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Short Communication

Synthesis of chiral fluorine-containing compounds via Pd-catalyzed asymmetrical allylations of dimethyl 2-fluoromalonate using sulfonamide-pyridine ligands

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ABSTRACT

Chiral *o*-aniline sulfoxides serving as chiral sulfurous source were synthesized, from which new sulfonamide-pyridine ligands were made in three-steps. These compounds proved to be efficient *S,N*-ligands for enantiocontrol of palladium-catalyzed allylic substitutions of dimethyl 2-fluoromalonate. The induced effect of the Pd/*S,N*-ligand catalyst on the enantioselectivity depends on the steric demand of the substituent on the sulfoxide moiety. This method provided the fluorine-containing allylic products with up to 94% *ee*.

1. Introduction

Asymmetric catalysis with transition metal complexes has been rapidly developing in synthetic chemistry. Chiral ligands play an essential role for the achievement of excellent stereoselectivity. In this regard, design and synthesis of novel effective ligands remain a big challenge [1]. Chiral sulfoxides were used as an auxiliary in asymmetric synthesis [2]. More recently, chiral sulfoxide ligands have attracted considerable attention for their utilization in asymmetric synthesis [3]. The sulfinyl group of such ligands is featured with both an intrinsic stereogenic center and binding site to transition metals. Therefore, it is reasoned that a structurally proper sulfoxide could possibly act as a sulfur ligand [4], which may offer sulfurous source for asymmetric catalysis. There were several examples focused on palladium (Pd)-catalyzed asymmetric allylations with using chiral sulfoxide ligands [5], which made from *tert*-butylsulfinyl group. [5g–j] To expand the chiral sources of sulfoxide ligands, a structural diversity of *o*-aniline sulfoxides has been envisioned, which may be synthesized according to our previous works (Scheme 1).

Fluorine-containing compounds are of great importance to pharmaceutical industry [6]. In particular, optically active monofluorinated compounds such as *Pharmacia, Clofarabin,* and *Difluprednate* are popular drugs [6d,7]. There are several methods reported for the synthesis of monofluorinated compounds [6a] however, transition metal-catalyzed asymmetrical allylic substitutions of fluorinated methylene derivatives are less disclosed [8], which could afford the monofluorinated allylic products. Herein we report the synthesis of new chiral sulfonamide-pyridine ligands stemmed from *o*-aniline sulfoxides and their application in Pd-catalyzed asymmetric allylic substitutions of dimethyl 2-fluoromalonate.

2. Results and discussion

We initially aimed at developing a method for the preparation of enantioenriched 2-allylthio-substituted aniline **3** on a large-scale (Scheme 1). This allylation reaction was carried out on a 4 mmol scale; and we found that the presence of a little water led to the reduction of the yield; and that the amount of iridium catalyst has an influence on this reaction. After avoiding the presence of water and reducing iridium catalyst from 2 mmol% to 1 mmol%, a large-scale synthetic method for **3** was developed on the basis of our previous work [9] (see: SI). The key intermediate **5** was prepared by a reduction of **3** with *o*-nitro benzenesulfonylhydrazide (NBSH) [10], following by an oxidation with *m*CPBA without loss of *ee* value (Scheme 1, see: SI).

As a result, two isomers (**5′** and **5**) were obtained and they can be separated by flash column chromatography. Among these isomers, the absolute configuration of **5b'** (R^1 = 3,5-*di*-$MeOC_6H_3$)

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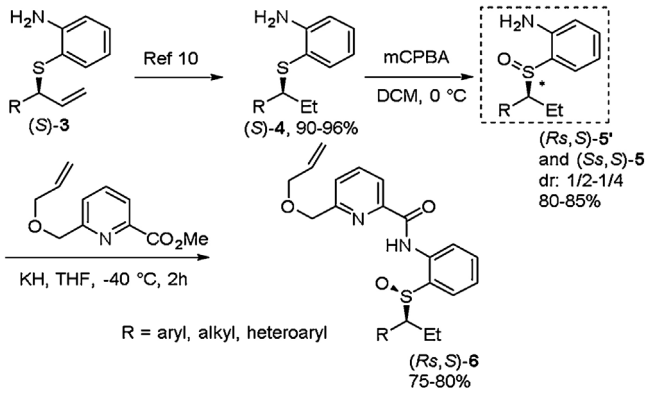


Scheme 1. Synthesis of new chiral sulfonamide-pyridine ligands **6**.

was established as (*Rs*,*S*) by its X-ray diffraction analysis (Fig. 1) [11]. Finally, the treatment of **5**, either (*Rs*,*S*)-**5** or (*Ss*,*R*)-**5′**, with potassium hydride (KH) at −40 °C, following by a reaction with methyl 6-((allyloxy)methyl)picolinate, gave the corresponding ligand **6** (Scheme 1 and Fig. 2) [12]. The 6-(allyloxymethyl) picolinamide, a substituent at 6-position of pyridine moiety, is optimal for these *N*,*S*-ligands, which were reported in our previous work [13]. We found that the *N*,*S*-ligands generated from *tert*-butylsulfinyl group are unsuitable for Pd-catalyzed asymmetrical allylations of 2-napthyl-substituted allylic acetate with dimethyl 2-fluoromalonate [13].

To evaluate the catalytic potential of the *S*,*N*-ligand **6**, a Pd-catalyzed reaction of (*E*)-1,3-bis(3-fluorophenyl)allyl acetate **7a** with dimethyl 2-fluoromalonate **8a** [14] was carried out (Table 1). In the presence of a catalyst [15] made from [Pd(C_3H_5)Cl_2] and (*Rs*,*S*)-**6b**, the reaction was performed in THF at room temperature without base and no allylic products were observed. When sodium hydride (NaH) was used as an additive, to our delight, the allylic product **9a** was formed in a 35% yield with 80% *ee*; a little amount of (*E*)-1,3-bis(3-fluorophenyl)prop-2-en-1-ol was observed as well (entry 1). Thus, a number of bases including potassium 2-methylpropan-2-olate (^{t}BuOK), K_3PO_4, LiCl, 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU), CsF and *tetra*-butylammonium fluoride (TBAF) was further investigated, we found that Cs_2CO_3 led to a superior result, whereas K_3PO_4, ^{t}BuOK and CsF gave moderate to good *ee* (entries 2, 3 and 6). Both LiCl and DBU were unsuitable for the reaction (entries 4 and 5). TBAF led to the highest yield but with an acceptable *ee* (entry 7). Variation of solvents has a significant impact on this reaction (entries 8 – 10). Chiral ligands are essential for the enantiocontrol of palladium-catalyzed allylic substitutions [5]. Consequently, a variety of the chiral sulfonamide-pyridine ligands was further explored. For instance, (*Ss*,*R*)-**6a** containing a phenyl group gave a somewhat lower *ee* than that of (*Rs*,*S*)-**6b**, which contains a 3,5-*di*-methoxy group on the phenyl ring (entry 8). The different configuration of ligand (*Ss*,*R*)-**6a** and (*Rs*,*S*)-**6b** resulted in the opposite configuration of **9a** (entry 8 vs entry 11). (*Rs*,*S*)-**6c** bearing a furanyl group gave a little lower *ee* than that of (*Ss*,*R*)-**6a** although it is structurally similar to (*Ss*,*R*)-**6a** (entry 12). Interestingly, (*Rs*,*R*)-**6d** with the least steric substituent such as a methyl group gave rise to good *ee* (entry 13). (*Rs*,*R*)-**6f** bearing a pyridine ring was also examined and it led to a poor outcome (entry 14). These results suggested that both the steric demand and nature of the substituent in **6** have a great influence on the enantioselectivity of this reaction. Furthermore, both Josiphos [16] and Trost ligands [17] were examined under the optimized conditions; Josiphos ligand gave **9a** in racemic form with a 83% yield (entry 15). Trost ligand led to a moderate result (entry16). It is noted that only trace amount of **9a** was formed when the reaction was carried out at 0 °C. Change of the ratio of reactants has a considerable influence, for example, **9a** was obtained in an improved yield (80%) albeit with a lowering *ee* (70%) when the ratio of **7a**/**8a** in 3/1 was employed at room temperature.

Analysis of **7a** which was recovered upon the completion of the reaction by HPLC on a chiral stationary phase illustrated that it was racemic.

Having established the optimized reaction conditions presented in entry 8 of Table 1, the scope of a series of (*E*)-1,3-disubstituted allyl acetates **7** was examined (Table 2). The substrates **7a** and **b** with the 3-substituted group, which is an

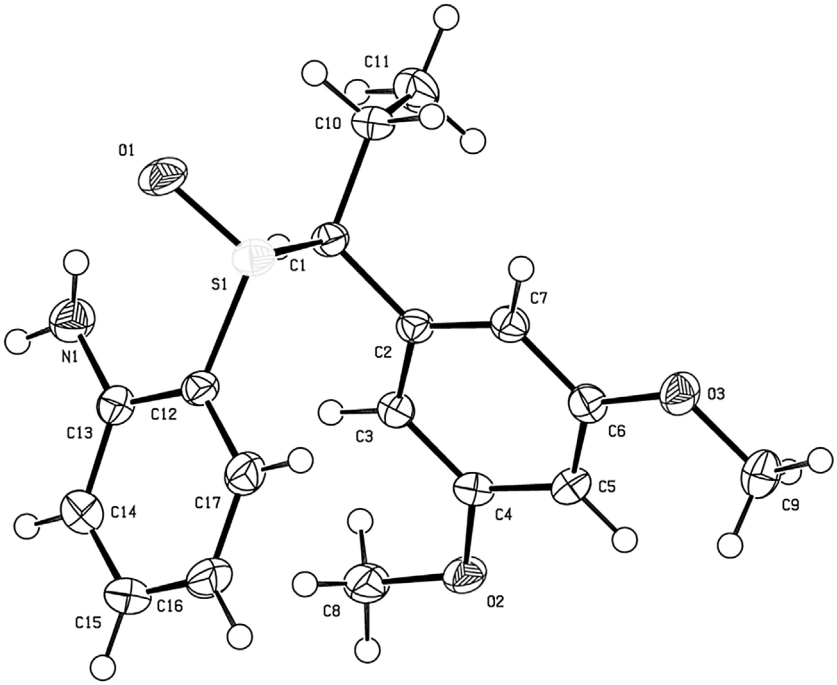


Fig. 1. X-ray structure of (*Rs*,*S*)-**5b'**.

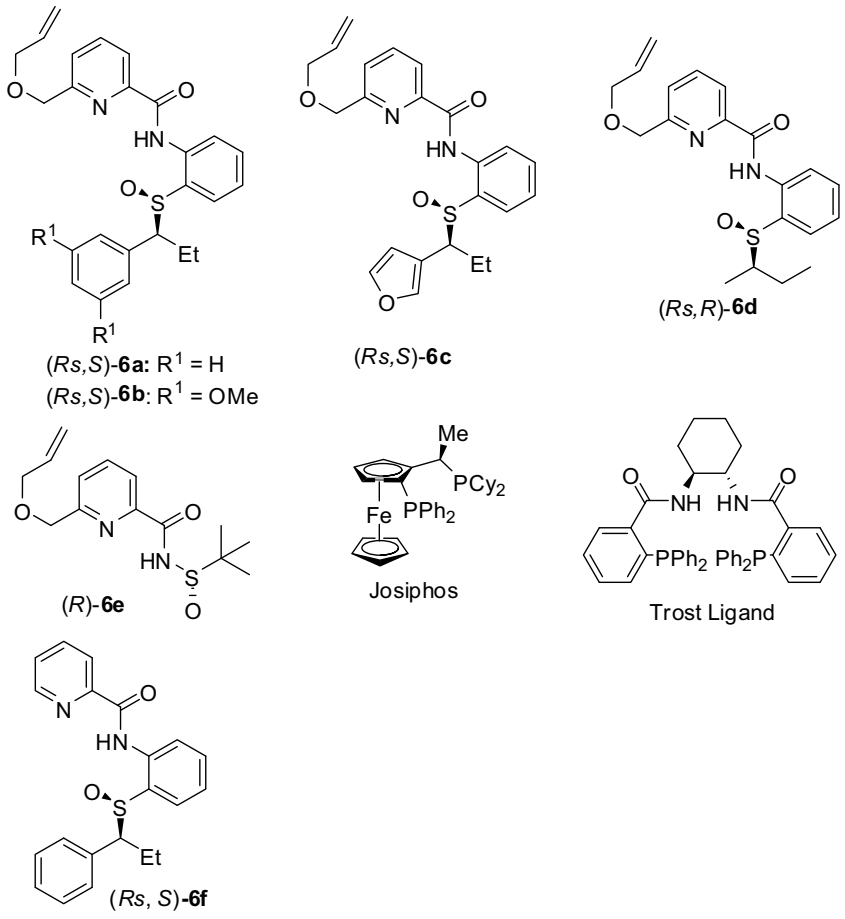


Fig. 2. Sulfonamide-pyridine ligands **6**, Josiphos, and Trost ligand.

Table 1
Screening the reaction conditions for a Pd-catalyzed allyic substitution using sulfoxide-pyridine ligands **6**.[a]

Entry	L	Add.	Sol.	Yield of **9a** (%)[b]	ee (%)[c]
1	**6b**	NaH	THF	35	80
2	**6b**	^{t}BuOK	THF	24	69
3	**6b**	K_3PO_4	THF	15	82
4	**6b**	LiCl	THF	NR	–
5	**6b**	DBU	THF	11	rac
6	**6b**	CsF	THF	15	66
7	**6b**	TBAF	THF	76	54
8	**6b**	Cs_2CO_3	THF	73	94
9	**6b**	Cs_2CO_3	DCM	11	47
10	**6b**	Cs_2CO_3	Tol.	10	80
11	**6a**	Cs_2CO_3	THF	51	−80
12	**6c**	Cs_2CO_3	THF	25	72
13	**6d**	Cs_2CO_3	THF	41	70
14	**6f**	Cs_2CO_3	THF	18	15
15	Josiphos	Cs_2CO_3	THF	83	rac.
16	Trost	Cs_2CO_3	THF	75	65

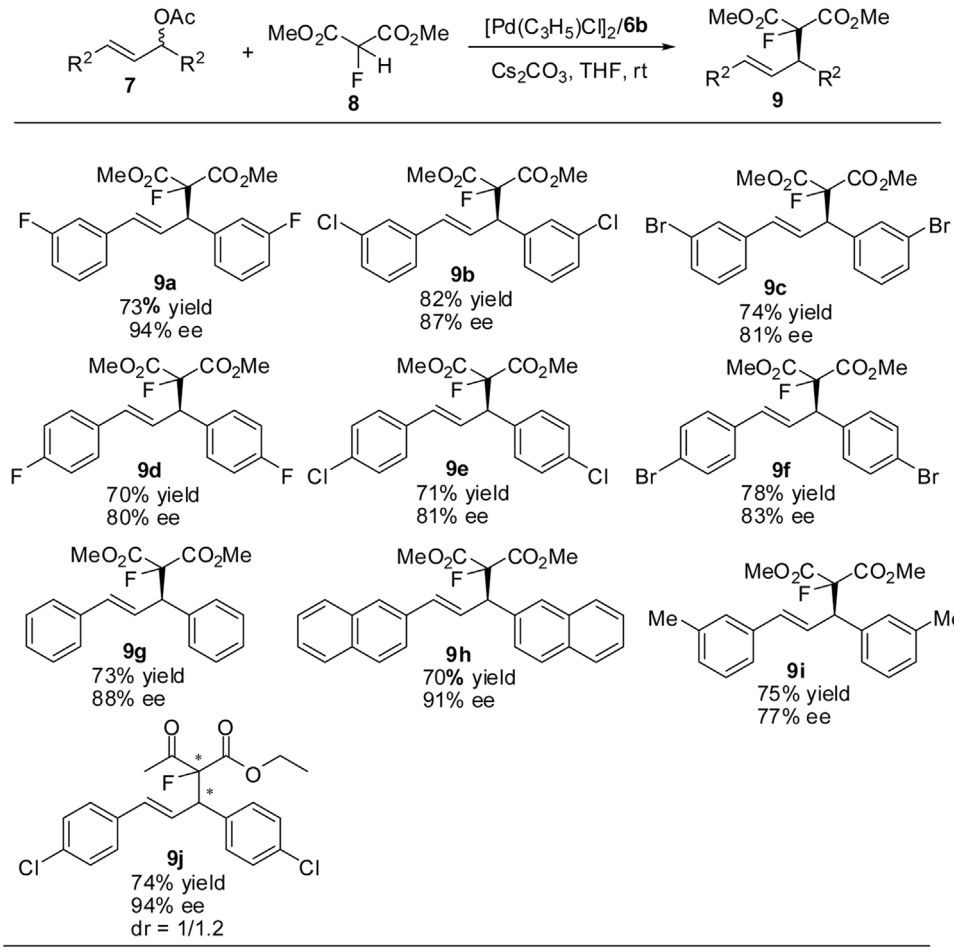
[a] Reaction conditions: $[Pd(C_3H_5)Cl]_2$ (4 mol%), **L** (8 mol%), **7a** (0.1 mmol), **8** (0.30 mmol) and additive (0.3 mmol) in solvent (2 mL) at room temperature.
[b] Isolated yield.
[c] Determined by a chiral HPLC analysis.

electron-withdrawing group (*e.g.*, 3-F and 3-Cl), on the phenyl ring offered the allylic products **9a** and **b** in good yields with high enantioselectivities (87–94% *ee*, Table 2). In contrast, replacing the same group, either –F or –Cl, from 3-position to 4-position respectively gave rise to the corresponding products **9d–e** with somewhat lower *ees* than that of **9a** and **b** (Table 2). The results indicated that either substituted position or electron-withdrawing nature of the substituent on the phenyl ring has a significant impact on the enantioselectivity of this reaction [18]. Both 3-bromo- and 4-bromo substituted substrates (**7c** and **f**) led to the similar results (Table 2).

With using (*E*)-1,3-diphenylallyl acetate **7g** as a substrate, **9g** was obtained in a 73% yield and 88% *ee* (Table 2). Significantly, substrate with a bulky group such as 2-napthyl-substituted allylic acetate **7h** provided **9h** in a moderate yield and a high *ee* value (Table 2). This method could be used for the synthesis of the 6-methoxy-2-napthyl-substituted allylic product, an analogue of **9h**, which could be transformed into fluorinated Naproxen [8c]. In contrast with our previous work [13], the ligand (*R*)-**6e** [13] (Fig. 2) other than **6b** was employed for the substrate **7h** under the similar conditions and it gave **9h** in a 82% yield and 65% *ee*. These results revealed that the sulfonamide moiety has a significant effect on the enantiocontrol. In this regard, the ligand **6b** in the induced effect on the enantioselectivity is supplementary to that of (*R*)-**6e**. The substrates **7i** with the 3-substituted group, which is an electron-donating group (*e.g.*, 3-Me), on the phenyl ring gave the allylic products **9i** in a 75% yield and 77% *ee* (Table 2). However, (*E*)-pent-3-en-2-yl acetate **7j** was tested and the desired allylic product was not obtained. The racemic fluorinated ethyl 3-oxobutanoate **8b** was used and it gave the corresponding allylic product **9j** in a 74% yield with 94% *ee* but 1/1.2 dr (Table 2).

The transformation of **9** made in this method was explored, for example, the treatment of (*E*)-dimethyl 2-(1,3-bis(4-chlorophenyl) allyl)-2-fluoromalona **9e** with lithium hydroxide monohydrate in

Table 2
Scope of Pd-catalyzed allylic substitutions using the ligand (*Rs*,*S*)-**6b**[a–c].



[a]Reaction conditions: $[Pd(C_3H_5)Cl]_2$ (4 mol%), **6** (8 mol%), **7** (0.1 mmol), **8** (0.30 mmol) and Cs_2CO_3 (0.3 mmol) in THF (2 mL) at room temperature.
[b]Isolated yield.
[c]ee was determined by a chiral HPLC analysis.

THF/H_2O at room temperature gave (*E*)-2-(1,3-bis(4-chlorophenyl) allyl)-2-fluoromalonic acid in 95% yield with $[\alpha]_D^{20} = +45.2^\circ$.

In order to determine their absolute configuration, **9c** was established as *R* by comparing with the known chiral compound [13].

On the basis of our observation in this reaction and other works [19], there are two presumed types of π-allyl-Pd intermidiates, M-type and W-type, in this allylation process (Fig. 3). M-type of π-allyl-Pd complex, in which the allyl phenyl group would assume a position remote from the pyridine- and sulfoxides moiety, is intended to bias allyl intermediate since the steric demand of both substituent at the 6-position of pyridine and sulfoxides moiety. The nucleophilic attack is more favoured at allyl carbon, which is trans

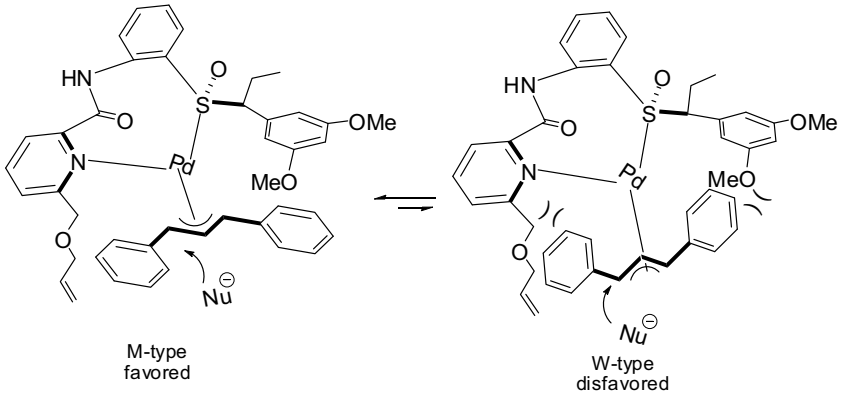


Fig. 3. Transition states in catalytic process.

to sulfur of M-type intermediate; and it thus gives the allylic product with *R* configuration [19b].

3. Conclusion

In conclusion, we have developed a new entrance to chiral *o*-aniline sulfoxides, which are used for the synthesis of chiral sulfoamide pyridine ligands. These ligands are effective for Pd-catalyzed allylic substitutions of dimethyl 2-fluoromalonate, which furnished monofluorinated allylic compounds in moderate yields with up to excellent enantioselectivity. This is the first example for the synthesis of multiple chiral *o*-aniline sulfoxides, which can serve as a new chiral sulfurous source for the synthesis of various *S*-ligands.

4. Experimental

4.1. General

All manipulations were carried out under the argon atmosphere using standard Schlenk techniques. All glassware was oven or flame dried immediately prior to use. All solvents were purified and dried according to standard methods prior to use, unless stated otherwise.

All reagents were obtained from commercial sources and used without further purification. ^{1}H NMR spectra were obtained at 400 MHz and recorded relative to tetramethylsilane signal (0 ppm) or residual protio-solvent. ^{13}C NMR spectra were obtained at 100 MHz and chemical shifts were recorded relative to the solvent resonance ($CDCl_3$, 77.0 ppm). Data for ^{1}H NMR are recorded as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet or unresolved, br = broad singlet, coupling constant(s) in Hz, integration). Data for ^{13}C NMR are reported in terms of chemical shift (δ, ppm).

4.2. General procedure for the synthesis of sulfoxide **5** and **5′**

To a solution of **4** (2.0 mmol) in DCM (10 mL) were added 3-chlorobenzoperoxoic acid (2.0 mmol) at 30 °C. The reaction was carried out 30 min with TLC-followed. Then the mixture was quenched by 10% $Na_2S_2O_4$ and sat. $NaHCO_3$ and extracted by DCM. The organic layer was washed with brine, dried by Na_2SO_4 and then concentrated. The crude residue was purified by flash column chromatography to give the desired products **5** and **5′**.

4.2.1. 2-((R)-((R)-1-Phenylpropyl)sulfinyl)aniline (**5a**)

White solid; mp: 95.1–95.9 °C; 26% yield; 96% *ee*. The *ee* of the product was determined by chiral HPLC [Daicel CHIRALCEL AD-H (0.46 cm × 25 cm); hexane/2-propanol = 90/10; flow rate = 1.2 mL/min; detection wavelength = 214 nm; t_R = 20.215 (minor), 31.227 (major) min]; $[\alpha]_D^{20}$ = +320.1° (c 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.33–7.25 (m, 3H), 7.18–7.10 (m, 3H), 7.00-6.95 (d, *J* = 7.6 Hz, 1H), 6.63 (t, *J* = 7.6 Hz, 1H), 6.56 (d, *J* = 8.0 Hz, 1H), 4.74 (br, 2H), 4.17 (dd, *J* = 5.6, 5.6 Hz, 1H), 2.02–1.93 (m, 2H), 0.87 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 147.5, 133.5, 131.9, 129.4, 128.2, 128.0, 127.4, 120.8, 117.0, 117.0, 68.3, 22.0, 11.6 ppm. IR (KBr): ν_{max} (cm^{-1}) = 3360, 3205, 3006, 2969, 2922, 2882, 1296, 1273, 1001, 743, 656. HRMS (ESI+) calcd for $C_{15}H_{17}NNaOS$ $[M+Na]^+$: 282.0923, Found: 282.0919

4.2.2. 2-((S)-((R)-1-Phenylpropyl)sulfinyl)aniline (**5a′**)

White solid; mp: 111.2–112.1 °C; 58% yield; 96% *ee*. The *ee* of the product was determined by chiral HPLC [Daicel CHIRALCEL AD-H (0.46 cm × 25 cm); hexane/2-propanol = 90/10; flow rate = 1.0 mL/min; detection wavelength = 214 nm; t_R = 15.449 (major), 17.066 (minor) min]; $[\alpha]_D^{20}$ = +303.3° (c 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.18–7.14 (m, 3H), 7.09 (dt, *J* = 6.8, 1.6 Hz, 1H), 7.00–6.93 (m, 2H), 6.59 (d, *J* = 8.0 Hz, 1H), 6.42 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.35 (dt, *J* = 8.0, 0.8 Hz, 1H), 5.01 (br, 2H), 4.49 (dd, *J* = 12.0, 12.0 Hz, 1H), 2.58-2.48 (m, 1H), 2.16–2.04 (m, 1H), 0.95 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 147.9, 133.9, 131.8, 128.7, 128.1, 127.8, 119.8, 116.8, 116.2, 116.2, 67.4, 22.2, 11.4 ppm. IR (KBr): ν_{max} (cm^{-1}) = 3365, 3200, 3006, 2969, 2922, 2852, 1276, 1253, 1001, 773, 726. HRMS (ESI+) calcd for $C_{15}H_{17}NNaOS$ $[M+Na]^+$: 282.0923, Found: 282.0921.

4.2.3. 2-((S)-((S)-1-(3, 5-Dimethoxyphenyl)propyl)sulfinyl)aniline (**5b**)

Thickness oil; 24% yield; 94% *ee*. The *ee* of the product was determined by chiral HPLC [Daicel CHIRALCEL OD-H (0.46 cm × 25 cm); hexane/2-propanol = 80/20; flow rate = 1.0 mL/min; detection wavelength = 214 nm; t_R = 13.402 (minor), 17.541 (major) min]; $[\alpha]_D^{20}$ = −284.1° (c 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.18 (dt, *J* = 8.0, 1.2 Hz, 1H), 7.02 (dd, *J* = 7.6, 1.2 Hz, 1H), 6.67 (dt, *J* = 7.6, 0.8 Hz, 1H), 6.60 (d, *J* = 8.0 Hz, 1H), 6.41 (s, 1H), 6.33-6.32 (m, 2H), 4.52 (br, 2H), 4.12 (dd, *J* = 10.0, 10.0 Hz, 1H), 3.71 (s, 6H), 1.94-1.85 (m, 2H), 0.87 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.5, 147.7, 136.0, 132.0, 127.7, 120.9, 117.1, 117.0, 107.3, 100.3, 68.6, 55.1, 22.0, 11.5 ppm. IR (KBr): ν_{max} (cm^{-1}) = 3445, 3322, 3220, 2969, 2938, 2857, 1470, 1205, 1150, 1061, 1009, 840, 758, 722. HRMS (ESI+) calcd for $C_{17}H_{21}NNaO_3S$ $[M+Na]^+$: 342.1134, Found: 342.1131.

4.2.4. 2-((R)-((S)-1-(3, 5-Dimethoxyphenyl)propyl)sulfinyl)aniline (**5b′**)

Thickness oil; 60% yield; 99.9% ee (after crystallization). The *ee* of the product was determined by chiral HPLC [Daicel CHIRALCEL OD-H (0.46 cm × 25 cm); hexane/2-propanol = 80/20; flow rate = 1.0 mL/min; detection wavelength = 214 nm; t_R = 7.785 (minor), 19.836 (major) min]; $[\alpha]_D^{20}$ = −255.3° (c 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.11 (dt, *J* = 8.0, 1.2 Hz, 1H), 6.62 (d, *J* = 8.4 Hz, 1H), 6.52 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.42 (dt, *J* = 7.6, 1.2 Hz, 1H), 6.28 (s, 1H), 6.10–6.09 (m, 2H), 4.67 (br, 2H), 4.41 (dd, *J* = 12.0, 12.0 Hz, 1H), 3.62 (s, 6H), 2.54–2.45 (m, 1H), 2.12–2.00 (m, 1H), 0.98 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.5, 147.8, 136.3, 132.0, 128.5, 120.6, 117.0, 116.8, 106.8, 100.3, 67.8, 55.2, 22.3, 11.5 ppm. IR (KBr): ν_{max} (cm^{-1}) = 3440, 3323, 3220, 2996, 2965, 2938, 2871, 2835, 1470, 1206, 1147, 1067, 1009, 839, 758, 722. HRMS (ESI+) calcd for $C_{17}H_{21}NNaO_3S$ $[M+Na]^+$: 342.1134, Found: 342.1132.

4.2.5. 2-((S)-((S)-1-(Furan-3-yl)propyl)sulfinyl)aniline (**5c**)

Thickness oil; 16% yield; 94% *ee*. The *ee* of the product was determined by chiral HPLC [Daicel CHIRALCEL AD-H (0.46 cm × 25 cm); hexane/2-propanol = 90/10; flow rate = 1.2 mL/min; detection wavelength = 214 nm; t_R = 21.742 (major), 25.416 (minor) min]; $[\alpha]_D^{20}$ = −27.5° (c 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.40 (s, 1H), 7.27 (s, 1H), 7.21 (dt, *J* = 8.4, 1.2 Hz, 1H), 7.04 (dd, *J* = 8.0, 1.2 Hz, 1H), 6.71 (dt, *J* = 7.6, 0.8 Hz, 1H), 6.20 (d, *J* = 8.0 Hz, 1H), 6.27 (s, 1H), 4.40 (dd, *J* = 9.2, 9.2 Hz, 1H), 3.65 (br, 2H), 1.97–1.79 (m, 2H), 0.96 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 147.8, 143.1, 142.2, 132.1, 127.7, 121.0, 118.2, 117.3, 117.2, 110.2, 60.7, 22.2, 11.8 ppm. IR (KBr): ν_{max} (cm^{-1}) = 3426, 3333, 3221, 3062, 2969, 2876, 1323, 1267, 1160, 1020, 870, 759, 605, 521. HRMS (ESI+) calcd for $C_{13}H_{15}NNaO_2S$ $[M+Na]^+$: 272.0716, Found: 272.0712.

4.2.6. 2-((R)-((S)-1-(Furan-3-yl)propyl)sulfinyl)aniline (**5c′**)

Thickness oil; 62% yield; $[\alpha]_D^{20}$ = −27.4° (c 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.28 (s, 1H), 7.16 (dt, *J* = 8.4, 1.2 Hz, 1H), 6.96 (s, 2H), 6.71 (dd, *J* = 8.0, 1.6 Hz, 1H), 6.63 (d, *J* = 8.0 Hz, 1H), 6.52 (t, *J* = 7.6 Hz, 1H), 6.09 (s, 1H), 5.08 (br, 2H), 4.44 (dd, *J* = 12.0, 12.0 Hz, 1H), 2.50–2.40 (m, 1H), 1.96–1.85 (m, 1H), 1.2 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 148.0, 143.1, 141.9, 132.2, 128.9, 120.4, 118.6, 117.1, 116.6, 109.6, 58.7, 22.4, 11.5 ppm. IR (KBr): ν_{max}

(cm^{-1}) = 3421, 3319, 3197, 3067, 2964, 2936, 2871, 1258, 1010, 866, 796, 749, 605, 530. HRMS (ESI+) calcd for $C_{13}H_{15}NNaO_2S$ $[M+Na]^+$: 272.0716, Found: 272.0715.

*4.2.7. 2-((R)-sec-Butylsulfinyl)aniline (**5d**)*

Light yellow oil; 48% yield; 88% *ee*. The *ee* of the product was determined by chiral HPLC [Daicel CHIRALCEL AD-H (0.46 cm × 25 cm); hexane/2-propanol = 90/10; flow rate = 1.2 mL/min; detection wavelength = 214 nm; t_R = 13.208 (minor), 15.979 (major) min]; $[\alpha]_D^{20} = -83.1^\circ$ (c 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.25–7.18 (m, 2H), 6.76 (dt, *J* = 7.6, 1.2 Hz, 1H), 6.66 (d, *J* = 8.0 Hz, 1H), 4.86 (br, 2H), 3.29–3.21 (m, 1H), 1.68-1.55 (m, 1H), 1.47–1.38 (m, 1H), 1.36 (d, *J* = 6.8 Hz, 3H), 0.97 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 147.9, 132.1, 128.0, 120.8, 117.4, 117.2, 57.3, 23.6, 12.3, 11.0 ppm. IR (KBr): ν_{max} (cm^{-1}) = 3431, 3324, 3207, 3022, 2969, 2922, 2875,1155, 1062, 1001, 759, 717, 525. HRMS (ESI+) calcd for $C_{10}H_{15}NNaOS$ $[M+Na]^+$: 220.0767, Found: 220.0768.

*4.2.8. 2-((S)-sec-Butylsulfinyl)aniline (**5d'**)*

Light yellow oil; 25% yield; 93% *ee*. The *ee* of the product was determined by chiral HPLC [Daicel CHIRALCEL AD-H (0.46 cm × 25 cm); hexane/2-propanol = 90/10; flow rate = 1.2 mL/min; detection wavelength = 214 nm; t_R = 12.301 (major), 13.549 (minor) min]; $[\alpha]_D^{20} = +107.3^\circ$ (c 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.24 (dt, *J* = 1.2, 8.0 Hz, 1H), 6.76 (dd, *J* = 7.6, 1.2 Hz, 1H), 6.72 (dt, *J* = 7.6, 0.8 Hz, 1H), 6.67 (dd, *J* = 8.0, 0.8 Hz, 1H), 5.02 (br, 2H), 3.52–3.44 (m, 1H), 2.15–2.04 (m, 1H), 1.67–1.60 (m, 1H), 1.07 (t, *J* = 7.2 Hz, 3H), 0.99 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 148.3, 132.3, 128.8, 1120.4, 117.4, 117.0, 56.0, 23.0, 13.0, 10.4 ppm. IR (KBr): ν_{max} (cm^{-1}) = 3421, 3309, 3197, 2969, 2922, 2857, 1309, 1001, 749, 721, 530. HRMS (ESI+) calcd for $C_{10}H_{15}NNaOS$ $[M+Na]^+$: 220.0767, Found: 220.0769.

*4.3. General procedure for the synthesis of new chiral sulfonamide-pyridine ligands **6***

An oven-dried round-bottomed flask equipped with a magnetic stir bar was charged with KH (0.5 mmol, 30% in mineral oil) and 3 mL of THF under argon atmosphere, the mixture was cool at −40 °C for 10 min, and **5′** (0.5 mmol) was added; and the mixture was stirred at −40 °C for 1 h. Then methyl 6-((allyloxy)methyl) picolinate (0.51 mmol) was added and stirred for another 1 h. The crude residue was concentrated in vacuo and purified by flash column chromatography (hexane/ethyl acetate) to provide the desired products **6**.

*4.3.1. 6-(Allyloxymethyl)-N-(2-((S)-((R)-1-phenylpropyl)sulfinyl) phenyl)picolinamide (**6a**)*

Thickness oil; 81% yield; $[\alpha]_D^{20} = -55.7^\circ$ (c 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ = 11.7 (br, 1H), 8.61 (d, *J* = 8.4 Hz, 1H), 8.13 (d, *J* = 7.6 Hz, 1H), 7.93 (t, *J* = 8.0 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 1H), 7.44 (t, *J* = 8.0 Hz, 1H), 7.10–6.91 (m, 5H), 6.86 (d, *J* = 7.6 Hz, 1H), 6.02 (ddt, *J* = 16.0, 10.4, 6.4 Hz, 1H), 5.40 (d, *J* = 17.2 Hz, 1H), 5.27 (d, *J* = 10.4 Hz, 1H), 4.84–4.76 (m, 2H), 4.20 (d, *J* = 5.6 Hz, 2H), 4.13 (dd, *J* = 11.2, 11.2 Hz, 1H), 2.59–2.47 (m, 1H), 2.13–2.03 (m, 1H), 0.89 (t, *J* = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 162.77, 157.8, 148.9, 138.9, 138.0, 134.2, 132.9, 132.2, 128.9, 128.3, 127.3, 123.9, 123.0, 121.7, 121.0, 117.3, 72.6, 71.9, 71.4, 22.3, 11.6 ppm. IR (KBr): ν_{max} (cm^{-1}) = 3450, 3053, 2964, 2932, 2880, 2848, 1682, 1575, 1318, 1020, 754, 698. HRMS (ESI+) calcd for $C_{25}H_{26}NaN_2O_3$ $[M+Na]^+$: 457.1556, Found: 457.1558.

*4.3.2. 6-(Allyloxymethyl)-N-(2-((R)-((S)-1-(3, 5-dimethoxyphenyl) propyl)sulfinyl)phenyl)picolinamide (**6b**)*

Thickness oil; 87% yield; 97% *ee*. The *ee* of the product was determined by chiral HPLC [Daicel CHIRALCEL AD-H (0.46 cm × 25 cm); hexane/2-propanol = 80/20; flow rate = 1.0 mL/min; detection wavelength = 214 nm; t_R = 7.395 (minor), 9.060 (major) min]; $[\alpha]_D^{20} = -105.0^\circ$ (c 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ = 11.6 (br, 1H), 8.63 (d, *J* = 8.0 Hz, 1H), 8.11 (d, *J* = 7.6 Hz, 1H), 7.92 (t, *J* = 8.0 Hz, 1H), 7.70 (d, *J* = 7.6 Hz, 1H), 7.46 (t, *J* = 8.8 Hz, 1H), 7.15 (d, *J* = 7.6 Hz, 1H), 7.03 (t, *J* = 7.6 Hz, 1H), 6.14 (t, *J* = 2.4 Hz, 1H), 6.03 (ddt, *J* = 16.0, 10.4, 5.2 Hz, 1H), 6.00 (d, *J* = 2.4 Hz, 2H), 5.37 (d, *J* = 17.2 Hz, 1H), 5.26 (d, *J* = 10.4 Hz, 1H), 4.84–4.76 (m, 2H), 4.20 (dt, *J* = 5.2, 1.6 Hz, 2H), 4.02 (dd, *J* = 11.2, 11.6 Hz, 1H), 3.46 (s, 6H), 2.56–2.46 (m, 1H), 2.13–1.97 (m, 1H), 0.93 (t, *J* = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 162.6, 160.5, 158.1, 148.8, 139.1, 138.0, 134.9, 134.4, 132.1, 127.8, 127.2, 123.8, 123.2, 121.6, 120.9, 117.3, 107.0, 100.2, 72.6, 72.2, 71.9, 22.3, 11.6 ppm. IR (KBr): ν_{max} (cm^{-1}) = 3448, 3090, 3002, 2969, 2918, 2852, 1514, 1150, 1211, 1066, 1020, 926, 824, 749. HRMS (ESI+) calcd for $C_{27}H_{30}NaN_2O_3$ $[M+Na]^+$: 517.1768, Found: 517.1765.

*4.3.3. 6-(Allyloxymethyl)-N-(2-((R)-((S)-1-(furan-3-yl)propyl) sulfinyl)phenyl)picolinamide (**6c**)*

Thickness oil; 82% yield; $[\alpha]_D^{20} = -47.8^\circ$ (c 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ = 11.8 (br, 1H), 8.66 (d, *J* = 8.4 Hz, 1H), 8.15 (d, *J* = 8.0 Hz, 1H), 7.93 (t, *J* = 7.6 Hz, 1H), 7.70 (d, *J* = 7.6 Hz, 1H), 7.50 (t, *J* = 8.4 Hz, 1H), 7.17–7.15 (m, 2H), 7.07 (t, *J* = 8.4 Hz, 1H), 7.00 (s, 1H), 6.03 (ddt, *J* = 16.0, 10.8, 5.6 Hz, 1H), 6.00 (d, *J* = 1.2 Hz, 1H), 5.38 (d, *J* = 17.2 Hz, 1H), 5.26 (dd, *J* = 10.4, 1.2 Hz, 1H), 4.82–4.75 (m, 2H), 4.19 (dt, *J* = 5.6, 1.6 Hz, 2H), 4.00 (dd, *J* = 11.2, 11.2 Hz, 1H), 2.48–2.38 (m, 1H), 1.92–1.84 (m, 1H), 0.96 (t, *J* = 7.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 162.8, 157.8, 148.9, 143.3, 142.0, 139.1, 138.0, 134.2, 132.4, 127.7, 127.2, 124.0, 123.1, 122.0, 121.0, 117.6, 117.3, 109.5, 72.6, 71.9, 62.5, 22.3, 11.5 ppm. IR (KBr): ν_{max} (cm^{-1}) = 3560, 3058, 2974, 2918, 2852, 1687, 1514, 1051, 1015, 870, 749. HRMS (ESI+) calcd for $C_{23}H_{24}NaN_2O_4$ $[M+Na]^+$: 447.1349, Found: 447.1346.

*4.3.4. 6-(Allyloxymethyl)-N-(2-((R)-sec-butylsulfinyl)phenyl) picolinamide (**6d**)*

Thickness oil; 88% yield; $[\alpha]_D^{20} = -8.3^\circ$ (c 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ = 12.0 (br, 1H), 8.72 (d, *J* = 8.4 Hz, 1H), 8.16 (d, *J* = 7.6 Hz, 1H), 7.92 (t, *J* = 8.0 Hz, 1H), 7.70 (d, *J* = 7.6 Hz, 1H), 7.56 (t, *J* = 8.4 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.20 (t, *J* = 8.4 Hz, 1H), 6.00 (ddt, *J* = 16.0, 10.8, 5.6 Hz, 1H), 6.00 (d, *J* = 1.2 Hz, 1H), 5.37 (d, *J* = 17.2 Hz, 1H), 5.25 (d, *J* = 10.4 Hz, 1H), 4.80–4.72 (m, 2H), 4.16 (d, *J* = 5.6 Hz, 2H), 3.28–3.19 (m, 1H), 2.12–2.02 (m, 1H), 1.72–1.61 (m, 1H), 1.03–0.99 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 163.0, 158.0, 148.8, 139.1, 138.1, 134.2, 132.4, 127.9, 127.3, 124.0, 123.4, 122.3, 121.1, 117.3, 72.6, 71.9, 58.8, 22.8, 12.7, 10.5 ppm. IR (KBr): ν_{max} (cm^{-1}) = 3557, 3193, 2978, 2848, 2922, 1533, 1034, 917, 824, 754. HRMS (ESI+) calcd for $C_{20}H_{24}NaN_2O_3$ $[M+Na]^+$: 395.1400, Found: 395.1403.

4.3.5. N-*(2-((R-((S)-1-Phenylpropyl)sulfinyl) phenyl)picolinamide (**6f**)*

Thickness oil; 86% yield. $[\alpha]_D^{20} = +43.9^\circ$ (c 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ = 11.58 (br, 1H), 8.73 (d, *J* = 4.4 Hz, 1H), 8.56 (d, *J* = 8.4 Hz, 1H), 8.23 (d, *J* = 6.8 Hz, 1H), 7.91 (dt, *J* = 8.0, 1.6 Hz, 1H), 7.50 (t, *J* = 6.8 Hz, 1H), 7.44 (t, *J* = 7.2 Hz, 1H), 7.07 (d, *J* = 7.2 Hz, 1H), 7.03–6.96 (m, 4H), 6.88 (d, *J* = 7.6 Hz, 1H), 4.12 (dd, *J* = 11.2, 11.2 Hz, 1H), 2.56–2.51 (m, 1H), 2.13–2.04 (m, 1H), 0.90 (t, *J* = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 162.8, 149.8, 148.3, 138.9, 137.2, 132.9, 132.1, 129.4, 128.9, 128.3, 127.7, 127.2, 126.4, 123.2, 124.5, 122.0, 71.6, 22.4, 11.6 ppm. IR(KBr): $_{max}$ (cm^{-1}) = 3420, 3022, 2964, 2928, 2898, 2882, 2848, 1674, 1562, 1311, 1020, 755, 674. HRMS (ESI+) calcd for $C_{21}H_{20}NaN_2O_2S$ $[M+Na]^+$: 387.1138, Found: 387.1132.

4.4. General procedure for the Pd-catalyzed enantioselective allylic alkylations

$[Pd(C_3H_5)Cl]_2$ (0.004 mmol, 4 mol%), [6-(allyloxymethyl)-*N*-(2-((*R*)-((*S*)-1-(3,5-dimethoxyphenyl)propyl)sulfinyl)phenyl)picolinamide] (**6b**, 0.008 mmol, 8 mol%), and (*E*)-1,3-disubstituted allyl acetates **7** (0.1 mmol) were dissolved in THF (2.0 mL) in a dry Schlenk tube filled with argon. The reaction mixture was stirred for 30 min at room temperature. Then Cs_2CO_3 (3.0 equiv) and dimethyl 2-fluoromalonate **8** (0.3 mmol, 3.0 equiv) were added. After the completion of the reaction monitoring by TLC, the crude reaction mixture was filtrated with celite and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (petroleum ether/ethyl acetate) to give the desired products **9**.

4.4.1. (E)-Dimethyl 2-(1, 3-bis(3-fluorophenyl)allyl)-2-fluoromalonate (**9a**)

White solid; mp: 93.1–94.2 °C, 73% yield; 94% *ee*. The *ee* of the product was determined by chiral HPLC [Daicel CHIRALCEL AD-H (0.46 cm × 25 cm); hexane/2-propanol = 90/10, flow rate = 1.0 mL/min; detection wavelength = 214 nm; t_R = 11.056 (minor), 11.827 (major) min]; $[\alpha]_D^{20}$ = +21.7° (c 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.33–7.23 (m, 2H), 7.16 (d, *J* = 7.2 Hz, 1H), 7.12–7.10 (m, 2H), 7.05 (d, *J* = 8.0 Hz, 1H), 7.01–6.91 (m, 2H), 6.54 (d, *J* = 16.0 Hz, 1H), 6.42 (dd, *J* = 16.0, 8.8 Hz, 1H), 4.53 (dd, *J* = 30.4, 8.8 Hz, 1H), 3.83 (s, 3H), 3.64 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ = −112.2, −113.3, −175.6. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 165.3 (d, *J* = 25.3 Hz), 164.9 (d, *J* = 25.8 Hz), 163.0 (d, *J* = 244.3 Hz), 162.7 (d, *J* = 245.1 Hz), 138.8 (d, *J* = 7.1 Hz), 138.5 (d, *J* = 7.6 Hz), 133.6 (d, *J* = 2.5 Hz), 130.1 (dd, *J* = 8.2, 8.4 Hz), 125.4 (d, *J* = 4.5 Hz), 124.5 (dd, *J* = 2.5, 2.5 Hz), 122.4 (d, *J* = 2.7 Hz), 116.2 (d, *J* = 2.5 Hz), 116.0 (d, *J* = 2.6 Hz), 115.0 (d, *J* = 3.4 Hz), 114.8 (d, *J* = 4.1 Hz), 113.0 (d, *J* = 21.7 Hz), 97.1 (d, *J* = 208.9 Hz), 53.7, 53.3, 53.1 (d, *J* = 19.6 Hz) ppm. IR (KBr): $\nu\nu_{max}$ (cm^{-1}) = 3057, 2956, 2910, 2833, 1759, 1438, 1280, 1270, 1148, 1051, 970, 904, 746. HRMS (ESI+) calcd for $C_{20}H_{17}F_3NaO_4$ $[M+Na]^+$: 401.0971, Found: 401.0775.

4.4.2. (E)-Dimethyl 2-(1, 3-bis(3-chlorophenyl)allyl)-2-fluoromalonate (**9b**)

Thickness oil; 82% yield; 87% *ee*. The *ee* of the product was determined by chiral HPLC [Daicel CHIRALCEL AD-H (0.46 cm × 25 cm); hexane/2-propanol = 90/10, flow rate = 1.0 mL/min; detection wavelength = 214 nm; t_R = 11.409 (minor), 12.319 (major) min]; $[\alpha]_D^{20}$ = +61.2° (c 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.37 (s, 1H), 7.33 (s, 1H), 7.27–7.26 (m, 3H), 7.23–7.21 (m, 3H), 6.51 (d, *J* = 15.6 Hz, 1H), 6.41 (dd, *J* = 15.6, 8.8 Hz, 1H), 4.50 (dd, *J* = 30.8, 8.8 Hz, 1H), 3.83 (s, 3H), 3.65 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ = −175.5. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 165.3 (d, *J* = 25.3 Hz), 164.9 (d, *J* = 25.6 Hz), 138.4, 138.0, 134.6, 134.5, 133.5, 129.9, 129.8, 129.3 (d, *J* = 2.4 Hz), 128.2, 128.1, 127.2 (d, *J* = 2.4 Hz), 126.4, 125.5 (d, *J* = 5.5 Hz), 124.8, 97.0 (d, *J* = 208.9 Hz), 53.7, 53.4, 53.4 (d, *J* = 18.4 Hz) ppm. IR (KBr): ν_{max} (cm^{-1}) = 3062, 3016, 2960, 2927, 1756, 1598, 1561, 1435, 1262, 1141, 1048, 959, 787, 703. HRMS (ESI+) calcd for $C_{20}H_{17}Cl_2FNaO_4$ $[M+Na]^+$: 433.0380, Found: 433.0381.

4.4.3. (E)-Dimethyl 2-(1, 3-bis(3-bromophenyl)allyl)-2-fluoromalonate (**9c**)

White solid; mp: 93.1–93.9 °C; 74% yield; 81% *ee*. The *ee* of the product was determined by chiral HPLC [Daicel CHIRALCEL AD-H (0.46 cm × 25 cm); hexane/2-propanol = 90/10, flow rate = 1.0 mL/min; detection wavelength = 214 nm; t_R = 11.602 (minor), 12.944 (major) min]; $[\alpha]_D^{20}$ = +61.2° (c 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.54–7.49 (m, 2H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.36 (d, *J* = 7.6 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.25–7.15 (m, 3H), 6.50 (d, *J* = 15.6 Hz, 1H), 6.40 (dd, *J* = 16.0, 8.8 Hz, 1H), 4.49 (dd, *J* = 30.8, 8.8 Hz, 1H), 3.83 (s, 3H), 3.65 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ = −175.5. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 165.2 (d, *J* = 25.3 Hz), 164.8 (d, *J* = 25.6 Hz), 138.6, 138.3, 133.4, 132.1 (d, *J* = 2.3 Hz), 131.1, 131.0, 130.3, 130.1, 129.3, 127.7 (d, *J* = 2.5 Hz), 125.5 (d, *J* = 5.4 Hz), 125.2, 122.8, 122.6, 97.0 (d, *J* = 209.0 Hz), 53.7, 53.4, 53.2 (d, *J* = 18.3 Hz) ppm. IR (KBr): ν_{max} (cm^{-1}) = 3053, 2997, 2969, 2927, 2848, 1766, 1593, 1561, 1477, 1467, 1435, 1248, 1141, 1043, 973, 777, 703, 614. HRMS (ESI+) calcd for $C_{20}H_{17}Br_2FNaO_4$ $[M+Na]^+$: 520.9370, Found: 520.9369.

4.4.4. (E)-Dimethyl 2-(1, 3-bis(4-fluorophenyl)allyl)-2-fluoromalonate (**9d**)

White solid; mp: 91.4–92.3 °C; 70% yield; 80% *ee*. The *ee* of the product was determined by chiral HPLC [Daicel CHIRALCEL AD-H (0.46 cm × 25 cm); hexane/2-propanol = 90/10, flow rate = 1.0 mL/min; detection wavelength = 214 nm; t_R = 16.966 (major), 18.703 (minor) min]; $[\alpha]_D^{20}$ = +59.3° (c 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.37–7.26 (m, 4H), 7.04–6.96 (m, 4H), 6.51 (d, *J* = 15.6 Hz, 1H), 6.33 (dd, *J* = 15.6, 9.2 Hz, 1H), 4.51 (dd, *J* = 30.8, 9.2 Hz, 1H), 3.83 (s, 3H), 3.62 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ = −113.6, −114.2, −176.1. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 165.4 (d, *J* = 25.1 Hz), 165.1 (d, *J* = 25.7 Hz), 162.5 (d, *J* = 246.1 Hz), 162.3 (d, *J* = 245.3 Hz), 133.2, 132.4 (d, *J* = 3.3 Hz), 130.8, 130.7, 128.1, 128.0, 124.2, 115.6 (d, *J* = 8.5 Hz), 115.4 (d, *J* = 9.1 Hz), 97.0 (d, *J* = 208.4 Hz), 53.5, 53.2, 52.9 (d, *J* = 18.4 Hz) ppm. IR (KBr): ν_{max} (cm^{-1}) = 3048, 3006, 2960, 2908, 2843, 1770, 1598, 1509, 1439, 1230, 1169, 1057, 978, 838, 740, 521, 507. HRMS (ESI+) calcd for $C_{20}H_{17}F_3NaO_4$ $[M+Na]^+$: 401.0971, Found: 401.0774.

4.4.5. (E)-Dimethyl 2-(1, 3-bis(4-chlorophenyl)allyl)-2-fluoromalonate (**9e**)

White solid; mp: 102.1–102.5 °C; 71% yield; 81% *ee*. The *ee* of the product was determined by chiral HPLC [Daicel CHIRALCEL AD-H (0.46 cm × 25 cm); hexane/2-propanol = 90/10, flow rate = 1.0 mL/min; detection wavelength = 214 nm; t_R = 14.625 (major), 16.354 (minor) min]; $[\alpha]_D^{20}$ = +65.6° (c 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.34–7.31 (m, 4H), 7.29–7.25 (m, 4H), 6.51 (d, *J* = 16.4 Hz, 1H), 6.39 (dd, *J* = 16.0, 8.8 Hz, 1H), 4.52 (dd, *J* = 30.8, 8.8 Hz, 1H), 3.83 (s, 3H), 3.63 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ = −175.7. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 165.2 (d, *J* = 25.4 Hz), 164.8 (d, *J* = 25.7 Hz), 134.9, 134.7, 133.8, 133.6, 133.3, 130.4, 130.3, 128.8, 128.6, 127.7, 124.8 (d, *J* = 4.3 Hz), 97.0 (d, *J* = 208.9 Hz), 53.5, 53.2, 52.9 (d, *J* = 18.4 Hz) ppm. IR (KBr): ν_{max} (cm^{-1}) = 3025, 3002, 2950, 2922, 2852, 1756, 1281, 1481, 1262, 1099, 978, 833, 763, 754, 511. HRMS (ESI+) calcd for $C_{20}H_{17}Cl_2FNaO_4$ $[M+Na]^+$: 433.0380, Found: 433.0385.

4.4.6. (E)-Dimethyl 2-(1, 3-bis(4-bromophenyl)allyl)-2-fluoromalonate (**9f**)

White solid; mp: 71.5–72.6 °C; 78% yield; 83% *ee*. The *ee* of the product was determined by chiral HPLC [Daicel CHIRALCEL AD-H (0.46 cm × 25 cm); hexane/2-propanol = 80/20, flow rate = 1.0 mL/min; detection wavelength = 214 nm; t_R = 17.997 (major), 21.487 (minor) min]; $[\alpha]_D^{20}$ = +27.3° (c 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.46 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.8 Hz, 2H), 7.25 (d, *J* = 6.4 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 6.49 (d, *J* = 15.6 Hz, 1H), 6.38 (dd, *J* = 15.6, 8.8 Hz, 1H), 4.49 (dd, *J* = 31.2, 8.8 Hz, 1H), 3.82 (s, 3H), 3.64 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ = −175.8. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 165.3 (d, *J* = 25.1 Hz), 164.9 (d, *J* = 25.7 Hz), 135.5, 135.1, 133.5, 131.9, 131.7, 130.8, 130.7, 128.0, 124.9 (d, *J* = 4.5 Hz), 122.1, 121.9, 97.0 (d, *J* = 208.7 Hz), 53.7, 53.4, 53.1 (d, *J* = 18.5 Hz) ppm. IR (KBr): ν_{max} (cm^{-1}) = 3039, 2964, 2927, 2843, 176, 1486, 1258, 1155, 1076, 1048, 1015, 964, 768, 563, 511. HRMS (ESI+) calcd for $C_{20}H_{17}Br_2FNaO_4$ $[M+Na]^+$: 520.9370, Found: 520.9374.

*4.4.7. (E)-Dimethyl 2-(1, 3-diphenylallyl)-2-fluoromalonate (**9g**) [4]*

White solid; 73% yield; 88% *ee*. The *ee* of the product was determined by chiral HPLC [Daicel CHIRALCEL AD-H (0.46 cm × 25 cm); hexane/2-propanol = 90/10, flow rate = 1.0 mL/min; detection wavelength = 214 nm; t_R = 13.931 (major), 16.480 (minor) min]; $[\alpha]_D^{20}$ = +24.4° (c 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.40–7.38 (m, 2H), 7.36–7.32 (m, 4H), 7.30–7.27 (m, 3H), 7.24–7.21 (m, 1H), 6.58 (d, *J* = 16.0 Hz, 1H), 6.46 (dd, *J* = 16.0, 8.8 Hz, 1H), 4.53 (dd, *J* = 31.6, 8.8 Hz, 1H), 3.82 (s, 3H), 3.61 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ = −175.9. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 165.6 (d, *J* = 25.5 Hz), 165.1 (d, *J* = 25.8 Hz), 136.9, 136.5, 134.3, 129.1, 129.0, 128.5, 127.8, 127.8, 126.5, 124.6 (d, *J* = 3.5 Hz), 97.5 (d, *J* = 208.5 Hz), 53.8 (d, *J* = 18.3 Hz), 53.5, 53.2 ppm.

*4.4.8. (E)-Dimethyl 2-(1, 3-bis(3-fluorophenyl)allyl)-2-fluoromalonate (**9h**)*

White solid; mp: 102.2–103.4 °C; 70% yield; 91% *ee*. The *ee* of the product was determined by chiral HPLC [Daicel CHIRALCEL AD-H (0.46 cm × 25 cm); hexane/2-propanol = 90/10, flow rate = 1.0 mL/min; detection wavelength = 214 nm; t_R = 29.258 (major), 35.442 (minor) min]; $[\alpha]_D^{20}$ = +45.0° (c 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.90 (s, 1H), 7.86–7.80 (m, 3H), 7.78–7.74 (m, 3H), 7.69 (s, 1H), 7.59–7.55 (m, 2H), 7.48–7.41 (m, 4H), 6.77 (d, *J* = 15.6 Hz, 1H), 6.68 (dd, *J* = 16.0, 8.8 Hz, 1H), 4.77 (dd, *J* = 31.6, 8.8 Hz, 1H), 3.85 (s, 3H), 3.57 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ = −175.4. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 165.7 (d, *J* = 25.4 Hz), 165.2 (d, *J* = 25.7 Hz), 134.6, 134.2, 133.9, 133.4, 133.3, 133.1, 132.8, 128.4, 128.2, 128.0, 127.9, 127.6, 127.5, 126.9, 126.9, 126.6, 126.3, 126.1, 126.1, 126.0, 124.9 (d, *J* = 4.4 Hz), 123.5, 97.9 (d, *J* = 208.5 Hz), 54.0 (d, *J* = 18.3 Hz), 53.6, 53.3 (d, *J* = 18.5 Hz) ppm. IR (KBr): ν_{max} (cm^{-1}) = 3057, 2951, 2925, 2844, 1759, 1265, 1133, 1036, 970, 919, 827, 751, 481. HRMS (ESI+) calcd for $C_{28}H_{23}FNaO_4$ $[M+Na]^+$: 465.1473, Found: 465.1470.

*4.4.9. (E)-Dimethyl 2-(1,3-di-m-tolylallyl)-2-fluoromalonate (**9i**)*

White solid; mp: 97.5–98.6 °C; 75% yield; 77% *ee*. The *ee* of the product was determined by chiral HPLC. [Daicel CHIRALCEL AD-H (0.46 cm × 25 cm); hexane/2-propanol = 90/10, flow rate = 1.0 mL/min; detection wavelength = 214 nm; t_R = 7.983 (major), 8.740 (minor) min]; $[\alpha]_D^{20}$ = +45.3° (c 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.18–7.14 (m, 6H), 7.07–7.03 (m, 2H), 6.54 (d, *J* = 15.6 Hz, 1H), 6.48–6.41 (m, 1H), 4.48 (dd, *J* = 31.2, 8.4 Hz, 1H), 3.80 (s, 3H), 3.60 (s, 3H), 2.32 (s, 3H), 2.31 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ = −175.7. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 165.6 (d, *J* = 25.5 Hz), 165.1 (d, *J* = 25.9 Hz), 138.0, 137.9, 136.6, 136.4, 134.1, 129.6 (d, *J* = 2.0 Hz), 128.5, 128.4, 128.3, 128.2, 127.0, 125.9 (d, *J* = 2.2 Hz), 124.4 (d, *J* = 4.5 Hz), 123.7, 97.0 (d, *J* = 208.0 Hz), 53.7 (d, *J* = 18.3 Hz), 53.4, 53.0, 21.3, 21.2 ppm. IR (KBr): ν_{max} (cm^{-1}) = 3045, 2969, 2925, 2843, 1766, 1480, 1244, 1153, 1070, 1048, 1015, 964, 777, 521. HRMS (ESI+) calcd for $C_{22}H_{23}FNaO_4$ $[M+Na]^+$:393.1473, Found: 393.1475.

*4.4.10. Ethyl (E)-2-acetyl-3,5-bis(4-chlorophenyl)-2-fluoropent-4-enoate (**9j**)*

White solid; mp: 121.3–122.4 °C; 74% yield; 94% *ee*; 1/1.2 dr. The *ee* of the product was determined by chiral HPLC [Daicel CHIRALCEL AD-H (0.46 cm × 25 cm); hexane/2-propanol = 95/5, flow rate = 0.8 mL/min; detection wavelength = 214 nm; t_R = 18.949 (major), 20.234 (minor) min]. $[\alpha]_D^{20}$ = +78.2° (c 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.35–7.29 (m, 8H), 7.26–7.24 (m, 8H), 6.51 (d, *J* = 15.6 Hz, 1H), 6.44–6.36 (m, 2H), 6.26 (dd, *J* = 15.6, 6.8 Hz, 1H), 4.58–4.55 (m, 1H), 4.50–4.47 (m, 1H), 4.32–4.21(m, 2H), 4.10–4.02 (m, 2H), 2.31 (d, *J* = 6.4 Hz, 3H), 1.98 (d, *J* = 6.4 Hz, 3H), 1.25 (t, *J* = 6.8 Hz, 3H), 1.06 (t, *J* = 7.2 Hz, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ = −174.7, −175.4. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 201.3(d, *J* = 29.5 Hz), 201.2 (d, *J* = 29.6 Hz), 164.6 (d, *J* = 27.9 Hz), 164.3 (d, *J* = 28.1 Hz), 135.6, 134.9, 134.7, 134.6, 133.8, 133.7, 133.4, 133.2, 130.7 (d, *J* = 2.3 Hz), 130.2(d, *J* = 2.7 Hz), 128.9, 128.8, 128.7, 128.7, 127.6, 127.6, 124.9 (d, *J* = 3.8 Hz), 124.8 (d, *J* = 5.0 Hz), 102.7 (d, *J* = 202.4 Hz), 102.6 (d, *J* = 206.1 Hz), 62.9, 62.7, 52.6(d, *J* = 18.1 Hz), 52.5 (d, *J* = 18.1 Hz), 26.8, 26.8, 14.1, 13.7 ppm. IR(KBr): ν_{max} (cm^{-1}) = 3063, 3022, 3006, 2950, 2928, 2855, 1731, 1756, 1280, 1262, 1181, 1090, 987, 863, 763, 754, 611. HRMS (ESI+) calcd for $C_{21}H_{19}Cl_2FNaO_3$ $[M+Na]^+$: 431.0587, Found: 431.0584.

*4.4.11. Synthesis of the allylic dicarboxylic acids (**10**)*

To a solution of **9e** (0.2 mmol) in the binary solvent composed of THF (3.0 mL) and H_2O (1.0 mL) was added $LiOH{\cdot}H_2O$ lithium hydroxide monohydrate (0.5 mmol). The mixture was stirred at 25 °C for 5 h and then poured into water (10 mL). After acidifying with diluted aqueous HCl solution, the precipitate was collected by filtration and washed with H_2O to give **10** (72.6 mg) as a light yellow solid. (*E*)-2-(1,3-Bis(4-chlorophenyl)allyl)-2-fluoromalonic acid (10): White solid; mp: 153.4 – 154.3 °C; 95% yield. $[\alpha]_D^{20}$ = +45.2° (c 0.5, $CHCl_3$). ^1H NMR (400 MHz, $(CD_3)_2SO$) δ = 13.95 (br, 2H), 7.46–7.35 (m, 8H), 6.62–6.52 (m, 2H), 4.49 (dd, *J* = 30.8, 7.6 Hz, 1H). ^{19}F NMR (376 MHz, $(CD_3)_2SO$) δ = −172.9. ^{13}C NMR (100 MHz, $(CD_3)_2SO$) δ = 166.3 (d, *J* = 25.8 Hz), 166.0 (d, *J* = 25.8 Hz), 136.7, 135.2, 132.2, 132.1, 131.1, 128.6, 128.3, 128.1, 126.4, 126.3, 96.5 (d, *J* = 202.6 Hz), 51.7 (d, *J* = 18.4 Hz) ppm. IR(KBr): ν_{max} (cm^{-1}) = 3650, 3062, 3022, 2960, 2852, 1710, 1655, 1281, 1120, 987, 833, 754. HRMS (ESI+) calcd for $C_{18}H_{12}Cl_2FO_4Na$ $[M+Na]^+$: 405.0067, Found: 405.0061.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jfluchem.2016.07.010.

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