Enantioselective Conjugate Addition of Fluoromalonate to Nitroalkenes Catalyzed by Chiral Nickel Complexes

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Received April 28, 2009, Accepted May 22, 2009

Key Words: Chiral nickel complexes, Michael reaction, Nitroalkenes, Asymmetric catalysis, Fluoromalonates

Fluorinated compounds are of importance in organic synthesis because of their use as medicines and agrochemicals and in fundamental studies of biochemical and metabolic processes.[1] Introduction of fluorine atom into biologically active compounds often leads to improvement of their biological characteristics due to unique properties of the fluorine atom.[2] Chiral organofluorine compounds have been utilized in studies of enzyme mechanisms and as intermediates in asymmetric syntheses.[3]

The Michael addition reaction is widely recognized as one of the most general and versatile methods for formation of C-C bonds in organic synthesis,[4] and the development of enantioselective catalytic protocols for this reaction has been subject of intensive research.[5,6] Michael reaction of nucleophiles to nitroalkenes represents a direct and most appealing approach to chiral nitroalkanes that are versatile intermediates in organic synthesis, which can be transformed into an amine, nitrile oxide, ketone, carboxylic acid, and hydrogen *etc.*[7]

Recently, several groups presented the catalytic asymmetric conjugate additions of active methine compounds to nitroalkenes in the presence of chiral metal complexes or organocatalysts.[8] Although catalytic enantioselective Michael additions of 1,3-dicarbonyl compounds have reported, up to now there is one example of these reactions with fluoromalonates using chiral Mg-box complex.[9b] However, a highly enantioselective conjugate addtion of fluoromalonates to nitroalkenes remains elusive; although, if successfully promoted with a practically accessible chiral catalyst under air- and moisture-tolerant conditions, it could provide a highly attractive, convergent approach toward optically active γ-nitro fluoromalonates.

As part of research program related to the development of synthetic methods for the enantioselective construction of stereogenic carbon centers,[10] we recently reported chiral nickel complexes **1** (Fig. 1) to be a highly selective catalyst for the enantioselective amination of active methines.[11] In this communications, we wish to describe the direct asymmetric Michael reaction of fluoromalonates to nitroalkenes catalyzed by air- and moisture-stable chiral nickel complexes.[12]

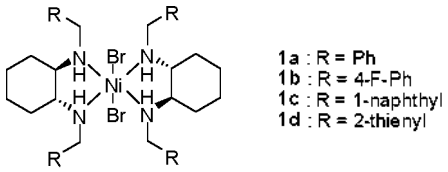
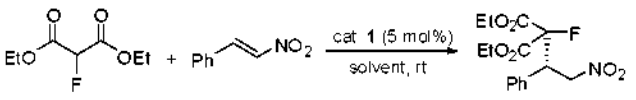


Figure 1. Structure of chiral nickel complexes.

A survey of some reaction parameters was performed, and some representative results are presented in Table 1. Our investigation began with the catalytic asymmetric Michael addition of ethyl fluoromalonate (**2**) with β-nitrostyrene (**3a**). When the reaction was performed in toluene at room temperature in the presence of 5 mol% catalyst **1a**, product **4a** was isolated in high yield with 97% ee (Table 1, entry 1). We first examined the impact of the structure of catalysts **1a-d** on enantioselectivities (Table 1, 87-97% ee, entries 1-4). The best results have been obtained with catalyst **1a**. Concerning the solvents (entries 1 and 5-11), the use of nonpolar solvents gave the good results in the yield and the enantiomeric excess.

To examine the generality of the catalytic asymmetric Michael reaction of fluoromalonates **2** by using chiral nickel catalyst **1a**, we studied the addition of fluoromalonates **2** to wide range of substituted aromatic and heteroaromatic nitroalkenes **3** in toluene.[13] As it can be seen by the results summarized in Table 2, the corresponding products **4a-h** were obtained in excellent yields (89-97%) and excellent enantioselectivities (90-97% ee). The absolute configuration was determined after transesterification[15] of **4** to corresponding dimethyl malonate derivatives by comparing chiral HPLC

Table 1. Optimization of the reaction conditions

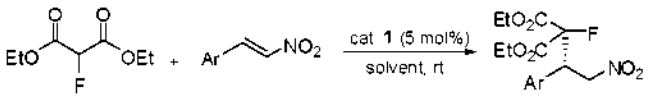


2 **3a** **4a**

entry	cat. **1**	solvent	time (h)	yield[a] (%)	ee[b] (%)
1	**1a**	toluene	20	97	97
2	**1b**	toluene	20	93	95
3	**1c**	toluene	20	91	87
4	**1d**	toluene	20	90	91
5	**1a**	CH_2Cl_2	15	90	93
6	**1a**	*o*-xylene	20	95	97
7	**1a**	*m*-xylene	20	95	96
8	**1a**	*p*-xylene	20	96	95
9	**1a**	EtOAc	24	85	95
10	**1a**	EtOH	12	96	91
11	**1a**	THF	16	91	92

[a]Isolated yields. [b]Enantiopurity of **4a** was determined by HPLC analysis with a Chiralpak AD-H column.

Table 2. Enantioselective conjugate addition of fluoromalonate to nitroalkenes



2 **3** **4**

entry	**3**, Ar	time (h)	yield[a] (%)	ee[b] (%)
1	C_6H_5	20	**4a**, 97	97
2	4-F-C_6H_4	11	**4b**, 92	93
3	4-OMe-C_6H_4	10	**4c**, 91	95
4	4-Me-C_6H_4	9	**4d**, 95	91
5	2-F-C_6H_4	9	**4e**, 92	91
6	2-Cl-C_6H_4	13	**4f**, 96	97
7	2-furyl	19	**4g**, 89	90
8	2-thienyl	10	**4h**, 90	91

[a]Isolated yields. [b]The ee value of **4** was determined by HPLC analysis with chiral columns (Chiralcel OD-H for **4c**. Chiralpak AD-H for **4a-b** and **4d-h**).

data and specific rotation with authentic samples.[14]

In conclusion, we have developed a highly efficient catalytic asymmetric Michael reaction of fluoromalonates **2** to nitroalkenes **3** using air- and moisture-stable chiral nickel catalyst **1a**. The desired γ-nitro-α-fluoro carbonyl compounds **4** were obtained in good to high yields and excellent enantioselectivities (90-97% ee) were observed.[14] We believe that this method provides an efficient route for the preparation of chiral γ-nitro-α-fluorocarboxylic acid derivatives, and the availability of these compounds should facilitate medicinal chemical studies in various fields. Further details and application of this Michael addition of fluoromalonates will be presented in due course.

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13. **General procedure for asymmetric conjugate addition of fluoromalonates to nitroalkenes**: To a stirred mixture of ethyl fluoromalonate (**2**, 64.1 mg, 0.36 mmol) and chiral nickel catalyst **1a** (24.2 mg, 0.03 mmol) in toluene (0.6 mL) was added nitroalkene **3** (0.3 mmol) at room temperature. After being stirred for 9-20 h, the reaction mixture was concentrated. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 5/1) to afford desired product **4**. **4a**: $[\alpha]_D^{23}$ = 15.4 (c = 1.8, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) 1.01 (t, *J* = 6.9 Hz, 3H), 1.35 (t, *J* = 7.0 Hz, 3H), 3.93-4.18 (m, 2H), 4.32-4.42 (m, 2H), 4.57 (ddd, *J* = 30.3, 9.5, 4.8 Hz, 1H), 4.81 (dd, *J* = 13.4, 9.5 Hz, 1H), 4.93 (dd, *J* = 13.4, 4.8 Hz, 1H), 7.29-7.32 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) 13.6, 13.9, 47.3 (d, *J* = 18.3 Hz), 62.9, 63.6, 75.5 (d, *J* = 5.8 Hz), 94.5 (d, *J* = 200.2 Hz), 128.8, 129.0, 129.2, 132.9, 163.6 (d, *J* = 26.1 Hz), 164.6 (d, *J* = 25.5 Hz); t_R HPLC (80:20, *n*-hexane: *i*-PrOH, 220 nm, 1.0 mL/min) Chiralpak AD-H, t_R = 5.4 min (minor), 6.1 min (major). 97% ee.
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