Tetrahedron: *Asymmetry* 20 (2009) 602–604

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

# Enantioselective alkynylation of aldehydes with chiral β-imino α-perfluoroalkylpropanol derivatives

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ARTICLE INFO

*Article history:*
Received 18 January 2009
Accepted 10 February 2009
Available online 3 April 2009

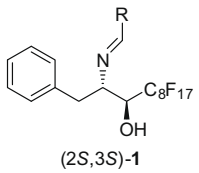
ABSTRACT

Chiral β-imino α-perfluoroalkylpropanol derivatives **1** were prepared by condensation of (2*S*,3*S*)-2-amino-3-perfluorooctyl-1-phenylpropan-3-ol **2** and aldehydes. Among them, (2*S*,3*S*)-**1d** prepared from **2** and salicylaldehyde catalyzed the asymmetric alkynylation of aldehydes using alkynylzincs to afford the product in up to 81% ee.



## 1. Introduction

The enantioselective alkynylation of an aldehyde has progressed significantly in the last decade. In 2000, a breakthrough was caused by the first report on the alkynylation using an alkynylzinc and *N*-methylephedrine.[1] The paper clarified the high catalytic performance of *N*-methylephedrine in that the amino alcohol participates in the chelation to zinc allowing both the activation of the alkynylzinc and the high stereocontrol of the reaction. Today, many researchers are addressing this study, and many chiral amino alcohols are elaborated as ligands.[2–4] On the other hand, we originated chiral ligands containing β-imino α-perfluoroalkylated alcohols (2*S*,3*S*)-**1**.[5] Their high asymmetric inductions were already confirmed in the ethylation of aldehydes using diethylzinc. The α-perfluoroalkylated alcohol of **1** seemed to chelate to the diethylzinc strongly. Thereby, the sterically hindered environment around the zinc could accelerate ethyl transfer. The successful result prompts us to apply **1** to the enantioselective alkynylation of aldehydes using alkynylzinc. This paper describes the preliminary results on the alkynylation catalyzed by (2*S*,3*S*)-**1** (see Fig. 1).




(2*S*,3*S*)-**1**

**Figure 1.** Structure of β-amino α-perfluoroalkylalcohol derivative.

## 2. Results and discussion

We have already synthesized (2*S*,3*S*)-**1a** (R = 1-naphthyl) of which the α-perfluoroalkylated alcohol was a characteristic.[6] The high catalytic performance of (2*S*,3*S*)-**1a** was observed in the enantioselective ethylation of benzaldehyde using diethylzinc to give 93% ee of the product quantitatively. Remarkably, the reaction time was shortened compared to the related reactions reported before. This is indicative of strong chelation of the α-perfluoroalkylated alcohol of **1** to zinc, affording a sterically hindered environment around the zinc, which is enough to accelerate the ethyl transfer. On the basis of this observation, we intended to apply **1** to the alkynylation of aldehydes using an alkynylzinc which is less reactive than diethylzinc. We initiated the study from conversion of **1** to several derivatives to search a suitable ligand for the alkynylation. The derivatives were prepared by condensation of **2** with aldehydes in the presence of $MgSO_4$. The suspended material was filtered off and the solvent was removed in vacuo to give **1a**–**h**. $^1H$ NMR analysis and low resolution MS spectra indicated the formation of **1**, and the peaks that originated from the formation of the oxazolidine derivative were not observed. The purities of crude **1a**–**h** were immediately confirmed by GC to be more than 95%, however, they were hydrolyzed gradually during operations owing to their instability toward moisture. These freshly prepared compounds **1a**–**h** were employed directly in the reaction. The results on the alkynylation are summarized in Table 1. As shown in entry 1, ligand **1a** was an effective chiral ligand in the ethylation giving 43% ee of the product in the alkynylation. Other ligands **1b** and **c** which were prepared from 2-naphthylaldehyde and benzaldehyde also gave low ee's of the products. In the case of **1d** (entry 4), the ee of the product was increased to 67%. The improved result for **1d** may be concerned with the phenolic alcohol capable of chelating to zinc. Other ligands, **1e**–**h**, were not suitable for this alkynylation. This study clarified that a phenolic alcohol could increase the

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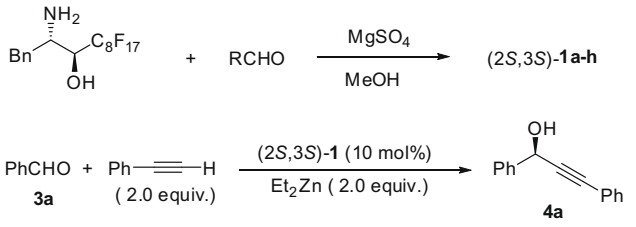
doi:10.1016/j.tetasy.2009.02.047

**Table 1**
Catalytic performance of several α-imino alcohols (2*S*,3*S*)-**1** on the reaction of benzaldehyde with phenylacetylene in toluene




| Entry | R | Ligand | Yield (%) | ee[a,b] (%) |
|---|---|---|---|---|
| 1 | 1-Naphthyl | **1a** | 97 | 43 |
| 2 | 2-Naphthyl | **1b** | 99 | 23 |
| 3 | Phenyl | **1c** | 96 | 45 |
| 4 | 2-Hydroxyphenyl | **1d** | 99 | 67 |
| 5 | 2-Pyridyl | **1e** | 98 | Racemic |
| 6 | 2-Hydroxy-1-naphthyl | **1f** | 92 | 44 |
| 7 | 1-Hydroxy-2-naphthyl | **1g** | 96 | Racemic |
| 8 | 3,5-Di-*tert*-butyl-2-hydroxyphenyl | **1h** | 99 | 30 |

[a] Determined by chiral HPLC analysis.
[b] All configurations were (*R*), and determined by comparing the sign of specific rotation with the reported ones.[7]

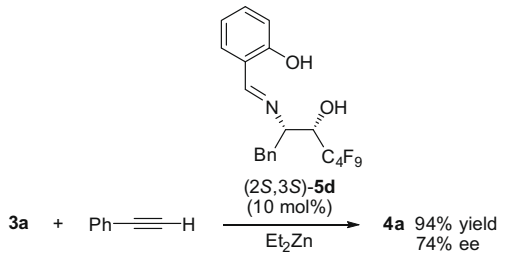
asymmetric induction of **1** but the steric environment around the phenolic alcohol was severe for the asymmetric induction.

Next, we searched for better reaction conditions based on a solvent and selection of different temperatures. The results are summarized in Table 2. The result indicated that the reaction was affected considerably by the solvent polarity. Use of non-polar solvent improved the asymmetric induction of **1d** (entries 1–4). The ee of the product was increased to 79% by the conditions in which the solvent was hexane and the reaction temperature was 0 °C at the beginning and then gradually warmed to rt (entry 5). Keeping the temperature at −10 °C caused a decrease of the ee to 56% due to elongation of the reaction (entry 6). The best result was marked when the reaction was conducted in hexane at a temperature of −10 °C to rt to give 81% ee of the product (entry 7) (see Scheme 1).

**Table 2**
Result of the alkynylation under different conditions using 10 mol % of (2*S*,3*S*)-**1d**

| Entry | Temperature (°C) | Solvent | Yield (%) | ee[a,b] (%) |
|---|---|---|---|---|
| 1 | rt | Toluene | 99 | 65 |
| 2 | rt | Hexane | 92 | 74 |
| 3 | rt | $CH_2Cl_2$ | 99 | 52 |
| 4 | rt | THF | 85 | 28 |
| 5 | 0 to rt | Hexane | 99 | 79 |
| 6 | −10 | Hexane | 60 | 56 |
| 7 | −10 to rt | Hexane | 93 | 81 |

[a] Determined by chiral HPLC analysis.
[b] All configurations were (*R*), and determined by comparing the sign of specific rotation with the reported ones.[7]




**Scheme 1.** Effect of the Rf group on the alkynylation.

To investigate the effect of the Rf group on the asymmetric induction in the alkynylation, (2*S*,3*S*)-**5d** containing perfluorobutyl group was subjected to the reaction under the same condition as entry 7 in Table 2. The reaction was completed within 7 h to give the product in 94% yield. The chemical yield was almost similar as the case of **1d**, however, the ee of the product was dropped to 74%. The result demonstrated that the Rf group played an important role to acquire the high catalytic performance of the ligand. The same tendency was observed in our previous result on the asymmetric ethyl addition to aldehyde using diethylzinc.[5] Next, we investigated the scope and limitation of the alkynylation of **1d** with different types of aldehyde. The results are summarized in Table 3. Several aromatic or aliphatic aldehydes were chosen for the study.

**Table 3**
Result of the alkynylation with different aldehydes using 10 mol % of (2*S*,3*S*)-**1d** in hexane

| Entry | R of **3** | Product | Yield (%) | ee[a] (%) |
|---|---|---|---|---|
| 1 | 2-Cl–$C_6H_4$– | **4b** | 72 | 61[b] |
| 2 | 4-$CF_3$–$C_6H_4$– | **4c** | 41 | 68 |
| 3 | 4-$CH_3$–$C_6H_4$– | **4d** | 40 | 73 |
| 4 | 3-$CH_3$–$C_6H_4$– | **4e** | 81 | 57 |
| 5 | 1-Naphthyl | **4f** | 69 | 55 |
| 6 | *n*-$C_7H_{15}$– | **4g** | 74 | 4 |
| 7 | Cyclohexyl | **4h** | 79 | 3 |

[a] Determined by chiral HPLC analysis.
[b] All configurations were *R*, and determined by comparing the sign of rotation with the reported ones.

As shown in entries 1–5, these aromatic aldehydes gave moderate ee's of the products regardless of the electron-withdrawing or -donating substituent. However, significant differences in the reactivity were observed on the *para*-substituted aldehydes (entries 2 and 3). In those aldehydes, ee's of the product were almost similar as other aromatic aldehydes, but their chemical yields dropped to around 40%. Entries 6 and 7 indicated inefficiency of this alkynylation on aliphatic aldehydes. The difference in the reactivity will be a useful hint for discussing the transition state.

## 3. Conclusions

In conclusion, we prepared imino alcohols, (2*S*,3*S*)-**1a**–**h**, and evaluated their catalytic asymmetric induction in the alkynylation of aldehyde using alkynylzinc. Among these, **1d** prepared from **2** and salicylaldehyde catalyzed the alkynylation of benzaldehyde to give the product in 81% ee quantitatively. Notably, the reaction was completed within 7 h. The shortened reaction time accounts for strongly activated alkynylzinc chelated by **1d**. The mechanistic study involving transition state of the zinc complex is now in progress.

## 4. Experimental

### 4.1. General

All reactions were conducted under an argon atmosphere unless noted otherwise. Chemicals were treated as follows: THF, ether, and toluene were distilled from Na/benzophenone; other chemicals were used as received. $^1H$ and $^{13}C$ NMR spectra were recorded on GSX-400 (400 MHz, JEOL) or ECA-600 (600 MHz, JEOL) spectrometers and $^{19}F$ NMR spectra were recorded on FT-NMR R-1500 (60 MHz, Hitachi) or ECP-600 (600 MHz, JEOL) spectrometers at ambient probe temperature and referenced as follows: $^1H$ and $^{13}C$, TMS; $^{19}F$, BTF. IR spectra were measured on a Hitachi 270-30 IR spectrophotometer. Mass spectra were recorded on JMS-DX-300 or JMS-700 T (JEOL) spectrometer. Ee was determined by GLC with GAMMA DEX™ 225 Capillary Column (30 m × 0.25 mm × 0.25 μm) or by HPLC with Chiralcel OD-H (0.46$\phi$ × 25 cm, Daicel). Optical rotations were measured by DIP-140 (JASCO).

#### 4.1.1. General procedure for the alkynylation

To a suspension of $MgSO_4$ (100 mg) in methanol (1.0 mL) were added **2** (0.05 mmol) and salicylaldehyde (0.05 mmol) under an atmosphere of Ar. After stirring for 30 min at room temperature, the solid was filtered off and the filtrate was evaporated. The crude **1d** was subjected directly to the next reaction. All amounts of diethylzinc, phenylacetylene, aldehyde, and solvent were adjusted based on that of **1d** obtained. To the solution of **1d** (0.05 mmol) in hexane (4.0 mL) were added diethylzinc (1.0 mmol, 1.0 M in hexane solution) and phenylacetylene (1.0 mmol) at room temperature. After stirring for 30 min at the same temperature, the mixture was cooled to −10 °C and the solution of benzaldehyde (0.5 mmol) in hexane (0.1 mL) was added slowly over an hour. After the addition, the cooling apparatus was removed and the mixture was stirred for 6 h at room temperature. The reaction was quenched by addition of 10% of aqueous HCl and the organic layer was collected. The aqueous layer was extracted with ether and the combined organic layers were dried ($MgSO_4$). After filtration of the solid, the solvent was removed in vacuo and the crude product was purified by silica gel column chromatography (ether:hexane = 1:9) to give **4a**.

#### 4.1.2. 2-(((2*S*,3*S*)-4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-Heptadecafluoro-3-hydroxy-1-phenylundecan-2-yl-imino)methyl)phenol (2*S*,2*S*)-1d

Yellow solid; mp 110.2–111.9 °C; $^1$H NMR ($CDCl_3$) $\delta$: 12.3 (1H, s), 8.02 (1H, s), 6.86–7.52 (9H, m), 4.32 (1H, d, $^3J_{H,F}$ = 22 Hz), 3.87 (1H, m), 3.19 (1H, dd, $^2J_{H,H}$ = 14.2 Hz, $^3J_{H,H}$ = 5.8 Hz), 3.06 (1H, dd, $^2J_{H,H}$ = 14.2 Hz, $^3J_{H,H}$ = 8.3 Hz), 2.8 (1H, s); MS *m*/*z* : 673 ($M^+$); HRMS Calcd for $C_{24}H_{16}F_{17}NO_2$: 673.0910 ($M^+$). Found: 673.0914 ($M^+$).

#### 4.1.3. (*R*)-1,3-Diphenylprop-2-yn-1-ol (4a)

Eighty-one percentage of ee was determined by HPLC analysis (10% IPA in hexanes, flow rate = 0.5 mL/min, 254 nm). Retention time: $t_{major}$ = 24.6 min and $t_{minor}$ = 30.6 min.

#### 4.1.4. (*R*)-1-(2-Chlorophenyl)-3-phenylprop-2-yn-1-ol (4b)

Sixty-one percentage of ee was determined by HPLC analysis (10% IPA in hexanes, flow rate = 0.5 mL/min, 254 nm). Retention time: $t_{major}$ = 36.9 min and $t_{minor}$ = 39.5 min.

#### 4.1.5. (*R*)-3-Phenyl-1-(4-(trifluoromethyl)phenyl)prop-2-yn-1-ol (4c)

Sixty-eight percentage of ee was determined by HPLC analysis (10% IPA in hexanes, flow rate = 0.5 mL/min, 254 nm). Retention time: $t_{major}$ = 16.2 min and $t_{minor}$ = 61.3 min.

#### 4.1.6. (*R*)-3-Phenyl-1-*p*-tolylprop-2-yn-1-ol (4d)

Seventy-three percentage of ee was determined by HPLC analysis (10% IPA in hexanes, flow rate = 0.5 mL/min, 254 nm). Retention time: $t_{major}$ = 20.0 min and $t_{minor}$ = 34.8 min.

#### 4.1.7. (*R*)-3-Phenyl-1-*m*-tolylprop-2-yn-1-ol (4e)

Fifty-seven percentage of ee was determined by HPLC analysis (10% IPA in hexanes, flow rate = 0.5 mL/min, 254 nm). Retention time: $t_{major}$ = 22.5 min and $t_{minor}$ = 43.2 min.

#### 4.1.8. (*R*)-1-(Naphthalen-1-yl)-3-phenylprop-2-yn-1-ol (4f)

Fifty-five percentage of ee was determined by HPLC analysis (10% IPA in hexanes, flow rate = 0.5 mL/min, 254 nm). Retention time: $t_{major}$ = 30.8 min and $t_{minor}$ = 61.4 min.

#### 4.1.9. (*R*)-1-Phenyldec-1-yn-3-ol (4g)

Four percentage of ee was determined by HPLC analysis (10% IPA in hexanes, flow rate = 0.5 mL/min, 254 nm). Retention time: $t_{major}$ = 10.2 min and $t_{minor}$ = 22.2 min.

#### 4.1.10. (*R*)-1-Cyclohexyl-3-phenylprop-2-yn-1-ol (4h)

Three percentage of ee was determined by HPLC analysis (10% IPA in hexanes, flow rate = 0.5 mL/min, 254 nm). Retention time: $t_{major}$ = 11.8 min and $t_{minor}$ = 21.0 min.

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