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Catalytic asymmetric Mannich-type reactions of fluorinated ketoesters with *N*-Boc aldimines in the presence of chiral palladium complexes

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ABSTRACT

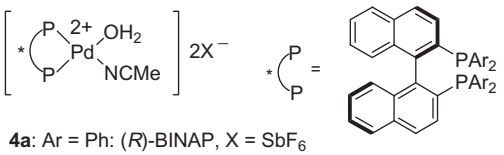
The catalytic enantioselective Mannich reaction promoted by chiral palladium complexes is described. The treatment of α-fluoro-β-ketoesters with *N*-Boc-aldimines under mild reaction conditions afforded the corresponding β-aminated α-fluoro-β-ketoesters with excellent enantioselectivities (up to 99% ee).

Fluorine-containing compounds are of importance in organic synthesis because of their use as medicinals 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 the unique properties of the fluorine atom.[2] Chiral fluorine-containing compounds are interesting and important materials with uses in analytical, biological, and medicinal chemistry and also in the chemistry of polymers and materials. In particular, Chiral organofluorine compounds containing a fluorine atom bonded directly to a stereogenic center have been utilized in the studies of enzyme mechanisms and as intermediates in asymmetric syntheses.[3]

Among various strategies, electrophilic fluorination of active methines and C–C bond formation of fluorocarbon nucleophiles are two typical approaches for the construction of fluorine-containing molecules, and their asymmetric versions are particularly attractive. Enantioselective electrophilic fluorination has been achieved with the aid of electrophilic fluorinating agents using chiral transition-metal catalysts and organocatalysts with excellent enantioselectivities.[4,5] On the other hand, the use of fluorinated active methine nucleophiles, such as fluoromalonate,[6] α-fluoro-β-ketoesters,[7] and fluorobis(phenylsulfonyl)methane[8] for a catalytic asymmetric reaction has become increasingly popular. Enantioselective Mannich reactions are efficient and powerful methods to prepare chiral β-amino carbonyl derivatives.[9] Tremendous efforts have been made in the development of efficient chiral catalysts for enantioselective Mannich reactions with preformed enolates[10] and enolizable β-dicarbonyl and related compounds.[11] Recently, several groups report the catalytic enantioselective Mannich reactions of α-fluoro-β-ketoesters with *N*-Boc-aldimines using various organocatalysts.[12]

As part of a research program related to the development of synthetic methods for the enantioselective construction of stereogenic carbon centers.[13] we recently reported chiral palladium complexes **4** (Fig. 1) to be highly selective catalysts for the enantioselective addition of active methines.[14] In this Letter, we wish to describe the direct enantioselective Mannich reaction of α-fluoro-β-ketoesters with simple *N*-Boc imines catalyzed by chiral palladium complexes **4** which are air- and moisture-stable.[15]

In an attempt to validate the feasibility of the catalytic enantioselective Mannich reaction of α-fluoro-β-ketoesters, we initially investigated the reaction system with α-fluoro-β-ketoester **1a**



4a: Ar = Ph: (*R*)-BINAP, X = SbF_6
4b: Ar = Ph: (*R*)-BINAP, X = PF_6
4c: Ar = Ph: (*R*)-BINAP, X = OTf
4d: Ar = Ph: (*R*)-BINAP, X = BF_4
4e: Ar = 4-Me-C_6H_4: (*R*)-Tol-BINAP, X = SbF_6
4f: Ar = 4-Me-C_6H_4: (*R*)-Tol-BINAP, X = BF_4
4g: Ar = 3,5-Me_2-C_6H_3: (*R*)-Xylyl-BINAP, X = SbF_6
4h: Ar = 3,5-Me_2-C_6H_3: (*R*)-Xylyl-BINAP, X = BF_4

Figure 1. Structure of chiral palladium catalysts.

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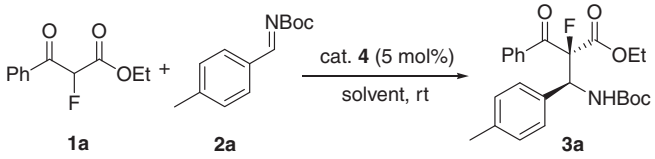
and *N*-Boc aldimine **2a** in the presence of 5 mol % of palladium complexes in toluene at room temperature. We first examined the impact of the structure of catalysts **4a–h** on enantioselectivities (Table 1, 34–99% ee, entries 1–8).

Catalyst **4d** gave the desired product **3a** with high enantioselectivity (99% ee, entry 4). Based on the exploratory studies, we decided to select catalyst **4d** for further optimization of reaction conditions. A survey of the reaction media indicated that many common solvents, such as toluene, DCM, acetone, and THF (entries 4 and 9–11), were well tolerated in this Mannich reaction with moderate to high enantioselectivities. Among the solvents probed, the best results (78% yield, 75:25 dr, and 99% ee) were achieved when the reaction was conducted in toluene (entry 4). We then explored the possibility of using a wide range of *N*-Boc protected substituted aromatic and heteroaromatic aldimines **2** with α-fluoro-β-ketoester **1a** under the optimized reaction condition.

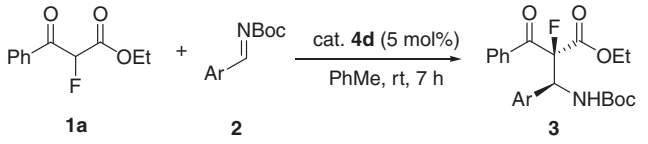
Table 1
Optimization of the reaction conditions



Entry	Cat	Solvent	Time (h)	Yield[a] (%)	dr[b] (%)	ee[c] (%)
1	**4a**	PhMe	5	72	70:30	67
2	**4b**	PhMe	5	74	74:26	64
3	**4c**	PhMe	5	65	42:58	34
4	**4d**	PhMe	7	78	75:25	99
5	**4e**	PhMe	5	73	67:33	92
6	**4f**	PhMe	5	75	66:34	93
7	**4g**	PhMe	5	62	61:39	41
8	**4h**	PhMe	5	90	63:37	73
9	**4d**	DCM	5	65	66:34	76
10	**4d**	Acetone	5	45	56:44	56
11	**4d**	THF	5	61	60:40	74

[a] Yield of isolated product.
[b] The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude product.
[c] Enantiomeric excess of major diastereomer was determined by HPLC analysis using Chiralpak AD-H column.

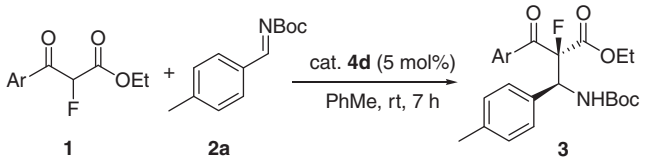
Table 2
Variation of *N*-Boc aldimines



Entry	**2**, Ar	Yield[a] (%)	dr[b] (%)	ee[c] (%)
1	**2a**, *p*-MeC_6H_4	**3a**, 78	75:25	99
2	**2b**, *p*-FC_6H_4	**3b**, 82	87:13	94
3	**2c**, *p*-ClC_6H_4	**3c**, 82	62:38	98
4	**2d**, Ph	**3d**, 88	77:23	94
5	**2e**, *o*-FC_6H_4	**3e**, 73	>99:1	95
6	**2f**, *o*-ClC_6H_4	**3f**, 77	67:33	97
7	**2g**, 2-naphthyl	**3g**, 83	74:26	94
8	**2h**, thienyl	**3h**, 85	72:28	95
9	**2i**, furyl	**3i**, 82	69:31	96

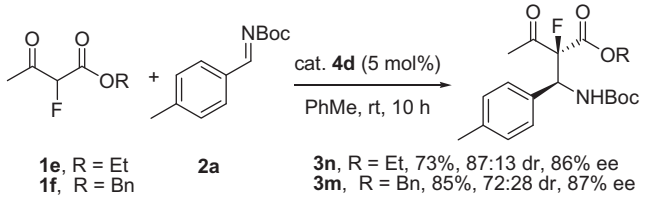
[a] Yield of isolated product.
[b] The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude product.
[c] Enantiopurity of major diastereomer of **3** was determined by HPLC analysis with Chiralpak AD-H (for **3a**), AS-H (for **3g**) and IA (for **3b**–**3f**, **3h**–**3i**) columns.

Table 3
Variation of α-fluoro-β-ketoesters



Entry	**1**, Ar	Yield[a] (%)	dr[b] (%)	ee[c] (%)
1	**1a**, *p*-Me-Ph	**3j**, 78	67:35	93
2	**1b**, *m*-Br-Ph	**3k**, 77	56:44	94
3	**1c**, *m*-Cl-Ph	**3l**, 80	59:41	99
4	**1d**, 2-thienyl	**3m**, 89	64:36	93

[a] Yield of the isolated product.
[b] The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude product.
[c] Enantiopurity of major diastereomer of **3j**–**3m** was determined by HPLC analysis with Chiralpak IC (for **3j**, **3l**), IA (for **3k**) and AS-H (for **3m**) columns.



Scheme 1.

As shown in Table 2, the products **3a–i** were formed in high yields (73–88%), excellent diastereoselectivities (62:38–>99:1), and excellent enantioselectivities (94–99%).

To examine the generality of the catalytic enantioselective Mannich reaction of α-fluoro-β-ketoesters **1** by using chiral palladium complex **4d**, we studied the addition of various α-fluoro-β-ketoesters **1** to *N*-Boc aldimine **2a**. As it can be seen by the results summarized in Table 3, the corresponding products **3j–m** were obtained in high to excellent yields (77–89%), high diastereoselectivities (59:41–67:35), and excellent enantioselectivities (93–99%).[16] Absolute configuration of major diastereomer of **3a** was determined to be (2*S*,3*S*) by comparison of the optical rotation and chiral HPLC data with the published values in literature.[12a]

We examined the direct enantioselective Mannich-type reaction of α-fluoro acetoacetate derivatives **1e–f** with *N*-Boc *p*-tolualdimine (**2a**) using chiral palladium catalyst **4d** in toluene at room temperature. In the presence of 5 mol % of catalyst **4d**, the reaction proceeded to afford the β-aminated product **3n–m** after 10 h with 86–87% ee (Scheme 1).

In conclusion, we have developed a highly efficient catalytic enantioselective Mannich reaction of α-fluoro-β-ketoesters using chiral palladium complexes **4** which are air- and moisture-stable. The desired β-aminated products were obtained in good to high yields, and high enantioselectivities (up to 99% ee) were observed for all the substrates examined in this work. We believe that this method provides a practical entry for the preparation of chiral β-aminated α-fluoro-β-ketoester derivatives. Further details and application of this Mannich-type reaction will be presented in due course.

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16. *Typical procedure for Mannich Reaction of ethyl 2-fluoro-3-oxo-3-phenylpropanoate* ***1a*** *with N-Boc p-tolualdimine* ***2a***: To a stirred solution of ethyl 2-fluoro-3-oxo-3-phenylpropanoate (**1a**, 0.3 mmol, 63.0 mg) and catalyst **4d** (0.015 mmol, 14.4 mg) in toluene (3 mL) was added *N*-Boc *p*-tolualdimine (**2a**, 0.45 mmol, 98.6 mg). Reaction mixture was stirred for 7 h at room temperature, concentrated, and purified by flash column chromatography (EtOAc/hexane: 1/7) to afford the Mannich adduct **3a** (100.4 mg, 78%). *(2S, 3S)-Ethyl 2-benzoyl-3-(tert-butoxycarbonylamino)-2-fluoro-3-p-tolylpropanoate (**3a**)*. Major diastereomer: $[\alpha]_D^{31}$ = 28.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.28 (t, *J* = 6.9 Hz, 3H), 1.39 (s, 9H), 2.26 (s, 3H), 4.18–4.39 (m, 2H), 5.44 (d, *J* = 10.4 Hz, 1H), 5.96 (dd, ^2J = 28.9 Hz, ^1J = 10.4 Hz, 1H), 7.04–7.08 (m, 2H), 7.26–7.29 (m, 2H), 7.34–7.39 (m, 2H), 7.49–7.54 (m, 1H), 7.81–7.84 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.77, 20.96, 28.11, 57.11 (d, *J* = 18.35 Hz), 63.01, 79.96, 102.21 (d, *J* = 203.75 Hz), 128.35, 128.56, 128.96, 129.33, 129.46, 133.54, 133.66, 137.71, 154.29, 165.49 (d, *J* = 26.9 Hz), 190.76 (d, *J* = 25.6 Hz); ESI-HRMS: *m*/*z* calcd for $C_{24}H_{29}FNO_5$ $[M+H]^+$: 430.2030; found 430.2034; HPLC (80:20, *n*-hexane: *i*-PrOH, 254 nm, 1.0 mL/min) Chiralpak AD-H column, t_R = 10.4 min (minor), t_R = 14.9 min (major), 99% ee.