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Formation of Chiral α-Monofluorinated-β-amino Esters through Organocatalytic Asymmetric Reduction of α-Fluoro-β-enamino Esters by Trichlorosilane

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A concise method was developed to prepare chiral α-monofluorinated-β-amino esters through *N*-sulfinyl urea catalyzed asymmetric hydrosilylation of α-fluoro-β-enamino esters, which affords high yields, good to high diastereoselectivities (up to＞99/1), and moderate to good enantioselectivities (up to 83% *ee*).

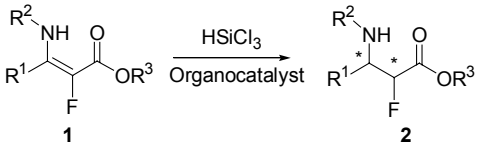
Keywords asymmetric reduction, sulfinyl urea, α-fluorinated-β-amino ester, stereoselectivity

Introduction

Due to the special properties of fluorine atom(s), including small steric size, high electronegativity and carbon-fluorine bond strength, the introduction of fluorine atom(s) into β-amino acids normally leads to remarkable changes of their physical, chemical, and biological properties.[1] For instance, the replacement of CH_2 with CF_2 in the β-amino acid fragment of Rhodopeptins, a family of cyclic tetrapeptides isolated from *Rhodococcus* species MerN1033, remarkably improved the toxicity profile of the compounds.[2]

The preparation of fluorinated β-amino acids has recently drawn a great deal of attentions in medicinal and bioorganic chemistry community. Abell presented the first example of preparing α-fluorinated-β-amino acids using Evan's chiral oxazolidinone auxiliary for asymmetric induction in the key fluorination step.[3] Later, Togni,[4] Shibata,[5] Sodeoka[6] and others presented a number of methods to construct α-fluorinated carbonyl compounds as the key intermediates for the synthesis of α-fluorinated-β-amino acids via transition metal catalyzed and organocatalytic asymmetric C—F bond formation.[7] Lu[8] and Tan[9] also reported a method utilizing catalytic asymmetric nucleophilic addition of fluorinated ketoesters to access α-fluorinated-β-amino esters. In principle, catalytic asymmetric reduction of α-fluorinated-β-enamino ester **1** should be an alternative straightforward pathway to construct chiral α-fluorinated-β-amino ester **2** (Scheme 1). However, to the best of our knowledge, so far no method has been reported to implement this transformation. This stimulated our strong interest to prepare chiral α-fluorinated-β-amino esters via asymmetric reduction of α-fluoro-β-enamino esters.

Scheme 1 Asymmetric organocatalytic reduction of α-fluoro-β-enamino ester **1** by trichlorosilane



1 **2**

In recent years, others and we have developed Lewis base catalyzed asymmetric reduction by trichlorosilane ($HSiCl_3$) into a viable asymmetric synthetic method.[10-12] Besides the reduction of imines and ketones for the synthesis of chiral amines and alcohols, this method has also proven to be highly effective for the reduction of some functionalized enamines[11] such as β-enamino esters, which affords chiral β-amino esters in high yields and excellent stereoselectivities.[11b-11e] Recently, we proceeded to explore if this method could also be applicable for the asymmetric reduction of α-fluorinated-β-enamino esters for the production of chiral α-fluorinated-β-amino esters. Herein, we wish to report our finding that good results could be obtained for the reduction of a broad range of α-fluorinated-β-enamino esters by this method when a special type of sulfinyl ureas was used as catalyst.

Results and Discussion

We began our studies by screening different types of Lewis base catalysts we previously developed for the

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asymmetric reduction by trichlorosilane. α-Fluoro-β-enamino ester **1a** was used as the testing substrate. The sulfinyl ureas **3a** and **3b**, a special type of catalysts we recently demonstrated to be highly efficient bifunctional activator for the reduction of β-enamino nitro compounds by $HSiCl_3$,[12] were found to exhibit good reactivity and diastereoselectivity (Table 1, Entries 2—3).[13] But unfortunately, they displayed poor enantioselectivity. Nonetheless, we felt that this type of catalysts, if appropriately modified, might have potentials to furnish good enantioselectivity. We speculated that replacement of the simple aryl R group with a sterically more hindered scaffold with additional chiral elements might be a solution to the low enantioselectivity problem with catalyst **3**. Thus, we prepared a set of catalysts **4**[14] bearing different substituents derived from (1*S*,2*R*)-indanol and tested their efficacies in the reduction of **1a**. Their diastereomers **5** and **6** were also prepared and tested for comparisons (Figure 1).

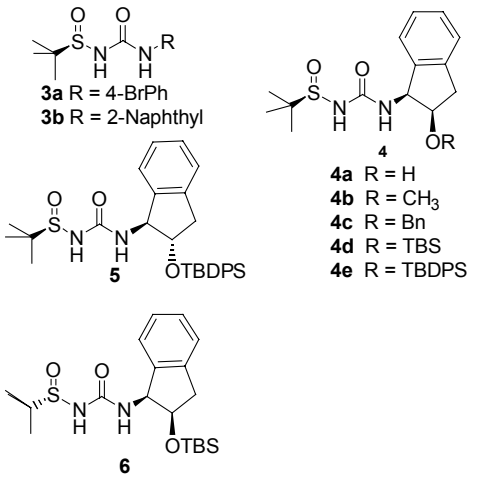
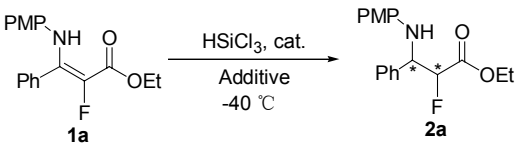


Figure 1 Catalyst structures.

As shown in Table 1, catalysts **4a** bearing a free hydroxyl group only gave slightly better results than catalysts **3** (Entry 4). The enantioselectivity is still very low. Either methylation (**4b**) or benzylation (**4c**) of the hydroxyl group had no beneficial effects on the enantioselectivity (Entries 5 and 6), but enhanced both the reactivity and the diastereoselectivity to a high level. Interestingly, when the hydroxyl group was protected with a bulkier TBS group (**4d**), the enantioselectivity was significantly improved and 58% *ee* value was obtained (Entry 7), meanwhile, the high reactivity and diastereoselectivity were still retained. Switch of the bulky protection group from TBS to TBDPS (**4e**) resulted in further improvement of the enantioselectivity, bringing the *ee* value up to 78% (Entry 8). The stereochemistry on the 2-position of the indanol scaffold had only marginal effects on the efficiency. Catalyst **5** derived from (1*S*,2*S*)-indanol afforded only slightly lower enantioselectivity than **4e** (Entry 9). Notably, when the configuration of the sulfur atom in the sulfinyl group of **4d** was changed from *R* to *S*, the resulting catalyst **6** exhibited almost unaffected diastereoselectivity, but afforded substantially decreased enantioselectivity with reversed sense of chirality (Entry 10), suggesting that the stereochemical match between the chiral sulfinyl group and the indanol moiety is crucial for the enantiocontrol.

Table 1 Asymmetric reduction of α-fluoro-β-enamino ester **1a** catalyzed by *N*-sulfinyl ureas[a]



Entry	Catalyst	Additive	Solvent	Yield[c]/%	*dr*[d]	*ee*[d]
1	—	H_2O	toluene	<5	—	—
2	**3a**	H_2O	toluene	88	72/28	<10
3	**3b**	H_2O	toluene	70	70/30	<10
4	**4a**	H_2O	toluene	88	86/14	14
5	**4b**	H_2O	toluene	73	91/9	<10
6	**4c**	H_2O	toluene	93	93/7	<10
7	**4d**	H_2O	toluene	90	95/5	58
8	**4e**	H_2O	toluene	95	95/5	78
9	**5**	H_2O	toluene	90	95/5	71
10	**6**	H_2O	toluene	95	90/10	−30[e]
11	**4e**	AcOH	toluene	78	93/7	73
12	**4e**	$PhCO_2H$	toluene	94	90/10	63
13	**4e**	EtOH	toluene	82	91/9	72
14	**4e**	—	toluene	70	89/11	40
15	**4e**	H_2O	CH_2Cl_2	40	95/5	69
16	**4e**	H_2O	MeCN	70	51/49	60
17	**4e**	H_2O	xylene	80	93/7	76
18	**4e**	H_2O	EA	85	61/39	72

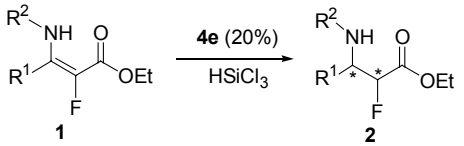
[a] Unless stated otherwise, reactions were carried out on a 0.05 mmol scale with $HSiCl_3$ (3.0 equiv.) and additive (1.0 equiv.) in solvent (0.5 mL) at −40 ℃ for 48 h. [b] Catalyst loading based on α-fluoro-β-enamino ester. [c] Isolated yield. [d] The *ee* and *dr* values were determined using chiral HPLC, *dr*=*anti*/*syn*. [e] The opposite enantiomer was formed.

With these results in hand, we next selected catalyst **4e** with the best overall performance for further optimizations. As we previously observed in the reduction of other enamine type substrates,[11a,11b] protonic additive is important for the reactivity and stereoselectivity, and water is superior to other additives such as acetic acid, benzoic acid, and ethanol (Entries 11—14). Other solvents such as dichloromethane, acetonitrile, xylene, and ethyl acetate were all found to be inferior to toluene.

Finally, the substrate scope of the **4e**-catalyzed reduction was examined. A broad range of α-fluoro-β-enamino esters were reduced in the presence of 20 mol% **4e** under optimal conditions. The results are summarized in Table 2. In general, all the reductions

proceeded smoothly to completion in 48 h and the desired products were obtained in excellent yields, good to high diastereoselectivities, and moderate to good enantioselectivities. *N*-PMP amine derived substrates with R^1 as an electron-rich aryl group (**1a**—**1e** and **1i**) generally gave good overall results (Entries 1—5 and 9). In particular, up to 94% yield, >99/1 *dr* and 83% *ee* were obtained for **1b** bearing PMP as R^1 (Entry 2). Substrates with a relatively electron-deficient aromatic R^1 group (**1f**—**1h**) afforded slightly lower diastereoselectivities and significantly decreased enantioselectivities (Entries 6—8). Further decreased enantioselectivity was observed for substrate **1j** with R^1 as an aliphatic methyl group (Entry 10). When R^2 was changed from PMP to less electronic-efficient aromatic groups such as *para*-fluorophenyl (**1k**) and phenyl (**1l**) or to aliphatic group such as benzyl (**1m**), only moderate enantioselectivites were achieved (Entries 11—13). Notably, although no substrate could afford enantioselectivity up to a high level (>90% *ee*), a single recrystallization of the product **2a** proved to be able to enrich the enantiomer to achieve excellent enantiopurity (98% *ee*, Entry 1), which further demonstrates the potential practical usefulness of the present catalytic reaction system.

Table 2 Asymmetric reduction of various *α*-fluoro-*β*-enamino esters **1** catalyzed by **4e**[a]



Entry	R^1	R^2	**1**	Yield[b]/%	*dr*[c]	*ee*[c]
1	Ph	PMP	**1a**	95	95/5	78 (98)[d]
2	PMP	PMP	**1b**	94	>99/1	83
3[e]	*m*-$MeOC_6H_4$	PMP	**1c**	96	97/3	72
4[e]	*p*-$CH_3C_6H_4$	PMP	**1d**	96	97/3	79
5	*p*-BrC_6H_4	PMP	**1e**	89	94/6	71
6	*p*-FC_6H_4	PMP	**1f**	92	86/14	38
7	*p*-ClC_6H_4h	PMP	**1g**	90	94/6	61
8	*p*-$CF_3C_6H_4$	PMP	**1h**	92	91/9	55
9	2-naphthyl	PMP	**1i**	95	90/10	70
10[e]	Me	PMP	**1j**	97	88/12	22
11	Ph	*p*-FC_6H_4	**1k**	91	78/22	56
12	Ph	Ph	**1l**	92	94/6	50
13	Ph	Bn	**1m**	86	85/15	48

[a] Reactions were carried out on a 0.05 mmol scale with $HSiCl_3$ (3.0 equiv.) in toluene (0.5 mL) at −40 ℃ for 48 h. [b] Isolated yield. [c] The *ee* and *dr* values were determined by HPLC. [d] Data in parentheses was obtained after a single recrystallization in ^{i}PrOH/hexane. [e] Due to the difficulty of enantiomeric separation by HPLC, the ester product was reduced to the corresponding alcohol for *ee* value measurement.

Conclusions

In conclusion, the asymmetric reduction of *α*-fluoro-*β*-enamino esters was successfully implemented using chiral *N*-sulfinyl ureas as catalyst and trichlorosilane as reducing agent. A broad range of *α*-fluoro-*β*-enamino esters were reduced to afford chiral *α*-fluoro-*β*-amino esters with high yields, good to high diastereoselectivities, and moderate to good enantioselectivities. This method provides an alternative straightforward approach to construct chiral *α*-fluoro-*β*-amino esters.

Experimental

General procedure for the synthesis of catalysts

Catalysts **3**—**6** were synthesized according to the literature procedures.[14] To a stirred solution of butanesulfinamide (1.0 equiv.) in anhydrous THF was added butyllithium (1.1 equiv.) dropwise at −78 ℃. The solution was stirred for 20 min and was then warmed to room temperature, followed by introduction of isocyanate (1.1 equiv.). Water was added to quench the reaction when completion. The resulting mixture was extracted with EtOAc. The combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under vacuum. The residue was purified on silica gel with column chromatography to afford pure product.

(*R*)-*N*-((1*S*,2*R*)-2-(*tert*-Butyldiphenylsilyloxy)-2,3-dihydro-1*H*-inden-1-ylcarbamoyl)-2-methylpropane-2-sulfinamide (4e)

White solid. ^{1}H NMR (600 MHz, $CDCl_3$) *δ*: 7.56 (d, *J*=6.7 Hz, 2H), 7.47 (d, *J*=7.1 Hz, 2H), 7.26—7.37 (m, 7H), 7.13—7.14 (m, 2H), 6.99 (s, 1H), 6.19 (t, *J*=11.5 Hz, 1H), 5.15 (t, *J*=11.8 Hz, 1H), 4.63 (s, 1H), 2.73 (d, *J*=16.0 Hz, 1H), 2.67 (d, *J*=16.3 Hz, 1H), 1.17 (s, 9H), 0.97 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) *δ*: 155.1, 141.2, 139.5, 135.7, 133.5, 132.9, 130.0, 129.9, 128.1, 127.9, 127.7, 127.0, 125.1, 124.8, 75.3, 58.1, 57.2, 39.7, 27.0, 22.3, 19.3; ESI HRMS calcd for $(C_{30}H_{38}NNaO_3SSi)^+$ 557.2265, found 557.2258.

General procedural for the reduction of 1

Under an argon atmosphere, trichlorosilane (0.15 mmol) was added dropwise to a stirred solution of **1** (0.05 mmol), catalyst **4e** (0.01 mmol), and water (0.05 mmol) in anhydrous toluene (0.35 mL) at −40 ℃. The mixture was stirred for 48 h at the same temperature. The reaction was then quenched with a saturated aqueous solution of $NaHCO_3$ and extracted with EtOAc. The combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under vacuum. The crude product was purified by column chromatography (silica gel, hexane) to afford pure products **2**.

Ethyl-2-fluoro-3-(4-methoxypheny-lamino)-3-phenyl-propanoate (2a)

White solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.17—7.30 (m, 5H), 6.62 (d, J=9.2 Hz, 2H), 6.47 (d, J=8.8 Hz, 2H), 5.06 (d, J=47.3 Hz, 1H), 4.86 (d, J=26.5 Hz, 1H), 4.34 (s, 1H), 4.12—4.17 (m, 2H), 3.61 (s, 3H), 1.15 (t, J=7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 167.8 (d, J=24.4 Hz), 152.7, 140.1, 138.0, 128.8, 128.0, 127.1, 115.4, 114.8, 92.0 (d, J=191.4 Hz), 61.9, 59.8 (d, J = 19.0 Hz), 55.7, 14.1. ESI HRMS calcd for $(C_{18}H_{20}FNNaO_3)^+$ 340.1319, found 340.1315.

Ethyl-2-fluoro-3-(4-methoxyphenyl)-3-(4-methoxy-phenyl-amino)propanoate (2b)

Colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.20 (d, J=8.3 Hz, 2H), 6.78 (d, J=8.4 Hz, 2H), 6.61 (d, J=8.4 Hz, 2H), 6.45 (d, J=8.4 Hz, 2H), 5.00 (d, J=47.7 Hz, 1H), 4.80 (d, J=26.5 Hz, 1H), 4.13—4.15 (m, 2H), 3.69 (s, 3H), 3.61 (s, 3H), 1.15 (t, J=7.3 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 167 (d, J=24.4 Hz), 158.2, 151.6, 139.0, 128.8, 127.1, 114.3, 113.7, 113.1, 91.1 (d, J=191.2 Hz), 60.78, 58.2 (d, J=19.3 Hz), 54.5, 54.1, 13.0. ESI HRMS calcd for $(C_{19}H_{22}NNaO_4)^+$ 370.1425, found 370.1416.

Ethyl 2-fluoro-3-(4-methoxyphenyl-amino)-3-*p*-tolyl-propanoate (2d)[15]

White oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.25 (d, J=7.9 Hz, 2H), 7.15 (d, J=7.9 Hz, 2H), 6.7 (d, J=7.9 Hz, 2H), 6.55 (d, J=7.9 Hz, 2H), 5.10 (dd, J=47.6, 2.7 Hz, 1H), 4.89 (d, J=26.9 Hz, 1H), 4.21—4.25 (m, 2H), 3.69 (s, 3H), 2.32 (s, 2.95), 1.23 (t, J=7.1 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 168 (d, J=23.8 Hz), 152.6, 140.2, 137.7, 134.9, 129.4, 126.9, 115.4, 114.8, 91.0 (d, J=191.1 Hz), 61.9, 59.5 (d, J=19.0), 55.7, 21.1, 14.1.

Ethyl-3-(4-bromophenyl)-2-fluoro-3-(4-methoxyphe-nyl-amino)propanoate (2e)

White oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.38 (d, J=8.4 Hz, 2H), 7.18 (d, J=8.4 Hz, 2H), 6.61 (d, J=10.5 Hz, 2H), 6.43 (d, J=8.9 Hz, 2H), 5.01 (dd, J=47.5, 2.7 Hz, 1H), 4.90 (d, J=26.8 Hz, 1H), 4.32 (s, 1H), 4.13—4.16 (m, 2H), 3.61 (s, 3H), 1.15 (t, J=7.8 Hz, 3H). ESI HRMS calcd for $(C_{18}H_{19}FBrNNaO_3)^+$ 418.0425, found 418.0415.

Ethyl-2-fluoro-3-(4-fluorophenyl)-3-(4-methoxyphe-nyl-amino)propanoate (2f)

Yellowish oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.26—7.28 (m, 2H), 6.94—6.97 (m, 2H), 6.62 (d, J=8.9 Hz, 2H), 6.45 (d, J=8.9 Hz, 2H), 5.0 (dd, J=47.5, 2.7 Hz, 1H), 4.86 (dd, J=26.3, 2.3 Hz, 1H), 4.13—4.17 (m, 2H), 3.62 (s, 3H), 1.16 (t, J=7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 167.6 (d, J=24.2 Hz), 162 (d, J=246.0 Hz), 152.8, 139.8, 133.7, 128.7, 115.7 (d, J=21.4 Hz), 115.3, 114.8, 91 (d, J=191.4 Hz), 61.9, 59.1 (d, J=19.1 Hz), 55.7, 14.1. ESI HRMS calcd for $(C_{18}H_{19}F_2NNaO_3)^+$ 358.1225, found 358.1242.

Ethyl-3-(4-chlorophenyl)-2-fluoro-3-(4-methoxyphe-nylamino)propanoate (2g)

Yellowish oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.23 (s, 4H), 6.15 (d, J=8.9 Hz, 2H), 6.44 (d, J=8.9 Hz, 2H), 5.05 (dd, J=47.8, 2.6 Hz, 1H), 4.83 (d, J=26.5 Hz, 1H), 4.32 (s, 1H), 4.13—4.18 (m, 2H), 3.62 (s, 3H), 1.15 (t, J=7.3 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 167.5 (d, J=24.2 Hz), 152.8, 139.6, 136.6, 133.9, 128.9, 128.5, 115.4, 114.9, 91.1 (d, J=191.2 Hz), 62.0, 59.1 (d, J=19.1 Hz), 55.6, 14.1. ESI calcd for $(C_{18}H_{19}ClFNNaO_3)^+$ 374.0930, found 374.0923.

Ethyl-2-fluoro-3-(4-methoxyphenyl-amino)-3-(4-(tri-fluoromethyl)phenyl)propanoate (2h)

White solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.51 (d, J=8.2 Hz, 2H), 7.42 (d, J=8.0 Hz, 2H), 6.60 (d, J=8.9 Hz, 2H), 6.43 (d, J=8.9 Hz, 2H), 5.05 (dd, J=47.4, 2.6 Hz, 1H), 4.90 (d, J=26.8 Hz, 1H), 4.35 (s, 1H), 4.13—4.17 (m, 2H), 3.59 (s, 3H), 1.14 (t, J=7.3 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 167.4 (d, J=24.4 Hz), 152.9, 142.2, 139.5, 130.3 (q, J=32.3 Hz), 127.5, 125.7, 123.0 (q, J=270.5 Hz), 115.3, 114.9, 90.5 (d, J=191.2 Hz), 62.1, 59.4 (d, J=18.9 Hz), 55.6, 14.0. ESI HRMS calcd for $(C_{19}H_{19}F_4NNaO_3)^+$ 408.1193, found 408.1191.

Ethyl-2-fluoro-3-(4-methoxyphenyl-amino)-3-(-2-naphthalenyl)propanoate (2i)

White solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.71—7.75 (m, 4H), 7.37—7.42 (m, 3H), 6.60 (d, J=8.9 Hz, 2H), 6.51 (d, J=8.9 Hz, 2H), 5.11 (dd, J=47.2, 2.7 Hz, 1H), 5.02 (d, J=26.4 Hz, 1H), 4.5 (s, 1H), 4.13—4.17 (m, 2H), 1.13 (t, J=7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 167.8 (d, J=18.9 Hz), 152.7, 140.1, 135.6, 133.3, 133.1, 128.6, 127.9, 127.7, 126.4, 126.3, 126.2, 115.4, 114.8, 91.5 (d, J=192.1 Hz), 61.9, 60.0 (d, J=18.9 Hz), 55.7, 14.1. ESI HRMS calcd for $(C_{22}H_{22}FNNaO_3)^+$ 390.1476, found 390.1474.

Ethyl-2-fluoro-3-(4-fluorophenyl-amino)-3-phenyl-propanoate (2j)

Yellowish oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.18—7.30 (m, 5H), 6.71—6.74 (m, 2H), 6.42—6.45 (m, 2H), 5.10 (dd, J=47.4, 2.52 Hz, 1H), 4.86 (d, J=26.6 Hz, 1H), 4.48 (s, 1H), 4.14—4.17 (m, 2H), 1.15 (t, J=7.2 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 167.7 (d, J=24.4 Hz), 156.0 (d, J=287.0 Hz), 142.3, 137.6, 128.8, 128.2, 127.0, 115.7 (d, J=22.4 Hz), 114.9 (d, J=7.5 Hz), 91.0 (d, J=191.2 Hz), 62.0, 59.5 (d, J=19.0 Hz), 14.1. ESI HRMS calcd for $(C_{17}H_{17}F_2NNaO_2)^+$ 328.1120, found 328.1120.

Ethyl-2-fluoro-3-phenyl-3-(phenylamino)propanoate (2k)

White solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.26—7.40 (m, 5H), 7.10—7.13 (m, 2H), 6.68—6.71 (m, 1H), 6.59 (d, J=7.9 Hz, 2H), 5.2 (dd, J=47.4, 2.5 Hz, 1H), 5.04 (d, J=27.0 Hz, 1H), 4.67 (s, 1H), 4.20—4.26 (m, 2H), 1.22 (t, J=7.1 Hz, 3H). ^{13}C NMR (150 MHz,

$CDCl_3$) δ: 167.8, 146.0, 137.8, 129.2, 128.8, 128.0, 127.0, 118.4, 113.9, 92.3 (d, J=192.0 Hz), 62.0, 58.75 (d, J=19.0 Hz), 14.1. ESI HRMS calcd for $(C_{17}H_{18}FNNaO_2)^+$ 310.214, found 320.1215.

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