Journal of Heterocyclic Chemistry

WILEY

JOURNAL OF HETEROCYCLIC CHEMISTRY

RESEARCH ARTICLE OPEN ACCESS

Organocatalytic Enantioselective Synthesis of Oxindole-4-Aminopyrazolone Derivatives via Mannich Reaction of 3-Substituted Oxindoles With Pyrazolinone Ketimines

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Received: 2 May 2025 | **Revised:** 16 June 2025 | **Accepted:** 23 June 2025

Funding: This work was supported by the Junta de Castilla y León (VA072G24).

Keywords: asymmetric organocatalysis | Mannich addition | oxindole | pyrazolinone-derived ketimines | quaternary stereocenters

ABSTRACT

The organocatalyzed Mannich reaction between pyrazolinone ketimines and 3-aryl-substituted oxindoles mediated by a hidroquinine-derived squaramide is reported. This method enables the synthesis of a diverse set of oxindole-4-aminopyrazolone derivatives bearing vicinal tetrasubstituted stereocenters, affording products in good yields (up to 95%), with excellent diastereoselectivity (> 20:1) and moderate enantioselectivity (up to 85:15 er) under mild conditions.

1 | Introduction

The Mannich reaction is a type of multicomponent process that introduces an aminoalkyl group at a position adjacent to a carbonyl group bearing an acidic hydrogen [1–4]. Reactions involving aldimines and α-methylene carbonyl compounds are also classified under this reaction type. The asymmetric Mannich reaction is a powerful tool in synthetic chemistry, increasingly explored through organocatalysis for its efficiency and stereoselectivity in constructing complex molecules relevant to drug discovery, materials science, and the development of bioactive compounds [5, 6].

The asymmetric synthesis of heterocyclic compounds bearing stereogenic centers has gained significant attention in the last decade due to the occurrence of these structures in natural and bioactive compounds [7]. Among them, pyrazolones and pyrazoles are two of the most important classes of nitrogen-containing heterocycles, owing to their widespread presence in medicinal chemistry and functional materials [8]. A notable example is the 4-substituted-4-aminopyrazolones, which possess a tetrasubstituted stereocenter at the C-4 position. This privileged heterocyclic structure is found in various biologically active molecules and pharmaceutical drugs [9–11]. One of the most efficient approaches for synthesizing chiral 4-substituted 4-aminopyrazolones involves the addition of nucleophiles to ketimines derived from pyrazole-4,5-diones [12–14]. A direct asymmetric Mannich reaction, utilizing these newly developed ketimines, offers a practical route for accessing such highly functionalized building blocks [15–18].

Among the different chiral oxindoles, 3-amino-3-substituted-2-oxindoles are key structures in natural products and biologically active compounds [19–21] whose pharmacological activity depends on the nature of the substituents at the C-3 position and the absolute configuration of the stereocenter. The asymmetric addition of carbon nucleophiles to isatin-derived ketimines is the most direct method for preparing this type of compound,

with organocatalyzed methods having grown in interest in recent years [22–24].

Given the relevance of pyrazole and oxindole, the incorporation of both structural units into a single molecule could lead to new derivatives with quaternary amino-substituted stereocenters and potentially interesting biological properties. Their synthesis can be achieved by two alternative strategies: (i) reaction of pyrazolones with Boc-ketimines derived from isatin or (ii) reaction of Boc-protected pyrazolinone ketimines with 3-substituted oxindoles (Scheme 1).

Following the first strategy, Pedro's group first described the organocatalyzed enantioselective Mannich reaction of isatin-derived ketimines with 4-unsubstituted pyrazolones followed by in situ acetylation, affording the corresponding acetylated pyrazoles in high yields and excellent enantioselectivities [25]. In a subsequent published work from this group, the enantioselective addition of 4-substituted pyrazolones to the same Boc-ketimines affords aminooxindole-pyrazolone adducts containing congested vicinal tetrasubstituted stereocentres with excellent diastereo- and enantioselectivity [26]. Zhang and co-workers [27] also reported a one-pot enantioselective Mannich addition/allylic alkylation cascade reaction between pyrazolones, isatin-derived ketimines, and allylic acetates.

According to the second strategy, Du and co-workers reported the highly diastereo- and enantioselective Mannich reaction of 3-fluorooxindole to N-aryl pyrazolinone ketimines using a dihydroquinine-derived squaramide as organocatalyst [28]. However, when using a N-Boc-protected ketimine as the starting product under the optimized reaction conditions, the results were not satisfactory neither in terms of chemical yield nor in terms of diastereo- and enantioselectivity.

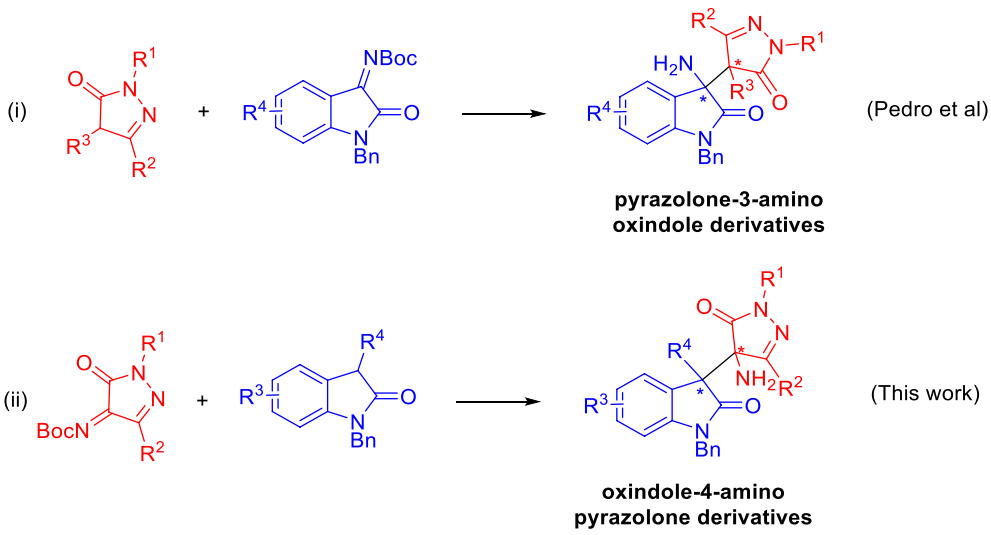
Herein we describe the unreported organocatalyzed addition of 3-aryl substituted oxindoles to Boc-protected pyrazolinone ketimines, providing novel oxindole-aminopyrazolone adducts in good yields, excellent diastereoselectivity, and moderate enantioselectivity.

2 | Results and Discussion

For the optimization process, we studied the reaction between the 3-phenyloxindole **2a** and the pyrazolinone-derived N-Boc ketimine **1a** in the presence of 10 mol% of organocatalyst in dichloromethane at room temperature (Table 1). A preliminary experiment showed that when **1a** was treated with **2a** in the absence of a catalyst, no reaction was observed.

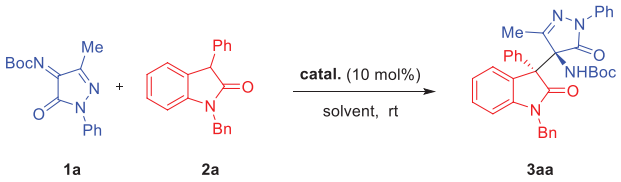
First, we studied the squaramides **C1**–**C3** derived from quinine (Table 1, entries 1–3) obtaining in all cases the adduct **3aa** as the only diastereomer (dr > 20:1) and the best enantiomeric ratio (62:38 er) with the phenethyl-substituted squaramide **C3**. Thiourea **C4**, derived from quinine, yielded worse results than its analogue, squaramide **C3**, in this reaction (compare entries 3–4). Next, two catalysts derived from cinchonidine and hydroquinine, **C5** and **C6**, were tested (entries 5–6), achieving the best results with squaramide **C6**, which yet again provided compound **3aa** as the sole diastereomer and with a slight increase in the enantiomeric ratio (67:33). Finally, quinidine-derived squaramide **C7**, a pseudoenantiomer of **C3**, also effectively catalyzed this reaction but gave the opposite enantiomer of **3aa** with similar enantioselectivity (entry 7).

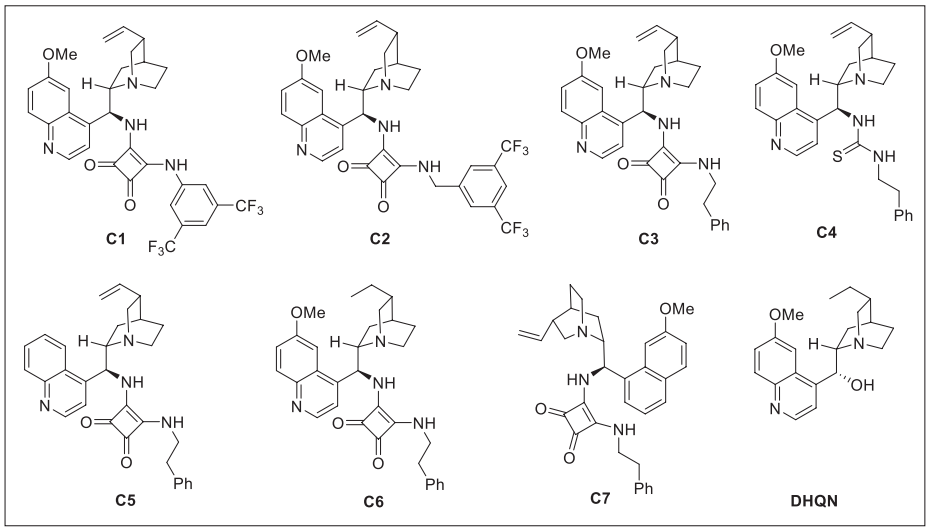
According to these results, we chose squaramide **C6** as the best catalyst for the reaction and proceeded to study other parameters such as solvent, temperature, and catalyst loading. First, we tested toluene and several ethereal solvents (entries 8–12), achieving the best enantiomeric ratio with 1,4-dioxane (72:28 er). More polar solvents such as acetonitrile, ethyl acetate, acetone, and isopropanol did not improve the previous results obtained with 1,4-dioxane. Finally, we studied other chlorinated solvents (entries 17–18) obtaining the best yield (85%) and enantiomeric ratio (75:25 er) with 1,2-dichloroethane (DCE). The poorer yield obtained in chloroform was due to the formation of the *N,O*-acetal **4a** produced by the reaction of ketimine **1a** with traces of ethanol used as a stabilizer of this solvent (see Experimental). Lowering the temperature to −18°C provided a decrease in both yield and enantiomeric ratio (entry 19). Decreasing the catalyst loading to 5 mol% did not improve the previous results either



SCHEME 1 | Strategies for the synthesis of pyrazole-3-amino oxindole and oxindole-4-amino pyrazolone adducts.

TABLE 1 | Optimization of reaction conditions[a].





Entry[a]	Catalyst	Solvent	*t* (h)	3aa (%)[b]	dr[c]	er[d]
1	**C1**	DCM	2	40	> 20:1	58:42
2	**C2**	DCM	2	82	> 20:1	60:40
3	**C3**	DCM	2	80	> 20:1	62:38
4	**C4**	DCM	4	71	> 20:1	55:45
5	**C5**	DCM	2	52	> 20:1	64:36
6	**C6**	DCM	2	68	> 20:1	67:33
7	**C7**	DCM	2	79	> 20:1	37:63
8	**C6**	PhMe	4	72	> 20:1	70:30
9	**C6**	Et_2O	6	75	> 20:1	62:38
10	**C6**	MTBE	3	58	> 20:1	63:37
11	**C6**	THF	2	89	> 20:1	65:35
12	**C6**	1,4-dioxane	3	75	> 20:1	72:28
13	**C6**	MeCN	2	72	> 20:1	67:33
14	**C6**	EtOAc	4	85	> 20:1	71:29
15	**C6**	acetone	2	78	> 20:1	70:30
16	**C6**	IPA	6	62	> 20:1	62:38
17	**C6**	$CHCl_3$	3	45	> 20:1	75:25
18	**C6**	DCE	2	85	> 20:1	**75:25**
19[e]	**C6**	DCE	6	60	> 20:1	73:27
20[f]	**C6**	DCE	2	80	> 20:1	73:27
21	**DHQN**	DCE	3	78	> 20:1	62:38

[a]Reactions performed with **1a** (0.11 mmol), **2a** (0.1 mmol), **catalyst** (0.01 mmol), solvent (1 mL), room temperature.
[b]Isolated yield.
[c]Determined by ^{1}H-RMN.
[d]Determined by chiral HPLC.
[e]Reaction performed at −18°C.
[f]Reaction performed with 0.005 mol of catalyst **C6**.

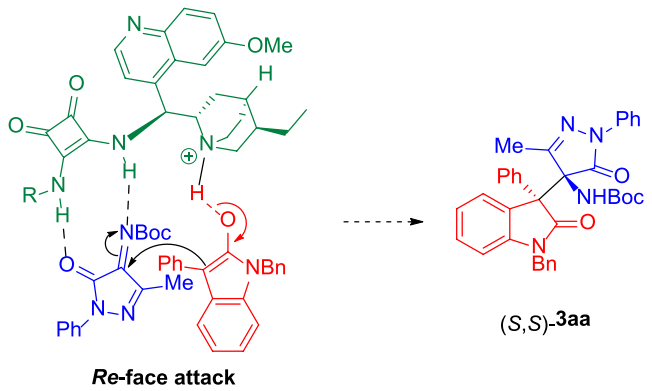


FIGURE 1 | Plausible transition-state model.

(entry 20). Finally, we performed a final experiment in DCE with dihydroquinine (DHQN) as catalyst, obtaining the adduct **3aa** with lower enantioselectivity than that achieved with squaramide **C6**.

Additional tests were also carried out in DCE using other organocatalysts derived from quinine, (1*R*,2*R*)-1,2-diaminocyclohexane, (1*R*, 2*R*)-1,2-diphenyl-ethanediamine, and *L*-valine, but no improvement was achieved with either (see Supporting Information).

On the basis of our results and those previously reported with quinine-derived organocatalysts, [15–17] we proposed the formation of the ternary complex depicted in Figure 1 to rationalize the (*S,S*)-configuration of the adduct **3aa**. The H-bonding activation of N-Boc ketimine **1a** by the squaramide moiety of catalyst **C6** facilitates the nucleophilic attack of the enolate of N-benzyl-3-aryloxindole **2a** from the *re*-face of the imine group, leading to the formation of adduct **3aa** with the (*S,S*) configuration.

With the best available reaction conditions (1,2-dichloroethane as a solvent, room temperature, with a 10 mol% of catalyst **C6**) we evaluated the scope and limitations of the reaction. First, a range of different N-Boc ketimines with a variety of substituents were tested with the N-benzyl 3-phenyl-2-oxindole **2a** (Scheme 2). To our delight, both electron-withdrawing (Cl) and electron-donating (Me) groups in the *para* position of the phenyl group at the N1 position of the pyrazolinone ring were tolerated, and the corresponding adducts **3ba** and **3ca** were obtained with excellent diastereomeric ratio (dr > 20:1), good yields (84%–95%) and a slightly better enantiomeric ratio for **3ac** (77:23 er). However, when the methyl group at the C-3 position of the pyrazolinone ring was substituted with an ethyl (**1d**) or a phenyl group (**1e**) both yields and enantiomeric ratio decreased.

Next, we studied different 3-substituted oxindoles bearing a variety of substituents in positions 1, 3, and 5. First, N-substitution of the oxindole nitrogen was investigated (Scheme 2), **3ab**. A group like methyl was well tolerated, and the corresponding adduct was obtained with high diastereo- and moderate enantioselectivity (68:32 er). The use of oxindoles containing a *p*-methoxyphenyl or a *p*-trifluoromethyl group at C3 led to compounds **3ac** and **3ad** in moderate yields, excellent diastereoselectivity, but very low enantiomeric ratio. A similar result was obtained in the reaction with oxindole **2e**, substituted with a bromine at the C5 position. Finally, oxindole **2f**, 4-ethoxycarbonyl-substituted, led to a 71:29 mixture of diastereoisomers and high enantiomeric ratio for the major *anti*-diastereomer (85:15 er).

Surprisingly, Boc-deprotection of **3aa** with TFA/DCM or with 6 M HCl in dioxane did not yield the expected amino derivative. Instead, a mixture of oxindole **2a** and a strongly colored compound **5a** was isolated (Scheme 3). Its structure was determined by ^{1}H- and ^{13}C-NMR and HRMS, resulting in the well-known rubazonic acid [29].

3 | Conclusions

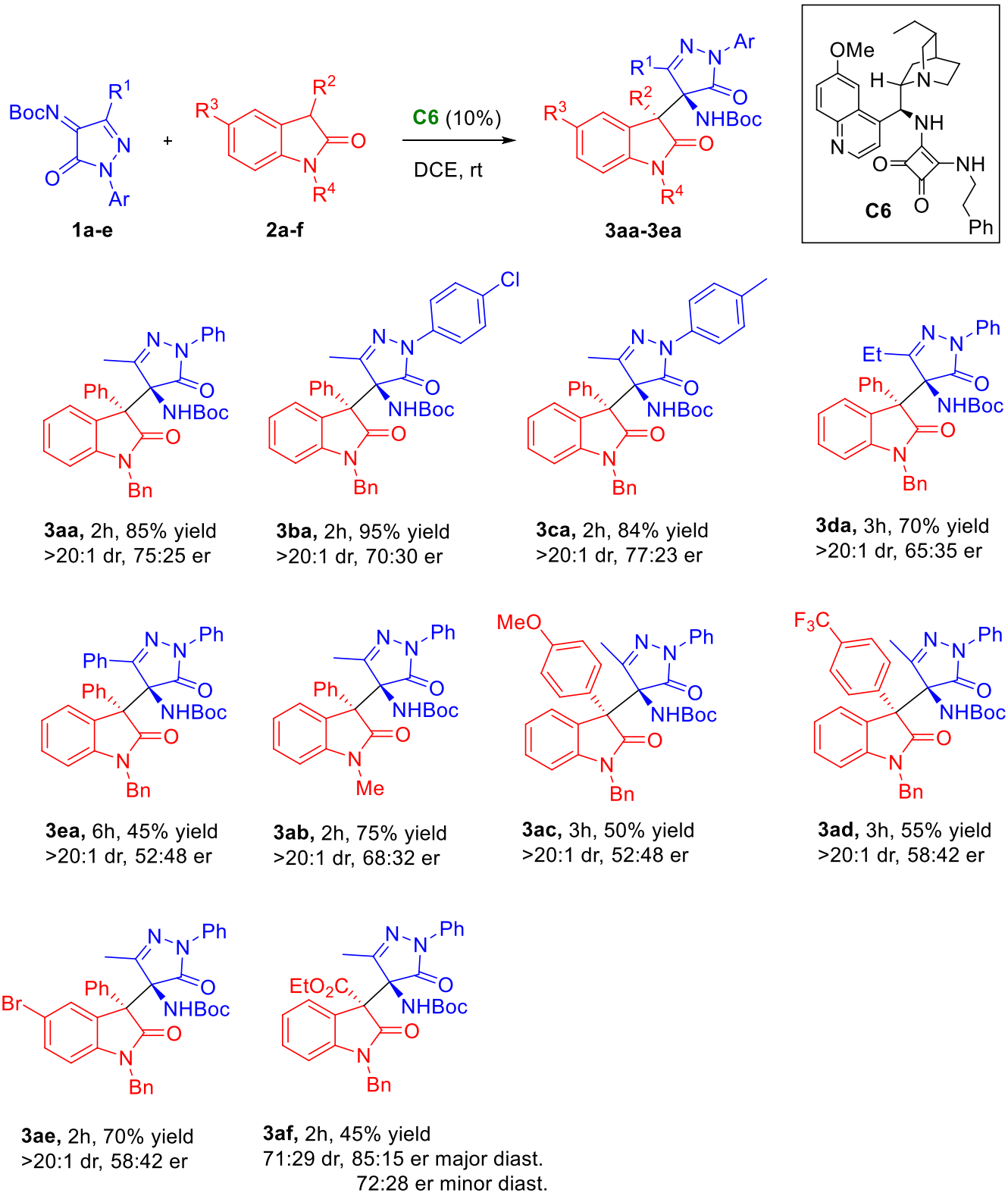
In summary, we have developed an organocatalytic enantioselective Mannich reaction of pyrazolinone-derived ketimines with 3-substituted oxindoles using hydroquinine-derived bifunctional squaramide as a catalyst. This method provides a direct pathway to access the chiral 4-aminopyrazolone derivatives containing two privileged structural motifs, the oxindole and pyrazolinone substructures. With the described methodology, the Boc-protected oxindole-4-aminopyrazolinones could be obtained in good yields, excellent diastereoselectivity, but moderate enantioselectivity.

4 | Experimental

^{1}H NMR (500 MHz, 400 MHz) and ^{13}C NMR (126 MHz, 101 MHz) spectra were recorded in $CDCl_3$ or DMSO-d_6 as solvent (Laboratory of Instrumental Techniques, University of Valladolid). Chemical shifts for protons are reported in ppm from TMS with the residual $CHCl_3$ resonance as an internal reference. Chemical shifts for carbons are reported in ppm from TMS and are referenced to the carbon resonance of the solvent. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad signal), coupling constants in Hertz, and integration. Specific rotations were measured on a Perkin-Elmer 341 digital polarimeter using a 5-mL cell with a 1-dm path length and a sodium lamp, and concentration is given in g per 100 mL.

Melting points were obtained with a micro melting point Cole-Parmer MP-200D and are uncorrected. Flash chromatography was carried out using silica gel (230–240 mesh). Chemical yields refer to pure isolated substances. TLC analysis was performed on glass-backed plates coated with silica gel 60 and an F_{254} indicator and visualized by either UV irradiation or by staining with phosphomolybdic acid solution. Chiral HPLC analysis was performed on a JASPO HPLC system (JASCO PU-2089 pump and UV-2075 UV/Vis detector) equipped with a quaternary pump using a Lux-i-Amylose-1 analytical column (250 × 4.6 mm). UV detection was monitored at 254 nm. ESI mass spectra were obtained on an Agilent 5973 inert GC/MS system.

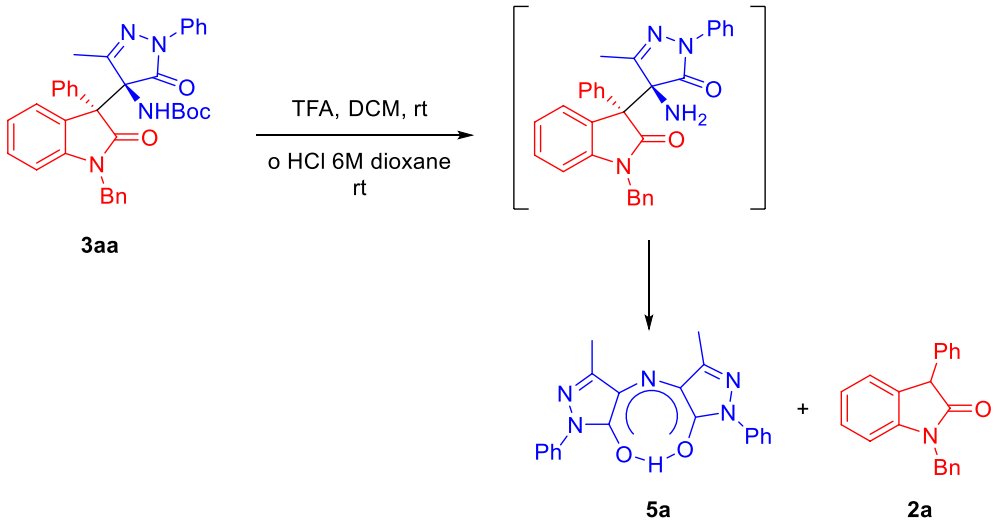
Commercially available organic and inorganic compounds were used without further purification. Solvents were dried and stored over microwave-activated 4 Å molecular sieves. Pyrazolinone ketimines [15], N-benzyloxindoles **2a–f** [30], squaramides **C1–C2** [31], **C3** [17] and thiourea **C4** [32] were prepared according to literature procedures. Racemic mixtures were synthesized according to the general procedure using an aquiral bifunctional



SCHEME 2 | Scope of the addition of 3-substituted oxindoles to N-Boc pyrazolinone-ketimines. *Reaction conditions*: **1a–e** (0.11 mmol), **2a–f** (0.1 mmol), **C1** (0.01 mmol), DCE (1 mL), rt. Isolated yield after column chromatography. Diastereomeric ratio determined by ^{1}H-NMR. Enantiomeric ratio determined by chiral HPLC analysis.

thiourea derived from N^1,N^1-dimethylethane-1,2-diamine [33] (0.01 mmol) as catalyst.

General procedure to enantioselective Mannich reaction of N-Boc pyrazolinone ketimines with 3-substituted oxindoles. To a mixture of N-Boc ketimine **1** (0.11 mmol, 1.1 equiv) and catalyst (0.01 mmol, 0.1 equiv) in 1.0 mL of the solvent, 3-substituted oxindole (0.1 mmol) was added and the reaction mixture was stirred in a Wheaton vial until consumption of the starting material (monitoring by TLC). After



SCHEME 3 | Boc-deprotection of **3aa**.

solvent removal under reduced pressure, the crude mixture was purified by flash column chromatography to afford the corresponding product. The diastereomeric ratio was determined by ^{1}H-NMR and the enantiomeric ratio by chiral-phase HPLC analysis using mixtures of hexane/isopropanol as eluent.

***tert*-Butyl ((*S*)-4-((*S*)-1-benzyl-2-oxo-3-phenylindolin-3-yl)-3-methyl-5-oxo-1-phenyl − 4,5-dihydro-1*H*-pyrazol-4-yl)carbamate (3aa)**. Product **3aa** was obtained according to the general procedure by the reaction of N-benzyl-3-phenyloxindole **2a** (30 mg, 0.1 mmol) with ketimine **1a** (32 mg, 0.11 mmol) using catalyst **C6** (5 mg, 0.01 mmol). Chromatography on a silica gel using hexane/DCM 1:4 as an eluent afforded compound **3aa** as a colorless solid (50 mg, 0.085 mmol, 85% yield). Mp 172°C–173°C. $[\alpha]_D^{25} = +46.5$ ($c = 0.4$, $CHCl_3$) (75:25 er). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.30 (br s, 1H, NH), 7.81 (m, 2H, Har), 7.47 (dd, J = 7.7, 1.2 Hz, 1H, Har), 7.39 (m, 3H, Har), 7.32 (m, 2H, Har), 7.29–7.25 (m, 5H, Har), 7.22 (m, 2H, Har), 7.14 (td, J = 7.8, 1.2 Hz, 1H, Har), 7.07 (tt, J = 7.4, 1.2 Hz, 1H, Har), 6.92 (td, J = 7.7, 1.1 Hz, 1H, Har), 6.71 (dd, J = 8.0, 1.0 Hz, 1H, Har), 5.09 (d, J = 16.0 Hz, 1H, CHHPh), 4.91 (d, J = 16.0 Hz, 1H, CHHPh), 1.65 (s, 3H, CH_3), 1.41 (s, 9H, $C(CH_3)_3$) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 175.0 (CO), 170.5 (CO), 157.9 (C=*N*), 154.7 (CO_2tBu), 143.0 (Car), 137.1 (Car), 135.0 (Car), 133.1 (Car), 129.8 (CHar), 129.5 (CHar), 128.9 (CHar), 128.8 (CHar), 128.7, 128.6 (CHar), 128.5 (CHar), 128.0, 127.6 (CHar), 127.0 (CHar), 126.3 (CHar), 125.1 (CHar), 124.6 (Car), 122.5 (CHar), 119.3 (CHar), 110.5 (CHar), 77.3 ($C(CH_3)_3$), 70.7 (CNH), 53.6 (CPh), 44.5 (CH_2), 28.2 ($C(CH_3)_3$), 15.9 (CH_3) ppm. **IR (ATR):** 3309, 2981, 2927, 1717, 1693, 1613, 1596, 1485, 1365, 1251, 1157, 755, 691 cm^{-1}. **HPLC**: Lux *i*-Amylose-1 column, hexane/*i*-PrOH 90:10, 0.5 mL/min, λ = 254 nm, minor enantiomer *t*r = 14.6 min, major enantiomer *t*r = 27.3 min. **HRMS** (ESI-QTOF) m/z: $[M+H]^+$ Calcd. For $C_{36}H_{35}N_4O_4$ 587.2653; Found 587.2658.

***tert*-Butyl ((*S*)-4-((*S*)-1-benzyl-2-oxo-3-phenylindolin-3-yl)-1-(4-chlorophenyl)-3-methyl-5-oxo-4,5-dihydro1*H*-pyrazol-4-yl)carbamate (3ba)**. Product **3ba** was obtained according to general procedure by reaction of N-benzyl-3-phenyloxindole **2a** (30 mg, 0.1 mmol) with ketimine **1b** (35 mg, 0.11 mmol) using catalyst **C6** (5 mg, 0.01 mmol). Chromatography on a silica gel using hexane/DCM 1:4 as an eluent afforded compound **3ba** as a colorless solid (59 mg, 0.095 mmol, 95% yield). Mp 216°C–217°C. $[\alpha]_D^{25} = +31.2$ ($c = 0.52$, $CHCl_3$) (70:30 er). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.29 (br s, 1H, NH), 7.80 (m, 2H, Har), 7.44 (dd, J = 7.7, 1.2 Hz, 1H, Har), 7.39 (m, 2H, Har), 7.32 (d, J = 9.0 Hz, 2H, Har), 7.29–7.22 (m, 6H, Har), 7.17 (d, J = 9.0 Hz, 2H, Har), 7.14 (td, J = 7.8, 1.2 Hz, 1H, Har), 6.90 (td, J = 7.7, 1.0 Hz, 1H, Har), 6.70 (dd, J = 8.0, 1.0 Hz, 1H, Har), 5.07 (d, J = 16.0 Hz, 1H, CHHPh), 4.91 (d, J = 16.0 Hz, 1H, CHHPh), 1.63 (s, 3H, CH_3), 1.41 (s, 9H, $C(CH_3)_3$) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 174.8 (CO), 170.5 (CO), 158.3 (C=*N*), 143.0 (Car), 135.7 (Car), 134.9 (Car), 132.9 (Car), 130.0 (Car), 129.9 (CHar), 129.4 (CHar), 128.9 (CHar), 128.8 (CHar), 128.7 (CHar), 128.5 (CHar), 127.7 (CHar), 127.2 (CHar), 127.0 (CHar), 126.2 (CHar), 124.4 (Car), 122.4 (CHar), 110.5 (CHar), 77.3 ($C(CH_3)_3$), 70.7 (CNH), 53.5 (CPh), 44.6 (CH_2), 28.2 ($C(CH_3)_3$), 15.8 (CH_3) ppm. **IR (ATR)**: 3333, 2981, 2927, 1703, 1489, 1362, 1257, 1159, 757, 728, 695 cm^{-1}. **HPLC**: Lux *i*-Amylose-1 column, hexane/*i*-PrOH 90:10, 0.5 mL/min, λ = 254 nm, minor enantiomer *t*r = 16.0 min, major enantiomer *t*r = 22.8 min. **HRMS** (ESI-QTOF) m/z: $[M+H]^+$ Calcd. For $C_{36}H_{34}ClN_4O_4$ 621.2263; Found 621.2295.

***tert*-Butyl ((*S*)-4-((*S*)-1-benzyl-2-oxo-3-phenylindolin-3-yl)-3-methyl-5-oxo-1-(*p*-tolyl)-4,5-dihydro-1*H*-pyrazol-4-yl)carbamate (3ca)**. Product **3ca** was obtained according to the general procedure by the reaction of N-benzyl-3-phenyloxindole **2a** (30 mg, 0.1 mmol) with ketimine **1c** (33 mg, 0.11 mmol) using catalyst **C6** (5 mg, 0.01 mmol). Chromatography on a silica gel using hexane/DCM 1:4 as an eluent afforded compound **3ca** as a colorless solid (50 mg, 0.084 mmol, 84% yield). Colorless solid, mp 208°C–209°C. $[\alpha]_D^{25} = +41.7$ ($c = 0.3$, $CHCl_3$) (77:23 er). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.27 (br s, 1H, NH), 7.81 (m, 2H, Har), 7.47 (dd, J = 7.7, 1.2 Hz, 1H, Har), 7.38 (m, 3H, Har), 7.30–7.22 (m, 5H, Har), 7.15 (m, 3H, Har), 7.01 (d, J = 8.1 Hz, 2H, Har), 6.93 (td, J = 7.7, 1.1 Hz, 1H, Har), 6.70 (dd, J = 8.0, 1.1 Hz, 1H, Har), 5.08 (d, J = 16.0 Hz, 1H, CHHPh), 4.91 (d, J = 16.0 Hz, 1H, CHHPh), 2.27 (s, 3H, $CH_3C_6H_4$), 1.64 (s, 3H, CH_3), 1.41 (s, 9H, $C(CH_3)_3$) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 175.0 (CO), 170.3 (CO), 157.7 (C=*N*), 143.0 (Car), 135.0 (Car), 134.8 (Car), 136.6 (Car), 133.1 (Car),

129.8 (CHar), 129.5 (CHar), 129.0 (CHar), 128.8 (CHar), 128.7 (CHar), 128.6 (CHar), 128.0 (CHar), 127.6 (CHar), 127.0 (CHar), 126.4 (CHar), 124.6 (Car), 122.5 (CHar), 110.5 (CHar), 77.3 ($C(CH_3)_3$), 70.6 (CNH), 53.6 (CPh), 44.5 (CH_2), 28.2 ($C(CH_3)_3$), 20.9 ($CH_3C_6H_4$), 15.9 (CH_3) ppm. **IR (ATR)**: 3333, 2935, 1710, 1608, 1485, 1362, 1253, 1163, 891, 815, 760, 695 cm^{-1}. **HPLC**: Lux *i*-Amylose-1 column, hexane/*i*-PrOH 90:10, 0.5 mL/min, λ = 254 nm, minor enantiomer *t*r = 14.9 min, major enantiomer *t*r = 25.8 min. **HRMS** (ESI-QTOF) m/z: $[M+H]^+$ Calcd. for $C_{37}H_{37}N_4O_4$ 601.2809; Found 601.2844.

***tert*-Butyl ((*S*)-4-((*S*)-1-benzyl-2-oxo-3-phenylindolin-3-yl)-3-ethyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)carbamate (3da)**. Product **3da** was obtained according to the general procedure by the reaction of N-benzyl-3-phenyloxindole **2a** (30 mg, 0.1 mmol) with ketimine **1d** (33 mg, 0.11 mmol) using catalyst **C6** (5 mg, 0.01 mmol). Chromatography on a silica gel using hexane/DCM 1:4 as an eluent afforded compound **3da** as a colorless solid (42 mg, 0.07 mmol, 70% yield). $[\alpha]_D^{25} = +21.5$ (*c* = 0.34, $CHCl_3$) (65:35 er). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.27 (br s, 1H, NH), 7.80 (m, 2H, Har), 7.43 (d, J = 7.6 Hz, 1H, Har), 7.38 (m, 5H, Har), 7.30–7.24 (m, 5H, Har), 7.21 (m, 2H, Har), 7.12 (td, J = 7.8, 1.2 Hz, 1H, Har), 7.06 (tt, J = 7.4, 1.2 Hz, 1H, Har), 6.90 (td, J = 7.7, 1.1 Hz, 1H, Har), 6.69 (dd, J = 7.9, 1.0 Hz, 1H, Har), 5.08 (d, J = 16.0 Hz, 1H, CHHPh), 4.90 (d, J = 16.0 Hz, 1H, CHHPh), 1.98 (m, 1H, CHHCH$_3$), 1.65 (m, 1H, CHHCH$_3$), 1.39 (s, 9H, $C(CH_3)_3$), 1.17 (t, J = 7.3 Hz, 3H, CH_3) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 175.0 (CO), 170.8 (CO), 161.5 (C=*N*), 143.0 (Car), 137.3 (Car), 135.0 (Car), 133.3 (Car), 129.8 (CHar), 129.4 (CHar), 128.8 (CHar), 128.7 (CHar), 128.6 (CHar), 128.4 (CHar), 128.0 (CHar), 127.6 (CHar), 127.0 (CHar), 126.3 (CHar), 124.9 (CHar), 124.6 (Car), 122.4 (CHar), 110.5 (CHar), 77.3 ($C(CH_3)_3$), 70.7 (CNH), 53.7 (CPh), 44.5 (CH_2), 28.1 ($C(CH_3)_3$), 23.0 (CH_2CH_3), 9.5 (CH_3CH_2) ppm. **IR (ATR)**: 3304, 2978, 2938, 1714, 1696, 1612, 1598, 1489, 1471, 1370, 1348, 1156, 753, 692 cm^{-1}. **HPLC**: Lux *i*-Amylose-1 column, hexane/*i*-PrOH 90:10, 0.5 mL/min, λ = 254 nm, minor enantiomer *t*r = 11.7 min, major enantiomer *t*r = 18.5 min. **HRMS** (ESI-QTOF) m/z: $[M+H]^+$ Calcd. For $C_{37}H_{37}N_4O_4$ 601.2809; Found 601.2836.

***tert*-Butyl ((*S*)-4-((*S*)-1-benzyl-2-oxo-3-phenylindolin-3-yl)-5-oxo-1,3-diphenyl-4,5-dihydro-1*H*-pyrazol-4-yl)carbamate (3ea)**. Product **3ea** was obtained according to general procedure by reaction of N-benzyl-3-phenyloxindole **2a** (30 mg, 0.1 mmol) with ketimine **1e** (38 mg, 0.11 mmol) using catalyst **C6** (5 mg, 0.01 mmol). Chromatography on a silica gel using hexane/DCM 1:4 as an eluent afforded compound **3ea** as a colorless solid (29 mg, 0.045 mmol, 45% yield). $[\alpha]_D^{25} = -3.0$ (*c* = 0.4, $CHCl_3$) (52:48 er). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.46 (br s, 1H, NH), 7.67 (m, 3H, Har), 7.55 (d, J = 7.1 Hz, 2H, Har), 7.45 (d, J = 7.4 Hz, 2H, Har), 7.30–7.23 (m, 7H, Har), 7.16 (m, 2H, Har), 7.11 (m, 3H, Har), 7.02 (m, 3H, Har), 6.94 (td, J = 7.7, 1.1 Hz, 1H, Har), 6.67 (dd, J = 7.9, 1.1 Hz, 1H, Har), 5.10 (d, J = 16.0 Hz, 1H, CHHPh), 4.97 (d, J = 16.0 Hz, 1H, CHHPh), 1.32 (s, 9H, $C(CH_3)_3$) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$): δ 170.9 (CO), 154.5 (CO_2tBu), 142.8 (Car), 137.2 (Car), 132.0 (Car), 135.0 (Car), 130.7 (Car), 130.0 (CHar), 129.6 (CHar), 129.2 (CHar), 128.8 (CHar), 128.6 (CHar), 128.5 (CHar), 128.3 (CHar), 127.8 (CHar), 127.7 (CHar), 127.6 (CHar), 127.2 (CHar), 127.1 (CHar), 126.7 (CHar), 126.4 (CHar), 125.4 (CHar), 124.4 (Car), 122.2 (CHar), 110.3 (CHar), 71.0 (CNH), 53.9 (CPh), 44.5 (CH_2Ph), 28.0 ($C(CH_3)_3$) ppm. **IR (ATR)**: 3332, 3058, 2975, 2928, 1705, 1611, 1593, 1489, 1467, 1250, 1153, 1109, 908, 889, 759, 731, 691 cm^{-1}. **HPLC**: Lux *i*-Amylose-1 column, hexane/*i*-PrOH 90:10, 0.5 mL/min, λ = 254 nm, minor enantiomer *t*r = 33.5 min, major enantiomer *t*r = 12.8 min. **HRMS** (ESI-QTOF) m/z: $[M+H]^+$ Calcd. for $C_{41}H_{37}N_4O_4$ 649.2415; Found 649.2849.

***tert*-Butyl ((*S*)-3-methyl-4-((*S*)-1-methyl-2-oxo-3-phenylindolin-3-yl)-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)carbamate (3ab)**. Product **3ab** was obtained according to general procedure by reaction of N-methyl-3-phenyloxindole **2b** (22 mg, 0.1 mmol) with ketimine **1a** (32 mg, 0.11 mmol) using catalyst **C6** (5 mg, 0.01 mmol). Chromatography on a silica gel using hexane/DCM 1:4 as an eluent afforded compound **3ab** as a colorless solid (38 mg, 0.075 mmol, 75% yield). Mp 163°C–164°C. $[\alpha]_D^{25} = +26.9$ (*c* = 0.5, $CHCl_3$) (68:32 er). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 8.25 (br s, 1H, NH), 7.80 (m, 2H, Har), 7.46 (dd, J = 7.5, 1.1 Hz, 1H, Har), 7.36 (m, 3H, Har), 7.28 (m, 3H, Har), 7.20 (m, 2H, Har), 7.06 (tt, J = 7.4, 1.2 Hz, 1H, Har), 6.95 (td, J = 7.7, 1.1 Hz, 1H, Har), 6.89 (m, 1H, Har), 3.26 (s, 3H, CH_3N), 1.61 (s, 3H, CH_3), 1.39 (s, 9H, $C(CH_3)_3$) ppm. **^{13}C-NMR** (101 MHz, $CDCl_3$) δ 174.6 (CO), 170.4 (CO), 157.8 (C=*N*), 143.9 (Car), 137.0 (Car), 132.9 (Car), 129.8 (CHar), 129.4 (CHar), 128.8 (CHar), 128.6 (CHar), 128.5 (CHar), 128.0, 127.6 (CHar), 127.0 (CHar), 126.3 (CHar), 125.1 (CHar), 124.4 (Car), 122.4 (CHar), 119.3 (CHar), 110.5 (CHar), 77.3 ($C(CH_3)_3$), 70.7 (CNH), 53.4 (CPh), 33.8 (CH_3N), 28.2 ($C(CH_3)_3$), 15.8 (CH_3) ppm. **IR (ATR)**: 3315, 2924, 2855, 1714, 1699, 14,859 1471, 1366, 1155, 753, 739, 692 cm^{-1}. **HPLC**: Lux-Amylose-1 column, hexane/*i*-PrOH 90:10, 1.0 mL/min, λ = 254 nm, minor enantiomer *t*r = 6.9 min, major enantiomer *t*r = 7.7 min. **HRMS** (ESI-QTOF) m/z: $[M+H]^+$ Calcd. For $C_{30}H_{31}N_4O_4$ 511.2345; Found 511.2362.

***tert*-Butyl ((*S*)-4-((*S*)-1-benzyl-3-(4-methoxyphenyl)-2-oxoindolin-3-yl)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)carbamate (3ac)**. Product **3ac** was obtained according to general procedure by reaction of N-benzyl-3-(4-methoxyphenyl)oxindole **2c** (33 mg, 0.1 mmol) with ketimine **1a** (32 mg, 0.11 mmol) in DCE using catalyst **C6** (5 mg, 0.01 mmol). Chromatography on a silica gel using hexane/EtOAc 8:1 as an eluent afforded compound **3ac** as a colorless solid (31 mg, 0.05 mmol, 50% yield). $[\alpha]_D^{25} = +17.7$ (*c* = 0.6, $CHCl_3$) (52:48 er). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.29 (br s, 1H, NH), 7.73 (d, *J* = 9.0 Hz, 2H, Har), 7.47 (d, *J* = 7.6 Hz, 1H, Har), 7.34–7.20 (m, 9H, Har), 7.13 (td, *J* = 7.8, 1.2 Hz, 1H, Har), 7.07 (ddd, *J* = 7.5, 4.3, 1.2 Hz, 1H, Har), 6.94–6.89 (m, 3H, Har), 6.72–6.69 (m, 1H, Har), 5.08 (d, *J* = 16.0 Hz, 1H, CHHPh), 4.92 (d, *J* = 16.0 Hz, 1H, CHHPh), 3.83 (s, 3H, OCH_3), 1.69 (s, 3H, CH_3), 1.42 (br s, 9H, $C(CH_3)_3$) ppm. **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 175.2 (CO), 170.6 (CO), 159.8 (CO_2tBu), 158.1 (C=*N*), 143.0 (Car), 137.1 (Car), 135.0 (Car), 131.1 (CHar), 130.7 (CHar), 129.7 (CHar), 128.9 (CHar), 128.8 (CHar), 128.6 (CHar), 128.5 (CHar), 127.6 (CHar), 127.1 (CHar), 127.0 (CHar), 126.2 (CHar), 125.1 (CHar), 124.8 (CHar), 124.8 (Car), 122.4 (CHar), 119.4 (CHar), 113.9 (CHar), 110.5 (CHar), 70.8 (CNBoc) 55.3 (OCH_3), 53.1 (CPh), 44.5 (NCH_2Ph), 28.2 ($C(CH_3)_3$), 16.0 (CH_3) ppm. **HPLC**: Lux *i*-Amylose-1 column, hexane/*i*-PrOH 90:10, 0.5 mL/min, λ = 254 nm, mayor enantiomer *t*r = 20.0 min, minor enantiomer *t*r = 38.4 min. **HRMS** (ESI-QTOF) m/z: $[M+Na]^+$ Calcd. For $C_{37}H_{36}N_4NaO_5$ 639.2578; Found 639.2577.

***tert*-Butyl ((*S*)-4-((*S*)-1-benzyl-2-oxo-3-(4-(trifluoromethyl) phenyl)indolin-3-yl)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)carbamate (3ad)**. Product **3ad** was obtained according to the general procedure by the reaction of N-benzyl-3-(4-(trifluoromethyl)phenyl)oxindole **2d** (37 mg, 0.1 mmol) with ketimine **1a** (32 mg, 0.11 mmol) in DCE using catalyst **C6** (5 mg, 0.01 mmol). Chromatography on a silica gel using hexane/EtOAc 8:1 as an eluent afforded compound **3ad** as a colorless solid (36 mg, 0.055 mmol, 55% yield). $[\alpha]_D^{25} = +19.3$ ($c = 0.56$, $CHCl_3$) (58:42 er). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.21 (br s, 1H, NH), 7.98 (d, J = 8.3 Hz, 2H, Har), 7.67 (d, $J = 8.3$ Hz, 2H, Har), 7.47 (d, $J = 7.7$ Hz, 1H, Har), 7.33–7.23 (m, 10H, Har), 7.09 (dt, $J = 9.0$, 3.8 Hz, 1H, Har),6.96 (t, $J = 7.6$ Hz, 1H, Har), 6.75 (d, $J = 7.9$ Hz, 1H, Har), 5.11 (d, $J = 16.0$ Hz, 1H, CHHPh), 4.91 (d, $J = 16.0$ Hz, 1H, CHHPh), 1.69 (s, 3H, CH_3), 1.43 (br s, 9H, $C(CH_3)_3$) ppm. **^{13}C-NMR** (126 MHz, $CDCl_3$) δ 174.4 (CO), 170.2 (CO), 157.2 (C=*N*), 143.1 (Car), 137.4 (Car), 136.9 (Car), 134.8 (Car), 131.0 (q, $J = 32.8$ Hz, CCF_3) 130.3 (CHar), 130.0 (CHar), 129.0 (CHar), 128.9 (CHar), 128.7 (CHar), 128.5 (CHar), 127.8 (CHar), 127.2 (CHar), 127.1 (CHar), 126.2 (CHar), 126.2 (CHar), 125.5 (q, $J = 3.7$ Hz, CHar), 125.3 (CHar), 124.0 (Car), 123.8 (q, $J = 272.4$ Hz, CF_3), 122.8 (CHar), 119.3 (CHar), 110.8 (CHar), 70.6 (CNHBoc), 53.5 (CPh), 44.7 (NCH_2Ph), 28.2 ($C(CH_3)_3$), 16.1 (CH_3) ppm. **^{19}F-NMR** (470 MHz, $CDCl_3$) δ −62.83 ppm. **HPLC**: Lux *i*-Amylose-1 column, hexane/*i*-PrOH 90:10, 0.5 mL/min, λ = 254 nm, minor enantiomer *t*r = 10.8 min, major enantiomer *t*r = 13.5 min. $[M+Na]^+$ Calcd. for $C_{37}H_{33}F_3N_4NaO$ 677.2346; Found 677.2357.

***tert*-Butyl ((*S*)-4-((*S*)-1-benzyl-5-bromo-2-oxo-3-phenylindolin-3-yl)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)carbamate (3ae)**. Product **3ae** was obtained according to general procedure by reaction of N-benzyl-5-bromo-3-phenyloxindole **2e** (38 mg, 0.1 mmol) with ketimine **1a** (32 mg, 0.11 mmol) in DCE using catalyst **C6** (5 mg, 0.01 mmol). Chromatography on a silica gel using hexane/EtOAc 8:1 as an eluent afforded compound **3ae** as a colorless solid (47 mg, 0.07 mmol, 70% yield). Mp 167°C–170°C. $[\alpha]_D^{25} = +13.9$ ($c = 0.36$, $CHCl_3$) (58:42 er). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.22 (s, 1H, NH), 7.77 (dd, $J = 6.7$, 3.3 Hz, 2H, Har), 7.61 (d, $J = 1.9$ Hz, 1H, Har), 7.48–7.33 (m, 5H, Har), 7.31–7.16 (m, 8H, Har), 7.14–7.05 (m, 1H, Har), 6.52 (d, $J = 8.4$ Hz, 1H, Har), 5.05 (d, $J = 16.0$ Hz, 1H, CHHPh), 4.84 (d, $J = 16.0$ Hz, 1H, CHHPh), 1.62 (s, 3H, CH_3), 1.41 (s, 9H, $C(CH_3)_3$) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.34 (CO), 157.99 ($NCO_2{}^tBu$), 142.04 (Car), 136.97 (Car), 134.43 (Car), 132.72 (CHar), 129.27 (CHar), 129.21 (CHar), 129.14 (CHar), 128.87 (CHar), 128.83 (CHar), 128.55 (CHar), 127.79 (CHar), 126.96 (CHar), 126.64 (Car), 125.29 (CHar), 119.36 (CHar), 115.35 (Car), 111.90 (CHar), 77.23 ($C(CH_3)_3$), 53.50 (CqPh), 44.57 (CH_2Ph), 28.14 ($C(CH_3)_3$), 15.81 (CH_3). ppm. **HPLC**: Lux *i*-Amylose-1 column, hexane/*i*-PrOH 90:10, 0.5 mL/min, λ = 254 nm, minor enantiomer *t*r = 13.4 min, major enantiomer *t*r = 27.0 min. **HRMS** (ESI-QTOF) m/z: $[M+H]^+$ Calcd. For $C_{36}H_{34}BrN_4O_4$ 665.1763; Found 665.1782.

Ethyl (*R*)-1-benzyl-3-((*S*)-4-((*tert*-butoxycarbonyl)amino)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)-2-oxoindoline-3-carboxylate (3af). Product **3af** was obtained according to general procedure by reaction of ethyl 1-benzyl-2-oxoindoline-3-carboxylate **2f** (30 mg, 0.1 mmol) with ketimine **1a** (32 mg, 0.11 mmol) in DCE using catalyst **C6** (5 mg, 0.01 mmol). Chromatography on a silica gel using hexane/EtOAc 8:1 as an eluent afforded compound **3af** as a colorless solid (26 mg, 0.045 mmol, 45% yield). (dr: 71:29; er: **85:15** major, **72:28** minor). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.76 (d, $J = 8.0$ Hz, 1H, Har), 7.62–7.44 (m, 2H, Har), 7.43–7.22 (m, 9H, Har), 7.21–7.14 (m, 2H, Har), 7.10 (t, $J = 7.4$ Hz, 2H, Har), 6.96 (d, $J = 8.2$ Hz, 1H, Har), 6.74 (d, $J = 7.9$ Hz, 1H, Har), 6.69 (d, $J = 7.9$ Hz, 1H, Har), 5.13 (d, $J = 15.7$ Hz, 1H, CHHPh), 4.82 (d, $J = 15.8$ Hz, 1H, CHHPh), 4.38–4.18 (m, 2H, CH_2), 1.41 (s, 9H, $C(CH_3)_3$), 1.25 (t, $J = 7.1$ Hz, 3H, CH_2CH_3) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 175.2 (CO), 169.0 (CO), 156.0 (COOEt), 143.3 (Car), 135.1 (Car), 134.6 (Car), 130.5 (CHar), 130.4 (CHar), 128.8 (CHar), 128.5 (CHar), 127.9 (CHar), 127.8 (CHar), 127.4 (CHar), 125.2 (CHar), 124.4 (CHar), 123.2 (CHar), 122.9 (CHar), 122.4 (CHar), 119.5 (CHar), 109.8 (CHar), 109.4 (CHar), 109.1 (CHar), 63.3 (CH_2CH_3), 44.5 (CH_2Ph), 43.8 (CH_2Ph), 29.7 (CH_2) 28.1 ($C(CH_3)_3$), 13.8 (CH_3) ppm. **HPLC**: Lux *i*-Amylose-1 column, hexane/*i*-PrOH 90:10, 0.5 mL/min, λ = 254 nm, mayor diastereomer: minor enantiomer *t*r = 19.6 min, mayor enantiomer *t*r = 27.5 min, minor diastereomer: mayor enantiomer *t*r = 35.0 min, minor enantiomer *t*r = 38.3 min. **HRMS** (ESI-QTOF) m/z: $[M+Na]^+$ Calcd. for $C_{33}H_{34}N_4NaO_6$ 605.2371; Found 605.2388.

***tert*-Butyl (4-ethoxy-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl) carbamate (4a)**. Product **4a** was obtained as a subproduct in the reaction of ketimine **1a** with 3-phenyloxindole **2a** in chloroform stabilized with ethanol. Colorless solid, mp 134°C–135°C. **^{1}H NMR** (500 MHz, $CDCl_3$): δ 7.91 (dd, $J = 8.8$, 1.1 Hz, 2H, Har), 7.40 (dd, $J = 8.7$, 7.4 Hz, 2H, Har), 7.19 (m, 1H, Har), 5.29 (br s, 1H, NH), 3.54 (m, 2H, CH_2O), 2.15 (s, 3H, CH_3), 1.35 (s, 9H, $C(CH_3)_3$), 1.20 (t, 3H, CH_3CH_2) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ 167.4 (CON), 157.4 (CO_2tBu), 152.5 (CCH_3), 137.7 (Car), 128.9 (CHar), 125.2 (CHar), 118.4 (CHar), 85.8 (CNHBoc), 81.9 ($C(CH_3)_3$), 60.2 (CH_2O), 28.0 ($C(CH_3)_3$), 15.1 (CH_3CH_2) 12.9 (CH_3) ppm. **IR (ATR)**: 3214, 3115, 2979, 2924, 1702, 1595, 1504, 1364, 1239, 1155, 1052, 1026, 846, 751, 692 cm^{-1}. **HRMS** (ESI-QTOF) m/z: $[M+Na]^+$ Calcd. for $C_{17}H_{23}N_3NaO_4$ 356.1581; Found 356.1592.

(*Z*)-4-((5-hydroxy-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)imino)-5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (5a). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 17.47 (s, 1H, OH), 7.92 (dd, $J = 8.8$, 1.2 Hz, 4H, Har), 7.47 (dd, $J = 8.6$, 7.4 Hz, 4H, Har), 7.32 (m, 2H, Har), 2.37 (s, 6H, CH_3) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$): δ 154.4 (CON), 152.3 (CCH_3), 137.5 (Car), 129.0 (CHar), 126.9 (CHar), 125.8 (CN), 120.7 (CHar), 12.0 (CH_3) ppm. **IR (ATR):** 3065, 2924, 1714, 1536, 1489, 1372, 1321, 1174, 1010, 1026, 751, 684 cm^{-1}. **HRMS** (ESI-QTOF) m/z: $[M+Na]^+$ Calcd. for $C_{20}H_{17}N_5NaO_2$ 382.1274; Found 382.1285.

Acknowledgments

Authors thank Junta de Castilla y León (Project VA072G24) for financial support. L.M., A.M., and J.M.A. thank the Laboratory of Instrumental Techniques (LTI) Research Facilities, Universidad de Valladolid.

Data Availability Statement

The data that supports the findings of this study are available in the Supporting Information of this article.

References

1. E. M. Afsah, "Double Mannich Reaction With Ketones as a Route to Heterocyclic Systems: A Mini Review," *Journal of Heterocyclic Chemistry* 61 (2024): 805–817.

2. S. Mohurle, V. Devi C, S. D. Pasuparthy, D. Talamarla, V. Kali, and B. Maiti, "[BCMIM][cl] Ionic Liquid Catalyzed Diastereoselective Synthesis of β-Amino Ketones via Facile, One-Pot, Multicomponent Mannich Reaction Under Solvent-Free Condition," *Journal of Heterocyclic Chemistry* 60 (2023): 1545–1557.

3. E. M. Afsah, E. M. Kandil, S. M. Abdelmageed, and F. T. Elbarhmtoushi, "Synthesis of Novel Mannich Bases and Hybrid Mannich Bases Related to Isoindolin-1,3-Dione," *Journal of Heterocyclic Chemistry* 57 (2020): 346–354.

4. E. M. Afsah, E. M. Keshk, A.-R. H. Abdel-Rahman, and N. F. Jomah, "Utility of Ketonic Mannich Bases in Synthesis of Some New Functionalized 2-Pyrazolines," *Journal of Heterocyclic Chemistry* 55 (2018): 326–334.

5. I. Bagheri, L. Mohammadi, V. Zadsirjan, and M. M. Heravi, "Organocatalyzed Asymmetric Mannich Reaction: An Update," *ChemistrySelect* 6 (2021): 1008–1066.

6. X.-Q. Houa and D.-M. Du, "Recent Advances in Squaramide-Catalyzed Asymmetric Mannich Reactions," *Advanced Synthesis & Catalysis* 362 (2020): 4487–4512.

7. T. T. Talele, "Opportunities for Tapping Into Three-Dimensional Chemical Space Through a Quaternary Carbon," *Journal of Medicinal Chemistry* 63 (2020): 13291–13315.

8. Z. Zhao, X. Dai, C. Li, et al., "Pyrazolone Structural Motif in Medicinal Chemistry: Retrospect and Prospect," *European Journal of Medicinal Chemistry* 186 (2020): 111893.

9. X. Bao, S. Wei, X. Qian, et al., "Asymmetric Construction of a Multi-Pharmacophore-Containing Dispirotriheterocyclic Scaffold and Identification of a Human Carboxylesterase 1 Inhibitor," *Organic Letters* 20 (2018): 3394–3398.

10. M. Bae, J. Oh, E. S. Bae, et al., "WS9326H, an Antiangiogenic Pyrazolone-Bearing Peptide From an Intertidal Mudflat Actinomycete," *Organic Letters* 20 (2018): 1999–2002.

11. M. Lusardi, A. Spallarossa, and C. Brullo, "Amino-Pyrazoles in Medicinal Chemistry: A Review," *International Journal of Molecular Sciences* 24 (2023): 7834.

12. X. Bao, X. Wang, J.-M. Tian, X. Ye, B. Wang, and H. Wang, "Recent Advances in the Applications of Pyrazolone Derivatives in Enantioselective Synthesis," *Organic & Biomolecular Chemistry* 20 (2022): 2370–2386.

13. X. Xie, L. Xiang, C. Peng, and B. Han, "Catalytic Asymmetric Synthesis of Spiropyrazolones and Their Application in Medicinal Chemistry," *Chemical Record* 19 (2019): 2209–2235.

14. P. Chauhan, S. Mahajan, and D. Enders, "Asymmetric Synthesis of Pyrazoles and Pyrazolones Employing the Reactivity of Pyrazolin-5-One Derivatives," *Chemical Communications* 51 (2015): 12890–12907.

15. P. Chauhan, S. Mahajan, U. Kaya, A. Peuronen, K. Rissanen, and D. Enders, "Asymmetric Synthesis of Amino-Bis-Pyrazolone Derivatives via an Organocatalytic Mannich Reaction," *Journal of Organic Chemistry* 82 (2017): 7050–7058.

16. Y. Zhou, Y. You, Z.-H. Wang, X.-M. Zhang, X.-Y. Xu, and W.-C. Yuan, "Organocatalyzed Enantioselective Decarboxylative Mannich Reaction of β-Ketoacids With Pyrazolinone Ketimines for the Construction of Chiral β-Amino Ketone-Pyrazolinone Derivatives," *European Journal of Organic Chemistry* 2019 (2019): 3112–3116.

17. M. Gil-Ordóñez, C. Aubry, C. Niño, A. Maestro, and J. M. Andrés, "Squaramide-Catalyzed Asymmetric Mannich Reaction Between 1,3-Dicarbonyl Compounds and Pyrazolinone Ketimines: A Pathway to Enantioenriched 4-Pyrazolyl- and 4-Isoxazolyl-4-Aminopyrazolone Derivatives," *Molecules* 27 (2022): 6983.

18. C. Li, W.-F. Zuo, J. Zhou, et al., "Catalytic Asymmetric Synthesis of 3,4′-Indole–Pyrazole Derivatives Featuring Axially Chiral Bis-Pentatomic Heteroaryls," *Organic Chemistry Frontiers* 9 (2022): 1808–1813.

19. C. V. Galliford and K. Scheidt, "Pyrrolidinyl-Spirooxindole Natural Products as Inspirations for the Development of Potential Therapeutic Agents," *Angewandte Chemie International Edition* 46 (2007): 8748–8758.

20. B. Yu, D.-Q. Yu, and H.-M. Liu, "Spirooxindoles: Promising Scaffolds for Anticancer Agents," *European Journal of Medicinal Chemistry* 97 (2015): 673–698.

21. P. Dhokne, A. P. Sakla, and N. Shankaraiah, "Structural Insights of Oxindole Based Kinase Inhibitors as Anticancer Agents: Recent Advances," *European Journal of Medicinal Chemistry* 216 (2021): 113334.

22. J. Kaur, B. P. Kaur, and S. S. Chimni, "Recent Advances in the Catalytic Synthesis of 3-Aminooxindoles: An Update," *Organic & Biomolecular Chemistry* 18 (2020): 4692–4708.

23. H. Pellisier, "Synthesis of Chiral 3-Substituted 3-Amino-2-Oxindoles Through Enantioselective Catalytic Nucleophilic Additions to Isatin Imines," *Beilstein Journal of Organic Chemistry* 14 (2018): 1349–1369.

24. Z. G. Mohammadi, R. Moradi, and N. Lashgari, "Asymmetric Synthesis of Chiral Oxindoles Using Isatin as Starting Material," *Tetrahedron* 74 (2018): 1323–1353.

25. C. Vila, F. I. Amr, G. Blay, M. C. Muñoz, and J. R. Pedro, "Organocatalytic Enantioselective Synthesis of Pyrazoles Bearing a Quaternary Stereocenter," *Chemistry, an Asian Journal* 11 (2016): 1532–1536.

26. F. I. Amr, C. Vila, G. Blay, M. C. Muñoz, and J. R. Pedro, "Organocatalytic Enantioselective Alkylation of Pyrazol-3-Ones With Isatin-Derived Ketimines: Stereocontrolled Construction of Vicinal Tetrasubstituted Stereocenters," *Advanced Synthesis & Catalysis* 358 (2016): 1583–1588.

27. G. Wu, H. Xu, Z. Liu, et al., "Asymmetric Organocatalysis Combined With Palladium Catalysis: Synergistic Effect on Enantioselective Mannich/α-Allylation Sequential Reactions of Pyrazolones in Constructing Vicinal Quaternary Stereocenters," *Organic Letters* 21 (2019): 7708–7712.

28. Q.-D. Zhang, B.-L. Zhao, B.-Y. Li, and D.-M. Du, "Squaramide-Catalyzed Asymmetric Mannich Reactions Between 3-Fluorooxindoles and Pyrazolinone Ketimines," *Organic & Biomolecular Chemistry* 17 (2019): 7182–7191.

29. M. L. Tong, L. T. Leusch, K. Holzschneider, and S. F. Kirsch, "Rubazonic Acids and Their Synthesis," *Journal of Organic Chemistry* 85 (2020): 6008–6016.

30. B. M. Trost, J. Xie, and J. D. Sieber, "The Palladium Catalyzed Asymmetric Addition of Oxindoles and Allenes: An Atom-Economical Versatile Method for the Construction of Chiral Indole Alkaloids," *Journal of the American Chemical Society* 133 (2011): 20611–20622.

31. S. Del Pozo, S. Vera, M. Oiarbide, and C. Palomo, "Catalytic Asymmetric Synthesis of Quaternary Barbituric Acids," *Journal of the American Chemical Society* 139 (2017): 15308–15311.

32. P. Rodríguez-Ferrer, M. Sanz-Novo, A. Maestro, J. M. Andrés, and R. Pedrosa, "Synthesis of Enantioenriched 3-Amino-3-Substituted Oxindoles by Stereoselective Mannich Reaction Catalyzed by Supported Bifunctional Thioureas," *Advanced Synthesis & Catalysis* 361 (2019): 3645–3655.

33. S. M. Opalka, J. L. Steinbacher, B. A. Lambiris, and D. T. McQuade, "Thiourea/Proline Derivative-Catalyzed Synthesis of Tetrahydrofuran Derivatives: A Mechanistic View," *Journal of Organic Chemistry* 76 (2011): 6503–6517.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.