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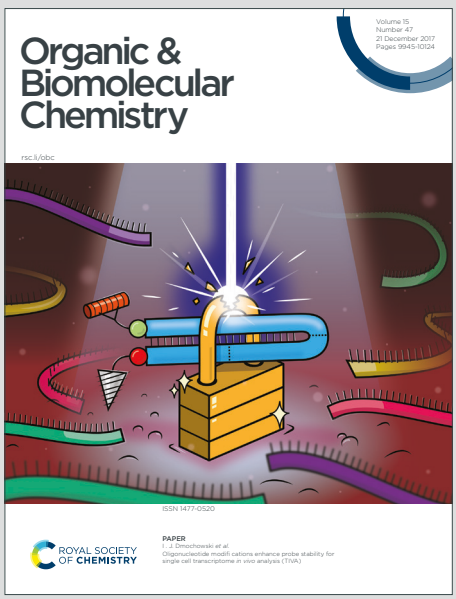

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ARTICLE

Squaramide-Catalyzed Asymmetric Mannich Reactions Between 3-Fluorooxindoles and Pyrazolinone Ketimines

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An Enantioselective Mannich reaction between 3-fluorooxindoles and pyrazolinone ketimines has been developed for the construction of amino-pyrazolone-oxindoles containing stereogenic C–F units. Depending on this new protocol that allows for the generation of two adjacent tetrasubstituted stereocenters, a variety of structurally diverse fluorinated amino-pyrazolone-oxindoles were obtained in good to excellent yields with excellent diastereoselectivities and enantioselectivities (up to 98% yield, >20:1 dr and >99% ee). What's more, good yield and high setreoselectivities were obtained in the gram-scale reaction.

Introduction

Pyrazolone is an important class of five-membered structural motif featuring two adjacent nitrogen atoms that has been widely found in various pharmaceuticals and agrochemicals.[1] Pyrazolone derivatives have been extensively used to synthesize a series of drugs such as anticancer, antimicrobial, antipyretic, HIV integrase inhibitors and anti-Alzheimer.[2] Therefore, new synthetic strategy for pyrazolone derivatives is always the focus that scientists dedicated to study.

On the other hand, as the atom with the strongest electronegativity and low polarizability, fluorine atom has significantly different physical and chemical properties compared with other atoms.[3] These unique properties can change the key factors of fluorinated compounds, such as solubility, lipophilicity and metabolic stability. Studies have shown that the introduction of fluorine atom into drug molecules can significantly alter the metabolic pathway and speed of the drugs, as well as improving the bioavailability and biological selection of the drugs.[4] For example, when the hydrogen atom is replaced by fluorine atom in the 9α position of the hydrocortisone, the biological activity of anti-inflammatory therapies can increase 10 times.[5] Consequently, organic-fluorine chemistry has an important position in the study of pharmaceuticals and agrochemicals.

Since Yuan and co-workers[6] reported the Michael addition reaction of pyrazolones with nitroolefins under the catalyst of chiral thiourea, the asymmetric synthesis of pyrazolones has been widely exploited in past decade.[7] Recently, Lu and co-workers[8] reported the one-pot Mannich reaction of pyrazolones to isatin ketimines and subsequent fluorination with N-fluorobenzenesulfonimide (NFSI) catalyzed by the porous carbon nanosheet-supported squaramide organocatalyst derived from quinine (Scheme 1a). Compared with fluorine substitution reaction, asymmetric reaction involving fluorine substituted substrates is an efficient way to construct fluorinated compounds with stereogenic C–F units. Among them, 3-fluorooxindoles are important nucleophiles that have been used in the asymmetric synthesis of fluorinated oxindole derivatives bearing stereogenic C–F units. More recently, our group[9] reported the squaramide-catalyzed enantioselective Mannich reaction between 3-fluorooxindoles and isatin-derived imines to synthesize the 3,3'-linked bisoxindoles containing stereogenic C–F units (Scheme 1b).

On account for the importance of fluorinated compounds and our recent research on bifunctional chiral squaramide organocatalysts to catalyze the asymmetric reactions for the synthesis of pyrazolones,[10] we reported herein a highly enantioselective Mannich reaction of 3-fluorooxindoles to pyrazolinone ketimines using chrial squaramide catalyst, which can afford the amino-pyrazolone-oxindole derivatives containing stereogenic C–F units with two adjacent tetrasubstituted stereocenters (Scheme 1c).

Results and discussion

In our initial investigation, we selected the Mannich reaction of pyrazolone-derived imine **1a** and 3-fluorooxindole **2a** as the model reaction. When **1a** and **2a** was added to the reaction with a ratio of 1:1, there was always a small amount of remaining **2a**. Thus, the molar ratio of **1a** to **2a** was changed to be 1.1:1. The model reaction was finished completely in CH_2Cl_2 with the presence of 10 mol% squaramide **C1** derived from quinine for 36 h at room temperature (25 °C). The corresponding product **3a** was obtained in high yield with high diastereoselectivity and

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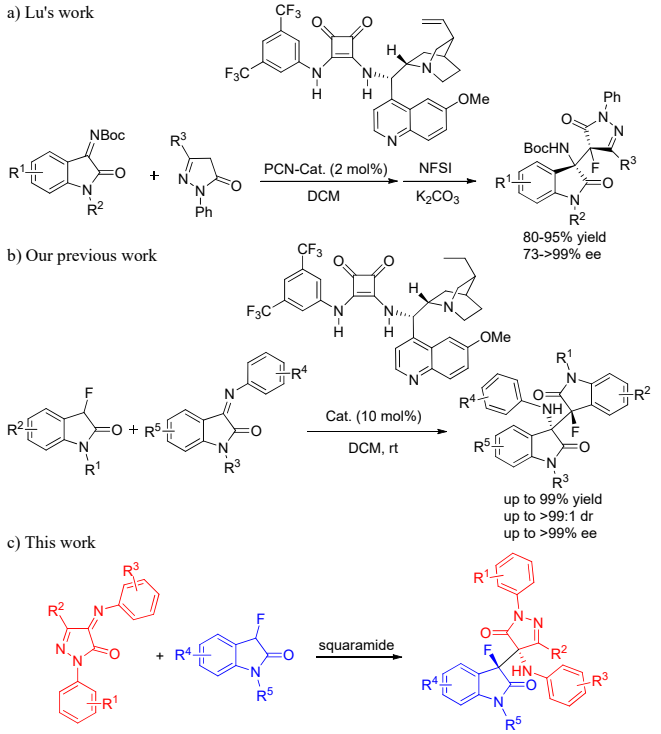
enantioselectivity (91% yield, 96:4 *dr* and 97% *ee*) (Table 1, entry 1).

Based on the above results, we continued to test a series of bifunctional squaramide catalyst with different privileged chiral scaffolds (Figure. 1). When (1*S*, 2*S*)-1,2-diaminocyclohexane-derived squaramide **C2** bearing 4-CF_3 group on the aromatic ring was used as catalyst, the yield and stereoselectivities of the target product dropped significantly (Table1, entry 2). Subsequently, five squaramide catalysts **C3**–**C7** derived from hydroquinine, cinchonidine or hydrocinchonidine were tested, the reaction results were better compared with the catalyst **C2** (Table1, entry 3–7). Among them, the squaramide catalyst **C5** derived from hydroquinine was the most efficient catalyst in both the yield (93%) and stereoselectivity (>99:1 *dr*, >99% *ee*) (Table1, entry 5). In addition, squaramide **C8** derived from quinidine could afford the product **3a** with moderate yield and opposite configuration (Table 1, entry 8).



Scheme 1 Asymmetric synthesis of fluorinated amino-pyrazolone-oxindoles.

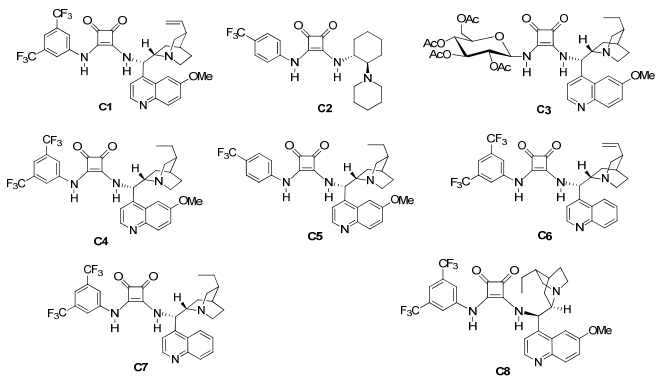
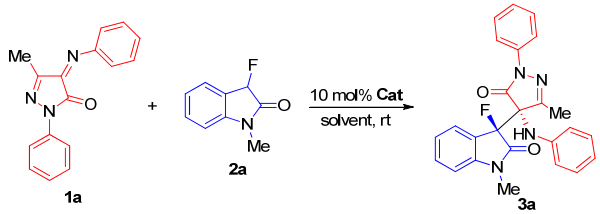


Fig. 1 Squaramide organocatalysts.

To further improve the yield of the product, we performed optimal conditions of solvent, catalyst loading and reaction temperature (Table 1, entries 9–17). Subsequent studies showed that the reaction solvent had significant influence on the reaction. When THF used as the solvent, the yield and stereoselectivities of the product **3a** reduced slightly (Table 1, entry 9). When $CHCl_3$, DCE or PhMe used as the solvent, both the yields and stereoselectivities of the product **3a** decreased significantly (Table 1, entries 10–12). CH_3CN was able to increase the yield of this reaction with excellent stereoselectivities (95% yield, >99:1 *dr* and >99% *ee*). Finally, CH_3CN was selected as the optimal solvent (Table 1, entry 13).

Subsequently, we studied the effect of catalyst loading on this Mannich reaction. However, when reducing the catalyst loading to 2.5 mol%, the yield of the product sharply decreased (Table 1, entry 14). When reducing the catalyst loading to 5 mol% or 7.5 mol%, the enantioselectivity and yield of the product **3a** were almost unaffected (Table 1, entries 15 and 16). Thus, according to the above results, 5 mol% catalyst loading was the best suitable option. When the reaction temperature was increased to 40 °C, the yield of the product could not be further improved. In conclusion, the optimal reaction conditions was 5 mol% catalyst **C5** in CH_3CN at room tempture for 36 h (Table 1, entry 15).

Table 1 Screening of organocatalysts and optimization of reaction conditions[a]



Entry	Slovent	Catalyst	Yield[b] (%)	*dr*[c]	*ee*[c] (%)
1	CH_2Cl_2	**C1**	91	96:4	97
2	CH_2Cl_2	**C2**	46	77:23	25
3	CH_2Cl_2	**C3**	81	99:1	89
4	CH_2Cl_2	**C4**	92	97:3	>99
5	CH_2Cl_2	**C5**	93	>99:1	>99
6	CH_2Cl_2	**C6**	91	96:4	97
7	CH_2Cl_2	**C7**	86	>99:1	96
8	CH_2Cl_2	**C8**	51	>99:1	–89
9	THF	**C5**	92	98:2	98
10	PhMe	**C5**	79	95:5	79
11	$CHCl_3$	**C5**	62	98:2	97
12	DCE	**C5**	72	98:2	97
13	CH_3CN	**C5**	95	>99:1	>99
14[d]	CH_3CN	**C5**	82	>99:1	99
15[e]	CH_3CN	**C5**	95	>99:1	>99
16[f]	CH_3CN	**C5**	95	99:1	99
17[e, g]	CH_3CN	**C5**	93	>99:1	>99

[a]Reactions were carried out by using **1a** (0.11 mmol), **2a** (0.1 mmol), and catalyst (5 mol%) in 1.0 mL of solvent at room temperature (25 °C) for 36 h. [b] Isolated yield after purification by column chromatography. [c] Determined by HPLC analysis. [d] 2.5 mol% catalyst was used. [e] 5.0 mol% catalyst was used. [f] 7.5 mol% catalyst was used. [g] The reaction was performed at 40 °C.

Having optimized the conditions of the reaction, we then explored the substrate scope for this Mannich reaction. The results are illustrated in Table 2. When the substituent at the R^1

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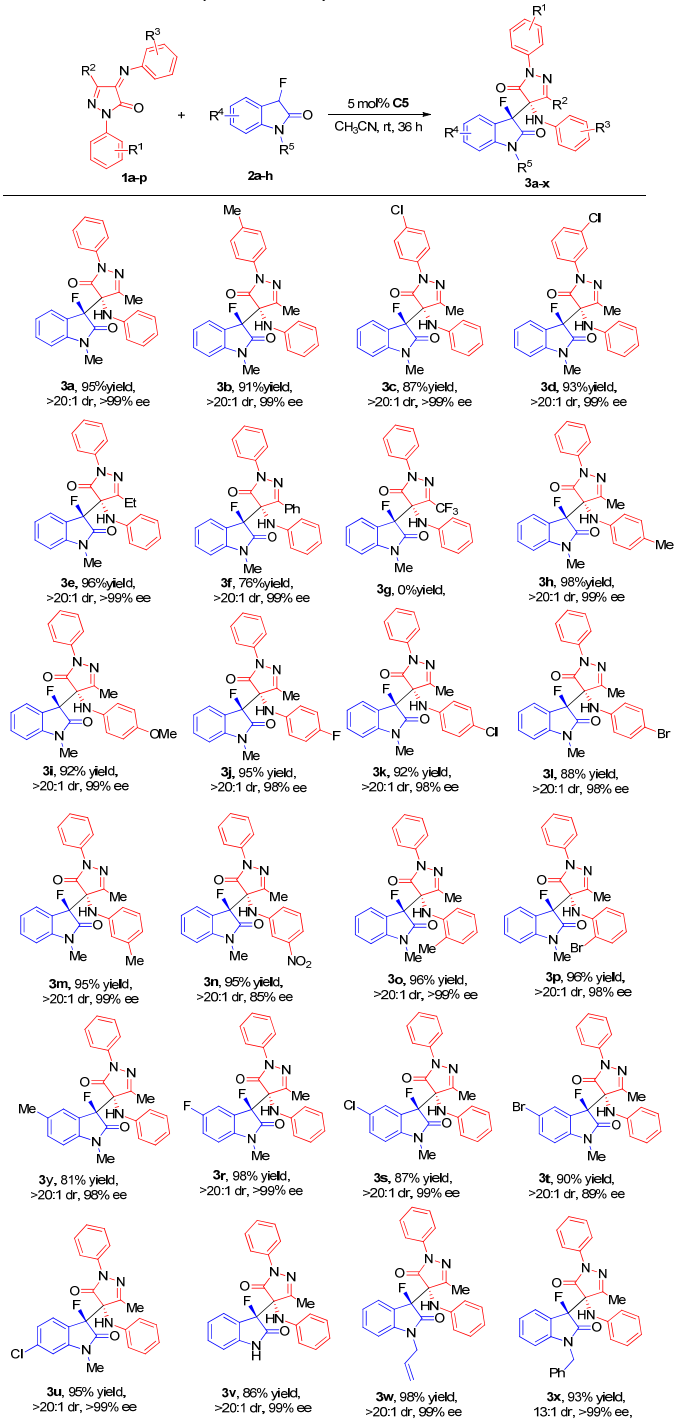
position of the pyrazolones, whether it was electron-donating (**3b**) or electron-withdrawing (**3c** and **3d**) substituents, the corresponding products were obtained in good to excellent yields with excellent diastereo- and enantioselectivities. When the substituent at the R^2 position of the pyrazolone, the electron-donating substituent was beneficial to the reaction (**3e**). When phenyl was at the R^2 position of pyrazolone, the corresponding product **3f** could be obtained with a slightly lower yield. However, the electron-withdrawing substituent such as $-CF_3$ was detrimental to this reaction (**3g**).

Table 2 Substrate scope for the asymmetric Mannich reaction[a]



[a] Reactions were carried out by using **1a** (0.22 mmol), **2a** (0.20 mmol), and catalyst **C5** (5 mol%) in 2.0 mL of CH_3CN at room temperature for 36 h. The *ee* values were determined by HPLC analysis and the *dr* values were determined by NMR analysis

When the R^3 position of the pyrazolone was *para*-substituted, the electron-donating and electron-withdrawing substituents are advantageous for maintaining the enantioselectivities and yields of the reactions (**3h**-**3l**), while the reaction with 4-Br substituted substrate had a slightly lower yield (**3l**). When the R^3 position of the pyrazolone was *meta*-substituted, the 3-Me substituent could maintain the enantioselectivity and yield of the target product **3m**, but the 3-NO_2 substituent caused a slight decrease in enantioselectivity of the product **3n**. When the R^3 position of the pyrazolone was *ortho*-substituted such as 2-Me or 2-Br substituted pyrazolinone ketimines, the enantioselectivities and yields of the products **3o** and **3p** could be well maintained.

After explored a series of pyrazolinone ketimines, the substrate scope of 3-fluorooxindole was further extended. When the 5-position of 3-fluorooxindole was substituted by Me, Cl or Br, the yields and enantioselectivities of the corresponding products **3q**, **3s** and **3t** were slightly decreased. When 5-F and 6-Cl substituted 3-fluorooxindoles were used as the substrates, the enantioselectivities and yields of the target products **3r** and **3u** were scarcely influenced. When the *N*-substituent of 3-fluorooxindole was H atom, the yield of the corresponding product **3v** significantly reduced. The reason may be that the free N-H group interfered the asymmetric induction effect through hydrogen bonding interaction. When the *N*-substituent of 3-fluorooxindole was benzyl (**3w**) or allyl (**3x**), the product's yield and enantioselectivity all could be well remained.

The absolute configuration of the target product was elucidated by single crystal X-ray diffraction analysis of **3p**.[11] The absolute configuration of **3p** was determined to be (3*S*, 4'*S*) (Figure. 2). The absolute configurations of the other products were assigned by analogy.

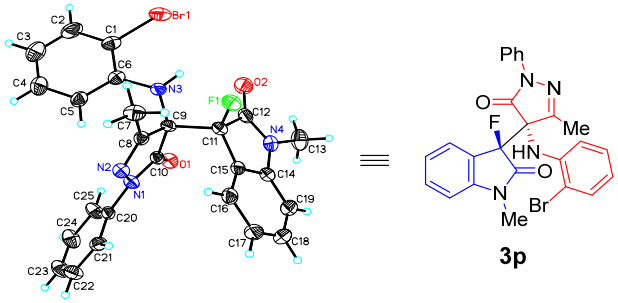


Fig. 2 X-ray crystal structure of **3p**.

To demonstrate the preparative utility and robustness of this Mannich reaction, the reaction between **1h** and **2a** was conducted on a gram scale using standard conditions (Scheme 2). The target product can be obtained in slightly lower yield with the same excellent diastereoselectivity and enantioselectivity (94% yield, >20:1 *dr* and 99% *ee*).

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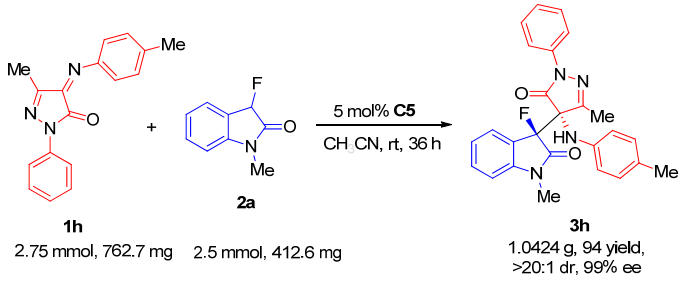
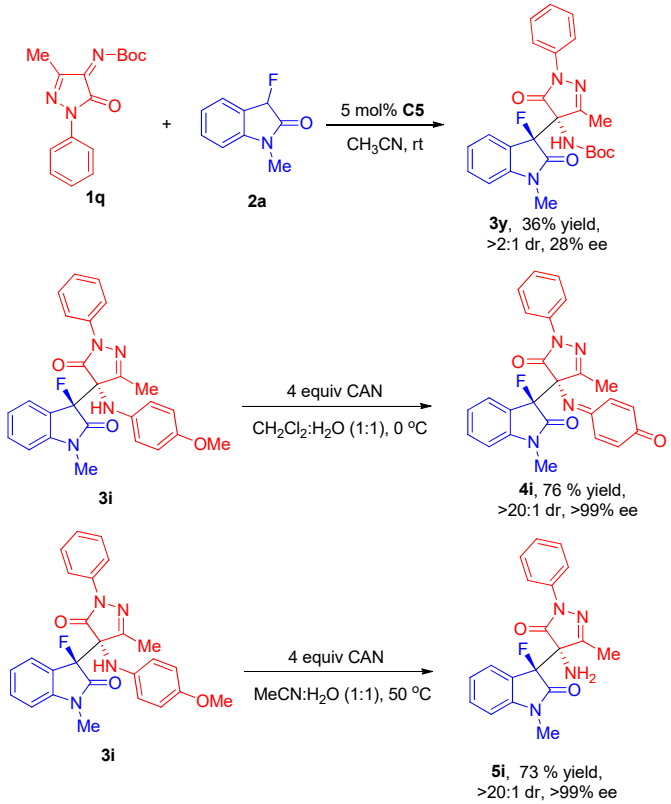
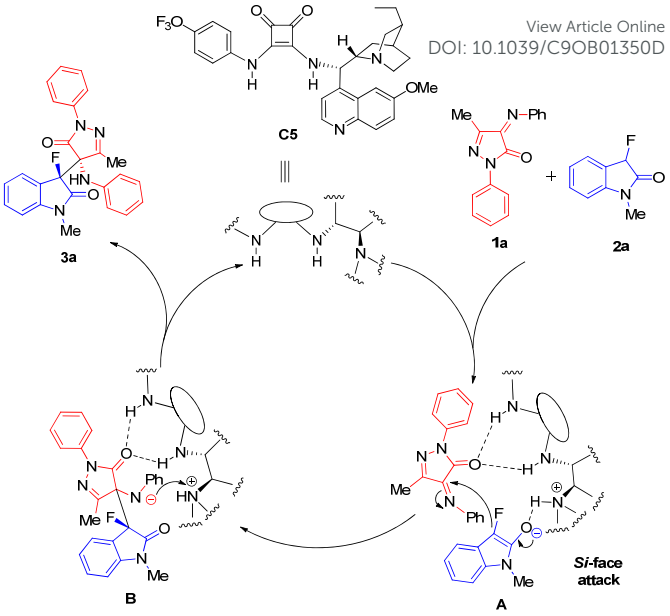


Scheme 2 Gram scale synthesis of **3h**.

In order to further increase the applicability of the developed catalytic method, we have tried to obtain primary amine pyrazolone-oxindoles. We have synthesized N-Boc protected pyrazolinone ketimine, and carried out corresponding catalytic experiment under the optimum reaction conditions. The reaction can take place, but the reaction results of the target product **3y** were not satisfactory. We also tried other synthetic route by choosing product **3i** as the starting material. As demonstrated in Scheme 3, with different reaction conditions,[12] the *p*-methoxy phenyl (PMP) group can be oxidized by cerium ammonium nitrate (CAN) to obtain different product **4i** and **5i**. The obtained product was quinonoid compound **4i** in CH_2Cl_2 at 0 °C, which it was primary amine pyrazolone-oxindole **5i** in CH_3CN at 50 °C due to complete imine hydrolysis in a homogeneous solution of CH_3CN and water.



Scheme 3 The synthesis of product **3y** and transformations of product **3i**.



Scheme 4 Proposed mechanism for the reaction.

On the basis of our experiments and previously reported, we proposed a reasonable mechanism for this Mannich reaction (Scheme 4). Under the action of the catalyst **C5**, 3-fluorooxindole forms an intermediate through the enol interconversion, at the same times, the chiral portion of the catalyst controls the spatial orientation of the pyrazolone-imine to form a transition state **A** by hydrogen bonding. And then the enolate of **2a** attacks imine **1a** to form transition state **B**, which eventually forms the target product **3a** and regenerated the bifunctional catalyst **C5** after a protonation process.

Conclusions

In summary, we have developed a highly enantioselective Mannich reaction of pyrazolinone ketimines with 3-fluorooxindoles in the presence of a chiral squaramide catalyst derived from hydroquinine. The target fluorinated pyrazolones with two adjacent tetrasubstituted stereocenters can be obtained in good to excellent yields (up to 98%) with excellent stereoselectivities (up to >20:1 *dr* and >99% *ee*). The gram-scale experiment was also successfully performed with the same excellent stereoselectivity. In addition, under the further transformation of the products, we found that with different reaction conditions, the *p*-methoxy phenyl (PMP) substituent of **3i** could be oxidized by cerium ammonium nitrate (CAN) to form the different product **4i** and **5i**. This methodology can provide a convenient method for the synthesis of fluorinated amino-pyrazolone-oxindoles with potentially pharmaceutical activities.

Experimental

General Methods: All solvents commercially and available chemicals were used without further purification. The column chromatography was performed with silica gel (200–300 mesh) using mixtures of petroleum ether and ethyl acetate. Melting points were determined

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with a XT-4 melting-point apparatus without corrected. ^{1}H NMR spectra were measured with Bruker Ascend 400 MHz spectrometer, and chemical shifts were reported in δ (ppm) units relative to tetramethylsilane (TMS) as the internal standard. ^{13}C NMR spectra were measured at 101 MHz with Bruker Ascend 400 MHz spectrometer or 176 MHz with Bruker Avance III HD 700 MHz spectrometer, and chemical shifts are reported in δ (ppm) units relative to tetramethylsilane and referenced to the solvent peak ($CDCl_3$, δ(C) = 77.00 ppm). ^{19}F NMR spectra were measured at 376 MHz with Bruker Ascend 400 MHz spectrometer. Proton coupling patterns are described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br). High-resolution mass spectra were obtained with an Agilent 6520 Accurate-Mass-Q-TOF MS system equipped with an electrospray ionization (ESI) source. The enantiomeric excesses were determined by chiral HPLC analysis using an Agilent 1200 LC instrument with Daicel Chiralpak IA, IB, IC or AD-H columns. Optical rotations were measured with Krüss P8000 polarimeter at the indicated concentration with the units of grams per 100 mL at 20 °C using sodium D light.

General procedure for asymmetric Mannich reaction for synthesis of fluorinated pyrazolone deratives 3

To a dried small bottle were added pyrazolinone ketimines **1** (0.22mmol), 3-fluorooxindoles **2** (0.2 mmol), and squaramide catalyst **C5** (5 mol%) in CH_3CN (2.0 mL) at room temperature. The reaction mixture was stirred for 36 h and the progress of the reaction was monitored by TLC analysis (Petroleum ether/ethyl acetate = 2:1). After the completion of the reaction, the crude product mixture was purified by flash column chromatography on silica (PE/EA= 5:1) to afford the pure product **3**. The racemic standard of **3** was prepared using non-chiral catalyst.

(*S*)-3-Fluoro-1-methyl-3-((*S*)-3-methyl-5-oxo-1-phenyl-4-(phenylamino)-4,5-dihydro-1*H*-pyrazol-4-yl)indolin-2-one (3a). 3a was obtained as a white solid (81.5 mg, 95% yield), m.p. 157−159 °C. HPLC (Daicel Chiralpak IA, *n*-hexane/2-propanol = 80:20, flow rate 1.0 mL/min, detection at 254 nm): major diastereoisomer, t_R = 8.9 min (minor), t_R = 16.0 min (major); >99% *ee* for the major diastereoisomer. $[\alpha]_D^{20}$ = +29.4 (*c* 4.19, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.36−7.33 (m, 3H, ArH), 7.24−7.17 (m, 3H, ArH), 7.09−7.03 (m, 3H, ArH), 6.94 (t, *J* = 7.6 Hz, 1H, ArH), 6.82 (s, 1H, NH), 6.73−6.67 (m, 2H, ArH), 6.51 (d, *J* = 8.0 Hz, 2H, ArH), 3.12 (s, 3H, CH_3), 2.44 (d, *J* = 1.6 Hz, 3H, CH_3) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): *δ* 169.5 (d, $^2J_{C\text{-}F}$ = 22.0 Hz), 168.7 (d, $^3J_{C\text{-}F}$ = 5.4 Hz), 158.3, 144.5, 144.4 (d, $^3J_{C\text{-}F}$ = 5.4 Hz), 136.8, 132.8, 129.5, 128.7, 125.8, 124.8, 123.1, 119.7, 119.7 (d, $^2J_{C\text{-}F}$ =18.4 Hz), 119.5, 114.0, 109.3, 89.6 (d, $^1J_{C\text{-}F}$ =209.8 Hz), 73.7 (d, $^2J_{C\text{-}F}$ = 23.4 Hz), 26.4, 16.0 (d, $^4J_{C\text{-}F}$ = 3.4 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): *δ* −170.5 ppm. HRMS (ESI): *m*/*z* calcd for $C_{25}H_{21}N_4O_2F$ $[M + H]^+$ 429.1721, found 429.1716.

(*S*)-3-Fluoro-1-methyl-3-((*S*)-3-methyl-5-oxo-4-(phenylamino)-1-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazol-4-yl)indolin-2-one (3b). 3b was obtained as a white solid (80.5 mg, 91% yield), m.p. 45−47 °C. HPLC (Daicel Chiralpak IA, *n*-hexane/2-propanol = 80:20, flow rate 1.0 mL/min, detection at 254 nm): diastereoisomer, t_R = 14.3 min (minor), t_R = 18.9 min (major); 99% *ee* for the major diastereoisomer. $[\alpha]_D^{20}$ = +15.8 (*c* 2.60, CH_2Cl_2): ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.41−7.28 (m, 2H, ArH), 7.17 (d, *J* = 8.5 Hz, 2H, ArH), 7.11−7.07 (m, 2H, ArH), 7.06−6.97 (m, 3H, ArH), 6.82−6.72 (m, 3H, NH+ArH), 6.56−6.48 (m, 2H, ArH), 3.21 (s, 3H, CH_3), 2.45 (d, *J* = 1.2 Hz, 3H, CH_3), 2.25 (s, 3H, CH_3) ppm; ^{13}C NMR (176 MHz, $CDCl_3$): *δ* 169.6 (d, $^2J_{C\text{-}F}$ = 22.0 Hz), 168.5 (d, $^3J_{C\text{-}F}$ = 5.1 Hz), 158.1, 144.6, 144.4 (d, $^3J_{C\text{-}F}$ = 5.1 Hz), 135.7, 134.3, 132.8, 129.5, 129.2, 124.8, 123.1, 119.8, 119.7, 119.6, 114.0, 109.3, 89.7 (d, $^1J_{C\text{-}F}$ = 208.4 Hz), 73.6 (d, $^2J_{C\text{-}F}$ = 23.6 Hz), 26.4, 20.9, 15.9 (d, $^4J_{C\text{-}F}$ =3.9 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): *δ* −170.5 ppm. HRMS (ESI): *m*/*z* calcd for $C_{26}H_{23}N_4O_2F$ $[M + H]^+$ 443.1878, found 443.1888.

(*S*)-3-((*S*)-1-(4-Chlorophenyl)-3-methyl-5-oxo-4-(phenylamino)-4,5-dihydro-1*H*-pyrazol-4-yl)-3-fluoro-1-methylindolin-2-one (3c). 3c was obtained as a white solid (80.4 mg, 87% yield), m.p. 60−62 °C. HPLC (Daicel Chiralpak IA, *n*-hexane/2-propanol = 80:20, flow rate 1.0 mL/min, detection at 254 nm): major diastereoisomer, t_R = 11.0 min (minor), t_R = 21.0 min (major); minor diastereoisomer, t_R = 40.3 min, t_R = 44.0 min; >99% *ee* for the major diastereoisomer. $[\alpha]_D^{20}$ = +30.7 (*c* 2.73, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.36−7.30 (m, 4H, ArH), 7.20−7.14 (m, 2H, ArH), 7.12−7.08 (m, 2H, ArH), 6.98 (t, *J* = 7.6 Hz, 1H, ArH), 6.80−6.74 (m, 3H, NH+ArH), 6.50 (d, *J* = 7.6 Hz, 2H, ArH), 3.23 (s, 3H, CH_3), 2.46 (d, *J* = 1.6 Hz, 3H, CH_3) ppm; ^{13}C NMR (176 MHz, $CDCl_3$) *δ* 169.4 (d, $^2J_{C\text{-}F}$ = 22.2 Hz), 168.7 (d, $^3J_{C\text{-}F}$ = 5.5 Hz) ,158.8, 144.4, 144.3 (d, $^3J_{C\text{-}F}$ = 5.1 Hz), 135.3, 132.9, 130.9, 129.6, 128.8, 124.7, 123.1, 120.2, 119.8, 119.5 (d, $^2J_{C\text{-}F}$ = 18.3 Hz), 114.0, 109.3, 89.6 (d, $^1J_{C\text{-}F}$ = 209.3 Hz), 73.8 (d, $^2J_{C\text{-}F}$ = 23.4 Hz), 26.4, 16.0 (d, $^4J_{C\text{-}F}$ = 4.0 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): *δ* −170.6 ppm. HRMS (ESI): *m*/*z* calcd for $C_{25}H_{20}N_4O_2F^{34.9689}Cl$ $[M + H]^+$ 463.1332, found 463.1327; $C_{25}H_{20}N_4O_2F^{36.9659}Cl$ $[M + H]^+$ 465.1308, found 465.1313.

(*S*)-3-((*S*)-1-(3-Chlorophenyl)-3-methyl-5-oxo-4-(phenylamino)-4,5-dihydro-1*H*-pyrazol-4-yl)-3-fluoro-1-methylindolin-2-one (3d). 3d was obtained as a white solid (86.2 mg, 93% yield), m.p. 136−138 °C. HPLC (Daicel Chiralpak IA, *n*-hexane/2-propanol = 80:20, flow rate 1.0 mL/min, detection at 254 nm): major diastereoisomer, t_R = 7.3 min (minor), t_R = 9.6 min (major); minor diastereoisomer, t_R = 13.8 min, t_R = 20.7 min; 99% *ee* for the major diastereoisomer. $[\alpha]_D^{20}$ = +17.3 (*c* 4.09, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.45 (t, *J* = 2.0 Hz, 1H, ArH), 7.35−7.28 (m, 3H), 7.15−7.04 (m, 4H, ArH), 6.98 (t, *J* = 7.6 Hz, 1H, ArH), 6.79−6.73 (m, 3H, NH+ArH), 6.49 (d, *J* = 7.6 Hz, 2H, ArH), 3.22 (s, 3H, CH_3), 2.46 (d, *J* = 1.2 Hz, 3H, CH_3) ppm; ^{13}C NMR (176 MHz, $CDCl_3$) *δ* 169.4 (d, $^2J_{C\text{-}F}$ = 22.0 Hz), 168.8 (d, $^3J_{C\text{-}F}$ = 5.1 Hz), 158.8, 144.4, 144.3 (d, $^3J_{C\text{-}F}$ = 5.1 Hz), 137.8, 134.3, 132.9, 129.7, 129.5, 125.6, 124.7, 123.1, 119.8, 119.4 (d, $^2J_{C\text{-}F}$ = 18.1 Hz) , 118.9, 116.8, 114.0, 109.3, 89.5 (d, $^1J_{C\text{-}F}$ = 209.3 Hz), 73.9 (d, $^2J_{C\text{-}F}$ = 23.4 Hz), 26.4, 15.9 (d, $^4J_{C\text{-}F}$ = 3.9 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): *δ* −170.4 ppm. HRMS (ESI): *m*/*z* calcd for $C_{25}H_{20}N_4O_2F^{34.9689}Cl$ $[M + H]^+$ 463.1332, found 463.1327; $C_{25}H_{20}N_4O_2F^{36.9659}Cl$ $[M + H]^+$ 465.1308, found 465.1309.

(*S*)-3-((*S*)-3-Ethyl-5-oxo-1-phenyl-4-(phenylamino)-4,5-dihydro-1*H*-pyrazol-4-yl)-3-fluoro-1-methylindolin-2-one (3e). 3e was obtained as a white solid (85.1 mg, 96% yield), m.p. 45−47 °C. HPLC (Daicel Chiralpak IA, *n*-hexane/2-propanol = 85:15, flow rate 1.0 mL/min, detection at 254 nm): major diastereoisomer, t_R = 9.6 min (minor), t_R = 14.6 min (major); >99% *ee* for the major diastereoisomer. $[\alpha]_D^{20}$ = +6.9 (*c* 3.20, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.36 (d, *J* = 7.2 Hz, 2H, ArH), 7.33−7.27 (m, 2H, ArH), 7.23 (t, *J* = 8.0 Hz, 2H, ArH), 7.11−7.07 (m, 3H, ArH), 6.98 (t, *J* = 7.8 Hz, 1H, ArH), 6.82 (s, 1H, NH), 6.77−6.71 (m, 2H, ArH), 6.49 (d, *J* = 7.6 Hz, 2H, ArH), 3.20 (s, 3H, CH_3), 2.88−2.76 (m, 2H), 1.41 (t, *J* = 7.4 Hz, 3H, CH_3) ppm; ^{13}C NMR (176 MHz, $CDCl_3$): *δ* 169.6 (d, $^2J_{C\text{-}F}$ = 22.2 Hz), 168.9 (d, $^3J_{C\text{-}F}$ = 5.3 Hz), 162.0,

144.6, 144.4 (d, $^3J_{C-F}$ = 5.3 Hz), 136.9, 132.8, 129.5, 128.7, 125.7, 124.7, 123.0, 119.7 (d, $^2J_{C-F}$ = 18.3 Hz), 119.5, 119.5, 113.8, 109.2, 89.7 (d, $^1J_{C-F}$ = 208.2 Hz), 73.7 (d, $^2J_{C-F}$ = 23.4 Hz), 26.4, 23.2 (d, $^4J_{C-F}$ = 4.6 Hz), 9.09; ^{19}F NMR (376 MHz, $CDCl_3$): δ −170.1 ppm. HRMS (ESI): *m/z* calcd for $C_{26}H_{23}N_4O_2F$ $[M + H]^+$ 443.1878, found 443.1884.

(*S*)-3-Fluoro-1-methyl-3-((*S*)-5-oxo-1,3-diphenyl-4-(phenylamino)-4,5-dihydro-1*H*-pyrazol-4-yl)indolin-2-one (3f). 3f was obtained as a white solid (74.5 mg, 76% yield), m.p. 102−104 °C. HPLC (Daicel Chiralpak IA, *n*-hexane/2-propanol = 80:20, flow rate 1.0 mL/min, detection at 254 nm): major diastereoisomer, t_R = 8.4 min (minor), t_R = 17.5 min (major); 99% *ee* for the major diastereoisomer. $[\alpha]_D^{20}$ = +47.6 (*c* 1.67, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.51−8.48 (m, 2H, ArH), 7.48−7.45 (m, 3H, ArH), 7.41−7.39 (m, 2H, ArH), 7.31 (d, *J* = 7.2 Hz, 1H, ArH), 7.27−7.23 (m, 3H, ArH), 7.15−7.04 (m, 4H, NH+ArH), 6.95 (t, *J* = 7.8 Hz, 1H, ArH), 6.76−6.70 (m, 2H, ArH), 6.65 (d, *J* = 7.6 Hz, 2H, ArH), 3.23 (s, 3H, CH_3) ppm; ^{13}C NMR (176 MHz, $CDCl_3$): δ 170.0 (d, $^2J_{C-F}$ = 22.2 Hz), 168.9 (d, $^3J_{C-F}$ = 6.3 Hz), 153.8, 144.7, 144.3 (d, $^3J_{C-F}$ = 5.3 Hz), 136.8, 132.7, 131.2, 131.1, 129.5, 128.7, 128.7, 127.8, 126.1, 125.6, 123.0, 120.0, 119.9 (d, $^2J_{C-F}$ = 18.0 Hz), 119.7, 114.9, 109.1, 89.7 (d, $^1J_{C-F}$ = 212.3 Hz), 74.4 (d, $^2J_{C-F}$ = 24.5 Hz), 26.4 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ −167.4 ppm. HRMS (ESI): *m/z* calcd for $C_{30}H_{23}N_4O_2F$ $[M + H]^+$ 491.1878, found 491.1876.

(*S*)-3-Fluoro-1-methyl-3-((*S*)-3-methyl-5-oxo-1-phenyl-4-(p-tolylamino)-4,5-dihydro-1*H*-pyrazol-4-yl) indolin-2-one (3h). 3h was obtained as a white solid (86.7 mg, 98% yield), m.p. 68−70 °C. HPLC (Daicel Chiralpak IA, *n*-hexane/2-propanol = 80:20, flow rate 1.0 mL/min, detection at 254 nm): major diastereoisomer, t_R = 10.6 min (minor), t_R = 18.2 min (major); 99% *ee* for the major diastereoisomer. $[\alpha]_D^{20}$ = +17.9 (*c* 3.80, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (d, *J* = 7.6 Hz, 1H, ArH), 7.33−7.29 (m, 3H, ArH), 7.25−7.20 (m, 2H, ArH), 7.09 (t, *J* = 7.2 Hz, 1H, ArH), 6.99 (t, *J* = 7.8 Hz, 1H, ArH), 6.90 (d, *J* = 8.4 Hz, 2H, ArH), 6.78 (d, *J* = 8.0 Hz, 1H, ArH), 6.66 (s, 1H, NH), 6.46 (d, *J* = 8.4 Hz, 2H, ArH), 3.22 (s, 3H, CH_3), 2.47 (d, *J* = 1.2 Hz, 3H, CH_3), 2.17 (s, 3H, CH_3) ppm; ^{13}C NMR (176 MHz, $CDCl_3$): δ 169.5 (d, $^2J_{C-F}$ = 22.2 Hz), 168.9 (d, $^3J_{C-F}$ = 5.3 Hz), 158.4, 144.4 (d, $^3J_{C-F}$ =5.1 Hz), 142.1, 136.8, 132.8, 130.0, 129.1, 128.7, 125.8, 124.8, 123.1, 119.8 (d, $^2J_{C-F}$ = 18.1 Hz), 119.5, 114.4, 109.2, 89.7 (d, $^1J_{C-F}$ = 208.7 Hz), 74.0 (d, $^2J_{C-F}$ = 23.4 Hz), 26.4, 20.4, 16.0 (d, $^4J_{C-F}$ = 3.7 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ −170.6 ppm. HRMS (ESI): *m/z* calcd for $C_{26}H_{23}N_4O_2F$ $[M + H]^+$ 443.1878, found 443.1892.

(*S*)-3-Fluoro-3-((*S*)-4-((4-methoxyphenyl)amino)-3-methyl-5-oxo-1-phenyl-4,5-dihydro- 1*H*-pyrazol-4-yl)-1-methylindolin-2-one (3i). 3i was obtained as a white solid (84.3 mg, 92% yield), m.p. 60−62 °C. HPLC (Daicel Chiralpak IB, *n*-hexane/2-propanol = 85:15, flow rate 1.0 mL/min, detection at 254 nm): major diastereoisomer, t_R = 9.0 min (minor), t_R = 7.8 min (major); 99% *ee* for the major diastereoisomer. $[\alpha]_D^{20}$ = +30.8 (*c* 2.90, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, *J* = 7.6 Hz, 1H, ArH), 7.32−7.28 (m, 3H, ArH), 7.22 (t, *J* = 7.8 Hz, 2H, ArH), 7.08 (t, *J* = 7.4 Hz, 1H, ArH), 6.98 (t, *J* = 7.6 Hz, 1H, ArH), 6.77 (d, *J* = 8.0 Hz, 1H, ArH), 6.67 (d, *J* = 9.2 Hz, 2H, ArH), 6.56 (d, *J* = 9.2 Hz, 2H, ArH), 6.50 (s, 1H, NH), 3.65 (s, 3H, CH_3), 3.21 (s, 3H, CH_3), 2.48 (d, *J* = 1.2 Hz, 3H, CH_3) ppm; ^{13}C NMR (176 MHz, $CDCl_3$): δ 169.5 (d, ^2J = 22.0 Hz), 169.0 (d, ^3J = 5.3 Hz), 158.3, 153.8, 144.3 (d, ^3J = 5.3 Hz), 138.0, 136.7, 132.8, 128.6, 125.7, 124.7, 123.0, 119.8 (d, ^2J = 18.1 Hz), 119.4, 116.9, 114.8, 109.2, 89.6 (d, ^1J = 209.1 Hz), 74.5 (d, ^2J = 23.4 Hz), 55.4, 26.4, 16.0 (d, ^4J = 3.7 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ −170.6 ppm. HRMS (ESI): *m/z* calcd for $C_{26}H_{23}N_4O_3F$ $[M + H]^+$ 459.1827, found 459.1840.

(*S*)-3-Fluoro-3-((*S*)-4-((4-fluorophenyl)amino)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)-1-methylindolin-2-one (3j). 3j was obtained as a white solid (84.8 mg, 95% yield), m.p. 47−49 °C. HPLC (Daicel Chiralpak IA, *n*-hexane/2-propanol = 85:15, flow rate 1.0 mL/min, detection at 254 nm): major diastereoisomer, t_R = 11.0 min (minor), t_R = 14.2 min (major); 98% *ee* for the major diastereoisomer. $[\alpha]_D^{20}$ = +4.5 (*c* 3.62, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, *J* = 7.6 Hz, 1H, ArH), 7.34−7.27 (m, 3H, ArH), 7.23 (t, *J* = 7.8 Hz, 2H, ArH), 7.10 (t, *J* = 7.2 Hz, 1H, ArH), 6.99 (t, *J* = 7.6 Hz, 1H, ArH), 6.84−6.77 (m, 3H, ArH), 6.71 (s, 1H, NH), 6.51−6.48 (m, 2H, ArH), 3.22 (s, 3H, CH_3), 2.47 (d, *J* = 1.6 Hz, 3H, CH_3) ppm; ^{13}C NMR (176 MHz, $CDCl_3$): δ 169.5 (d, $^2J_{C-F}$ = 21.8 Hz), 168.6 (d, $^3J_{C-F}$ = 5.6 Hz), 158.1, 157.1 (d, $^1J_{C-F}$ = 238.8 Hz), 144.3 (d, $^3J_{C-F}$ = 5.3 Hz), 140.7, 136.6, 132.9, 128.7, 125.9, 124.7, 123.1, 119.6 (d, $^2J_{C-F}$ = 17.6 Hz), 119.4, 116.0 (d, $^2J_{C-F}$ = 22.5 Hz), 115.8 (d, $^3J_{C-F}$ = 7.6 Hz), 109.3, 89.5 (d, $^1J_{C-F}$ = 208.2 Hz), 74.1 (d, $^2J_{C-F}$ = 23.2 Hz), 26.4, 15.9 (d, $^4J_{C-F}$ = 4.0 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ −124.5, −170.5 ppm. HRMS (ESI): *m/z* calcd for $C_{25}H_{20}N_4O_2F_2$ $[M + H]^+$ 447.1627, found 447.1631.

(*S*)-3-((*S*)-4-((4-Chlorophenyl)amino)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)-3-fluoro-1-methylindolin-2-one (3k). 3k was obtained as a white solid (85.1 mg, 92% yield), m.p. 62−64 °C. HPLC (Daicel Chiralpak IA, *n*-hexane/2-propanol = 80:20, flow rate 1.0 mL/min, detection at 254 nm): major diastereoisomer, t_R = 9.4 min (minor), t_R = 14.9 min (major); 98% *ee* for the major diastereoisomer. $[\alpha]_D^{20}$ = +22.9 (*c* 3.39, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38−7.30 (m, 4H, ArH), 7.26−7.22 (m, 2H, ArH), 7.14−7.10 (m, 1H, ArH), 7.08−7.04 (m, 2H, ArH), 7.01 (tt, J_1 = 7.6 Hz, J_2 = 0.9 Hz, 1H, ArH), 6.84 (s, 1H, NH), 6.81 (d, *J* = 8.0 Hz, 1H, ArH), 6.47−6.43 (m, 2H, ArH), 3.24 (s, 3H, CH_3), 2.46 (d, *J* = 1.6 Hz, 3H, CH_3) ppm; ^{13}C NMR (176 MHz, $CDCl_3$): δ 169.4 (d, $^2J_{C-F}$ = 22.2 Hz), 168.3 (d, $^3J_{C-F}$ = 5.3 Hz), 158.0, 144.3 (d, $^3J_{C-F}$ = 5.1 Hz), 143.2, 136.6, 132.9, 129.4, 128.7, 126.0, 124.7, 124.5, 123.2, 119.5, 119.4 (d, $^2J_{C-F}$ = 17.8 Hz), 115.2, 109.3, 89.5 (d, $^1J_{C-F}$ = 209.3 Hz), 73.7 (d, $^2J_{C-F}$ = 23.4 Hz), 26.4, 15.9 (d, $^4J_{C-F}$ = 3.9 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ −170.3 ppm. HRMS (ESI): *m/z* calcd for $C_{25}H_{20}N_4O_2F^{34.9689}Cl$ $[M + H]^+$ 463.1332, found 463.1339; $C_{25}H_{20}N_4O_2F^{36.9659}Cl$ $[M + H]^+$ 465.1308, found 465.1328.

(*S*)-3-((*S*)-4-((4-Bromophenyl)amino)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)-3-fluoro-1-methylindolin-2-one (3l). 3l was obtained as a white solid (89.1 mg, 88% yield), m.p. 61−63 °C. HPLC (Daicel Chiralpak IA, *n*-hexane/2-propanol = 80:20, flow rate 1.0 mL/min, detection at 254 nm): major diastereoisomer, t_R = 9.9 min (minor), t_R = 15.4 min (major); 98% *ee* for the major diastereoisomer. $[\alpha]_D^{20}$ = +11.7 (*c* 4.14, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38−7.30 (m, 4H, ArH), 7.26−7.23 (m, 2H, ArH), 7.22−7.18 (m, 2H, ArH), 7.12 (t, *J* = 7.4 Hz, 1H, ArH), 7.00 (t, *J* = 7.8 Hz, 1H, ArH), 6.86 (s, 1H, NH), 6.80 (d, *J* = 8.0 Hz, 1H, ArH), 6.40 (d, *J* = 8.8 Hz, 2H, ArH), 3.23 (s, 3H, CH_3), 2.45 (d, *J* = 1.6 Hz, 3H, CH_3) ppm; ^{13}C NMR (176 MHz, $CDCl_3$): δ 169.5 (d, ^2J = 21.6 Hz), 168.3 (d, ^3J = 5.3 Hz), 157.9, 144.3 (d, ^3J = 5.3 Hz), 143.7, 136.6, 133.0, 132.3, 128.8, 126.0, 124.8, 123.2, 119.48, 119.47 (d, ^2J = 17.6 Hz), 115.6, 111.7, 109.4, 89.5 (d, ^1J = 209.1 Hz), 73.6 (d, ^2J = 23.2 Hz), 26.5, 16.0 (d, ^4J = 3.9 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ −170.3 ppm. HRMS (ESI): *m/z* calcd for $C_{25}H_{20}N_4O_2F^{78.9183}Br$ [M +

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H]$^+$ 507.0826, found 507.0835; $C_{25}H_{20}N_4O_2F^{80.9163}Br$ [M + H]$^+$ 509.0806, found 509.0817.

(*S*)-3-Fluoro-1-methyl-3-((*S*)-3-methyl-5-oxo-1-phenyl-4-(m-tolyl-amino)-4,5-dihydro-1*H*-pyrazol-4-yl) indolin-2-one (3m). 3m was obtained as a white solid (83.9 mg, 95% yield), m.p. 136-138 °C. HPLC (Daicel Chiralpak IA, *n*-hexane/2-propanol = 80:20, flow rate 1.0 mL/min, detection at 254 nm): major diastereoisomer, t_R = 6.0 min (minor), t_R = 10.5 min (major); 99% *ee* for the major diastereoisomer. $[\alpha]_D^{20}$ = –7.1 (*c* 4.01, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (d, J = 7.6 Hz, 1H, ArH), 7.33–7.29 (m, 3H, ArH), 7.25–7.21 (m, 2H, ArH), 7.10 (tt, J_1 = 7.4 Hz, J_2 = 1.2 Hz, 1H, ArH), 7.01–6.94 (m, 2H, ArH), 6.78 (d, J = 7.6 Hz, 1H, ArH), 6.73 (s, 1H, NH), 6.56 (d, J = 7.6 Hz, 1H, ArH), 6.43 (s, 1H, ArH), 6.26 (dd, J_1 = 8.2 Hz, J_2 = 2.6 Hz, 1H, ArH), 3.21 (s, 3H, CH_3), 2.46 (d, J = 1.2 Hz, 3H, CH_3), 2.18 (s, 3H, CH_3) ppm; ^{13}C NMR (176 MHz, $CDCl_3$): δ 169.5 (d, $^2J_{C\text{-}F}$ =19.4 Hz), 168.8 (d, $^3J_{C\text{-}F}$ =5.1 Hz), 158.4, 144.6, 144.3 (d, $^3J_{C\text{-}F}$ = 5.5 Hz), 139.2, 136.7, 132.8, 129.4, 128.7, 125.9, 124.7, 123.0, 120.6, 119.6 (d, $^2J_{C\text{-}F}$ = 18.1 Hz), 119.6, 115.4, 110.3, 109.2, 89.6 (d, $^1J_{C\text{-}F}$ = 209.1 Hz), 73.7 (d, $^2J_{C\text{-}F}$ = 23.4 Hz), 26.4, 21.4, 15.9 (d, $^4J_{C\text{-}F}$ = 4.0 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ –170.5 ppm. HRMS (ESI): *m/z* calcd for $C_{26}H_{23}N_4O_2F$ [M + H]$^+$ 443.1878, found 443.1878.

(*S*)-3-Fluoro-1-methyl-3-((*S*)-3-methyl-4-((3-nitrophenyl)amino)-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl) indolin-2-one (3n). 3n was obtained as a yellow solid (90.3 mg, 95% yield), m.p. 73–75 °C. HPLC (Daicel Chiralpak IA, *n*-hexane/2-propanol = 80:20, flow rate 1.0 mL/min, detection at 254 nm): major diastereoisomer, t_R = 13.3 min (minor), t_R = 17.3 min (major); 85% *ee* for the major diastereoisomer. $[\alpha]_D^{20}$ = –15.6 (*c* 1.99, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (dd, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 1H, ArH), 7.41–7.37 (m, 2H, ArH), 7.30–7.24 (m, 7H, ArH), 7.18–7.13 (m, 1H, ArH), 7.04 (t, J = 7.6 Hz, 1H, ArH), 6.88–6.84 (m, 2H, NH+ArH), 3.27 (s, 3H, CH_3), 2.47 (d, J = 1.2 Hz, 3H, CH_3) ppm; ^{13}C NMR (176 MHz, $CDCl_3$): δ 169.4 (d, $^2J_{C\text{-}F}$ = 22.0 Hz), 167.8 (d, $^3J_{C\text{-}F}$ = 5.1 Hz), 157.1, 149.4, 145.5, 144.4 (d, $^3J_{C\text{-}F}$ = 5.1 Hz), 136.3, 133.1, 130.3, 128.8, 126.5, 124.9, 123.5, 120.3, 120.1, 119.3 (d, $^2J_{C\text{-}F}$ = 18.3 Hz), 114.3, 109.5, 107.4, 89.3 (d, $^1J_{C\text{-}F}$ = 209.3 Hz), 73.2 (d, $^2J_{C\text{-}F}$ = 23.2 Hz), 26.5, 15.9 (d, $^4J_{C\text{-}F}$ = 4.0 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ –170.0 ppm. HRMS (ESI): *m/z* calcd for $C_{25}H_{20}N_5O_4F$ [M + H]$^+$ 474.1572, found 474.1578.

(*S*)-3-Fluoro-1-methyl-3-((*S*)-3-methyl-5-oxo-1-phenyl-4-(o-tolyl-amino)-4,5-dihydro-1*H*-pyrazol-4-yl) indolin-2-one (3o). 3o was obtained as a white solid (84.7 mg, 96% yield), m.p. 168–170 °C. HPLC (Daicel Chiralpak IA, *n*-hexane/2-propanol = 95:5, flow rate 1.0 mL/min, detection at 254 nm): major diastereoisomer, t_R = 12.0 min (minor), t_R = 13.7 min (major); >99% *ee* for the major diastereoisomer. $[\alpha]_D^{20}$ = –31.9 (*c* 2.08, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, J = 7.6 Hz, 1H, ArH), 7.35–7.29 (m, 3H, ArH), 7.26–7.21 (m, 2H, ArH), 7.13–7.07 (m, 2H, ArH), 7.00 (t, J = 7.6 Hz, 1H, ArH), 6.88 (td, J_1 = 7.8 Hz, J_2 = 1.6 Hz, 1H, ArH), 6.82 (s, 1H, NH), 6.78 (d, J = 8.0 Hz, 1H, ArH), 6.67 (td, J_1 = 7.4 Hz, J_2 = 1.2 Hz, 1H, ArH), 6.05 (d, J = 8.0 Hz, 1H, ArH), 3.22 (s, 3H, CH_3), 2.44–2.43 (m, 6H, CH_3) ppm; ^{13}C NMR (176 MHz, $CDCl_3$): δ 169.6 (d, $^2J_{C\text{-}F}$ = 22.0 Hz), 168.9 (d, $^3J_{C\text{-}F}$ = 5.1 Hz), 158.4, 144.4 (d, $^3J_{C\text{-}F}$ = 5.3 Hz), 142.7, 136.8, 132.8, 130.7, 128.7, 127.2, 125.9, 124.8, 124.6, 123.1, 119.7 (d, $^2J_{C\text{-}F}$ = 18.3 Hz), 119.5, 119.1, 109.5, 109.3, 89.3 (d, $^1J_{C\text{-}F}$ = 209.4 Hz), 73.8 (d, $^2J_{C\text{-}F}$ = 23.4 Hz), 26.4, 17.6, 15.9 (d, $^4J_{C\text{-}F}$ = 4.0 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ –170.4 ppm. HRMS (ESI): *m/z* calcd for $C_{26}H_{23}N_4O_2F$ [M + H]$^+$ 443.1878, found 443.1879.

(*S*)-3-((*S*)-4-((2-Bromophenyl)amino)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)-3-fluoro-1-methylindolin-2-one (3p). 3p was obtained as a white solid (97.3 mg, 96% yield), m.p. 163–165 °C. HPLC (Daicel Chiralpak ADH, *n*-hexane/2-propanol = 95:5, flow rate 1.0 mL/min, detection at 254 nm): major diastereoisomer, t_R = 20.4 min (minor), t_R = 25.3 min (major); minor diastereoisomer, t_R = 41.0 min; 98% *ee* for the major diastereoisomer. $[\alpha]_D^{20}$ = –82.4 (c 2.88, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (dd, J_1 = 7.8 Hz, J_2 = 1.4 Hz, 1H, ArH), 7.42–7.30 (m, 5H, ArH), 7.27–7.23 (m, 2H, ArH), 7.15–7.10 (m, 1H, ArH), 7.01–6.95 (m, 2H, NH+ArH), 6.80 (d, J = 8.0 Hz, 1H, ArH), 6.60 (td, J_1 = 7.6 Hz, J_2 = 1.6 Hz, 1H, ArH), 6.05 (dd, J_1 = 8.2 Hz, J_2 = 1.4 Hz, 1H, ArH), 3.23 (s, 3H, CH_3), 2.38 (d, J = 1.6 Hz, 3H, CH_3) ppm; ^{13}C NMR (176 MHz, $CDCl_3$): δ 169.1 (d, $^2J_{C\text{-}F}$ = 22.0 Hz), 168.0 (d, $^3J_{C\text{-}F}$ = 5.3 Hz), 157.7, 144.5 (d, $^3J_{C\text{-}F}$ = 5.1 Hz), 141.5, 136.7, 133.2, 133.0, 128.7, 128.7, 126.0, 124.9, 123.0, 120.0, 119.44, 119.36 (d, $^2J_{C\text{-}F}$ = 18.7 Hz), 111.2, 110.5, 109.3, 89.7 (d, $^1J_{C\text{-}F}$ = 209.4 Hz), 73.4 (d, $^2J_{C\text{-}F}$ = 23.4 Hz), 26.4, 15.9 (d, $^4J_{C\text{-}F}$ = 4.0 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ –170.1 ppm. HRMS (ESI): *m/z* calcd for $C_{25}H_{20}N_4O_2F^{78.9183}Br$ [M + H]$^+$ 507.0826, found 507.0825; $C_{25}H_{20}N_4O_2F^{80.9163}Br$ [M + H]$^+$ 509.0806, found 509.0808.

(*S*)-3-Fluoro-1,5-dimethyl-3-((*S*)-3-methyl-5-oxo-1-phenyl-4-(phenylamino)-4,5-dihydro-1*H*-pyrazol-4-yl) indolin-2-one (3q). 3q was obtained as a white solid (71.6 mg, 81% yield), m.p. 180–182 °C. HPLC (Daicel Chiralpak IA, *n*-hexane/2-propanol = 85:15, flow rate 1.0 mL/min, detection at 254 nm): major diastereoisomer, t_R = 9.3 min (minor), t_R = 13.4 min (major); minor diastereoisomer, t_R = 28.8 min (major), t_R = 35.0 min (minor); 98% *ee* for the major diastereoisomer. $[\alpha]_D^{20}$ = –35.7 (*c* 1.08, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, J = 8.0 Hz, 2H, ArH), 7.27–7.21 (m, 2H, ArH), 7.18 (s, 1H, ArH), 7.13–7.09 (m, 4H, ArH), 6.85 (s, 1H, NH), 6.75 (t, J = 7.4 Hz, 1H, ArH), 6.67 (d, J = 8.0 Hz, 1H, ArH), 6.52 (d, J = 8.0 Hz, 2H, ArH), 3.21 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 2.25 (s, 3H, CH_3) ppm; ^{13}C NMR (176 MHz, $CDCl_3$): δ 169.5 (d, $^2J_{C\text{-}F}$ = 22.0 Hz), 168.7 (d, $^3J_{C\text{-}F}$ = 5.3 Hz), 158.4, 144.6, 141.9 (d, $^3J_{C\text{-}F}$ = 5.3 Hz), 136.9, 133.0, 132.8, 129.5, 128.7, 125.7, 125.4, 119.7 (d, $^2J_{C\text{-}F}$ = 18.1 Hz), 119.6, 119.3, 114.0, 109.1, 89.7 (d, $^1J_{C\text{-}F}$ = 209.3 Hz), 73.8 (d, $^2J_{C\text{-}F}$ = 23.4 Hz), 26.5, 20.9, 16.0 (d, $^4J_{C\text{-}F}$ = 3.9 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ –170.2 ppm. HRMS (ESI): *m/z* calcd for $C_{26}H_{23}N_4O_2F$ [M + H]$^+$ 443.1878, found 443.1882.

(*S*)-3,5-Difluoro-1-methyl-3-((*S*)-3-methyl-5-oxo-1-phenyl-4-(phenylamino)-4,5-dihydro-1*H*-pyrazol-4-yl) indolin-2-one (3r). 3r was obtained as a white solid (88.1 mg, 98% yield), m.p. 166–168 °C. HPLC (Daicel Chiralpak IA, *n*-hexane/2-propanol = 80:20, flow rate 1.0 mL/min, detection at 254 nm): major diastereoisomer, t_R = 8.1 min (minor), t_R = 12.1 min (major); >99% *ee* for the major diastereoisomer. $[\alpha]_D^{20}$ = +26.2 (*c* 4.12, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, J = 8.0 Hz, 2H, ArH), 7.25 (t, J = 8.0 Hz, 2H, ArH), 7.18–7.06 (m, 4H, ArH), 6.99 (t, J = 8.8 Hz, 1H, ArH), 6.77–6.73 (m, 2H, NH+ArH), 6.67 (dd, J_1 = 8.0 Hz, J_2 = 4.0 Hz, 1H, ArH), 6.51 (d, J = 8.0 Hz, 2H, ArH), 3.17 (s, 3H, CH_3), 2.44 (d, J = 1.6 Hz, 3H, CH_3) ppm; ^{13}C NMR (176 MHz, $CDCl_3$): δ 169.1 (d, $^2J_{C\text{-}F}$ = 21.3 Hz), 168.5 (d, $^3J_{C\text{-}F}$ = 5.1 Hz), 158.7 (d, $^1J_{C\text{-}F}$ = 241.8 Hz), 158.1, 144.3, 140.3 (d, $^4J_{C\text{-}F}$ = 4.6 Hz), 136.7, 129.5, 128.8, 125.9, 120.9 (dd, $^3J_{C\text{-}F}$ = 8.2, $^2J_{C\text{-}F}$ = 18.0 Hz), 119.8, 119.2, 119.1, 114.0, 112.9 (d, $^2J_{C\text{-}F}$ = 24.6 Hz), 110.1 (d, $^3J_{C\text{-}F}$ = 7.7 Hz), 89.3 (d, $^1J_{C\text{-}F}$ = 209.8 Hz), 73.6 (d, $^2J_{C\text{-}F}$ = 23.4 Hz), 26.5, 15.9 (d, $^4J_{C\text{-}F}$ = 3.7 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ –118.4, –170.8 ppm. HRMS (ESI): *m/z* calcd for $C_{25}H_{20}N_4O_2F_2$ [M + H]$^+$ 447.1627, found 447.1629.

(*S*)-5-Chloro-3-fluoro-1-methyl-3-((*S*)-3-methyl-5-oxo-1-phenyl-4-(phenylamino)-4,5-dihydro-1*H*-pyrazol-4-yl) indolin-2-one (3s). 3s was obtained as a white solid (80.7 mg, 87% yield), m.p. 178-180 °C. HPLC (Daicel Chiralpak IA, *n*-hexane/2-propanol = 80:20, flow rate 1.0 mL/min, detection at 254 nm): major diastereoisomer, t_R = 8.8 min (minor), t_R = 11.1 min (major); 99% *ee* for the major diastereoisomer. $[\alpha]_D^{20}$ = –99.0 (*c* 1.56, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (t, *J* = 7.6 Hz, 3H, ArH), 7.27 (t, *J* = 8.2 Hz, 3H, ArH), 7.15–7.09 (m, 3H, ArH), 6.79–6.67 (m, 3H, NH+ArH), 6.52 (d, *J* = 8.0 Hz, 2H, ArH), 3.19 (s, 3H, CH_3), 2.45 (s, 3H, CH_3) ppm; ^{13}C NMR (176 MHz, $CDCl_3$): δ 169.0 (d, $^2J_{C\text{-}F}$ = 21.1 Hz), 168.5 (d, $^3J_{C\text{-}F}$ =5.3 Hz), 158.2, 144.3, 142.9 (d, $^3J_{C\text{-}F}$ = 5.3 Hz), 136.7, 132.6, 129.6, 128.8, 128.6, 126.0, 125.1, 121.1 (d, $^2J_{C\text{-}F}$ = 18.1 Hz), 119.9, 119.4, 114.0, 110.3, 89.2 (d, $^1J_{C\text{-}F}$ = 209.8 Hz), 73.7 (d, $^2J_{C\text{-}F}$ = 23.2 Hz), 26.6, 15.9 (d, $^4J_{C\text{-}F}$ = 4.7 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ –171.0 ppm. HRMS (ESI): *m/z* calcd for $C_{25}H_{20}N_4O_2F^{34.9689}Cl$ $[M + H]^+$ 463.1332, found 463.1334; $C_{25}H_{20}N_4O_2F^{36.9659}Cl$ $[M + H]^+$ 465.1308, found 465.1317.

(*S*)-5-Bromo-3-fluoro-1-methyl-3-((*S*)-3-methyl-5-oxo-1-phenyl-4-(phenylamino)-4,5-dihydro-1*H*-pyrazol-4-yl) indolin-2-one (3t). 3t was obtained as a white solid (91.3 mg, 90% yield), m.p. 175–177 °C. HPLC (Daicel Chiralpak IB, n-hexane/2-propanol = 90:10, flow rate 1.0 mL/min, detection at 254 nm): major diastereoisomer, t_R = 9.7 min (minor), t_R = 8.1 min (major); minor diastereoisomer, t_R = 20.5 min, t_R = 25.4 min; 89% *ee* for the major diastereoisomer. $[\alpha]_D^{20}$ = –13.3 (*c* 0.73, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (s, 1H, ArH), 7.43–7.39 (m, 3H, ArH), 7.28 (t, *J* = 7.8 Hz, 2H, ArH), 7.16–7.10 (m, 3H, ArH), 6.78 (t, *J* = 7.4 Hz, 1H, ArH), 6.71 (s, 1H, NH), 6.65 (d, *J* = 8.4 Hz, 1H, ArH), 6.52 (d, *J* = 8.0 Hz, 2H, ArH), 3.21 (s, 3H, CH_3), 2.45 (s, 3H, CH_3) ppm; ^{13}C NMR (176 MHz, $CDCl_3$): δ 168.9 (d, $^2J_{C\text{-}F}$ = 22.0 Hz), 168.5 (d, $^3J_{C\text{-}F}$ = 5.3 Hz), 158.2, 144.3, 143.4 (d, $^3J_{C\text{-}F}$ = 5.1 Hz), 136.7, 135.6, 129.6, 128.8, 127.9, 126.0, 121.5 (d, $^2J_{C\text{-}F}$ = 18.1 Hz), 119.9, 119.5, 115.6, 114.0, 110.8, 89.2 (d, $^1J_{C\text{-}F}$ = 210.5 Hz), 73.8 (d, $^2J_{C\text{-}F}$ = 23,2 Hz), 26.6, 16.0 (d, $^4J_{C\text{-}F}$ = 3.9 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ –171.1 ppm. HRMS (ESI): *m/z* calcd for $C_{25}H_{20}N_4O_2F^{78.9183}Br$ $[M + H]^+$ 507.0826, found 507.0835; $C_{25}H_{20}N_4O_2F^{80.9163}Br$ $[M + H]^+$ 509.0806, found 509.0819.

(*S*)-6-Chloro-3-fluoro-1-methyl-3-((S)-3-methyl-5-oxo-1-phenyl-4-(phenylamino)-4,5-dihydro-1*H*-pyrazol-4-yl)indolin-2-one (3u). 3u was obtained as a white solid (88.0 mg, 95% yield), m.p. 78–80 °C. HPLC (Daicel Chiralpak IA, *n*-hexane/2-propanol = 85:15, flow rate 1.0 mL/min, detection at 254 nm): major diastereoisomer, t_R = 9.1 min (minor), t_R = 14.1 min (major); >99% *ee* for the major diastereoisomer. $[\alpha]_D^{20}$ = +35.5 (*c* 4.70, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38–7.34 (m, 2H, ArH), 7.30–7.22 (m, 3H, ArH), 7.14–7.07 (m, 3H, ArH), 6.96 (dd, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H, ArH), 6.79–6.69 (m, 3H, NH+ArH), 6.52 (d, *J* = 7.6 Hz, 2H, ArH), 3.18 (s, 3H, CH_3), 2.44 (d, *J* = 1.6 Hz, 3H, CH_3) ppm; ^{13}C NMR (176 MHz, $CDCl_3$): δ 169.4 (d, $^2J_{C\text{-}F}$ = 22.0 Hz), 168.5 (d, $^3J_{C\text{-}F}$ = 5.1 Hz), 158.2, 145.6 (d, $^3J_{C\text{-}F}$ = 5.1 Hz), 144.3, 139.0, 136.6, 129.5, 128.8, 126.0, 125.7, 122.9, 119.8, 119.4, 118.0 (d, $^2J_{C\text{-}F}$ = 18.3 Hz), 114.0, 110.1, 89.1 (d, $^1J_{C\text{-}F}$ = 209.4 Hz), 73.6 (d, $^2J_{C\text{-}F}$ = 21.8 Hz), 26.5, 15.9 (d, $^4J_{C\text{-}F}$ = 3.9 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ –169.8 ppm. HRMS (ESI): *m/z* calcd for $C_{25}H_{20}N_4O_2F^{34.9689}Cl$ $[M + H]^+$ 463.1332, found 463.1346; $C_{25}H_{20}N_4O_2F^{36.9659}Cl$ $[M + H]^+$ 465.1308, found 465.1330.

(*S*)-3-Fluoro-3-((*S*)-3-methyl-5-oxo-1-phenyl-4-(phenylamino)-4,5-dihydro-1*H*-pyrazol-4-yl) indolin-2-one (3v). 3v was obtained as a white solid (71.4 mg, 86% yield), m.p. 65–67 °C. HPLC (Daicel Chiralpak IA, *n*-hexane/2-propanol = 75:25, flow rate 1.0 mL/min, detection at 254 nm): major diastereoisomer, t_R = 36.5 min (major); minor diastereoisomer, t_R = 7.2 min, t_R = 12.8 min; >99% *ee* for the major diastereoisomer. $[\alpha]_D^{20}$ = +10.8 (*c* 1.72, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.85 (s, 1H, NH), 7.34–7.29 (m, 3H, ArH), 7.20 (t, *J* = 7.8 Hz, 2H, ArH), 7.14–7.03 (m, 4H, ArH), 6.91 (t, *J* = 7.6 Hz, 1H, ArH), 6.79–6.74 (m, 2H, NH+ArH), 6.54–6.49 (m, 3H, ArH), 2.46 (d, *J* = 1.6 Hz, 3H, CH_3) ppm; ^{13}C NMR (176 MHz, $CDCl_3$): δ 170.8 (d, $^2J_{C\text{-}F}$ = 22.0 Hz), 169.2 (d, $^3J_{C\text{-}F}$ = 5.3 Hz), 158.9, 144.5, 141.8 (d, $^3J_{C\text{-}F}$ = 6.3 Hz), 136.5, 132.8, 129.6, 128.8, 126.2, 125.0, 122.8, 120.0, 119.7, 119.7 (d, $^2J_{C\text{-}F}$ = 18.8 Hz), 113.9, 111.7, 89.8 (d, $^1J_{C\text{-}F}$ = 210.5 Hz), 74.0 (d, $^2J_{C\text{-}F}$ = 23.6 Hz), 15.9 (d, $^4J_{C\text{-}F}$ = 3.9 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ –169.8 ppm. HRMS (ESI): *m/z* calcd for $C_{24}H_{19}N_4O_2F$ $[M + H]^+$ 415.1565, found 415.1561.

(*S*)-1-Allyl-3-fluoro-3-((*S*)-3-methyl-5-oxo-1-phenyl-4-(phenyl-amino)-4,5-dihydro-1*H*-pyrazol-4-yl) indolin-2-one (3w). 3w was obtained as a white solid (89.5 mg, 98% yield), m.p. 99–101 °C. HPLC (Daicel Chiralpak IA, *n*-hexane/2-propanol = 85:15, flow rate 1.0 mL/min, detection at 254 nm): major diastereoisomer, t_R = 9.0 min (minor), t_R = 22.3 min (major); minor diastereoisomer, t_R = 31.0 min; 99% *ee* for the major diastereoisomer. $[\alpha]_D^{20}$ = +8.5 (*c* 3.26, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–7.34 (m, 3H, ArH), 7.29–7.20 (m, 3H, ArH), 7.11–7.06 (m, 3H, ArH), 6.97 (t, *J* = 7.6 Hz, 1H, ArH), 6.80–6.77 (m, 2H, NH+ArH), 6.74 (t, *J* = 7.4 Hz, 1H, ArH), 6.52 (d, *J* = 7.6 Hz, 2H, ArH), 5.89–5,79 (m, 1H, =CH), 5.33 (d, *J* = 16.8 Hz, 1H, =CH_2), 5.25 (d, *J* = 10.4 Hz, 1H, =CH_2), 4.46 (dd, J_1 = 16.4 Hz, J_2 = 4.8 Hz, 1H, CH_2), 4.24 (dd, *J* = 16.2, 5.8 Hz, 1H, CH_2), 2.46 (d, *J* = 1.2 Hz, 3H, CH_3) ppm; ^{13}C NMR (176 MHz, $CDCl_3$): δ 169.3 (d, $^2J_{C\text{-}F}$ = 21.5 Hz), 168.6 (d, $^3J_{C\text{-}F}$ = 5.1 Hz), 158.2, 144.5, 143.7 (d, $^3J_{C\text{-}F}$ = 5.3 Hz), 136.8, 132.7, 130.3, 129.5, 128.7, 125.7, 124.8, 123.0, 119.6, 119.6 (d, $^2J_{C\text{-}F}$ = 18.1 Hz), 119.3, 118.4, 114.0, 110.3, 89.5 (d, $^1J_{C\text{-}F}$ = 208.0 Hz), 73.7 (d, $^2J_{C\text{-}F}$ = 23.4 Hz), 42.9, 15.9 (d, $^4J_{C\text{-}F}$ = 3.9 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ –169.2 ppm. HRMS (ESI): *m/z* calcd for $C_{27}H_{23}N_4O_2F$ $[M + H]^+$ 455.1878, found 455.1883.

(*S*)-1-Benzyl-3-fluoro-3-((*S*)-3-methyl-5-oxo-1-phenyl-4-(phenyl-amino)-4,5-dihydro-1*H*- pyrazol-4-yl) indolin-2-one (3x). 3x was obtained as a white solid (94.0 mg, 93% yield), m.p. 60–62 °C. HPLC (Daicel Chiralpak IC, *n*-hexane/2-propanol = 95:5, flow rate 1.0 mL/min, detection at 254 nm): major diastereoisomer, t_R = 13.8 min (major); >99% *ee* for the major diastereoisomer. $[\alpha]_D^{20}$ = +54.2 (*c* 4.55, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.36 (m, 5H, ArH), 7.31–7.18 (m, 5H, ArH), 7.13–7.04 (m, 4H, ArH), 6.90 (t, *J* = 7.6 Hz, 1H, ArH), 6.86 (s, 1H, NH), 6.73 (t, *J* = 7.4 Hz, 1H, ArH), 6.57–6.53 (m, 3H, ArH), 4.97 (d, *J* = 16.0 Hz, 1H, CH_2), 4.97 (d, *J* = 16.0 Hz, 1H, 1H, CH_2), 2.46 (d, *J* = 1.6 Hz, 3H, CH_3) ppm; ^{13}C NMR (176 MHz, $CDCl_3$): δ 169.8 (d, $^2J_{C\text{-}F}$ = 22.2 Hz), 168.6 (d, $^3J_{C\text{-}F}$ = 5.3 Hz), 158.3, 144.4, 143.6 (d, $^3J_{C\text{-}F}$ = 5.3 Hz), 136.7, 134.2, 132.7, 129.5, 128.7, 128.6, 127.8, 127.3, 125.7, 124.9, 123.1, 119.7, 119.6, 119.2, 113.9, 110.5, 89.6 (d, $^1J_{C\text{-}F}$ = 208.0 Hz), 73.6 (d, $^2J_{C\text{-}F}$ = 23.6 Hz), 44.4, 15.9 (d, $^4J_{C\text{-}F}$ = 4.0 Hz) ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ –167.6 ppm. HRMS (ESI): *m/z* calcd for $C_{31}H_{25}N_4O_2F$ $[M + H]^+$ 505.2034, found 505.2038.

***Tert*-butyl ((*S*)-4-((*S*)-3-fluoro-1-methyl-2-oxoindolin-3-yl)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)carbamate (3y). 3y** was obtained as a white solid (32.5 mg, 36% yield), m.p. 62–64 °C. HPLC (Daicel Chiralpak IA, *n*-hexane/2-propanol = 80:20, flow rate 1.0 mL/min, detection at 254 nm): major diastereoisomer, t_R = 6.4 min (minor), t_R = 9.6 min (major); 28% *ee* for the major diastereoisomer. $[\alpha]_D^{20}$ = −31.8 (*c* 1.12, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, *J* = 8.0 Hz, 2H, ArH), 7.43–7.36 (m, 3H, ArH), 7.30 (d, *J* = 7.6 Hz, 1H, ArH), 7.21–7.17 (m, 1H, ArH), 6.92 (t, *J* = 7.6 Hz, 1H, ArH), 6.87 (d, *J* = 8.0 Hz, 1H, ArH), 3.23 (s, 3H, CH_3), 1.87 (br s, 3H, CH_3), 1.62 (s, 1H, NH), 1.45 (s, 3H, CH_3), 1.43 (br s, 6H, CH_3) ppm; ^{13}C NMR (176 MHz, $CDCl_3$): δ 167.3, 143.6 (d, $^3J_{C\text{-}F}$ = 5.1 Hz), 137.5, 133.0 (d, $^4J_{C\text{-}F}$ = 2.8 Hz), 128.8, 125.8, 125.4, 123.9, 119.9 (d, $^2J_{C\text{-}F}$ = 18.1 Hz), 119.3, 109.1, 28.2, 28.1, 26.4, 13.4 ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ –175.8, –176.7 ppm. HRMS (ESI): *m/z* calcd for $C_{24}H_{25}FN_4NaO_4$ [M + Na]$^+$ 475.1752, found 475.1746.

Procedure for synthesis of compound 4i: To the solution of product **3i** (0.2 mmol) in CH_2Cl_2 (1.0 mL), the cerium ammonium nitrate (CAN) (0.8 mmol, 4 equiv) in H_2O (1.0 mL) was dropwise added at 0 °C. The progress of the reaction was monitored by TLC analysis (petroleum ether/ ethyl acetate = 3:2). After the completion of the reaction, a solution of NaOH (1.0 N) was added to the aqueous phase and then extracted with MTBE. The combined organic phases dried with $MgSO_4$ and concentrated under reduced pressure. The crude reaction mixture was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 4:1) to give pure compound **4i.**

(*S*)-3-Fluoro-3-((*S*)-3-methyl-5-oxo-4-((4-oxocyclohexa-2,5-dien-1-ylidene)amino)-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl) indolin-2-one (4i). 4i was obtained as a yellow solid (67.2 mg, 76% yield), m.p. 82–84 °C. HPLC (Daicel Chiralpak IB, n-hexane/2-propanol = 90:10, flow rate 1.0 mL/min, detection at 254 nm): major diastereoisomer, t_R = 22.5 min (major), t_R = 42.6 min (minor); minor diastereoisomer, t_R = 18.5 min (minor), t_R = 21.7 min (major); >99% *ee* for the major diastereoisomer. $[\alpha]_D^{20}$ = +368.9 (*c* 1.36, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, *J* = 7.6 Hz, 3H, ArH), 7.43–7.34 (m, 4H, ArH), 7.21 (t, *J* = 7.4 Hz, 1H, ArH), 7.08 (t, *J* = 7.6 Hz, 1H, ArH), 6.85 (d, *J* = 8.0 Hz, 1H, =CH), 6.64 (d, *J* = 10.0 Hz, 1H, =CH), 6.43 (s, 2H, =CH), 3.19 (s, 3H, CH_3), 1.91 (s, 3H, CH_3). ppm; ^{13}C NMR (176 MHz, $CDCl_3$): δ 186.3, 168.5 (d, $^2J_{C\text{-}F}$ = 22.0 Hz), 168.0, 161.7, 156.7, 144.7 (d, $^3J_{C\text{-}F}$ = 6.2 Hz), 142.6, 136.5, 134.9, 132.6, 132.5, 129.0, 126.6, 126.2, 126.1, 123.0, 121.3 (d, $^2J_{C\text{-}F}$ = 19.2 Hz), 119.5, 108.7, 92.7 (d, $^1J_{C\text{-}F}$ = 210.8 Hz), 78.1 (d, $^2J_{C\text{-}F}$ = 23.9 Hz), 26.4, 15.5. ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ –169.3 ppm. HRMS (ESI): *m/z* calcd for $C_{25}H_{19}N_4O_3F$ [M + H]$^+$ 443.1514, found 443.1526.

Procedure for synthesis of compound 5i: To the solution of product **3i** (0.2 mmol) in CH_3CN (1.0 mL), the cerium ammonium nitrate (CAN) (0.8 mmol, 4 equiv) in H_2O (1.0 mL) was dropwise added at 50 °C. The progress of the reaction was monitored by TLC analysis (Petroleum ether/ethyl acetate = 3:2). After the completion of the reaction, a solution of NaOH (1.0 N) was added to the aqueous phase and then extracted with MTBE. The combined organic phases dried with $MgSO_4$ and concentrated under reduced pressure. The crude reaction mixture was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 5:1) to give pure compound **5i.**

(*S*)-3-((*S*)-4-amino-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)-3-fluoro-1-methylindolin-2-one (5i). 5i was obtained as a yellow solid (43.9 mg, 73% yield), m.p. 143–145 °C. HPLC (Daicel Chiralpak ADH, *n*-hexane/2-propanol = 70:30, flow rate 1.0 mL/min, detection at 254 nm): major diastereoisomer, t_R = 9.8 min (major), t_R = 17.3 min (minor); >99% ee for the major diastereoisomer. $[\alpha]_D^{20}$ = +16.9 (*c* 0.86, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.37 (m, 2H, ArH), 7.32 (tt, J_1 = 7.8 Hz, J_2 = 1.4 Hz, 1H, ArH), 7.27–7.20 (m, 3H, ArH), 7.12–7.07 (m, 1H, ArH), 6.97 (t, *J* = 7.6 Hz, 1H, ArH), 6.79 (d, *J* = 7.6 Hz, 1H, ArH), 3.22 (s, 3H, CH_3), 2.56 (s, 2H, NH), 2.44 (d, *J* = 1.6 Hz, 3H, CH_3). ppm; ^{13}C NMR (176 MHz, $CDCl_3$): δ 169.4 (d, $^3J_{C\text{-}F}$ = 7.6 Hz), 169.2 (d, $^2J_{C\text{-}F}$ = 20.8 Hz), 157.5, 144.4 (d, $^3J_{C\text{-}F}$ = 5.3 Hz), 136.7, 132.5, 128.7, 125.6, 124.4, 123.0, 120.3 (d, $^2J_{C\text{-}F}$ = 19.2 Hz), 119.4, 109.0, 90.3 (d, $^1J_{C\text{-}F}$ = 200.3 Hz), 78.1 (d, $^2J_{C\text{-}F}$ = 26.0 Hz), 26.2, 15.4 (d, $^4J_{C\text{-}F}$ = 3.9 Hz). ppm; ^{19}F NMR (376 MHz, $CDCl_3$): δ –172.9 ppm. HRMS (ESI): *m/z* calcd for $C_{19}H_{17}N_4O_2F$ [M + H]$^+$ 353.1408, found 353.1402.

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Notes and references

1 (a) S.-C. Kuo, L.-J. Huang and H. Nakamura, *J. Med. Chem.*, 1984, **27**, 539−544; (b) D.-A. Horton, G.-T. Bourne and M.-L. Smythe, *Chem. Rev.*, 2003, **103**, 893−930; (c) N. Foloppe, L.-M. Fisher and A.-E. Surgenor, *Bioorg. Med. Chem.*, 2006, **14**, 4792−4802; (d) P.-L. McCormack, *Drugs*, 2011, **71**, 2457−2489; (e) Y. Zhang, R. Benmohamed, H. Huang, T. Chen, C. Voisine, R.-I. Morimoto, D.-R. Kirsch and R.-B. Silverman, *J. Med. Chem.*, 2013, **56**, 2665−2675.

2 (a) G. Saretzki, *Cancer Lett.*, 2003, **194**, 209−219; (b) A. Kimata, H. Nakagawa, R. Ohyama, T. Fukuuchi and N. Miyata, *J. Med. Chem.*, 2007, **50**, 5053−5056; (c) D.-M. Bradley, W.-N. Chan, K.-M. Thewlis and S.-E. Ward, PCT/EP2007/061794, WO2008053031A1, 2008; (d) V. Hadi, Y.-H. Koh, T.-W. Sanchez, D. Barrios, N. Neamati and K.-W. Jung, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 6854−6857; (e) Y. Zhang, R. Benmohamed, H. Huang, T. Chen, C. Voisine, R.-I. Morimoto, D.-R. Kirsch and R.-B. Silverman, *J. Med. Chem.*, 2013, **56**, 2665−2675.

3 Y. Hamashima, T. Suzuki, H. Takano, Y. Shimura and M. Sodeoka, *J. Am. Chem. Soc.*, 2005, **127**, 10164−10165.

4 (a) P. Hewawasam, V.-K. Gribkoff, Y. Pendri, S.-I. Dworetzky, N.-A. Meanwell, J. Knipe, Q. Gao, R. Perrone and J.-E. Starrett, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 1023−1026; (b) K. Muller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881−1886; (c) C.-V. Galliford and K.-A. Scheidt, *Angew. Chem. Int. Edit.*, 2007, **46**, 8748−8758; (d) Z. Bian, C.-C. Marvin, M. Pettersson and S.-F. Martin, *J. Am. Chem. Soc.*, 2014, **136**, 14184−14192; (e) T. Fujiwara, T. Seki, T. Yakura and Y. Takeuchi, *J. Fluorine Chem.*, 2014, **165**, 7−13.

5 F. Josef and F.-S. Emily, *J. Am. Chem. Soc.*, 1954, **76**, 1455−1456.

6 Y.-H. Liao, W.-B. Chen, Z.-J. Wu, X.-L. Du, L.-F. Cun, X.-M. Zhang and W.-C. Yuan, *Adv. Synth. Catal.*, 2010, **352**, 827−832.

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DOI: 10.1039/C9OB01350D

7 (a) P. Chauhan, S. Mahajian and D. Enders, *Chem. Commun.*, 2015, **51**, 12890–12907; (b) D. Hack, P. Chauhan, N. Seling, L. Rübenach, L. Mertens, G. Raabe, F. Schoenebeck and D. Enders, *Angew. Chem. Int. Edit.*, 2016, **55**, 1797−1800; (c) S. Liu, X.-Z. Bao and B.-M. Wang, *Chem. Commun.*, 2018, **54**, 11515−11529.
8 L. Zhao, X. Bao, Q. Hu, B. Wang and A.-H. Lu, *ChemCatChem*, 2018, **10**, 1248−1252.
9 B.-Y. Li and D.-M. Du, *Adv. Synth. Catal.*, 2018, **360**, 3164–3170.
10 (a) J.-H. Li and D.-M. Du, *Org. Biomol. Chem.*, 2013, **11**, 6215–6223; (b) J.-H. Li and D.-M. Du, *Adv. Synth. Catal.*, 2015, **357**, 3986–3994; (c) J.-H. Li, H.-L. Wen, L. Liu and D.-M. Du, *Eur. J. Org. Chem.*, 2016, **2016**, 2492–2499; (d) J.-H. Li, Z.-H. Cui and D.-M. Du, Org. Chem. Front., 2016, **3**, 1087−1090.
11 CCDC 1912247 (for **3p**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.
12 D.-Y. Park, K.-H. Kim and C.-H. Cheon, *Adv. Synth. Catal.*, 2018, **360**, 462−467.