 2 summarizes the results obtained for the reaction of a variety of aliphatic aldehydes with 1.5 or 10 equiv of allylsilane **3** at -78°C in propionitrile or acetone (entries 1-7). The obtained enantiomeric excesses ranged from 68 to 98%. The characteristic features of the results are as follows: (1) all reactions resulted in remarkable enantioselectivities, with the exception of straight-chain substrates; (2) the reaction with straight-chain substrates gave relatively low chemical yields and enantioselectivities; (3) acetone is more effective than propionitrile for the enantioselectivity with straight-chain substrates although the reaction rate in acetone is rather low compared with that in propionitrile; (4) the chiral catalyst **1** was recovered in >95% yield by column chromatography. A typical aromatic aldehyde, benzaldehyde, gave the corresponding homoallylic alcohol in a good chemical yield (94%) but with a very low enantiomeric excess (8% ee, entry 8).

Finally, the crotylation of aldehydes with (*E*)-crotyltrichlorosilane (**21**)<sup>13</sup> was also achieved highly diastereo- and enantioselectively using formamide **1**. For example, the reaction of aldehyde **2** with 40 mol% of the catalyst and 200 mol% of HMPA in propionitrile at -78°C for 3 w afforded only the corresponding optically active *anti* homoallylic alcohol **22**<sup>14</sup> in 92% yield with 98% ee. The major enantiomer was found to have the (1*S*,2*R*)-configuration by comparison to literature rotation.<sup>15</sup> In the same manner, the reaction of

hydrocinnamaldehyde (7) gave *anti*-alcohol 23<sup>14</sup> exclusively in 97% yield with 94% ee (Scheme 1). The *anti*-diastereocontrolled outcome is consistent with a chair-like cyclic silicate transition structure.<sup>1a,c,16</sup>

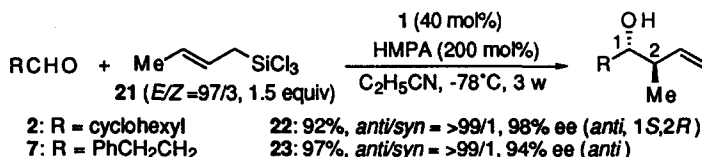
**Table 2.** Catalytic Enantioselective Allylations of Various Aldehydes with Allylsilane 3 Catalyzed by Formamide 1<sup>a</sup>

$$\text{RCHO} + \text{CH}_2=\text{CH}-\text{SiCl}_3 \xrightarrow[\text{C}_2\text{H}_5\text{CN}, -78^\circ\text{C}]{\text{catalyst 1, HMPA}} \text{R}-\text{CH}(\text{OH})-\text{CH}=\text{CH}_2$$

3 (1.5 equiv)

Entry	R	Catalyst 1 (mol%)	HMPA (mol%)	Time (w)	Product	Yield <sup>b</sup> (%)	ee <sup>c</sup> (%)
1	cyclopentyl (5)	20	100	2	6	72	91
2	PhCH <sub>2</sub> CH <sub>2</sub> (7) <sup>d</sup>	20	100	3	8	84	95 (S) <sup>e</sup>
3	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> CH (9)	20	100	3	10	74	93
4	<i>tert</i> -butyl (11)	40	200	4	12	61	98
5	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>5</sub> (13) <sup>d,f</sup>	40	200	4	14	53	68
6	CH <sub>2</sub> =CH(CH <sub>2</sub> ) <sub>2</sub> (15) <sup>d</sup>	20	100	3	16	56 <sup>g</sup>	86
7	3-butynyl (17) <sup>d</sup>	40	200	3	18	51 <sup>g</sup>	88
8	Ph (19)	20	100	1	20	94	8 <sup>h</sup>

a) Unless otherwise specified, the reaction was done with an aldehyde (1 mmol), allylsilane 3 (1.5 mmol), the catalyst 1 (0.2 or 0.4 mmol), and HMPA (1 or 2 mmol) in propionitrile (2 mL) at -78°C; b) Isolated yield; c) All ee values were determined by HPLC analysis of the corresponding 3,5-dinitrobenzoates (Chiralcel OD-H or AD, Daicel Chemical Industries, Ltd.); d) Carried out in acetone; e) The absolute configuration was assigned by comparison of the sign of the optical rotation with reported data.<sup>11b</sup>; f) 10 equiv of 3 was used; g) Because homoallylic alcohols are volatile, values reported are those for the corresponding 3,5-dinitrobenzoates; h) Determined by HPLC using a Daicel Chiralcel OD-H column.



**Scheme 1**

In conclusion, we have succeeded in developing a highly efficient Lewis base catalyst, chiral formamide 1, for catalytic asymmetric allylations. This catalyst can promote the crotylation of aliphatic aldehydes with (*E*)-crotylsilane 21 stereoselectively to give the corresponding *anti*-homoallylic alcohols with high diastereo- and enantiomeric excesses. Further applications of catalyst 1 to other catalytic asymmetric reactions are now being carried out.

**Typical Procedure for Allylation with Allyltrichlorosilane (3).** (*R*)-1-Cyclohexyl-3-buten-1-ol [(*R*)-4]: To a solution of cyclohexanecarboxaldehyde 2 (112 mg, 1.0 mmol), catalyst 1 (50.7 mg, 0.2 mmol) and HMPA (175  $\mu$ L, 1.0 mmol) in C<sub>2</sub>H<sub>5</sub>CN (2 mL) was added dropwise allylsilane 3 (263 mg, 1.5 mmol) at -78°C under argon. After stirring at -78°C for 2 w, the reaction mixture was poured into an ice-cooled mixture of Et<sub>2</sub>O (30 mL) and saturated aqueous NaHCO<sub>3</sub> (30 mL) and stirred for 15 min. The organic layer was separated and the aqueous phase extracted with Et<sub>2</sub>O (2 x 30 mL). The combined organic extracts were dried (MgSO<sub>4</sub>) and concentrated in vacuo. The oily residue was purified by flash chromatography (SiO<sub>2</sub>, EtOAc:*n*-hexane 1:20) to afford 4 (123 mg, 80% yield) as a colorless oil. [ $\alpha$ ]<sub>D</sub><sup>24</sup> +9.7° (*c* 1.00, ethanol) (98% ee); <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  5.95–5.74 (m, 1H), 5.20–5.08 (m, 2H), 3.46–3.34 (m, 1H), 2.42–2.04 (m, 2H), 2.40–0.80 (m, 12H); IR (neat): 3384, 2925, 1640, 1450, 986, 910 cm<sup>-1</sup>; MS: *m/z* 113 [M<sup>+</sup>-41], 95, 67, 55. Elution with *n*-hexane-EtOAc (3:1) recovered the chiral formamide 1 (49.1 mg) without racemization.

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10. Allyltrichlorosilane (**3**) was purchased from Aldrich Chemical Company, Inc. and distilled before use.
11. (a) The absolute configuration of the major enantiomer was determined to be *R* by comparison of the  $[\alpha]_D$  value with reported data. Observed  $[\alpha]_D$  value of **4** with 68% ee:  $[\alpha]_D^{24} +6.7^\circ$  (*c* 1.24, ethanol). For (*S*)-enriched alcohol **4** (92.6% ee), see: Costa, A.L.; Piazza, M.G.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Am. Chem. Soc.* **1993**, *115*, 7001-7002;  $[\alpha]_D^{25} -8.94^\circ$  (*c* 0.56, ethanol); (b) Observed  $[\alpha]_D$  value of **8** with 95% ee:  $[\alpha]_D^{25} -21.6^\circ$  (*c* 1.19, CHCl<sub>3</sub>). For (*R*)-enriched alcohol **8**, see: Imwinkelried, R.; Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 765-766;  $[\alpha]_D^{20} +16.9^\circ$  (*c* 1.00, CHCl<sub>3</sub>) (80% ee).
12. The reason why HMPA improves the enantioselectivity remains unclear. However, the HMPA-enhanced catalytic activity may be explained by assuming that HMPA dissociates formamide **1** from the reaction product to facilitate regeneration of the chiral catalyst.
13. (*E*)- and (*Z*)-Crotyltrichlorosilanes are readily prepared by using literature procedures, see: (a) Kira, M.; Kobayashi, M.; Sakurai, H. *Tetrahedron Lett.* **1987**, *28*, 4081-4084. (b) Kira, M.; Hino, T.; Sakurai, H. *Tetrahedron Lett.* **1989**, *30*, 1099-1102.
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15. Observed  $[\alpha]_D$  value of **22** with 98% ee:  $[\alpha]_D^{23} +18.4^\circ$  (*c* 1.29, CHCl<sub>3</sub>). For (1*R*,2*S*)-**22** (86% ee), see ref 14;  $[\alpha]_D^{25} -15.8^\circ$  (*c* 1.02, CHCl<sub>3</sub>).
16. (*Z*)-Crotyltrichlorosilane is not considered to be a sterically favorable substrate for the chair-like cyclic silicate transition structure. The reaction of aldehydes with the (*Z*)-crotylsilane (*Z/E* = 99/1) was very sluggish in the present method. Reaction of **2** with the silane (1.5 equiv) in the presence of **1** (40 mol%) and HMPA (200 mol%) in C<sub>2</sub>H<sub>5</sub>CN at -78°C for 3 w gave the corresponding *anti* (**22**) and *syn* homoallylic alcohols in the ratio of 61:39 (19% yield), and the enantiomeric excess of the *anti*-isomer was 98% [(1*S*,2*R*)-**22**]. The reaction carried out at -20°C for 3 w was *syn*-selective (*syn/anti* = 95/5, 34% yield). However, the enantioselectivity was very low [3% ee (the *syn*-isomer)].