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Short communication

Enantioselective α-hydrazination of α-fluoro-β-ketoesters catalyzed by chiral nickel complexes

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ABSTRACT

The catalytic enantioselective electrophilic α-hydrazination promoted by chiral nickel complexes is described. Treatment of α-fluoro-β-ketoesters with azodicarboxylates as electrophilic amination reagents under mild reaction conditions afforded the corresponding α-amino α-fluoro-β-ketoesters with high yields (80–96%) and enantioselectivities (up to 78% ee).

1. Introduction

Chiral organofluorine compounds containing a fluorine atom bonded directly to a stereogenic center have been utilized in studies of enzyme mechanisms and as intermediates in asymmetric syntheses [1]. The development of effective methodologies for the preparation of new selectively fluorinated, stereochemically defined compounds is critical to further advances of fluorine chemistry [2]. Fluorinated amino acids are becoming increasingly important in pharmaceuticals and other biological applications [3] such as the development of anticancer drugs for the control of tumor growth, drugs for control of blood pressure and allergies [4], enzyme inhibitors [5]. The catalytic enantioselective electrophilic amination of α-substituted esters seems to be alternate method for the synthesis of chiral α-amino acid derivatives. The catalytic, enantioselective, direct C–N bond formation reaction of active methine compounds represents an efficient and the simplest procedures to generate stereogenic carbon center attached to a nitrogen atom [6]. Several groups presented the direct enantioselective amination of active methine compounds such as β-ketoester [7], β-ketophosphonates [8], α-cyanoacetates [9], and α-cyanoketones [10] in the presence of chiral metal complexes or organocatalysts. Recently, Togni reported hydrazination of α-fluoro-β-ketoesters using chiral Cu-bisoxazoline complexes afforded α-fluoro-α-hydrazino-β-ketoesters [11]. While several efficient asymmetric amination reactions using chiral Lewic acids have been developed, a drawback is that most Lewis acids are unstable in the presence of water and even sensitive to moisture. Therefore, the development of amination reaction using moisture-stable chiral Lewis acid is still in great demand.

2. Results and discussion

As part of research program related to the development of synthetic methods for the enantioselective construction of stereogenic carbon centers [12], we report the catalytic enantioselective amination of ester derivatives promoted by organocatalyst or chiral palladium complexes [7]. In this communications, we wish to report the direct α-hydrazination of α-fluoro-β-ketoesters catalyzed by air- and moisture-stable chiral nickel complexes [13] with azodicarboxylates as the electrophilic nitrogen source.

To determine optimum reaction conditions for the catalytic enantioselective electrophilic amination of α-fluoro-β-ketoesters using air- and moisture-stable chiral nickel complexes **4** (Fig. 1), we initially investigated the reaction of α-fluoro benzoylacetate **1** with azodicarboxylates **2** as the electrophilic aminating agent in the presence of 5 mol% of catalyst in toluene at room temperature. We first examined the nature of ester group of azodicarboxylates on enantioselectivity (Table 1, entries 1–4). When employing *t*-butyl azodicarboxylate (**2d**), the corresponding aminated adduct **3ad** was isolated with high enantioselectivity of 69% ee (entry 4). Concerning the solvent (entries 4–12), the use of toluene gave the best results in the yield and the enantiomeric excess (entry 4). We examined the impact of the structure of catalysts

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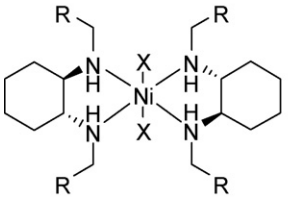


4a : R=Ph, X=Br
4b : R=Ph, X=Cl
4c : R=Ph, X=BF_4
4d : R=Ph, X=OTf
4e : R=Ph, X=PF_6
4f : R=Ph, X=SbF_6
4g : R=thiophen-2-yl, X=Br
4h : R=4-nitrophenyl, X=Br
4i : R=4-fluorophenyl, X=Br
4j : R=1-naphthyl, X=Br

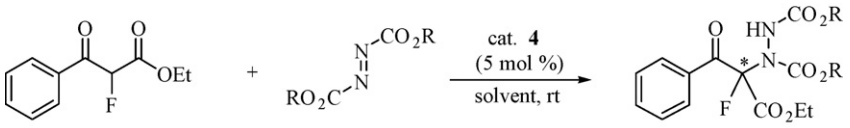
Fig. 1. Structure of chiral Ni(II) complexes.

on enantioselectivity (entries 4 and 13–21). The high selectivity was obtained with catalysts **4i**, which is prepared from 1,2-diaminocyclohexane with *p*-fluorobenzaldehyde.

To examine the generality of the catalytic enantioselective amination of α-fluoro-β-ketoesters **1** using air- and moisture-stable chiral nickel complex **4i**, we studied the amination of various α-fluoro-β-ketoesters **1a–f**. As it can be seen by the results summarized in Table 2, the corresponding α-aminated β-ketoesters **3ad–fd** were obtained in high yields (80–96%) and enantioselectivities (61–74% ee).

To show substrate scope of the catalytic enantioselective amination of β-ketoester derivatives **1g–j** by using chiral nickel

Table 1
Optimization of the reaction conditions.

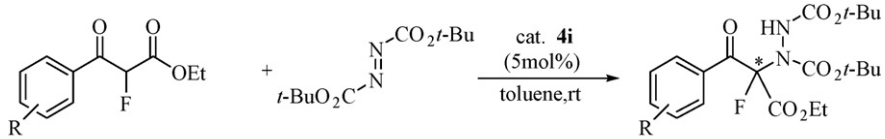


1a **2** **3**

Entry	**2**, R	Cat.	Solvent	Time (h)	Yield[a] (%)	ee[b] (%)
1	**2a**, Et	**4a**	Toluene	15	91	57
2	**2b**, *i*-Pr	**4a**	Toluene	20	85	51
3	**2c**, Bn	**4a**	Toluene	15	80	57
4	**2d**, *t*-Bu	**4a**	Toluene	20	73	69
5	**2d**, *t*-Bu	**4a**	Benzene	20	50	63
6	**2d**, *t*-Bu	**4a**	*p*-Xylene	25	50	43
7	**2d**, *t*-Bu	**4a**	Hexane	22	51	63
8	**2d**, *t*-Bu	**4a**	Pentane	21	54	61
9	**2d**, *t*-Bu	**4a**	THF	23	50	57
10	**2d**, *t*-Bu	**4a**	1,4-Dioxane	22	72	57
11	**2d**, *t*-Bu	**4a**	Ether	22	66	51
12	**2d**, *t*-Bu	**4a**	EtOH	20	63	35
13	**2d**, *t*-Bu	**4b**	Toluene	22	80	17
14	**2d**, *t*-Bu	**4c**	Toluene	20	84	25
15	**2d**, *t*-Bu	**4d**	Toluene	20	78	5
16	**2d**, *t*-Bu	**4e**	Toluene	20	89	21
17	**2d**, *t*-Bu	**4f**	Toluene	21	87	23
18	**2d**, *t*-Bu	**4g**	Toluene	20	85	51
19	**2d**, *t*-Bu	**4h**	Toluene	25	78	30
20	**2d**, *t*-Bu	**4i**	Toluene	25	86	73
21	**2d**, *t*-Bu	**4j**	Toluene	22	79	63

[a] Yield of isolated product.
[b] Enantiopurity of **3** was determined by HPLC analysis with Chiralpak AD column.

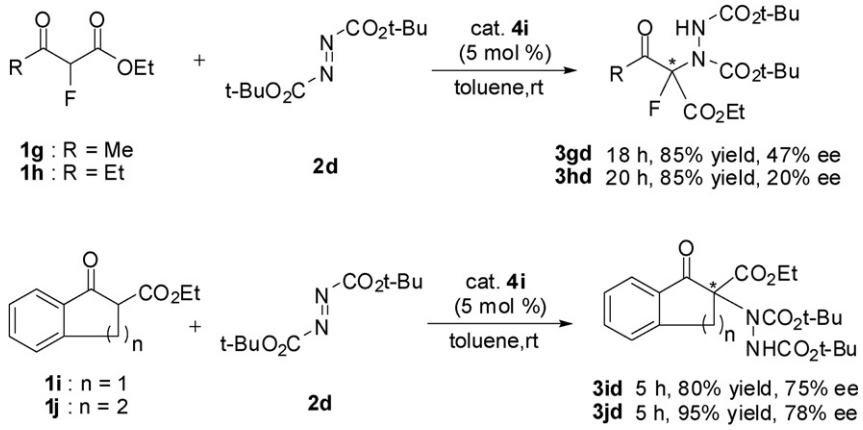
Table 2
Catalytic enantioselective amination of α-fluoro-β-ketoesters **1**.



1 **2d** **3**

Entry	**1**, R	Time (h)	Yield (%)	ee[a] (%)
1	**1a**, H	20	**3ad**, 86	73
2	**1b**, *p*-OMe	28	**3bd**, 84	73
3	**1c**, *p*-CF_3	26	**3cd**, 81	74
4[b]	**1d**, *p*-Me	14	**3dd**, 84	65
5[b]	**1e**, *p*-Br	28	**3ed**, 80	65
6	**1f**, *m*-Br	34	**3fd**, 80	61

[a] Enantiopurity of **3** was determined by HPLC analysis with Chiralpak AD column.
[b] Reaction carried out using catalyst **4a**.



Scheme 1.

complex **4i**, we studied the amination of aliphatic α-fluoro-β-ketoesters **1g–h** and cyclic β-ketoesters **1i–j**. As it can be seen by the results summarized in Scheme 1, the corresponding α-aminated β-ketoester derivatives **3g–j** were obtained in excellent yields and low to high enantioselectivities (20–78% ee).

3. Conclusions

In conclusion, we have developed a highly efficient catalytic enantioselective α-amination of α-fluoro-β-ketoesters using air- and moisture-stable chiral nickel complex **4i**. The desired α-aminated products were obtained in good to high yields, and high enantioselectivities (up to 78% ee) were observed. We believe that this method provides a practical entry for the preparation of chiral α-fluoro-α-amino acid derivatives, and the availability of these compounds should facilitate medicinal chemical studies in various fields. Further details and application of this amination will be presented in due course.

4. Experimental

General procedure for the α-hydrazination of α-fluoro-β-ketoesters **1**: a mixture of α-fluoro-β-ketoester **1** (0.2 mmol) and catalyst **4i** (8.79 mg, 0.01 mmol) in toluene (0.12 mL) was stirred for 10 min. A solution of *t*-butyl azodicarboxylate (**2**, 46.05 mg, 0.4 mmol) in toluene (0.2 mL) was added dropwise over a period of 5 min. The reaction mixture was stirred for 14–34 h at room temperature. After completion of the reaction, the resulting solution was concentrated and purified by flash chromatography (hexane/ethyl acetate = 5/1) to afford the α-aminated α-fluoro-β-ketoester **3**.

2-Fluoro-*N*′,*N*-bis(tert-butoxycarbonyl)-2-hydrazino-3-oxo-3-phenylbutyric acid ethyl ester (**3ad**): $[\alpha]_D^{16} = -10.76$ (c = 1.00, $CHCl_3$, 73% ee); ^{1}H NMR (200 MHz, $CDCl_3$) 1.26–1.51 (m, 21H), 4.11–4.35 (m, 2H), 6.63 (br, 1H), 7.41 (t, J = 7.8 Hz, 2H), 7.57 (t, J = 7.2 Hz, 1H), 8.15–8.28 (br, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.7, 27.5, 27.9, 63.2, 82.0, 84.7, 102.5 (d, J = 255.5 Hz), 128.1, 129.9, 130.3, 133.5 (d, J = 15 Hz), 150.2, 154.3, 162.2 (d, J = 25 Hz), 186.7 (d, J = 30 Hz); ESI-HRMS: m/z calcd for $C_{21}H_{29}FN_2O_7$ $[M+H]^+$: 441.2037; found: 441.2041; R_t HPLC (80:20, *n*-hexane: *i*-PrOH, 254 nm, 1.0 mL/min) Chiralcel AD, t_R = 11 min (minor), t_R 14 min (major).

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