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Short Communication

Catalytic asymmetric conjugate addition of α-fluoro β-ketophosphonates to nitroalkenes in the presence of nickel complexes

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ABSTRACT

The catalytic enantioselective conjugate addition reaction of α-fluoro β-ketophosphonates to nitroalkenes promoted by chiral nickel complexes is described. Treatment of α-fluoro β-ketophosphonates with nitroalkenes under mild reaction conditions afforded the corresponding Michael adducts containing fluorinated quaternary stereogenic center with excellent enantioselectivity (up to >99% ee).

1. Introduction

Fluorinated molecules have attracted increased interest in pharmaceutical and material science because of their utility as medicines, agrochemicals, and functional materials [1]. The introduction of fluorine atom into organic compounds often leads to improvement of their biological and physiological characteristics due to unique physical and chemical properties of the fluorine atom [2]. Especially, chiral fluorinated molecules are interesting and important materials with uses in medicinal and biological chemistry [3]. Construction of chiral fluorinated quaternary carbon centers is one of the most challenging topics in organic synthesis. General approaches for the synthesis of chiral fluorine-containing molecules are electrophilic fluorination of active methines and C–C bond formation of fluorocarbon nucleophiles [4]. A number of excellent examples for enantioselective fluorination of tertiary carbon nucleophiles were reported by using chiral transition metal complexes and organocatalysts [5–8]. On the other hand, the use of fluorinated active methine nucleophiles for a catalytic asymmetric reaction has become increasingly popular [9].

α-Fluoroalkylphosphonates are good mimics of phosphates which exist in a number of natural and biologically active molecules [10]. The enantioselective construction of α-fluoroalkylphosphonates is extremely important because the stereochemistry of α-carbon affects biological activity [11]. A number of excellent examples for enantioselective fluorination of phosphonate derivatives were reported by using chiral catalysts [12]. However, until now, only one synthetic method was reported for the synthesis of chiral α-fluoroalkylphosphonates by the catalytic enantioselective C–C bond formation from α-fluoro β-ketophosphonates [13]. There are still some drawbacks to the previously reported procedure, such as the high catalyst loading and longer reaction time required for the high yield and enantioselectivity. Accordingly, the development of alternative catalysts for the catalytic effective enantioselective Michael reaction of α-fluoro β-ketophosphonates with nitroalkenes is highly desirable.

2. Results and discussion

In the framework of our research program for the development of synthetic methods for the catalytic enantioselective construction of stereogenic carbon centers [14], we recently reported enantioselective conjugate addition of active methines to nitroalkenes [15]. In this letter, we wish to describe enantioselective conjugate addition of α-fluoro β-ketophosphonates to nitroalkenes catalyzed by air- and moisture-stable chiral nickel complexes (Fig. 1) [16].

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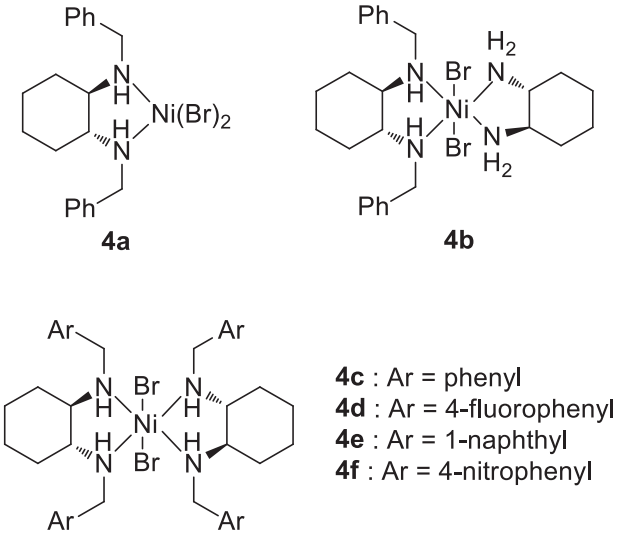


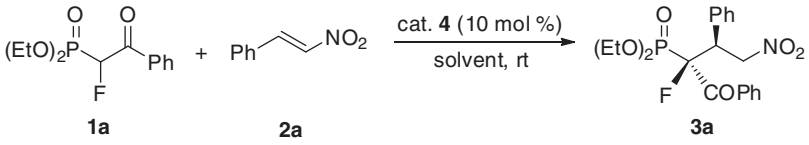
Fig. 1. Structures of chiral nickel catalysts.

To determine suitable reaction conditions for the catalytic enantioselective conjugate addition of α-fluoro β-ketophosphonates [17], we examined the conjugate addition of diethyl (1-fluoro-2-oxo-2-phenylethyl)phosphonate (**1a**) to β-nitrostyrene (**2a**) in the presence of 10 mol% of dicationic nickel complexes **4** in toluene at room temperature (Table 1). By screening chiral nickel (II) complexes **4a-f**, we found that catalyst **4c** was the best catalyst for this asymmetric conjugate addition, affording the corresponding product **3a** 70% yield and 99% ee (Table 1, entry 3). Next, we examined the reaction in various solvents (entries 3 and 7–13). A survey of the reaction media indicated that many common solvents, such as toluene, benzene, *p*-xylene, mesitylene, ether, THF, CH_2Cl_2, and ethanol were well tolerated in this conjugate addition without significant decrease in enantioselectivity. Among the solvents probed, the best results (70% yield and 99% ee) were achieved when the reaction was conducted in toluene (Table 1, entry 3). The present catalytic system tolerates catalyst loading down to 5, 2.5, 1, 0.5 or 0.1 mol% without compromising the enantioselectivity, but yields were slightly decreased (Table 1, entries 14–18). To overcome this limitation, elevated temperatures were used. Increasing the temperature of the reaction to 50 °C afforded the desired Michael adduct **3a** in high yield and excellent enantioselectivity (Table 1, entry 19). The absolute configuration of **3** was established by comparison of the specific rotation value and chiral HPLC analysis with previously reported values [13].

To examine the generality of the catalytic enantioselective conjugate addition reaction of α-fluoro β-ketophosphonates **1**, we studied the addition of various α-fluoro β-ketophosphonates **1** to β-nitrostyrene (**2a**) in the presence of 1 mol% of nickel catalyst **4c** in toluene at 50 °C. As it can be seen by the results summarized in Table 2, the corresponding products **3a–3f** were obtained in high yields, high diastereoselectivities, and excellent enantioselectivities (93–99% ee).

With optimal reaction conditions in hand, we then explored the possibility of using a wide range of nitroalkene derivatives **2** with diethyl (1-fluoro-2-oxo-2-phenylethyl)phosphonate (**1a**) in the presence of 1 mol% of catalyst **4c** in toluene at 50 °C (Table 3). The corresponding γ-nitro α-fluorophosphonates **3g–3n** were formed

Table 1
Optimization of the reaction conditions.[a]



Entry	Cat. **4**	Solvent	Time (h)	Yield[b] (%)	dr[c]	ee[d] (%)
1	**4a**	PhMe	9	57	30:1	86
2	**4b**	PhMe	9	47	30:1	92
3	**4c**	PhMe	6	70	30:1	99
4	**4d**	PhMe	6	65	30:1	98
5	**4e**	PhMe	6	61	25:1	97
6	**4f**	PhMe	6	67	25:1	97
7	**4c**	benzene	6	70	30:1	98
8	**4c**	*p*-xylene	6	67	30:1	98
9	**4c**	mesitylene	6	69	30:1	98
10	**4c**	Et_2O	6	77	30:1	93
11	**4c**	THF	6	62	30:1	95
12	**4c**	CH_2Cl_2	6	64	30:1	98
13	**4c**	EtOH	6	62	30:1	98
14[e]	**4c**	PhMe	24	69	30:1	99
15[f]	**4c**	PhMe	24	60	30:1	99
16[g]	**4c**	PhMe	24	45	30:1	99
17[h]	**4c**	PhMe	24	40	30:1	99
18[i]	**4c**	PhMe	24	30	30:1	99
19[g,j]	**4c**	PhMe	7	90	30:1	99

[a] Reaction conditions: α-Fluoro β-ketophosphonates (**1a**, 0.3 mmol), β-nitrostyrene (**2a**, 0.3 mmol), catalyst **4** (0.03 mmol), solvent (1.2 mL) at room temperature.
[b] Isolated yield.
[c] Determined by ^1H NMR analysis of the crude mixture.
[d] Enantiopurity was determined by HPLC analysis using Chiralpak IA-3 column
[e] 5 mol% catalyst loading.
[f] 2.5 mol% catalyst loading.
[g] 1 mol% catalyst loading.
[h] 0.5 mol% catalyst loading.
[i] 0.1 mol% catalyst loading.
[j] Reaction carried out at 50 °C.