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# Asymmetric allenylation of aliphatic aldehydes catalyzed by a chiral formamide

Katsuhiko Iseki,* Yoshichika Kuroki and Yoshiro Kobayashi

*MEC Laboratory, Daikin Industries, Ltd, Miyukigaoka, Tsukuba, Ibaraki 305-0841, Japan*

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## Abstract

(*S*,*S*)-*N*,*N*-Bis(α-methylbenzyl)formamide in combination with HMPA catalyzes the allenylation of aliphatic aldehydes with propargyltrichlorosilane with good enantioselectivity (up to 95% e.e.). © 1998 Elsevier Science Ltd. All rights reserved.

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## 1. Introduction

The present paper discloses the first catalytic enantioselective allenylation of aldehydes.[1] *N*,*N*-Dimethylformamide (DMF) is an effective Lewis base that catalyzes some important reactions such as allylation[2] and allenylation[3] of carbonyl compounds. We have previously succeeded in the asymmetric allylation of aliphatic aldehydes with allyl- and crotyltrichlorosilanes mediated by the chiral DMF analog, (*S*,*S*)-*N*,*N*-bis(α-methylbenzyl)formamide **1**.[4] The present addition of a propa-1,2-dienyl group to aliphatic aldehydes is carried out enantioselectively using the chiral catalyst **1** in combination with the additive, hexamethylphosphoramide (HMPA).

## 2. Results and discussion

Treatment of cyclohexanecarboxaldehyde **2a** with 1.5 equiv. of a mixture of propargyl- and allenyltrichlorosilanes (**3**:**4**=75:25)[5] in the presence of catalyst **1** (20 mol%) and HMPA (100 mol%) in dichloromethane at −78°C for 14 days produced (*S*)-enriched propa-1,2-dienyl carbinol **5a** in 71% yield with 79% e.e. (Table 1, entry 1).[6] However, propargyl carbinol **6a** was obtained in only a small amount (**5a**:**6a**=98:2), suggesting that formamide **1** catalyzes reaction of the aldehyde with allenylsilane **4** very sluggishly.[7] Although a decrease in the amount of catalyst **1** (10 mol%) retained

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* Corresponding author. Tel: 81-298-58-5060; fax: 81-298-58-5082; e-mail: iseki@mec.daikin.co.jp

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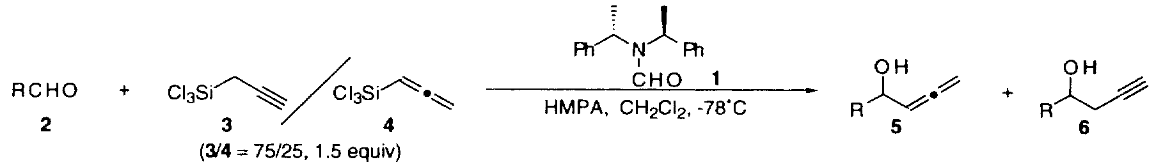
Table 1
Asymmetric allenylation of aliphatic aldehydes **2** with propagyltrichlorosilane **3** catalyzed by formamide **1**



| Entry | Aldehyde (RCHO 2) R | Formamide 1 (mol%) | HMPA (mol%) | Time (d) | Yield (5 + 6)[a] (%) | 5/6[b] | e.e. (5)[c] (%) | |
|---|---|---|---|---|---|---|---|---|
| 1 | cyclohexyl (**2a**) | 20 | 100 | 14 | 71 | 98/2 | 79 (*S*) | (**5a**) |
| 2 | cyclohexyl (**2a**) | 10 | 50 | 14 | 35 | 98/2 | 79 (*S*) | (**5a**) |
| 3 | cyclohexyl (**2a**) | 10 | 0 | 7 | 28 | 98/2 | 43 (*S*) | (**5a**) |
| 4 | $PhCH_2CH_2$ (**2b**) | 20 | 100 | 14 | 71 | 99/1 | 79 | (**5b**) |
| 5 | $(C_2H_5)_2CH$ (**2c**) | 20 | 100 | 14 | 70 | 96/4 | 77 | (**5c**) |
| 6 | *tert*-butyl (**2d**) | 20 | 100 | 14 | 55 | 94/6 | 95 | (**5d**) |
| 7[d] | $CH_3(CH_2)_5$ (**2e**) | 20 | 100 | 14 | 37 | 93/7 | 56 | (**5e**) |
| 8 | Ph (**2f**) | 40 | 200 | 4 | 59 | 96/4 | 0 | (**5f**) |

[a] Isolated yield. [b] Determined by GC analysis. [c] Determined by HPLC analysis of the corresponding 3,5-dinitrobenzoate (Chiralcel OD-H or AD, Daicel Chemical Industries, Ltd.). [d] Carried out in acetone.

the enantioselectivity (entry 2, 79% e.e.), the absence of HMPA markedly suppressed it (entry 3, 43% e.e.).[8] Hydrocinnamaldehyde **2b** and 2-ethylbutanal **2c** provided the corresponding propa-1,2-dienyl carbinols, **5b** and **5c**, with an enantiomeric excess of 79% and 77%, respectively (entries 4 and 5). The highest enantioselectivity was attained with 2,2-dimethylpropanal **2d** (entry 6, 95% e.e.). With heptanal **2e**, the reaction in acetone was found to be more effective in terms of enantioselectivity than that in dichloromethane (entry 7, 56% e.e.).[9] A typical aromatic aldehyde, benzaldehyde **2f**, gave the corresponding alcohol **5f** in essentially racemic form (entry 8).[10,11]

In conclusion, we have succeeded in the first catalytic enantioselective allenylation of aliphatic aldehydes using the chiral formamide **1**. Attempts are presently being made to improve the allenylation, especially the catalytic activity,[12] and to apply the catalyst **1** to other catalytic asymmetric reactions.

## 3. Experimental

### *3.1. General*

All reactions were carried out under an argon atmosphere with magnetic stirring in oven-dried glassware. Dichloromethane and acetone were distilled from $CaH_2$ and $K_2CO_3$, respectively, immediately before use. Other solvents and reagents were used as supplied or purified. Anhydrous $MgSO_4$ was used as the drying agent. TLC was carried out with pre-coated Kieselgel $60F_{254}$ plates (Merck). Silica gel 60 (Merck, 230–400 mesh) was used for column chromatography. GLC analysis was carried out on a Shimadzu GC-17A instrument using a J&W Scientific (30 m×0.25 mm) DB-1 capillary column whose film thickness was 0.25 μm. Liquid chromatographic analysis was performed on a Shimadzu LC-10A at 254 nm using a chiral column (Daicel Chiralcel OD-H and AD columns). Optical rotations were measured at 589 nm using a 1.0 dm cell with a total volume of 1 mL on a JASCO DIP-370 polarimeter.

Melting points were measured on a Yanaco MP-500D micro melting point apparatus and are uncorrected. Infrared spectra were taken either neat or as KBr pellets on a Perkin–Elmer 1600 FT-IR. Absorption was expressed in reciprocal centimeters ($cm^{-1}$). $^1H$ NMR and $^{13}C$ NMR spectra were recorded at 200 MHz and 50 MHz, respectively, on a Varian Gemini-200 instrument. $^1H$ NMR signals were expressed in parts per million (ppm) downfield from TMS as the internal standard ($\delta$). $^{13}C$ NMR spectra were given with $CHCl_3$ (77.0 ppm) as the internal standard. Coupling constants are in hertz. $CDCl_3$ served as solvent for $^1H$ and $^{13}C$ NMR. Low- and high-resolution mass spectral analyses were performed at 70 eV electron-impact (EI) using a Kratos CONCEPT-1H double-focusing magnetic sector spectrometer. Elemental analysis was carried out at the Toray Research Center, Inc., Tokyo.

### 3.2. *Materials*

(*S*,*S*)-Bis(α-methylbenzyl)amine was purchased from AZmax Co. Ltd., Chiba, Japan. Acetic formic anhydride was prepared according to reported procedures.[13]

### 3.3. *Preparation of (S,S)-N,N-bis(α-methylbenzyl)formamide* **1**

To a solution of (*S*,*S*)-bis(α-methylbenzyl)amine (5 g, 22.2 mmol) in dichloromethane (50 mL) was added dropwise acetic formic anhydride (96% purity, 5.1 g, 55.6 mmol) at room temperature. After stirring for 1 h, the reaction was quenched with saturated aqueous $NaHCO_3$ (50 mL). The organic layer was separated and the aqueous phase extracted with dichloromethane (2×50 mL). The combined extracts were washed with brine and dried. After evaporation of the solvent, the residue was purified by flash chromatography ($SiO_2$, EtOAc:*n*-hexane=1:3) and recrystallized from $Et_2O$:*n*-hexane to give **1** (5.5 g, 98% yield) as colourless needles: m.p. 80.2–81.8°C; $[\alpha]_D^{25}$ −214.1 (*c* 1.02, $CHCl_3$); IR (KBr): 2976, 1645, 1248, 697 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 1.67 (d, *J*=7.2 Hz, 3H), 1.71 (d, *J*=7.2 Hz, 3H), 4.50 (q, *J*=7.2 Hz, 1H), 5.69 (q, *J*=7.2 Hz, 1H), 7.30–6.78 (m, 10H), 8.33 (s, 1H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 17.1, 22.4, 50.7, 52.9, 126.7, 127.4, 127.7, 128.1, 128.3, 139.8, 141.0, 162.6; MS: *m/z* 253 [$M^+$], 148, 120, 105; anal. calcd for $C_{17}H_{19}NO$: C, 80.6; H, 7.6; N, 5.5. Found: C, 80.6; H, 7.5; N, 5.5.

### 3.4. *Preparation of propargyltrichlorosilane* **3**

A mixture of trichlorosilane (25 g, 184.6 mmol), propargyl chloride (13.4 mL, 184.6 mmol) and $Et_2O$ (150 mL) was added dropwise to a suspension of CuCl (1.83 g, 18.5 mmol) and $Et_3N$ (24.4 mL, 175.4 mmol) in $Et_2O$ (150 mL) at room temperature. After 16 h at this temperature, the reaction mixture was filtered. Distillation of the filtrate gave a mixture of **3** and **4** (**3**:**4**=75:25, 6.65 g, 21%) at 55–58°C/85 torr.

**3**: $^1H$ NMR ($CDCl_3$): $\delta$ 2.11 (t, *J*=3.0 Hz, 1H), 2.42 (d, *J*=3.0 Hz, 2H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 15.4, 71.3, 109.2; MS: *m/z* 176 [$M^+$], 174 [$M^+$], 172 [$M^+$]; HRMS calcd for $C_3H_3Cl_3Si$ [$M^+$]: 171.9070. Found: 171.9073.

**4**: $^1H$ NMR ($CDCl_3$): $\delta$ 4.92 (d, *J*=6.8 Hz, 2H), 5.33 (t, *J*=6.8 Hz, 1H); $^{13}C$ NMR ($CDCl_3$): $\delta$ 74.1, 84.4, 216.4; MS: *m/z* 176 [$M^+$], 174 [$M^+$], 172 [$M^+$]; HRMS calcd for $C_3H_3Cl_3Si$ [$M^+$]: 171.9070. Found: 171.9077.

### *3.5. General procedure for the preparation of 3,5-dinitrobenzoate derivatives of propa-1,2-dienyl carbinols **5***

To a solution of an optically active propa-1,2-dienyl carbinol **5** (65 μmol) in dichloromethane (2 mL) were added $Et_3N$ (0.5 mL, 3.59 mmol), 3,5-dinitrobenzoyl chloride (77 mg, 0.33 mmol), and a catalytic amount of 4-dimethylaminopyridine at room temperature. The reaction mixture was stirred for 18 h, poured into ice water and extracted with $Et_2O$. The combined extracts were washed with 0.5 N HCl, saturated aqueous $NaHCO_3$ and brine, dried and filtered. After evaporation of the solvent, a solution of the residue in dichloromethane was passed through a short silica gel column. The 3,5-dinitrobenzoate was recovered completely by elution with dichloromethane and the combined fractions were concentrated *in vacuo*. The obtained residue was analyzed by HPLC using a chiral column (Daicel Chiralcel OD-H and AD columns) to determine the enantiomeric excess.

### *3.6. Typical procedure for allenylation catalyzed by the chiral formamide **1**. (S)-1-Cyclohexylbuta-2,3-dien-1-ol **5a***

To a solution of cyclohexanecarboxaldehyde **2** (112 mg, 1.0 mmol), catalyst **1** (50.7 mg, 0.2 mmol) and HMPA (175 μL, 1.0 mmol) in dichloromethane (2 mL) was added dropwise a mixture of **3** and **4** (263 mg, 1.5 mmol) at −78°C. After stirring at −78°C for 14 days, the reaction mixture was poured into an ice-cooled mixture of $Et_2O$ (30 mL) and saturated aqueous $NaHCO_3$ (30 mL) and stirred for 15 min. The organic layer was separated and the aqueous phase extracted with $Et_2O$ (2×30 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The oily residue was purified by flash chromatography ($SiO_2$, EtOAc:*n*-hexane=1:20) to afford **5a** and **6a** (**5a**:**6a**=98:2, 108 mg, 71% yield) as a colourless oil. $[\alpha]_D^{24}$ +10.5 (*c* 1.02, benzene) (79% e.e.); IR (neat): 3360, 2924, 1955, 1450, 1015, 841 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 0.82–1.91 (m, 11H), 1.75 (s, 1H), 3.92 (ddt, *J*=2.2, 6.6, 6.6 Hz, 1H), 4.83 (dd, *J*=2.2, 6.5 Hz, 2H), 5.21 (dt, *J*=6.5, 6.6 Hz, 1H); $^{13}C$ NMR ($CDCl_3$): δ 26.1, 26.5, 28.3, 28.6, 44.1, 74.0, 77.1, 93.2, 112.3, 207.2; MS: *m/z* 152 [$M^+$], 113, 95; HRMS calcd for $C_{10}H_{16}O$ [$M^+$]: 152.1201. Found: 152.1196. HPLC analysis of the corresponding 3,5-dinitrobenzoate: $t_R$ (retention time) (minor), 4.1 min (10.4%); $t_R$ (major), 7.7 min (89.6%) (Chiralcel AD, *n*-hexane:EtOH=9:1, 2.0 mL/min). Elution with *n*-hexane:EtOAc (3:1) recovered the chiral formamide **1** (49.1 mg) without racemization.

### *3.7. 6-Phenylhexa-1,2-dien-4-ol **5b***

Compound **5b** (**5b**:**6b**=99:1, 71%) was obtained by the same procedure as **5a**: a colourless oil; $[\alpha]_D^{23}$ −2.4 (*c* 1.41, $CHCl_3$) (79% e.e.); IR (neat): 3384, 2928, 1955, 1716, 1454, 700 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): δ 1.69 (d, *J*=4.9 Hz, 1H), 1.93 (dt, *J*=7.6, 7.7 Hz, 2H), 2.77 (dt, *J*=4.4, 7.7 Hz, 2H), 4.12–4.30 (m, 1H), 4.91 (dd, *J*=2.5, 6.5 Hz, 2H), 5.31 (dt, *J*=6.5, 6.8 Hz, 1H), 7.12–7.39 (m, 5H); $^{13}C$ NMR ($CDCl_3$): δ 31.7, 39.0, 68.9, 77.8, 94.7, 125.9, 128.4, 128.5, 141.8, 207.1; MS: *m/z* 174 [$M^+$], 156, 91; HRMS calcd for $C_{12}H_{14}O$ [$M^+$]: 174.1045. Found: 174.1042. HPLC analysis of the corresponding 3,5-dinitrobenzoate: $t_R$ (major), 16.7 min (89.5%); $t_R$ (minor), 22.0 min (10.5%) (Chiralcel AD, *n*-hexane:EtOH=9:1, 1.0 mL/min).

### *3.8. 5-Ethylhepta-1,2-dien-4-ol **5c***

Compound **5c** (**5c**:**6c**=96:4, 70%) was obtained by the same procedure as **5a**: a colourless oil; $[\alpha]_D^{23}$ +38.8 (*c* 0.90, $CHCl_3$) (77% e.e.); IR (neat): 3360, 2963, 1956, 1461, 1021, 841 $cm^{-1}$; $^1H$ NMR ($CDCl_3$):

δ 0.92 (t, $J$=7.3 Hz, 6H), 1.20–1.60 (m, 5H), 1.62 (s, 1H), 4.13–4.28 (m, 1H), 4.86 (dd, $J$=2.2, 6.4 Hz, 2H), 5.23 (dt, $J$=6.4, 6.9 Hz, 1H); $^{13}$C NMR ($CDCl_3$): δ 11.5, 11.6, 21.5, 21.8, 47.1, 71.2, 77.3, 93.3, 208.9; MS: $m/z$ 140 [$M^+$], 125, 111, 101; HRMS calcd for $C_9H_{16}O$ [$M^+$]: 140.1201. Found: 140.1208. HPLC analysis of the corresponding 3,5-dinitrobenzoate: $t_R$ (minor), 4.2 min (11.6%); $t_R$ (major), 7.8 min (88.4%) (Chiralcel AD, $n$-hexane:EtOH=20:1, 2.0 mL/min).

### 3.9. 5,5-Dimethylhexa-1,2-dien-4-ol **5d**

The 3,5-dinitrobenzoate of compound **5d** (**5d**:**6d**=94:6, 55%) was obtained by the same procedure as **5a**: $[\alpha]_D^{24}$ +78.5 ($c$ 0.87, $CHCl_3$) (95% e.e.); IR (KBr): 3103, 2969, 1732, 1548, 1345, 1278, 1167 cm$^{-1}$; $^1$H NMR ($CDCl_3$): δ 1.08 (s, 9H), 4.78–4.97 (m, 2H), 5.25–5.42 (m, 2H), 9.15–9.25 (m, 3H); $^{13}$C NMR ($CDCl_3$): δ 25.7, 35.3, 77.1, 81.9, 87.2, 122.3, 129.3, 134.3, 148.6, 161.7, 209.2; MS: $m/z$ 320 [$M^+$], 305, 281, 195; HRMS calcd for $C_{15}H_{16}N_2O_6$ [$M^+$]: 320.1008. Found: 320.1013. HPLC analysis of the 3,5-dinitrobenzoate: $t_R$ (minor), 14.3 min (2.7%); $t_R$ (major), 15.8 min (97.3%) (Chiralcel OD-H, $n$-hexane:EtOH=20:1, 1.0 mL/min).

### 3.10. Deca-1,2-dien-4-ol **5e**

Compound **5e** (**5e**:**6e**=93:7, 37%) was obtained by the same procedure as **5a**, except using acetone instead of dichloromethane: a colourless oil; $[\alpha]_D^{25}$ +4.1 ($c$ 0.93, $CHCl_3$) (56% e.e.); IR (neat): 3334, 2929, 1957, 1467, 841 cm$^{-1}$; $^1$H NMR ($CDCl_3$): δ 0.88 (t, $J$=6.7 Hz, 3H), 1.20–1.65 (m, 10H), 1.69 (s, 1H), 4.10–4.23 (m, 1H), 4.85 (dd, $J$=2.4, 6.8 Hz, 2H), 5.24 (dt, $J$=6.3, 6.8 Hz, 1H); $^{13}$C NMR ($CDCl_3$): δ 14.1, 22.6, 25.4, 29.2, 31.8, 37.5, 69.7, 77.4, 94.9, 206.9; MS: $m/z$ 154 [$M^+$], 139, 115, 84, 70; HRMS calcd for $C_{10}H_{18}O$ [$M^+$]: 154.1358. Found: 154.1354. HPLC analysis of the corresponding 3,5-dinitrobenzoate: $t_R$ (minor), 11.8 min (21.8%); $t_R$ (major), 13.7 min (78.1%) (Chiralcel OD-H, $n$-hexane:EtOH=20:1, 1.0 mL/min).

### 3.11. 1-Phenylbuta-2,3-dien-1-ol **5f**

Compound **5f** (**5f**:**6f**=96:4, 59%) was obtained by the same procedure as **5a**: a colourless oil; $[\alpha]_D^{23}$ 0.0 ($c$ 0.65, $CHCl_3$) (0% e.e.); IR (neat): 3380, 1955, 1452, 1024, 850, 700 cm$^{-1}$; $^1$H NMR ($CDCl_3$): δ 2.14 (s, 1H), 4.94 (dd, $J$=2.2, 6.5 Hz, 2H), 5.23–5.33 (m, 1H), 5.46 (dt, $J$=6.5, 6.5 Hz, 1H), 7.23–7.60 (m, 5H); $^{13}$C NMR ($CDCl_3$): δ 72.0, 78.2, 95.2, 126.1, 127.8, 128.5, 142.8, 207.0; MS: $m/z$ 146 [$M^+$], 145, 108, 77; HRMS calcd for $C_{10}H_{10}O$ [$M^+$]: 146.0732. Found: 146.0736.

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2. (a) Kobayashi, S.; Nishio, K. *Tetrahedron Lett.* **1993**, *34*, 3453–3456; (b) Kobayashi, S.; Nishio, K. *Synthesis* **1994**, 457–459; (c) Kobayashi, S.; Nishio, K. *J. Org. Chem.* **1994**, *59*, 6620–6628; (d) Wang, Z.; Wang, D.; Sui, X. *J. Chem. Soc., Chem. Commun.* **1996**, 2261–2262.
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4. Iseki, K.; Mizuno, S.; Kuroki, Y.; Kobayashi, Y. *Tetrahedron Lett.* **1998**, *39*, 2767–2770.
5. Reaction of propargyl chloride with trichlorosilane in the presence of CuCl and $Et_3N$ in $Et_2O$ at room temperature for 16 h generated **3** selectively (**3**:**4**=86:14); see Ref. 3. However, the distillation (55–58°C/85 torr) from the reaction mixture caused the isomerization between **3** and **4** (**3**:**4**=75:25).

6. The absolute configuration of the major enantiomer was determined to be *S* by comparison of the $[\alpha]_D$ value with reported data. Observed $[\alpha]_D$ value of **5a** with 79% e.e.: $[\alpha]_D^{24}$ +10.5 (*c* 1.02, benzene). For (*R*)-enriched alcohol **5a** (85% e.e.), see: Lautens, M.; Delanghe, P. H. M. *J. Am. Chem. Soc.* **1994**, *116*, 8526–8535; $[\alpha]_D$ −10.2 (*c* 2.1, benzene).
7. Kobayashi and Nishio have shown that **3** and **4** react with aldehydes in DMF to afford **5** and **6**, respectively; see Ref. 3.
8. The reason why HMPA improves the enantioselectivity remains unclear. Both HMPA and **1** may coordinate with **3** to generate a hexavalent silicate.
9. The allenylation of **2e** using 40 mol% of **1** and 200 mol% of HMPA in dichloromethane at −78°C for 7 days gave **5e** in 74% yield with 28% ee (**5e**:**6e**=99:1). Acetone provides higher enantiomeric excesses than dichloromethane in the allenylation of straight-chain aldehydes.
10. For (*S*)-enriched alcohol **5f** (47% e.e.), see Ref. 1a; $[\alpha]_D^{22}$ +45.6 (*c* 1.2, $CCl_4$).
11. Although HMPA itself catalyzes the allenylation of aromatic aldehydes at −78°C, **1** is not effective in terms of enantioselectivity even in the absence of HMPA; see Ref. 4.
12. The present allenylation is very sluggish at −78°C. Elevating the temperature improves the reaction rate but dramatically suppresses the enantioselectivity; the allenylation of **2a** in the presence of **1** (40 mol%) and HMPA (200 mol%) was carried out at −40°C for 7 days to afford (*S*)-**5a** (**5a**:**6a**=91:9) in 84% yield with 19% e.e.
13. Krimen, L. I. *Organic Synthesis*; John Wiley: New York, 1988; Collect. Vol. 6, pp. 8–9.