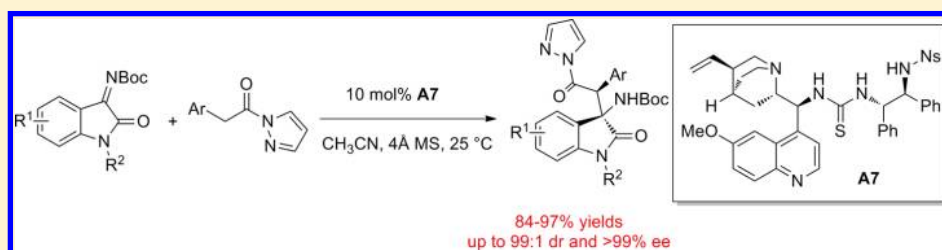


Organocatalyzed Enantioselective Mannich Reaction of Pyrazoleamides with Isatin-Derived Ketimines

Tian-Ze Li, Xi-Bo Wang, Feng Sha,* and Xin-Yan Wu*

Key Laboratory for Advanced Materials and Institute of Fine Chemicals, East China University of Science and Technology, Shanghai 200237, PR China

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ABSTRACT: The first organocatalytic enantioselective Mannich reaction of pyrazoleamides with isatin-derived *N*-Boc ketimines has been developed to afford 2-oxindole-based chiral β -amino amides in good yields (84–97%) with excellent diastereo- and enantioselectivities (up to 99:1 dr and >99% ee).

INTRODUCTION

The Mannich reaction represents one of the most effective C–C bond formation processes for the construction of β -aminocarbonyl compounds.¹ In the past decade, remarkable progress has been made on the organocatalytic asymmetric Mannich-type reactions.² In these examples, whereas aldimines are widely used as electrophiles, attempts on the utilization of ketimines are scarce.³ In addition, former investigations mainly focused on the use of ketones or aldehydes as the nucleophile, while, to the best of our knowledge, organocatalytic Mannich reaction using amides as a nucleophile has never been described.⁴ A drawback of using ketones or aldehydes as donors in the said reactions lies in that an additional oxidation of the formed β -amino aldehyde/ketone is required to obtain β -amino acids, a class of important structural motifs widely found in bioactive natural products and pharmaceuticals.⁵ Therefore, development of a simplified protocol for the enantioselective synthesis of β -amino acid via the Mannich reaction is of great interest.

3-Substituted 3-amino-2-oxindoles are privileged core structural motifs in many biologically active natural and synthetic compounds.⁶ Because of their importance, a diverse range of tactics have been developed for their asymmetric synthesis,⁷ involving the addition of various nucleophiles to ketimines derived from isatins^{3d–f,8} and α -amination of oxindoles.⁹ In 2012, Shibata's group reported the first, still the only, means available to obtaining oxindole-based β -amino thioesters by an enantioselective decarboxylative addition of malonic acid half thioesters to isatin-derived *N*-Boc ketimines.^{3e} As a consequence, it remains highly desirable to explore novel catalytic approaches for construction of oxindole-based chiral β -amino acids.

Recently, Barbas and co-workers described the use of pyrazoleamides as a special donor in an asymmetric Michael reaction.¹⁰ Substrates that feature pyrazoleamides with an electron-withdrawing aromatic group yielded the best results. We hypothesize the employment of pyrazoleamide as a nucleophile in the asymmetric Mannich reaction with isatin-derived ketimines toward the access of isatin-derived β -amino amides with potentially large medicinal values. As part of our ongoing research interest in the asymmetric synthesis of 3,3-disubstituted-2-oxindoles,¹¹ herein we report the first asymmetric organocatalytic Mannich reaction of amides with isatin-derived ketimines.

RESULTS AND DISCUSSION

Initially a Mannich reaction of isatin-derived *N*-Boc ketimine **1a** with pyrazoleamide **2a** was conducted as a model reaction to screen a suitable chiral bifunctional organocatalyst (Figure 1). As illustrated in Table 1, the reaction proceeded smoothly in CH_2Cl_2 with addition of 10 mol % of the Takemoto catalyst¹² **A1** at room temperature, which afforded the desired product in good yield with moderate diastereoselectivity and enantioselectivity (entry 1). Cinchonine and quinine derived tertiary amine-thiourea catalysts **A2** and **A3** provided better enantioselectivities than **A1** (entries 2 and 3). With tertiary amine-squaramide **A4**, an excellent stereoselectivity was obtained (96:4 dr, 95% ee, entry 4). These results indicate that the hydrogen-bonding effect of the catalysts might play an important role in controlling the stereoselectivity.

We therefore examined the catalytic activities of quinine-derived organocatalysts **A5–7** bearing sulfonamide as a

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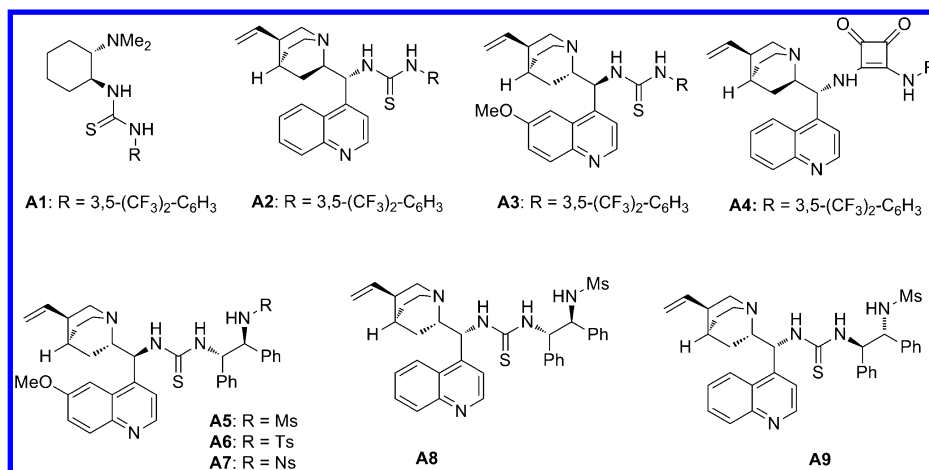


Figure 1. Structures of the screened organocatalysts.

Table 1. Screening of the Catalysts for the Mannich Reaction of Ketimine **1a** with Pyrazoleamide **2a**^a

entry	cat.	<i>t</i> (h)	yield (%) ^b	dr ^c	ee (%) ^c
1	A1	72	79	87:13	−62
2	A2	96	69	88:12	−87
3	A3	96	72	80:20	82
4	A4	96	63	96:4	−95
5	A5	96	63	96:4	97
6	A6	74	53	97:3	96
7	A7	74	60	98:2	97
8	A8	96	31	83:17	−88
9	A9	96	48	96:4	−98
10 ^d	A7	65	68	98:2	99

^aThe reactions were carried out with ketimine **1a** (0.2 mmol), amide **2a** (0.24 mmol), and catalyst (0.02 mmol) in 1 mL of CH₂Cl₂ at 25 °C. ^bIsolated yields. ^cDetermined by chiral HPLC analysis. ^d50 mg of 4 Å molecular sieves was added.

multiple hydrogen-bonding donor¹³ (entries 5–7). Up to 97% ee with excellent diastereoselectivity were obtained in the presence of 10 mol % of **A7** (entry 7). Using **A8** as the catalyst, the corresponding stereoselectivities and yield decreased obviously, presumably due to a poor chirality match between 9-amino(9-deoxy) epicinchonine and the (S,S)-1,2-diphenyl-ethane-1,2-diamine moiety. Although cinchonine derived catalyst **A9** provided an excellent enantioselectivity, the yield was unsatisfactory (entry 9). In addition, presence of 4 Å molecular sieves improved the reaction rate and enantioselectivity (entry 10 vs 7). In terms of both yield and enantioselectivity, **A7** was selected as the catalyst for further optimization of the reaction conditions.

Next, the solvent effect was investigated. As shown in Table 2, in all the solvents examined except DMF, product **3aa** could be obtained in excellent diastereoselectivity and enantioselectivity (entries 1–7). In relatively less polar solvents such as toluene and CH₂Cl₂, the product was obtained in moderate yields (entries 1–2), and use of CH₃CN gave the optimal

Table 2. Optimization of the Reaction Conditions^a

entry	solvent	<i>t</i> (h)	yield (%) ^b	dr ^c	ee (%) ^c
1	CH ₂ Cl ₂	65	68	98:2	99
2	toluene	96	62	98:2	97
3	Et ₂ O	36	78	99:1	98
4	THF	96	73	98:2	96
5	EtOAc	36	81	98:2	98
6	CH ₃ CN	18	91	99:1	99
7	DMF	36	81	33:67	10
8 ^d	CH ₃ CN	48	73	98:2	99
9 ^e	CH ₃ CN	96	15	99:1	99
10 ^f	CH ₃ CN	12	92	95:5	97
11 ^g	CH ₃ CN	36	72	98:2	99
12 ^h	CH ₃ CN	13	92	99:1	99

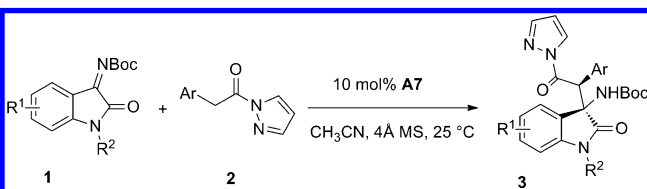
^aUnless stated otherwise, the reactions were carried out with **1a** (0.2 mmol), amide **2a** (0.24 mmol), **A3** (0.02 mmol), 4 Å molecular sieves (50 mg) at 25 °C in 1 mL of solvent. ^bIsolated yields. ^cDetermined by chiral HPLC analysis. ^dThe catalyst loading of **A7** was 5 mol %. ^eThe reaction temperature was 0 °C. ^fThe reaction temperature was 40 °C. ^gThe concentration of **1a** was 0.1 M. ^hThe concentration of **1a** was 0.3 M.

result. In CH₃CN, the reaction was completed in the shortest reaction time with a high yield and excellent enantioselectivity and diastereoselectivity (entry 6). Reducing the catalyst loading from 10 to 5 mol % resulted in an obvious decrease of yield, but with a retained enantioselectivity (entry 8 vs 6). A slightly decreased enantioselectivity was observed when the reaction was carried out at 40 °C (entry 10). On the other hand, the reaction became sluggish at 0 °C, and only 15% yield was achieved after stirring for 96 h (entry 9). When the concentration of **1a** was increased to 0.3 M, the reaction was completed in a shorter time with unchanged yield and stereoselectivities (entry 12). In contrast, lowering the substrate concentration (0.1 M) led to an obvious decrease of yield with a lower conversion rate (entry 11). On the basis of these results, the optimal reaction condition was established to be 0.3 M ketimines **1** in CH₃CN with addition of 1.2 equiv of

pyrazoleamides **2**, 50 mg of 4 Å molecular sieves, and 10 mol % catalyst A7 at 25 °C.

The substrate scope of the reaction by using differently substituted pyrazoleamides was examined under the optimized reaction condition (Table 3, entries 1–14). Being distinct from

Table 3. Substrate Scope of the Enantioselective Mannich Reaction^a



entry	Ar	R ¹	R ²	t (h)	yield (%) ^b	dr ^c	ee (%) ^c
1	Ph	H	Me	13	3aa, 92	99:1	99
2	4-CF ₃ C ₆ H ₄	H	Me	3	3ab, 91	96:4	96
3	4-BrC ₆ H ₄	H	Me	4	3ac, 94	97:3	97
4	4-ClC ₆ H ₄	H	Me	5	3ad, 93	97:3	97
5	4-FC ₆ H ₄	H	Me	8	3ae, 91	96:4	98
6	4-PhC ₆ H ₄	H	Me	9	3af, 96	99:1	>99
7	4-MeOC ₆ H ₄	H	Me	16	3ag, 93	96:4	>99
8	3-MeOC ₆ H ₄	H	Me	12	3ah, 97	98:2	99
9	3-BrC ₆ H ₄	H	Me	3	3ai, 92	98:2	99
10	2-MeOC ₆ H ₄	H	Me	84	3aj, 87	98:2	>99
11	2-BrC ₆ H ₄	H	Me	72	3ak, 91	95:5	99
12	1-naphthyl	H	Me	72	3al, 84	95:5	98
13	2-naphthyl	H	Me	5	3am, 96	99:1	97
14	2-thienyl	H	Me	1.5	3an, 93	94:6	97
15	Ph	5-F	Me	12	3ba, 93	97:3	98
16	Ph	5-Cl	Me	11	3ca, 91	96:4	98
17	Ph	5-Br	Me	11	3da, 92	95:5	98
18	Ph	5-Me	Me	24	3ea, 90	96:4	99
19	Ph	5-MeO	Me	18	3fa, 93	98:2	>99
20	Ph	6-Cl	Me	12	3ga, 94	97:3	99
21	Ph	6-Br	Me	12	3ha, 95	97:3	99
22	Ph	7-F	Me	12	3ia, 95	98:2	99
23	Ph	7-Cl	Me	12	3ja, 94	98:2	98
24	Ph	7-Br	Me	12	3ka, 94	98:2	98
25	Ph	7-CF ₃	Me	10	3la, 91	99:1	96
26	Ph	7-Me	Me	18	3ma, 94	98:2	>99
27	Ph	H	Bn	36	3na, 87	98:2	>99

^aThe reactions were carried out with ketimines (0.2 mmol), amides (0.24 mmol), 4 Å molecular sieves (50 mg), and A7 (0.02 mmol) in 0.66 mL of CH₃CN at 25 °C. ^bIsolated yields. ^cDetermined by chiral HPLC analysis.

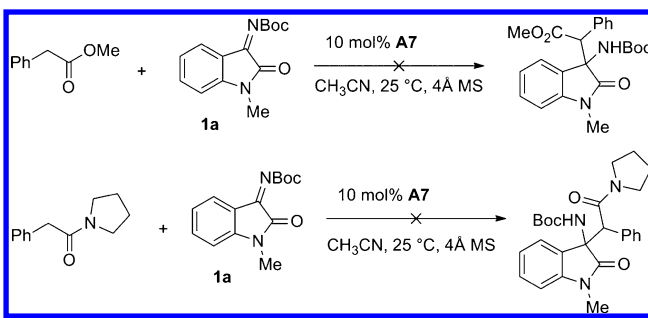
Barbas's work where the majority of the good results were produced from pyrazoleamides containing an electron-withdrawing aromatic group,¹⁰ all the pyrazoleamides examined underwent smoothly the Mannich reaction developed here to afford the desired adducts in excellent yields and stereoselectivities. Substrates **2** with an electron-withdrawing group at the 4-position gave slightly lower enantioselectivities than those without substituents or with electron-donating groups. Pyrazoleamides bearing either an electron-withdrawing or an electron-donating group at *para*- or *meta*-position afforded the desired products in excellent diastereoselectivities. Substitution at the *ortho*-position also provided excellent stereoselectivities, despite a longer reaction time required, probably due to a steric hindrance. To our disappointment, aliphatic substituted

pyrazoleamides are unreactive nucleophiles under the typical reaction condition.

Further exploration of the scope of the reaction was focused on varying the substituents on the isatin-derived ketimines (entries 15–26). To our delight, the reaction tolerated well all the *N*-Boc-1-methyl ketimine substrates with either an electron-withdrawing or an electron-donating group at different substitution positions, affording the corresponding adducts **3** in excellent yields, enantioselectivities, and diastereoselectivities. *N*-Benzyl substituted ketimine **1n** also gave the corresponding product **3na** in high yield along with excellent stereoselectivity (entry 27).

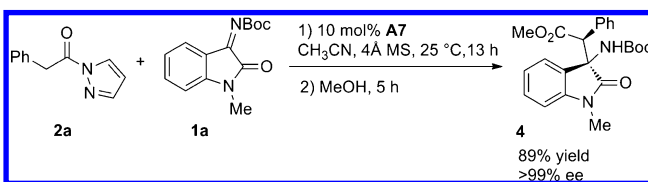
As predicted, methyl 2-phenylacetate and 2-phenyl-1-(pyrrolidin-1-yl)ethanone are unreactive nucleophiles under the typical reaction condition (Scheme 1), suggesting the importance of a pyrazol group to facilitate the Mannich reaction.

Scheme 1. Control Reaction of Methyl 2-Phenylacetate or Pyrrolidinyl 2-Phenylacetate with 1a



To further explore the synthetic application of the Mannich reaction developed, we investigated the transformation of the product **3aa** to its corresponding β -amino acid derivative. Pyrazole amide can be easily transformed to β -amino ester by a one-pot alcoholysis with high yield and excellent enantioselectivity (Scheme 2).

Scheme 2. One-Pot Esterification



A single crystal of **3da** was obtained by recrystallizing from *n*-hexane/CHCl₃, and the configuration of the two contiguous stereocenters was determined as 3*R* and 1'*S* by X-ray analysis (see the Supporting Information). The configurations of other adducts **3** were assigned by analogy. According to the result and the related literatures,^{3e,10} a possible transition-state structure was proposed as shown in Figure 2. Pyrazoleamide is deprotonated by the tertiary amine and then forms hydrogen bonds with the thiourea moiety of the catalyst. While another weak H-bonding interaction might be formed concurrently between the protonated amine and the ketimine, which forced the enolized pyrazoleamide attack of the ketimine from the *Si*-face, affording the adduct **3** with (3*R*,1'*S*)-configuration.

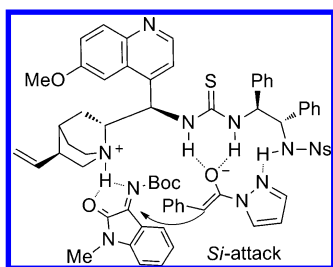


Figure 2. Proposed transition state.

CONCLUSION

In conclusion, we have first developed an organocatalytic enantioselective Mannich reaction of pyrazoleamides with isatin-derived *N*-Boc ketimines. In the presence of a quinone-based tertiary amine-thiourea catalyst, the corresponding isatin-derived chiral β -amino amides were obtained in good yields with excellent diastereo- and enantioselectivities. The method established here paves a new way for the asymmetric construction of β -amino acids.

EXPERIMENTAL SECTION

General Information. Melting points were taken without correction. High resolution mass spectra (HRMS) were performed on an electron spray ionization time-of-flight (ESI-TOF) mass spectrometer. The values of the specific rotation were derived from mixtures of diastereomers.

Catalyst **A1** was commercially available; catalysts **A2–A9** were prepared according to literature procedures.^{13a,14} *N*-Boc ketimines were synthesized according to literature.^{3d} Pyrazoleamide derivatives were prepared by following the literature procedure.^{10,15}

General Procedure for the Reaction of Pyrazoleamides with *N*-Boc Ketimines. To a solution of catalyst **A7** (0.02 mmol, 15.3 mg), pyrazoleamide **2** (0.24 mmol), and 4 Å molecular sieves (50.0 mg) in 0.66 mL of CH₃CN was added isatin-derived *N*-Boc ketimine **1** (0.2 mmol) at 25 °C, and the resulting mixture was stirred at this temperature until the reaction completed (monitored by TLC). The solvent was removed under reduced pressure, and the residue was purified by column chromatography (20/1 CH₂Cl₂/ethyl acetate) to give the desired product **3**.

***tert*-Butyl((*R*)-1-methyl-2-oxo-3-((*S*)-2-oxo-1-phenyl-2-(1*H*-pyrazol-1-yl)ethyl)indolin-3-yl)carbamate (**3aa**).** Yield: 92% (82 mg), white solid, mp 104.1–106.0 °C, $[\alpha]_D^{20} +56.7$ (c 1.7, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 8.17 (d, *J* = 2.8 Hz, 1H), 7.60 (s, 1H), 7.39–7.37 (m, 2H), 7.31–7.22 (m, 4H), 7.03 (d, *J* = 6.8 Hz, 1H), 6.94 (t, *J* = 7.6 Hz, 1H), 6.74 (d, *J* = 7.6 Hz, 1H), 6.36–6.35 (m, 1H), 6.17 (s, 1H), 5.61 (s, 1H), 3.17 (s, 3H), 1.17 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 174.0, 167.8, 153.6, 144.4, 143.9, 131.9, 130.4, 129.1, 129.0, 128.7, 128.6, 128.3, 123.5, 122.0, 110.3, 107.7, 80.4, 62.9, 53.1, 27.9, 26.4; IR (KBr, cm^{−1}) ν 3415, 2978, 1717, 1616, 1472, 1385, 1165, 1088, 1026, 753; HRMS calcd for C₂₅H₂₆N₄O₄ [M + H]⁺ 447.2032, found 447.2040; HPLC analysis (Daicel Chiralcel OD-H column, *n*-Hexane/*i*-PrOH = 90:10, 0.9 mL/min, λ = 254 nm) *t*_R = 13.1 min (major), 18.3 min (minor).

***tert*-Butyl((*R*)-1-methyl-2-oxo-3-((*S*)-2-oxo-2-(1*H*-pyrazol-1-yl)-1-(4-(trifluoromethyl)phenyl)ethyl)indolin-3-yl)carbamate (**3ab**).** Yield: 91% (94 mg), white solid, mp 87.5–89.3 °C, $[\alpha]_D^{20} +76.8$ (c 0.42, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 8.23 (d, *J* = 2.8 Hz, 1H), 7.62 (s, 1H), 7.53 (s, 4H), 7.25 (t, *J* = 7.6 Hz, 1H), 7.13 (d, *J* = 7.2 Hz, 1H), 6.95 (t, *J* = 7.6 Hz, 1H), 6.74 (d, *J* = 7.6 Hz, 1H), 6.47 (s, 1H), 6.42–6.41 (m, 1H), 5.62 (s, 1H), 3.18 (s, 3H), 1.19 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 173.3, 167.8, 153.7, 144.8, 143.5, 135.2, 130.8, 130.7, 130.4, 129.4, 128.9, 125.2, 125.0 (q, *J* = 3.6 Hz), 123.1, 122.4, 110.8, 108.1, 80.7, 63.2, 52.6, 28.0, 26.5; IR (KBr, cm^{−1}) ν 3475, 3414, 1740, 1725, 1617, 1385, 1324, 1071, 1020; HRMS calcd for C₂₆H₂₅F₃N₄NaO₄ [M + Na]⁺ 537.1726, found 537.1722; HPLC

analysis (Daicel Chiralcel OD-H column, *n*-Hexane/*i*-PrOH = 90:10, 0.9 mL/min, λ = 254 nm) *t*_R = 10.4 min (major), 13.1 min (minor).

***tert*-Butyl((*R*)-3-((*S*)-1-(4-bromophenyl)-2-oxo-2-(1*H*-pyrazol-1-yl)ethyl)-1-methyl-2-oxoindolin-3-yl)carbamate (**3ac**).** Yield: 94% (84 mg), white solid, mp 93.1–95.0 °C, $[\alpha]_D^{20} +73.9$ (c 0.47, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 8.20 (d, *J* = 2.8 Hz, 1H), 7.61 (s, 1H), 7.40 (d, *J* = 8.4 Hz, 2H), 7.27–7.23 (m, 3H), 7.10 (d, *J* = 7.2 Hz, 1H), 6.94 (t, *J* = 7.6 Hz, 1H), 6.74 (d, *J* = 7.6 Hz, 1H), 6.40–6.39 (m, 1H), 6.34 (s, 1H), 5.52 (s, 1H), 3.17 (s, 3H), 1.19 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 173.5, 167.8, 153.7, 144.6, 143.6, 132.0, 131.4, 130.1, 129.3, 128.9, 128.8, 123.2, 123.0, 122.2, 110.6, 108.0, 80.5, 62.9, 52.3, 27.9, 26.4; IR (KBr, cm^{−1}) ν 3421, 2981, 1720, 1620, 1388, 1327, 1165, 1126, 1072, 926, 536; HRMS calcd for C₂₅H₂₅BrN₄NaO₄ [M + Na]⁺ 547.0957, found 547.0950; HPLC analysis (Daicel Chiralcel OD-H column, *n*-Hexane/*i*-PrOH = 90:10, 0.9 mL/min, λ = 254 nm) *t*_R = 12.7 min (major), 14.8 min (minor).

***tert*-Butyl((*R*)-3-((*S*)-1-(4-chlorophenyl)-2-oxo-2-(1*H*-pyrazol-1-yl)ethyl)-1-methyl-2-oxoindolin-3-yl)carbamate (**3ad**).** Yield: 93% (89 mg), white solid, mp 95.3–97.1 °C, $[\alpha]_D^{20} +75.2$ (c 0.59, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 8.20 (d, *J* = 2.0 Hz, 1H), 7.61 (s, 1H), 7.33–7.23 (m, 5H), 7.11 (d, *J* = 7.2 Hz, 1H), 6.94 (t, *J* = 7.6 Hz, 1H), 6.73 (d, *J* = 7.6 Hz, 1H), 6.39 (s, 1H), 6.35 (s, 1H), 5.54 (s, 1H), 3.17 (s, 3H), 1.18 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 173.5, 167.8, 153.7, 144.6, 143.6, 134.7, 131.7, 129.6, 129.3, 129.0, 128.8, 128.4, 123.2, 122.2, 110.6, 107.9, 80.5, 63.0, 52.2, 27.9, 26.4; IR (KBr, cm^{−1}) ν 3417, 2978, 1720, 1616, 1493, 1388, 1254, 1165, 1088, 926, 756, 671; HRMS calcd for C₂₅H₂₅ClN₄NaO₄ [M + Na]⁺ 503.1462, found 503.1458; HPLC analysis (Daicel Chiralcel OD-H column, *n*-Hexane/*i*-PrOH = 90:10, 0.5 mL/min, λ = 254 nm) *t*_R = 21.2 min (major), 24.6 min (minor).

***tert*-Butyl((*R*)-3-((*S*)-1-(4-fluorophenyl)-2-oxo-2-(1*H*-pyrazol-1-yl)ethyl)-1-methyl-2-oxoindolin-3-yl)carbamate (**3ae**).** Yield: 91% (85 mg), white solid, mp 173.8–175.1 °C, $[\alpha]_D^{20} +84.0$ (c 0.29, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 8.21 (d, *J* = 2.8 Hz, 1H), 7.63 (s, 1H), 7.38–7.34 (m, 2H), 7.24 (t, *J* = 7.6 Hz, 1H), 7.11 (d, *J* = 7.2 Hz, 1H), 6.98–6.93 (m, 3H), 6.72 (d, *J* = 7.6 Hz, 1H), 6.41–6.40 (m, 1H), 6.35 (s, 1H), 5.57 (s, 1H), 3.16 (s, 3H), 1.17 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 173.6, 168.0, 162.8 (d, *J* = 246.9 Hz), 153.7, 144.6, 143.7, 132.1 (d, *J* = 8.1 Hz), 129.2, 129.0, 128.9, 126.8 (d, *J* = 3.0 Hz), 123.2, 122.2, 115.2 (d, *J* = 21.4 Hz), 110.6, 107.9, 80.5, 63.1, 52.0, 27.9, 26.4; IR (KBr, cm^{−1}) ν 3417, 2985, 1720, 1620, 1385, 1165, 764, 532; HRMS calcd for C₂₅H₂₅FN₄NaO₄ [M + Na]⁺ 487.1758, found 487.1757; HPLC analysis (Daicel Chiralcel OD-H column, *n*-Hexane/*i*-PrOH = 90:10, 0.9 mL/min, λ = 254 nm) *t*_R = 12.0 min (major), 14.5 min (minor).

***tert*-Butyl((*R*)-3-((*S*)-1-([1,1'-biphenyl]-4-yl)-2-oxo-2-(1*H*-pyrazol-1-yl)ethyl)-1-methyl-2-oxoindolin-3-yl)carbamate (**3af**).** Yield: 96% (100 mg), white solid, mp 188.2–189.3 °C, $[\alpha]_D^{20} +54.7$ (c 0.76, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 8.19 (d, *J* = 2.8 Hz, 1H), 7.62 (s, 1H), 7.56–7.52 (m, 4H), 7.47–7.40 (m, 4H), 7.35–7.32 (m, 1H), 7.28–7.24 (m, 1H), 7.08 (d, *J* = 7.2 Hz, 1H), 6.95 (t, *J* = 7.6 Hz, 1H), 6.76 (d, *J* = 8 Hz, 1H), 6.38–6.37 (m, 1H), 6.21 (s, 1H), 5.65 (s, 1H), 3.20 (s, 3H), 1.18 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 174.0, 168.0, 153.7, 144.5, 144.0, 141.4, 140.2, 130.9, 129.9, 129.2, 129.1, 128.7, 128.7, 127.5, 127.0, 126.9, 123.6, 122.1, 110.5, 107.9, 80.5, 62.9, 52.8, 27.9, 26.5; IR (KBr, cm^{−1}) ν 3417, 2981, 1720, 1616, 1388, 1165, 1088, 926, 756; HRMS calcd for C₃₁H₃₀N₄NaO₄ [M + Na]⁺ 545.2165, found 545.2164; HPLC analysis (Daicel Chiralcel OD-H column, *n*-Hexane/EtOH = 95:5, 0.3 mL/min, λ = 254 nm) *t*_R = 57.5 min (major), 68.1 min (minor).

***tert*-Butyl((*R*)-3-((*S*)-1-(4-methoxyphenyl)-2-oxo-2-(1*H*-pyrazol-1-yl)ethyl)-1-methyl-2-oxoindolin-3-yl)carbamate (**3ag**).** Yield: 93% (89 mg), white solid, mp 109.0–110.0 °C, $[\alpha]_D^{20} +51.2$ (c 0.52, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 8.16 (d, *J* = 2.8 Hz, 1H), 7.59 (s, 1H), 7.11 (d, *J* = 8.8 Hz, 2H), 7.26 (t, *J* = 8.0 Hz, 1H), 7.04 (d, *J* = 7.2 Hz, 1H), 6.94 (t, *J* = 7.6 Hz, 1H), 6.83 (d, *J* = 8.4 Hz, 2H), 6.76 (d, *J* = 7.6 Hz, 1H), 6.36–6.34 (m, 1H), 6.11 (s, 1H), 5.54 (s, 1H), 3.77 (s, 3H), 3.18 (s, 3H), 1.17 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 174.1, 168.1, 159.8, 153.7, 144.3, 144.0, 131.6, 129.1, 129.1, 128.7, 123.5, 122.8, 122.0, 113.8, 110.3, 107.8, 80.4, 62.9, 55.1, 52.3, 27.9,

26.5; IR (KBr, cm^{-1}) ν 3417, 2978, 1720, 1612, 1388, 1254, 1165, 1030, 926, 756, 532; HRMS calcd for $\text{C}_{26}\text{H}_{28}\text{N}_4\text{NaO}_5$ $[\text{M} + \text{Na}]^+$ 499.1957, found 499.1956; HPLC analysis (Daicel Chiralcel OD-H column, *n*-Hexane/*i*-PrOH = 90:10, 0.9 mL/min, λ = 254 nm) t_R = 11.5 min (major), 14.2 min (minor).

tert-Butyl((R)-3-((S)-1-(3-methoxyphenyl)-2-oxo-2-(1H-pyrazol-1-yl)ethyl)-1-methyl-2-oxoindolin-3-yl)carbamate (3ah). Yield: 97% (92 mg), white solid, mp 70.1–72.2 °C, $[\alpha]_D^{20} + 21.4$ (c 0.61, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3) δ 8.14 (d, J = 2.8 Hz, 1H), 7.60 (s, 1H), 7.29–7.21 (m, 2H), 7.04–6.90 (m, 4H), 6.85 (d, J = 8.4 Hz, 1H), 6.77 (d, J = 7.6 Hz, 1H), 6.36–6.35 (m, 1H), 6.03 (s, 1H), 5.62 (s, 1H), 3.74 (s, 3H), 3.18 (s, 3H), 1.17 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.1, 167.6, 159.3, 153.6, 144.4, 144.1, 132.3, 129.4, 129.2, 128.9, 128.6, 123.8, 122.8, 121.9, 115.9, 114.4, 110.3, 107.8, 80.4, 62.7, 55.2, 53.2, 27.9, 26.5; IR (KBr, cm^{-1}) ν 3421, 2978, 1720, 1612, 1493, 1385, 1254, 1165, 1088, 756; HRMS calcd for $\text{C}_{26}\text{H}_{28}\text{N}_4\text{NaO}_5$ $[\text{M} + \text{Na}]^+$ 499.1957, found 499.1953; HPLC analysis (Daicel Chiralcel OD-H column, *n*-Hexane/*i*-PrOH = 80:20, 0.2 mL/min, λ = 254 nm) t_R = 41.1 min (major), 52.0 min (minor).

tert-Butyl((R)-3-((S)-1-(3-bromophenyl)-2-oxo-2-(1H-pyrazol-1-yl)ethyl)-1-methyl-2-oxoindolin-3-yl)carbamate (3ai). Yield: 92% (97 mg), white solid, mp 77.2–79.5 °C, $[\alpha]_D^{20} + 61.5$ (c 0.65, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3) δ 8.22 (d, J = 2.8 Hz, 1H), 6.54 (s, 1H), 6.53 (s, 1H), 6.39 (d, J = 8.0 Hz, 1H), 7.30–7.22 (m, 2H), 7.14–7.09 (m, 2H), 6.96 (t, J = 7.6 Hz, 1H), 6.71 (d, J = 7.6 Hz, 1H), 6.42–6.41 (m, 1H), 6.36 (s, 1H), 5.56 (s, 1H), 3.18 (s, 3H), 1.18 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 173.4, 167.4, 153.6, 144.7, 143.6, 133.3, 133.1, 131.6, 129.5, 129.3, 129.3, 129.0, 128.8, 123.3, 122.2, 122.0, 110.7, 107.9, 80.5, 63.1, 52.4, 27.9, 26.4; IR (KBr, cm^{-1}) ν 3421, 2978, 1720, 1616, 1473, 1388, 1254, 1165, 1088, 926, 756; HRMS calcd for $\text{C}_{25}\text{H}_{26}\text{BrN}_4\text{O}_4$ $[\text{M} + \text{H}]^+$ 525.1137, found 525.1134; HPLC analysis (Daicel Chiralcel OD-H column, *n*-Hexane/*i*-PrOH = 90:10, 0.2 mL/min, λ = 254 nm) t_R = 58.0 min (major), 69.6 min (minor).

tert-Butyl((R)-3-((S)-1-(2-methoxyphenyl)-2-oxo-2-(1H-pyrazol-1-yl)ethyl)-1-methyl-2-oxoindolin-3-yl)carbamate (3aj). Yield: 87% (83 mg), white solid, mp 109.8–111.9 °C, $[\alpha]_D^{20} - 58.9$ (c 0.44, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3) δ 8.05 (d, J = 2.8 Hz, 1H), 7.52 (s, 1H), 7.33–7.28 (m, 2H), 7.00 (d, J = 8.4 Hz, 1H), 6.96 (d, J = 7.2 Hz, 1H), 6.87–6.83 (m, 4H), 6.53 (d, J = 6.8 Hz, 1H), 6.30 (s, 1H), 6.28–6.27 (m, 1H), 4.03 (s, 3H), 3.24 (s, 3H), 1.26 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 175.3, 168.0, 156.9, 145.0, 144.1, 130.7, 129.9, 129.7, 128.9, 128.5, 128.5, 124.4, 121.4, 120.6, 120.5, 111.7, 109.9, 107.5, 79.9, 63.5, 56.1, 46.3, 27.9, 26.4; IR (KBr, cm^{-1}) ν 3421, 2978, 1720, 1616, 1477, 1388, 1254, 1084, 926, 756, 532; HRMS calcd for $\text{C}_{26}\text{H}_{28}\text{N}_4\text{NaO}_5$ $[\text{M} + \text{Na}]^+$ 499.1957, found 499.1954; HPLC analysis (Daicel Chiralcel OD-H column, *n*-Hexane/*i*-PrOH = 95:5, 0.5 mL/min, λ = 254 nm) t_R = 54.6 min (major), 63.7 min (minor).

tert-Butyl((R)-3-((S)-1-(2-bromophenyl)-2-oxo-2-(1H-pyrazol-1-yl)ethyl)-1-methyl-2-oxoindolin-3-yl)carbamate (3ak). Yield: 91% (96 mg), white solid, mp 92.1–94.0 °C, $[\alpha]_D^{20} + 79.0$ (c 0.66, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3) δ 8.22 (d, J = 2.8 Hz, 1H), 7.64 (s, 1H), 7.60 (dd, J = 8.0, 1.2 Hz, 1H), 7.51 (dd, J = 8.0, 1.2 Hz, 1H), 7.26–7.20 (m, 2H), 7.16–7.09 (m, 2H), 6.98 (s, 1H), 6.89 (t, J = 7.2 Hz, 1H), 6.75 (d, J = 7.6 Hz, 1H), 6.40–6.39 (m, 1H), 6.17 (s, 1H), 3.22 (s, 3H), 1.17 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 173.1, 168.3, 153.7, 144.7, 143.6, 133.0, 130.8, 130.7, 129.9, 129.2, 129.2, 128.9, 127.0, 126.9, 123.1, 122.0, 110.7, 107.8, 80.3, 63.5, 50.7, 27.9, 26.4; IR (KBr, cm^{-1}) ν 3413, 2978, 1720, 1612, 1473, 1385, 1254, 1165, 1088, 922, 752, 529; HRMS calcd for $\text{C}_{25}\text{H}_{25}\text{BrN}_4\text{NaO}_4$ $[\text{M} + \text{Na}]^+$ 547.0957, found 547.0951; HPLC analysis (Daicel Chiralcel OD-H column, *n*-Hexane/*i*-PrOH = 90:10, 0.5 mL/min, λ = 254 nm) t_R = 24.5 min (major), 34.9 min (minor).

tert-Butyl((R)-1-methyl-3-((S)-1-(naphthalen-1-yl)-2-oxo-2-(1H-pyrazol-1-yl)ethyl)-2-oxoindolin-3-yl)carbamate (3al). Yield: 84% (83 mg), white solid, mp 154.7–156.3 °C, $[\alpha]_D^{20} - 75.2$ (c 0.56, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3) δ 8.45 (d, J = 8.4 Hz, 1H), 8.10 (d, J = 2.8 Hz, 1H), 7.83 (t, J = 8.8 Hz, 2H), 7.65 (t, J = 7.2 Hz, 2H), 7.59 (d, J = 7.2 Hz, 1H), 7.43–7.38 (m, 2H), 7.28–7.25 (m, 1H), 6.93–6.87 (m, 2H), 6.81 (d, J = 7.6 Hz, 1H), 6.71 (s, 1H), 6.25–

6.24 (m, 1H), 5.99 (s, 1H), 3.19 (s, 3H), 1.11 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.4, 168.3, 153.5, 144.3, 144.2, 134.0, 132.4, 129.6, 129.1, 129.1, 128.9, 128.4, 128.1, 127.1, 127.0, 125.9, 124.6, 124.0, 122.9, 121.8, 110.2, 107.7, 80.3, 63.5, 47.0, 27.8, 26.5; IR (KBr, cm^{-1}) ν 3429, 2978, 1720, 1612, 1473, 1385, 1250, 1165, 1088, 922, 756, 522; HRMS calcd for $\text{C}_{29}\text{H}_{29}\text{N}_4\text{O}_4$ $[\text{M} + \text{H}]^+$ 497.2189, found 497.2195; HPLC analysis (Daicel Chiralcel OD-H column, *n*-Hexane/*i*-PrOH = 95:5, 0.5 mL/min, λ = 254 nm) t_R = 28.1 min (major), 36.0 min (minor).

tert-Butyl((R)-1-methyl-3-((S)-1-(naphthalen-2-yl)-2-oxo-2-(1H-pyrazol-1-yl)ethyl)-2-oxoindolin-3-yl)carbamate (3am). Yield: 96% (95 mg), white solid, mp 129.8–130.7 °C, $[\alpha]_D^{20} + 40.5$ (c 0.48, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3) δ 8.16 (d, J = 2.8 Hz, 1H), 7.88 (s, 1H), 7.82–7.76 (m, 3H), 7.58 (s, 1H), 7.48–7.45 (m, 3H), 7.25 (t, J = 7.6 Hz, 1H), 7.03 (d, J = 7.2 Hz, 1H), 6.93 (t, J = 7.2 Hz, 1H), 6.74 (d, J = 8.0 Hz, 1H), 7.33–7.32 (m, 1H), 6.17 (s, 1H), 5.79 (s, 1H), 3.19 (s, 3H), 1.16 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.1, 167.8, 153.6, 144.4, 144.1, 133.0, 132.9, 129.9, 129.2, 129.0, 128.87, 128.5, 128.2, 128.0, 127.9, 127.5, 126.6, 126.3, 123.7, 122.0, 110.4, 107.8, 80.4, 62.9, 53.3, 27.9, 26.5; IR (KBr, cm^{-1}) ν 3417, 2978, 1720, 1616, 1388, 1250, 1165, 1088, 926, 756; HRMS calcd for $\text{C}_{29}\text{H}_{28}\text{N}_4\text{NaO}_4$ $[\text{M} + \text{Na}]^+$ 519.2008, found 519.2005; HPLC analysis (Daicel Chiralcel OD-H column, *n*-Hexane/*i*-PrOH = 80:20, 0.3 mL/min, λ = 254 nm) t_R = 29.4 min (major), 33.3 min (minor).

tert-Butyl((R)-1-methyl-2-oxo-3-((S)-2-oxo-2-(1H-pyrazol-1-yl)-1-(thiophen-2-yl)ethyl)indolin-3-yl)carbamate (3an). Yield: 93% (84 mg), white solid, mp 102.3–103.9 °C, $[\alpha]_D^{20} + 72.7$ (c 0.68, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3) δ 8.23 (s, 1H), 7.66 (s, 1H), 7.27–7.21 (m, 2H), 7.13 (d, J = 7.2 Hz, 1H), 7.02–6.89 (m, 3H), 6.72 (d, J = 7.6 Hz, 1H), 6.52 (s, 1H), 6.42 (s, 1H), 5.92 (s, 1H), 3.15 (s, 3H), 1.18 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 173.3, 167.4, 153.6, 144.6, 143.6, 131.8, 129.7, 129.2, 129.0, 128.8, 127.0, 126.4, 123.0, 122.1, 110.8, 107.8, 80.4, 63.1, 48.1, 27.9, 26.4; IR (KBr, cm^{-1}) ν 3417, 2981, 1720, 1616, 1388, 1250, 1165, 1088, 922; HRMS calcd for $\text{C}_{23}\text{H}_{24}\text{N}_4\text{NaO}_4\text{S}$ $[\text{M} + \text{Na}]^+$ 475.1416, found 475.1418; HPLC analysis (Daicel Chiralpak AD-H column, *n*-Hexane/*i*-PrOH = 70:30, 0.9 mL/min, λ = 254 nm) t_R = 12.6 min (major), 31.0 min (minor).

tert-Butyl((R)-5-fluoro-1-methyl-2-oxo-3-((S)-2-oxo-1-phenyl-2-(1H-pyrazol-1-yl)ethyl)indolin-3-yl)carbamate (3ba). Yield: 93% (86 mg), white solid, mp 99.1–100.9 °C, $[\alpha]_D^{20} + 42.3$ (c 0.13, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3) δ 8.16 (d, J = 2.8 Hz, 1H), 7.61 (s, 1H), 7.39–7.35 (m, 2H), 7.32–7.30 (m, 3H), 6.95 (td, J = 8.8, 2.4 Hz, 1H), 6.80 (dd, J = 8.0, 2.4 Hz, 1H), 6.66 (dd, J = 8.4, 4.0 Hz, 1H), 6.37–6.36 (m, 1H), 6.13 (s, 1H), 5.61 (s, 1H), 3.16 (s, 3H), 1.21 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 173.8, 167.6, 158.8 (d, J = 239.1 Hz), 153.4, 144.5, 140.1, 130.7, 130.3, 128.8, 128.7, 128.5, 115.2 (d, J = 23.4 Hz), 111.9 (d, J = 25.3 Hz), 110.5, 108.2 (d, J = 7.9 Hz), 80.6, 62.9, 53.2, 27.9, 26.6; IR (KBr, cm^{-1}) ν 3429, 2981, 1720, 1624, 1500, 1388, 1034, 930, 775; HRMS calcd for $\text{C}_{25}\text{H}_{25}\text{FN}_4\text{NaO}_4$ $[\text{M} + \text{Na}]^+$ 487.1758, found 487.1759; HPLC analysis (Daicel Chiralpak AD-H column, *n*-Hexane/*i*-PrOH = 85:15, 0.9 mL/min, λ = 254 nm) t_R = 24.4 min (major), 55.7 min (minor).

tert-Butyl((R)-5-chloro-1-methyl-2-oxo-3-((S)-2-oxo-1-phenyl-2-(1H-pyrazol-1-yl)ethyl)indolin-3-yl)carbamate (3ca). Yield: 91% (88 mg), white solid, mp 97.8–99.9 °C, $[\alpha]_D^{20} + 11.6$ (c 0.60, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3) δ 8.16 (d, J = 2.8 Hz, 1H), 7.61 (s, 1H), 7.38–7.34 (m, 2H), 7.33–7.30 (m, 3H), 7.22 (dd, J = 8.0, 2.0 Hz, 1H), 6.98 (d, J = 2.0 Hz, 1H), 6.66 (d, J = 8.0 Hz, 1H), 6.38–6.36 (m, 1H), 6.08 (s, 1H), 5.61 (s, 1H), 3.16 (s, 3H), 1.21 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 173.7, 167.5, 153.4, 144.5, 142.7, 130.7, 130.6, 130.4, 128.9, 128.9, 128.8, 128.5, 127.4, 124.2, 110.5, 108.7, 80.7, 62.7, 53.2, 28.0, 26.6; IR (KBr, cm^{-1}) ν 3425, 2981, 1724, 1612, 1493, 1388, 1250, 1165, 1095, 926, 525; HRMS calcd for $\text{C}_{25}\text{H}_{25}\text{ClN}_4\text{NaO}_4$ $[\text{M} + \text{Na}]^+$ 503.1462, found 503.1468; HPLC analysis (Daicel Chiralpak AD-H column, *n*-Hexane/*i*-PrOH = 80:20, 0.9 mL/min, λ = 254 nm) t_R = 15.6 min (major), 33.6 min (minor).

tert-Butyl((R)-5-bromo-1-methyl-2-oxo-3-((S)-2-oxo-1-phenyl-2-(1H-pyrazol-1-yl)ethyl)indolin-3-yl)carbamate (3da). Yield: 91% (96 mg), white solid, mp 105.3–107.4 °C, $[\alpha]_D^{20} + 18.9$ (c 0.16, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3) δ 8.16 (d, J = 2.8 Hz, 1H), 7.61 (s, 1H),

7.39–7.34 (m, 3H), 7.33–7.31 (m, 3H), 7.09 (d, $J = 2.0$ Hz, 1H), 6.62 (d, $J = 8.4$ Hz, 1H), 6.37–6.36 (m, 1H), 6.06 (s, 1H), 5.61 (s, 1H), 3.15 (s, 3H), 1.21 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 173.6, 167.5, 153.4, 144.5, 143.2, 131.8, 130.9, 130.7, 130.4, 128.9, 128.7, 128.5, 126.9, 114.5, 110.5, 109.2, 80.7, 62.6, 53.2, 27.9, 26.5; IR (KBr, cm^{-1}) ν 3448, 2980, 1720, 1665, 1388, 1250, 1161, 1092, 532; HRMS calcd for $\text{C}_{25}\text{H}_{25}\text{BrN}_4\text{NaO}_4$ $[\text{M} + \text{Na}]^+$ 547.0957, found 547.0952; HPLC analysis (Daicel Chiralpak AD-H column, n -Hexane/ i -PrOH = 80:20, 0.9 mL/min, $\lambda = 254$ nm) $t_R = 16.8$ min (major), 35.8 min (minor).

tert-Butyl((R)-1,5-dimethyl-2-oxo-3-((S)-2-oxo-1-phenyl-2-(1H-pyrazol-1-yl)ethyl)indolin-3-yl)carbamate (3ea). Yield: 90% (83 mg), white solid, mp 96.8–97.9 °C, $[\alpha]_D^{20} +26.9$ (c 0.52, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3) δ 8.17 (d, $J = 2.8$ Hz, 1H), 7.59 (d, $J = 0.8$ Hz, 1H), 7.39–7.36 (m, 2H), 7.30–7.27 (m, 3H), 7.04 (d, $J = 8.0$ Hz, 1H), 6.85 (s, 1H), 6.21 (d, $J = 7.6$ Hz, 1H), 6.35–6.34 (m, 1H), 6.11 (s, 1H), 5.62 (s, 1H), 3.13 (s, 3H), 2.23 (s, 3H), 1.17 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 173.8, 167.9, 153.7, 144.3, 141.5, 131.4, 131.1, 130.4, 129.2, 128.9, 128.6, 128.2, 124.4, 110.3, 107.4, 80.3, 63.0, 53.1, 27.9, 26.4, 21.0; IR (KBr, cm^{-1}) ν 3429, 2978, 1720, 1624, 1500, 1388, 1250, 1165, 1092, 930, 771, 525; HRMS calcd for $\text{C}_{26}\text{H}_{28}\text{N}_4\text{NaO}_4$ $[\text{M} + \text{Na}]^+$ 483.2008, found 483.2019; HPLC analysis (Daicel Chiralcel OD-H column, n -Hexane/ i -PrOH = 95:5, 0.9 mL/min, $\lambda = 254$ nm) $t_R = 17.0$ min (major), 28.1 min (minor).

tert-Butyl((R)-5-methoxy-1-methyl-2-oxo-3-((S)-2-oxo-1-phenyl-2-(1H-pyrazol-1-yl)ethyl)indolin-3-yl)carbamate (3fa). Yield: 93% (89 mg), white solid, mp 97.8–99.2 °C, $[\alpha]_D^{20} +26.2$ (c 0.61, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3) δ 8.16 (d, $J = 2.8$ Hz, 1H), 7.60 (s, 1H), 7.41–7.38 (m, 2H), 7.30–7.29 (m, 3H), 6.78 (dd, $J = 8.4$, 2.4 Hz, 1H), 6.66–6.64 (m, 2H), 6.36–6.35 (m, 1H), 6.11 (s, 1H), 5.62 (s, 1H), 3.69 (s, 3H), 3.14 (s, 3H), 1.19 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 173.7, 167.8, 155.5, 153.6, 144.4, 137.6, 131.0, 130.4, 130.1, 128.6, 128.4, 128.3, 113.7, 111.0, 110.3, 108.1, 80.4, 63.1, 55.8, 53.2, 27.9, 26.5; IR (KBr, cm^{-1}) ν 3417, 2978, 1720, 1616, 1500, 1388, 1165, 1034, 926, 771; HRMS calcd for $\text{C}_{26}\text{H}_{28}\text{N}_4\text{NaO}_5$ $[\text{M} + \text{Na}]^+$ 499.1957, found 499.1954; HPLC analysis (Daicel Chiralpak AD-H column, n -Hexane/ i -PrOH = 80:20, 0.9 mL/min, $\lambda = 254$ nm) $t_R = 22.5$ min (major), 64.3 min (minor).

tert-Butyl((R)-6-chloro-1-methyl-2-oxo-3-((S)-2-oxo-1-phenyl-2-(1H-pyrazol-1-yl)ethyl)indolin-3-yl)carbamate (3ga). Yield: 94% (90 mg), white solid, mp 127.1–129.0 °C, $[\alpha]_D^{20} +27.5$ (c 0.71, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3) δ 8.15 (d, $J = 2.8$ Hz, 1H), 7.60 (d, $J = 0.8$ Hz, 1H), 7.38–7.34 (m, 2H), 7.33–7.30 (m, 3H), 6.93–6.88 (m, 2H), 6.76 (s, 1H), 6.36–6.35 (m, 1H), 6.08 (s, 1H), 5.60 (s, 1H), 3.16 (s, 3H), 1.20 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.0, 167.7, 153.4, 145.3, 144.5, 134.9, 130.8, 130.3, 128.8, 128.7, 128.5, 127.3, 124.6, 121.8, 110.5, 108.6, 80.6, 62.4, 53.2, 27.9, 26.6; IR (KBr, cm^{-1}) ν 3417, 2981, 1720, 1616, 1493, 1388, 1250, 1165, 1095, 528; HRMS calcd for $\text{C}_{25}\text{H}_{25}\text{ClN}_4\text{NaO}_4$ $[\text{M} + \text{Na}]^+$ 503.1462, found 503.1484; HPLC analysis (Daicel Chiralpak AD-H column, n -Hexane/ i -PrOH = 90:10, 0.9 mL/min, $\lambda = 254$ nm) $t_R = 32.0$ min (major), 74.3 min (minor).

tert-Butyl((R)-6-bromo-1-methyl-2-oxo-3-((S)-2-oxo-1-phenyl-2-(1H-pyrazol-1-yl)ethyl)indolin-3-yl)carbamate (3ha). Yield: 95% (100 mg), white solid, mp 130.9–132.6 °C, $[\alpha]_D^{20} +19.2$ (c 0.78, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3) δ 8.15 (d, $J = 2.8$ Hz, 1H), 7.60 (d, $J = 1.2$ Hz, 1H), 7.37–7.31 (m, 5H), 7.07 (dd, $J = 7.6$, 1.6 Hz, 1H), 6.91 (d, $J = 1.6$ Hz, 1H), 6.83 (d, $J = 8.0$ Hz, 1H), 6.36–6.35 (m, 1H), 6.06 (s, 1H), 5.59 (s, 1H), 3.16 (s, 3H), 1.21 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.0, 167.7, 153.4, 145.5, 144.5, 130.8, 130.4, 128.9, 128.7, 128.5, 127.9, 124.9, 124.7, 122.8, 111.4, 110.5, 80.7, 62.4, 53.2, 28.0, 26.6; IR (KBr, cm^{-1}) ν 3417, 2978, 1720, 1608, 1493, 1388, 1246, 1165, 1092, 598; HRMS calcd for $\text{C}_{25}\text{H}_{25}\text{BrN}_4\text{NaO}_4$ $[\text{M} + \text{Na}]^+$ 547.0957, found 547.0966; HPLC analysis (Daicel Chiralpak AD-H column, n -Hexane/ i -PrOH = 90:10, 0.9 mL/min, $\lambda = 254$ nm) $t_R = 30.3$ min (major), 66.9 min (minor).

tert-Butyl((R)-7-fluoro-1-methyl-2-oxo-3-((S)-2-oxo-1-phenyl-2-(1H-pyrazol-1-yl)ethyl)indolin-3-yl)carbamate (3ia). Yield: 95% (88 mg), white solid, mp 77.1–79.0 °C, $[\alpha]_D^{20} +27.5$ (c 0.66, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3) δ 8.18 (d, $J = 2.8$ Hz, 1H), 7.61 (d, $J = 1.2$

Hz, 1H), 7.39–7.34 (m, 2H), 7.32–7.28 (m, 3H), 6.99–6.93 (m, 1H), 6.88–6.80 (m, 2H), 6.37–6.36 (m, 1H), 6.23 (s, 1H), 5.57 (s, 1H), 3.38 (d, $J = 2.4$ Hz, 3H), 1.20 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 173.7, 167.7, 153.5, 147.5 (d, $J = 241.9$ Hz), 144.5, 132.1, 130.7, 130.6 (d, $J = 8.1$ Hz), 130.4, 128.8, 128.7, 128.4, 122.5 (d, $J = 6.3$ Hz), 119.3 (d, $J = 2.8$ Hz), 117.1 (d, $J = 19.2$ Hz), 110.5, 80.6, 62.9, 53.2, 29.0 (d, $J = 5.8$ Hz), 27.9; IR (KBr, cm^{-1}) ν 3421, 2981, 1724, 1631, 1489, 1388, 1242, 1165, 775, 733; HRMS calcd for $\text{C}_{25}\text{H}_{26}\text{FN}_4\text{O}_4$ $[\text{M} + \text{H}]^+$ 465.1938, found 465.1938; HPLC analysis (Daicel Chiralpak AD-H column, n -Hexane/ i -PrOH = 85:15, 0.9 mL/min, $\lambda = 254$ nm) $t_R = 19.7$ min (major), 70.2 min (minor).

tert-Butyl((R)-7-chloro-1-methyl-2-oxo-3-((S)-2-oxo-1-phenyl-2-(1H-pyrazol-1-yl)ethyl)indolin-3-yl)carbamate (3ja). Yield: 94% (90 mg), white solid, mp 144.6–146.8 °C, $[\alpha]_D^{20} +41.2$ (c 0.56, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3) δ 8.18 (d, $J = 2.8$ Hz, 1H), 7.62 (d, $J = 0.8$ Hz, 1H), 7.36–7.28 (m, 5H), 7.15 (dd, $J = 8.0$, 1.2 Hz, 1H), 6.90 (dd, $J = 7.6$, 1.2 Hz, 1H), 6.83 (t, $J = 8.0$ Hz, 1H), 6.38–6.37 (m, 1H), 6.25 (s, 1H), 5.55 (s, 1H), 3.54 (s, 3H), 1.20 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.3, 167.6, 153.5, 144.5, 140.0, 132.1, 131.4, 130.7, 130.4, 128.8, 128.8, 128.4, 122.7, 121.9, 115.3, 110.5, 80.7, 62.6, 53.3, 29.8, 27.9; IR (KBr, cm^{-1}) ν 3417, 2981, 1720, 1466, 1388, 1250, 1165, 930, 737, 528; HRMS calcd for $\text{C}_{25}\text{H}_{25}\text{ClN}_4\text{NaO}_4$ $[\text{M} + \text{Na}]^+$ 503.1462, found 503.1461; HPLC analysis (Daicel Chiralpak AD-H column, n -Hexane/ i -PrOH = 80:20, 0.9 mL/min, $\lambda = 254$ nm) $t_R = 19.3$ min (major), 66.8 min (minor).

tert-Butyl((R)-7-bromo-1-methyl-2-oxo-3-((S)-2-oxo-1-phenyl-2-(1H-pyrazol-1-yl)ethyl)indolin-3-yl)carbamate (3ka). Yield: 94% (99 mg), white solid, mp 102.6–103.5 °C, $[\alpha]_D^{20} +45.9$ (c 0.57, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3) δ 8.18 (d, $J = 2.8$ Hz, 1H), 7.62 (d, $J = 0.8$ Hz, 1H), 7.35–7.27 (m, 6H), 6.94 (d, $J = 6.4$ Hz, 1H), 6.77 (t, $J = 8.0$ Hz, 1H), 6.38–6.37 (m, 1H), 6.27 (s, 1H), 5.54 (s, 1H), 3.55 (s, 3H), 1.20 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.4, 167.6, 153.4, 144.5, 141.3, 134.7, 132.4, 130.6, 130.4, 128.8, 128.4, 127.9, 123.1, 122.4, 110.5, 102.2, 80.7, 62.6, 53.3, 30.0, 27.9; IR (KBr, cm^{-1}) ν 3417, 2981, 1720, 1462, 1388, 1250, 1165, 926, 771, 737; HRMS calcd for $\text{C}_{25}\text{H}_{25}\text{BrN}_4\text{NaO}_4$ $[\text{M} + \text{Na}]^+$ 547.0957, found 547.0953; HPLC analysis (Daicel Chiralpak AD-H column, n -Hexane/ i -PrOH = 80:20, 0.9 mL/min, $\lambda = 254$ nm) $t_R = 19.8$ min (major), 65.8 min (minor).

tert-Butyl((R)-1-methyl-2-oxo-3-((S)-2-oxo-1-phenyl-2-(1H-pyrazol-1-yl)ethyl)-7-(trifluoromethyl)indolin-3-yl)carbamate (3la). Yield: 91% (94 mg), white solid, mp 69–71 °C, $[\alpha]_D^{20} +60.0$ (c 0.53, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3) δ 8.20 (d, $J = 2.8$ Hz, 1H), 7.65 (d, $J = 0.8$ Hz, 1H), 7.51 (d, $J = 7.6$ Hz, 1H), 7.31–7.22 (m, 6H), 7.01 (t, $J = 8.0$ Hz, 1H), 6.40–6.39 (m, 1H), 6.32 (s, 1H), 5.58 (s, 1H), 3.36–3.35 (m, 3H), 1.16 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.8, 167.2, 153.3, 144.6, 141.9, 131.9, 130.5, 130.4, 129.0, 128.9, 128.3, 126.9 (q, $J = 5.9$ Hz), 126.7, 124.8, 122.1, 121.3, 110.5, 80.9, 61.7, 53.3, 29.0 (q, $J = 6.4$ Hz), 27.8; IR (KBr, cm^{-1}) ν 3421, 2981, 1736, 1601, 1388, 1173, 1122, 1092, 748, 525; HRMS calcd for $\text{C}_{26}\text{H}_{25}\text{F}_3\text{N}_4\text{NaO}_4$ $[\text{M} + \text{Na}]^+$ 537.1726, found 537.1719; HPLC analysis (Daicel Chiralpak AD-H column, n -Hexane/ i -PrOH = 80:20, 0.9 mL/min, $\lambda = 254$ nm) $t_R = 13.4$ min (major), 43.4 min (minor).

tert-Butyl((R)-1,7-dimethyl-2-oxo-3-((S)-2-oxo-1-phenyl-2-(1H-pyrazol-1-yl)ethyl)indolin-3-yl)carbamate (3ma). Yield: 94% (87 mg), white solid, mp 84.5–86.6 °C, $[\alpha]_D^{20} +62.5$ (c 0.54, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3) δ 8.19 (d, $J = 2.8$ Hz, 1H), 7.61 (s, 1H), 7.37–7.34 (m, 2H), 7.28–7.25 (m, 3H), 6.94 (d, $J = 7.6$ Hz, 1H), 6.88 (d, $J = 7.2$ Hz, 1H), 6.80 (t, $J = 7.6$ Hz, 1H), 6.36–6.35 (m, 1H), 6.29 (s, 1H), 5.54 (s, 1H), 3.43 (s, 3H), 2.47 (s, 3H), 1.19 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 174.5, 167.9, 153.6, 144.3, 141.5, 132.8, 131.1, 130.4, 129.8, 128.7, 128.5, 128.1, 121.9, 121.3, 119.2, 110.3, 80.3, 62.6, 53.3, 29.8, 27.9, 18.9; IR (KBr, cm^{-1}) ν 3425, 2978, 1720, 1604, 1388, 1165, 1084, 930, 744; HRMS calcd for $\text{C}_{26}\text{H}_{28}\text{N}_4\text{NaO}_4$ $[\text{M} + \text{Na}]^+$ 483.2008, found 483.2008; HPLC analysis (Daicel Chiralpak AD-H column, n -Hexane/ i -PrOH = 80:20, 0.9 mL/min, $\lambda = 254$ nm) $t_R = 19.3$ min (major), 61.5 min (minor).

tert-Butyl((R)-1-benzyl-2-oxo-3-((S)-2-oxo-1-phenyl-2-(1H-pyrazol-1-yl)ethyl)indolin-3-yl)carbamate (3na). Yield: 87% (91 mg), white solid, mp 78.9–80.1 °C, $[\alpha]_D^{20} +27.7$ (c 0.38, CH_2Cl_2), ^1H

NMR (400 MHz, CDCl₃) δ 8.12 (d, J = 2.4 Hz, 1H), 7.60 (s, 1H), 7.39 (d, J = 7.2 Hz, 2H), 7.32–7.25 (m, 8H), 7.15 (t, J = 7.6 Hz, 1H), 7.06 (d, J = 7.6 Hz, 1H), 6.92 (t, J = 7.6 Hz, 1H), 6.66 (d, J = 7.6 Hz, 1H), 6.35 (s, 1H), 6.08 (s, 1H), 5.73 (s, 1H), 5.11–5.07 (m, 1H), 4.68–4.66 (m, 1H), 1.21 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 174.3, 167.8, 153.6, 144.4, 143.4, 135.8, 131.0, 130.5, 129.0, 128.9, 128.7, 128.6, 128.5, 127.5, 127.4, 123.9, 122.1, 110.4, 108.8, 80.4, 82.8, 53.1, 44.3, 28.0; IR (KBr, cm⁻¹) ν 3415, 2988, 1717, 1488, 1386, 1366, 1167, 746; HRMS calcd for C₃₁H₃₁N₄O₄ [M + H]⁺ 523.2345, found 523.2340; HPLC analysis (Daicel Chiralpak AD-H column, *n*-Hexane/EtOH = 90:10, 0.9 mL/min, λ = 254 nm) t_R = 25.4 min (major), 119.7 min (minor).

Procedure for One-Pot Esterification. To a solution of catalyst A7 (0.02 mmol, 15.3 mg), pyrazoleamide **2a** (0.24 mmol) and 4 Å molecular sieves (50.0 mg) in 0.66 mL of CH₃CN was added isatin-derived *N*-Boc ketimine **1a** (0.2 mmol) at 25 °C, and the resulting mixture was stirred at this temperature until the reaction completed and then added 2 mL of MeOH. After 5 h, the solvent was removed under reduced pressure and the residue was purified by column chromatography (20/1 CH₂Cl₂/ethyl acetate) to give the desired product **4**.

(*S*)-Methyl-2-((*S*)-3-((*tert*-butoxycarbonyl)amino)-1-methyl-2-oxoindolin-3-yl)-2-phenylacetate (**4**). Yield: 89% (73 mg), white solid, mp 114.1–115.3 °C, [α]_D²⁰ +32.9 (c 0.2, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 6.28–6.21 (m, 6H), 7.10 (d, J = 7.6 Hz, 1H), 6.97 (td, J = 7.6, 0.8 Hz, 1H), 6.88 (d, J = 7.6 Hz, 1H), 5.92 (s, 1H), 4.11 (s, 1H), 3.63 (s, 3H), 3.14 (s, 3H), 1.20 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 174.4, 170.1, 153.7, 143.8, 131.5, 130.2, 129.0, 128.8, 123.5, 122.0, 107.7, 80.3, 62.7, 56.1, 52.3, 27.9, 26.3; HRMS calcd for C₂₃H₂₆N₂NaO₅ [M + Na]⁺ 433.1739, found 433.1745; IR (KBr, cm⁻¹) ν 3419, 2978, 1720, 1615, 1495, 1384, 1253, 1165, 753; HPLC analysis (Daicel Chiralpak AD-H column, *n*-Hexane/*i*-PrOH = 80:20, 0.9 mL/min, λ = 254 nm) t_R = 27.9 min (major), 59.1 min (minor).

Preparation of Pyrazoleamides. A toluene (5 mL) solution of thionyl chloride (13 mmol) were added dropwise to a mixture consisting of pyrazole (10 mmol), carboxylic acid (13 mmol), triethylamine (40 mmol), and 25 mL of toluene. The resultant solution was stirred for 2 h at room temperature. After being quenched in succession with 0.1 M HCl solution (10 mL $\times$ 3), 0.1 M NaOH solution (10 mL $\times$ 3), and brine (20 mL), the organic phase was separated, dried over anhydrous MgSO₄, filtered, and concentrated under reduced pressure, the crude product was purified by chromatography on silica gel with petroleum ether/ethyl acetate as eluent.

2-Phenyl-1-(1H-pyrazol-1-yl)ethanone (**2a**).¹⁰ Yield: 91% (1.69 g), colorless liquid; ¹H NMR (400 MHz, CDCl₃) δ 8.23 (d, J = 2.4 Hz, 1H), 7.72 (s, 1H), 7.31–7.25 (m, 5H), 6.41–6.40 (m, 1H), 4.44 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 169.9, 144.0, 133.2, 129.7, 128.5, 128.5, 127.2, 109.8, 40.3; IR (KBr, cm⁻¹) ν 3413, 1716, 1497, 1384, 1241, 1039, 768, 723, 607; HRMS calcd for C₁₁H₁₁N₂O [M + H]⁺ 187.0866, found 187.0862.

1-(1H-Pyrazol-1-yl)-2-(4-(trifluoromethyl)phenyl)ethanone (**2b**).¹⁰ Yield: 88% (2.23 g), white solid, mp 127.9–128.4 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.27 (d, J = 2.8 Hz, 1H), 7.76 (s, 1H), 7.60 (d, J = 8.0 Hz, 2H), 7.50 (d, J = 7.50 Hz, 2H), 6.49–6.47 (m, 1H), 4.53 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 169.2, 144.4, 137.2, 130.2, 129.8, 129.4, 128.6, 125.5 (q, J = 37 Hz), 110.2, 40.2; IR (KBr, cm⁻¹) ν 3417, 1727, 1618, 1385, 1329, 1125, 1068, 604; HRMS calcd for C₁₂H₁₀F₃N₂O [M + H]⁺ 255.0740, found 255.0748.

2-(4-Bromophenyl)-1-(1H-pyrazol-1-yl)ethanone (**2c**).¹⁰ Yield: 92% (2.43 g), white solid, mp 77.0–77.1 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.25 (d, J = 2.8 Hz, 1H), 7.75 (s, 1H), 7.48–7.45 (m, 2H), 7.26–7.24 (m, 2H), 6.47–6.46 (m, 1H), 4.42 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 169.5, 144.3, 132.2, 131.7, 131.5, 128.6, 121.4, 110.1, 39.8; IR (KBr, cm⁻¹) ν 3416, 1736, 1384, 1352, 1200, 1088, 921, 762; HRMS calcd for C₁₁H₁₀BrN₂O [M + H]⁺ 264.9977, found 264.9973.

2-(4-Chlorophenyl)-1-(1H-pyrazol-1-yl)ethanone (**2d**).¹⁰ Yield: 92% (1.98 g), white solid, mp 70.0–70.5 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.25 (d, J = 2.8 Hz, 1H), 7.75 (s, 1H), 7.31 (s, 4H), 6.47–6.46 (m, 1H), 4.29 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 169.5,

142.2, 133.2, 131.6, 131.1, 128.7, 128.5, 110.0, 39.7; IR (KBr, cm⁻¹) ν 3415, 1735, 1638, 1400, 1384, 1091, 921, 771; HRMS calcd for C₁₁H₉ClN₂NaO [M + Na]⁺ 243.0301, found 243.0301.

2-(4-Fluorophenyl)-1-(1H-pyrazol-1-yl)ethanone (**2e**).¹⁰ Yield: 87% (1.78 g), white solid, mp 53.4–53.9 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.25 (d, J = 2.8 Hz, 1H), 7.75 (s, 1H), 7.36–7.32 (m, 2 H), 7.02 (t, J = 6.8 Hz, 2H), 6.46–6.45 (m, 1H), 4.43 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 169.8, 162.0 (d, J = 244.3 Hz), 144.1, 131.3 (d, J = 8.0 Hz), 128.9 (d, J = 3.3 Hz), 128.5, 115.4 (d, J = 21.5 Hz), 110.0, 39.5; IR (KBr, cm⁻¹) ν 3413, 1729, 1384, 1226, 1160, 1090, 922, 773, 517; HRMS calcd for C₁₁H₉FN₂NaO [M + Na]⁺ 227.0597, found 227.0607.

2-([1,1'-Biphenyl]-4-yl)-1-(1H-pyrazol-1-yl)ethanone (**2f**). Yield: 93% (2.44 g), white solid, mp 101.8–102.0 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.29 (d, J = 2.8 Hz, 1H), 7.77 (s, 1H), 7.59–7.56 (m, 4H), 7.46–7.41 (m, 4H), 7.34 (t, J = 6.8 Hz, 1H), 6.48–6.47 (m, 1H), 4.51 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 169.9, 144.1, 140.6, 140.2, 132.2, 130.1, 128.7, 128.5, 127.3, 127.2, 127.0, 109.9, 40.0; IR (KBr, cm⁻¹) ν 3415, 1740, 1637, 1618, 1385, 922, 752; HRMS calcd for C₁₇H₁₅N₂O [M + H]⁺ 263.1184, found 263.1190.

2-(4-Methoxyphenyl)-1-(1H-pyrazol-1-yl)ethanone (**2g**). Yield: 95% (2.05 g), white solid, mp 38.7–39.2 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.24 (d, J = 2.8 Hz, 1H), 7.74 (s, 1H), 7.29 (d, J = 8.8 Hz, 2H), 6.87 (d, J = 8.8 Hz, 2H), 6.44–6.43 (m, 1H), 4.39 (s, 2H), 3.77 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 170.2, 158.7, 144.0, 130.7, 128.5, 125.2, 114.0, 109.8, 55.1, 39.4; IR (KBr, cm⁻¹) ν 3417, 1738, 1513, 1411, 1246, 1177, 1033, 920, 770; HRMS calcd for C₁₂H₁₂N₂NaO₂ [M + Na]⁺ 239.0796, found 239.0804.

2-(3-Methoxyphenyl)-1-(1H-pyrazol-1-yl)ethanone (**2h**). Yield: 92% (1.99 g), colorless liquid; ¹H NMR (400 MHz, CDCl₃) δ 8.25 (d, J = 2.8 Hz, 1H), 7.74 (s, 1H), 7.24 (t, J = 8.0 Hz, 1H), 6.96–6.93 (m, 2H), 6.82 (dd, J = 8.0, 1.6 Hz, 1H), 6.44–6.43 (m, 1H), 4.43 (s, 2H), 3.78 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 169.8, 159.6, 144.1, 134.6, 129.5, 128.5, 122.0, 115.3, 112.8, 109.9, 55.1, 40.3; IR (KBr, cm⁻¹) ν 3414, 1735, 1599, 1491, 1384, 1260, 1041, 921, 769; HRMS calcd for C₁₂H₁₂N₂NaO₂ [M + Na]⁺ 239.0796, found 239.0806.

2-(3-Bromophenyl)-1-(1H-pyrazol-1-yl)ethanone (**2i**). Yield: 91% (2.41 g), white solid, mp 34.1–34.3 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.25 (d, J = 2.4 Hz, 1H), 7.75 (s, 1H), 7.54 (s, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.30 (d, J = 7.6 Hz, 1H), 7.20 (t, J = 8.0 Hz, 1H), 6.47–6.46 (m, 1H), 4.43 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 169.3, 144.3, 135.4, 132.7, 130.4, 130.1, 128.5, 128.4, 122.5, 110.1, 39.9; IR (KBr, cm⁻¹) ν 3415, 1735, 1384, 1350, 1240, 1087, 921, 763; HRMS calcd for C₁₁H₁₀BrN₂O [M + H]⁺ 264.9977, found 264.9985.

2-(2-Methoxyphenyl)-1-(1H-pyrazol-1-yl)ethanone (**2j**). Yield: 90% (1.94 g), white solid, mp 41.0–41.6 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.28 (d, J = 2.4 Hz, 1H), 7.74 (s, 1H), 7.29 (td, J = 7.6, 1.2 Hz, 1H), 7.21 (dd, J = 3.6, 1.2 Hz, 1H), 6.94 (td, J = 7.6, 1.2 Hz, 1H), 6.90 (d, J = 8.4 Hz, 1H), 6.45–6.44 (m, 1H), 4.48 (s, 2H), 3.77 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 169.9, 157.6, 143.8, 131.2, 128.8, 128.4, 122.2, 120.5, 110.5, 109.4, 55.4, 35.5; IR (KBr, cm⁻¹) ν 3415, 1739, 1618, 1384, 1248, 1088, 921, 755; HRMS calcd for C₁₂H₁₂N₂NaO₂ [M + Na]⁺ 239.0796, found 239.0812.

2-(2-Bromophenyl)-1-(1H-pyrazol-1-yl)ethanone (**2k**). Yield: 86% (2.28 g), colorless liquid; ¹H NMR (400 MHz, CDCl₃) δ 8.27 (d, J = 2.8 Hz, 1H), 7.76 (s, 1H), 7.60 (d, J = 7.6 Hz, 1H), 7.33–7.27 (m, 2H), 7.19–7.14 (m, 1H), 6.46–6.45 (m, 1H), 4.65 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 168.7, 144.1, 133.5, 132.7, 131.8, 129.1, 128.4, 127.5, 125.2, 109.8, 41.2; IR (KBr, cm⁻¹) ν 3417, 1738, 1384, 1355, 1196, 1088, 1030, 919, 746; HRMS calcd for C₁₁H₁₀BrN₂O [M + H]⁺ 264.9977, found 264.9981.

2-(Naphthalen-1-yl)-1-(1H-pyrazol-1-yl)ethanone (**2l**). Yield: 90% (2.13 g), white solid, mp 53.9–54.3 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.24 (d, J = 2.8 Hz, 1H), 8.01–7.98 (m, 1H), 7.85–7.83 (m, 1H), 7.80–7.76 (m, 2H), 7.51–7.40 (m, 4H), 7.42–7.41 (m, 1H), 4.91 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 169.8, 144.1, 133.8, 132.2, 129.8, 128.7, 128.6, 128.4, 128.2, 126.4, 125.7, 125.4, 123.8, 109.9, 37.8; IR (KBr, cm⁻¹) ν 3415, 1736, 1618, 1384, 1351, 1203, 1092, 784; HRMS calcd for C₁₅H₁₂N₂NaO [M + Na]⁺ 259.0847, found 259.0859.

2-(Naphthalen-2-yl)-1-(1H-pyrazol-1-yl)ethanone (**2m**). Yield: 87% (2.06 g), white solid, mp 57.8–58.5 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.25 (d, *J* = 2.8 Hz, 1H), 7.81–7.74 (m, 5H), 7.50–7.42 (m, 3H), 6.42–6.41 (m, 1H), 4.61 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 169.9, 144.1, 133.4, 132.5, 130.7, 128.6, 128.5, 128.2, 127.7, 127.6, 127.6, 126.1, 125.8, 109.9, 40.5; IR (KBr, cm⁻¹) ν 3415, 1745, 1385, 1239, 1203, 1088, 925, 803, 608; HRMS calcd for C₁₅H₁₃N₂O [M + H]⁺ 237.1028, found 237.1037.

1-(1H-Pyrazol-1-yl)-2-(thiophen-2-yl)ethanone (**2n**).¹⁰ Yield: 81% (1.56 g), colorless liquid; ¹H NMR (400 MHz, CDCl₃) δ 8.25 (d, *J* = 2.8 Hz, 1H), 7.75 (s, 1H), 7.23 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.03–7.02 (m, 1H), 6.98–6.96 (m, 1H), 6.46–6.45 (m, 1H), 4.67 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 158.7, 144.2, 133.9, 128.6, 127.5, 126.8, 125.4, 110.1, 34.7; IR (KBr, cm⁻¹) ν 3415, 1740, 1618, 1384, 1088, 922; HRMS calcd for C₉H₉N₂OS [M + H]⁺ 193.0436, found 193.0444.

■ ASSOCIATED CONTENT

■ Supporting Information

NMR spectra of pyrazoleamides **2**, NMR spectra and HPLC chromatograms of the products **3**, CIF file of enantiopure **3da**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: shaf@ecust.edu.cn.

*E-mail: xinyanwu@ecust.edu.cn.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) For reviews on Mannich reaction, see: (a) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044–1070. (b) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069–1094.
- (2) For reviews, see: (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138–5175. (b) Marques, M. M. B. *Angew. Chem., Int. Ed.* **2006**, *45*, 348–352. (c) Verkade, J. M. M.; van Hemert, L. J. C.; Quaedflieg, P. J. L. M.; Rutjes, F. P. J. T. *Chem. Soc. Rev.* **2008**, *37*, 29–41. (d) Xu, L.-W.; Lu, Y. *Org. Biomol. Chem.* **2008**, *6*, 2047–2053. (e) Bhadury, P. S.; Song, B. A. *Curr. Org. Chem.* **2010**, *14*, 1989–2006. (f) Kobayashi, S.; Mori, Y.; Fossey, J. S.; Salter, M. M. *Chem. Rev.* **2011**, *111*, 2626–2704.
- (3) For metal-free asymmetric Mannich-type reaction of ketimines, see: (a) Zhuang, W.; Saaby, S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 4476–4478. (b) Jiang, B.; Dong, J. J.; Si, Y. G.; Zhao, X. L.; Huang, Z. G.; Xu, M. *Adv. Synth. Catal.* **2008**, *350*, 1360–1366. (c) Kano, T.; Song, S.; Kubota, Y.; Maruoka, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 1191–1194. (d) Yan, W.; Wang, D.; Feng, J.; Li, P.; Zhao, D.; Wang, R. *Org. Lett.* **2012**, *14*, 2512–2515. (e) Hara, N.; Nakamura, S.; Sano, M.; Tamura, R.; Funahashi, Y.; Shibata, N. *Chem.—Eur. J.* **2012**, *18*, 9276–9280. (f) Chen, X.; Chen, H.; Ji, X.; Jiang, H.; Yao, Z.-J.; Liu, H. *Org. Lett.* **2013**, *15*, 1846–1849. (g) Yuan, H.-N.; Wang, S.; Nie, J.; Meng, W.; Yao, Q.; Ma, J.-A. *Angew. Chem., Int. Ed.* **2013**, *52*, 3869–3873.
- (4) For metal-catalytic enantioselective Mannich-type reaction of amides, see: (a) Harada, S.; Handa, S.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4365–4368. (b) Cutting, G. A.; Stainforth, N. E.; John, M. P.; Kociok-Köhn, G.; Willis, M. C. *J. Am. Chem. Soc.* **2007**, *129*, 10632–10633.
- (5) Juaristi, E. *Enantioselective Synthesis β-Amino Acids*; Wiley-VCH: New York, 1997.
- (6) For reviews, see: (a) Zhou, F.; Liu, Y.-L.; Zhou, J. *Adv. Synth. Catal.* **2010**, *352*, 1381–1407. (b) Klein, J.; Taylor, R. J. K. *Eur. J. Org. Chem.* **2011**, 6821–6841. (c) Dalpozzo, R.; Bartoli, G.; Bencivenni, G. *Chem. Soc. Rev.* **2012**, *41*, 7247–7290. (d) Shen, K.; Liu, X.; Lin, L.; Feng, X. *Chem. Sci.* **2012**, *3*, 327–334.
- (7) For reviews, see: (a) Chauhan, P.; Chimni, S. S. *Tetrahedron: Asymmetry* **2013**, *24*, 343–356. (b) Cheng, D.; Ishihara, Y.; Tan, B.; Barbas, C. F., III. *ACS Catal.* **2014**, *4*, 743–762.
- (8) (a) Lesma, G.; Landoni, N.; Pilati, T.; Sacchetti, A.; Silvani, A. *J. Org. Chem.* **2009**, *74*, 4537–4541. (b) Liu, Y.-L.; Zhou, F.; Cao, J.-J.; Ji, C.-B.; Ding, M.; Zhou, J. *Org. Biomol. Chem.* **2010**, *8*, 3847–3850. (c) Yan, W.; Wang, D.; Feng, J.; Li, P.; Wang, R. *J. Org. Chem.* **2012**, *77*, 3311–3317. (d) Guo, Q.-X.; Liu, Y.-W.; Li, X.-C.; Zhong, L.-Z.; Peng, Y.-G. *J. Org. Chem.* **2012**, *77*, 3589–3594. (e) Feng, J.; Yan, W.; Wang, D.; Li, P.; Sun, Q.; Wang, R. *Chem. Commun.* **2012**, *48*, 8003–8005. (f) Lv, H.; Tiwari, B.; Mo, J.; Xing, C.; Chi, Y. R. *Org. Lett.* **2012**, *14*, 5412–5415. (g) Liu, Y.-L.; Zhou, J. *Chem. Commun.* **2013**, *49*, 4421–4423. (h) Wang, D.; Liang, J.; Feng, J.; Wang, K.; Sun, Q.; Zhao, L.; Li, D.; Yan, W.; Wang, R. *Adv. Synth. Catal.* **2013**, *355*, 548–558.
- (9) (a) Cheng, L.; Liu, L.; Wang, D.; Chen, Y.-J. *Org. Lett.* **2009**, *11*, 3874–3877. (b) Qian, Z.-Q.; Zhou, F.; Du, T.-P.; Wang, B.-L.; Ding, M.; Zhao, X.-L.; Zhou, J. *Chem. Commun.* **2009**, 6753–6755. (c) Bui, T.; Hernández-Torres, G.; Milite, C.; Barbas, C. F., III. *Org. Lett.* **2010**, *12*, 5696–5699. (d) Yang, Z.; Wang, Z.; Bai, S.; Shen, K.; Chen, D.; Liu, X.; Lin, L.; Feng, X. *Chem.—Eur. J.* **2010**, *16*, 6632–6637. (e) Mouri, S.; Chen, Z.; Mitsunuma, H.; Furutachi, M.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2010**, *132*, 1255–1257. (f) Shen, K.; Liu, X.; Wang, G.; Lin, L.; Feng, X. *Angew. Chem., Int. Ed.* **2011**, *50*, 4684–4688.
- (10) Tan, B.; Hernández-Torres, G.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2012**, *51*, 5381–5385.
- (11) (a) Wang, C.-C.; Wu, X.-Y. *Tetrahedron* **2011**, *67*, 2974–2978. (b) Qian, J.-Y.; Wang, C.-C.; Sha, F.; Wu, X.-Y. *RSC Adv.* **2012**, *2*, 6042–6048. (c) Li, T.-Z.; Wang, X.-B.; Sha, F.; Wu, X.-Y. *Tetrahedron* **2013**, *69*, 7314–7319. (d) Wang, X.-B.; Li, T.-Z.; Sha, F.; Wu, X.-Y. *Eur. J. Org. Chem.* **2013**, 739–744.
- (12) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673.
- (13) (a) Li, W.; Wu, W.; Yu, F.; Huang, H.; Liang, X.; Ye, J. *Org. Biomol. Chem.* **2011**, *9*, 2505–2511. (b) Zhao, M.-X.; Tang, W.-H.; Chen, M.-X.; Wei, D.-K.; Dai, T.-L.; Shi, M. *Eur. J. Org. Chem.* **2011**, 6078–6084. (c) Ogura, Y.; Akakura, M.; Sakakura, A.; Ishihara, K. *Angew. Chem., Int. Ed.* **2013**, *52*, 8299–8303.
- (14) (a) Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett.* **2005**, *7*, 1967–1969. (b) Shi, M.; Lei, Z.-Y.; Zhao, M.-X.; Shi, J.-W. *Tetrahedron Lett.* **2007**, *48*, 5743–5746. (c) Yang, W.; Du, D.-M. *Org. Lett.* **2010**, *12*, 5450–5453.
- (15) Choji, K.; Hajime, H.; Isanobu, K.; Iwao, F.; Akira, H. *Synthesis* **1994**, 61–63.