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Asymmetric Synthesis of Fused Polycyclic Indazoles through Aminocatalyzed Aza-Michael Addition/Intramolecular Cyclization

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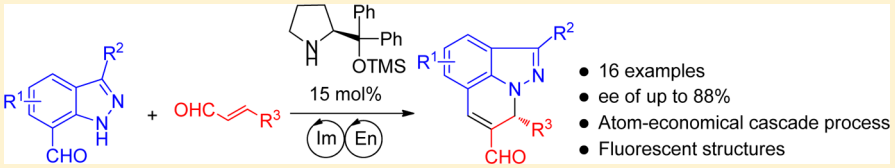
Supporting Information

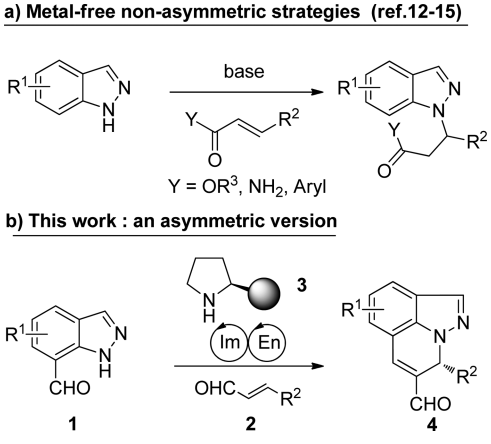


ABSTRACT: The first example of an asymmetric aminocatalyzed aza-Michael addition of 1*H*-indazole derivatives to *α,β*-unsaturated aldehydes is described. The iminium/enamine cascade process lies at the heart of our strategy, leading to enantioenriched fused polycyclic indazole architectures. Variations on both the *α,β*-unsaturated aldehydes and the indazole-7-carbaldehyde heterocycles were studied in order to broaden the scope of the transformation in synthetically interesting directions. The fused polycyclic indazoles exhibit fluorescence properties and can undergo synthetic transformations.

The decoration of nitrogen-containing aromatic systems is of utmost importance in synthetic chemistry due to the ubiquity of these architectures in biologically relevant compounds. Among the reactions available in the chemist's toolbox, the aza-Michael addition has become an established method for the selective functionalization of the nitrogen atom.[1] In particular, the development of asymmetric organocatalysis over the past decades has fueled the synthetic possibilities of aza-Michael additions by providing a vast number of combinations between nitrogen-containing heteroaromatic systems and Michael acceptors.[2] In recent years, the field of asymmetric aminocatalyzed aza-Michael addition to *α,β*-unsaturated carbonyl compounds has grown at a rapid pace to include numerous nitrogenated heteroaromatic compounds such as benzotriazole,[3] benzimidazole,[3a] imidazole,[3a,d,4] indole,[5] purine bases,[6] pyrazole,[3a,7] pyrrole,[8] tetrazole,[3] or triazole.[3a,c,9] To the best of our knowledge, 1*H*-indazole has never been investigated in organocatalyzed asymmetric aza-Michael addition with *α,β*-unsaturated carbonyl compounds while this reaction could lead to interesting motifs. For example, *N*-substituted indazoles are found in AG035029, which exhibits antidiabetic effects[10] and the tetracyclic compound KW-2170, a DNA intercalating antitumor agent.[11]

Considering the nonasymmetric version, a scant number of metal-free synthetic methods have been reported in the literature for promoting aza-Michael addition of 1*H*-indazoles to *α,β*-unsaturated carbonyl compounds. For instance, Goya and co-workers showed that 1*H*-indazole derivatives undergo *N*-alkylation with acrylamide under basic conditions.[12] The use of different bases (e.g., DBU, Cs_2CO_3, *t*BuOK) also turned out to be suitable conditions for the aza-Michael addition with alkyl acrylates[13] or enones.[14,15] Because of the lack of an organocatalytic method allowing the asymmetric aza-Michael addition of 1*H*-indazole to *α,β*-unsaturated carbonyl compounds, we decided to explore an aminocatalytic strategy to tackle this challenge. This approach will take advantage of the ability of chiral secondary amines **3** to condense with enals **2**, affording chiral reactive iminium species which could undergo a stereoselective nucleophilic addition (Scheme 1). In light of our continuing interest in the preparation of enantioenriched polycyclic architectures,[5d,16] we surmised that 1*H*-indazole-7-carbaldehyde motifs **1** could act as suitable starting materials to generate enantioenriched fused polycyclic indazoles **4** through an iminium−enamine process involving an aza-Michael addition, followed by an intramolecular cyclization/dehydration

Scheme 1. Synthetic Strategies for Aza-Michael Addition of 1*H*-Indazoles



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sequence.[17] This strategy will pave the way to the enantioselective preparation of functionalized 1,7-annulated indazole, which is the core framework of the antitumor agent KW-2170 (Figure 1).

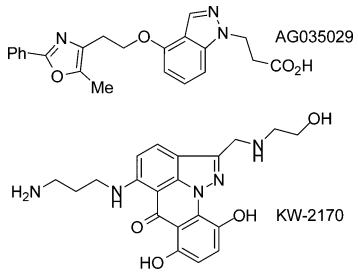
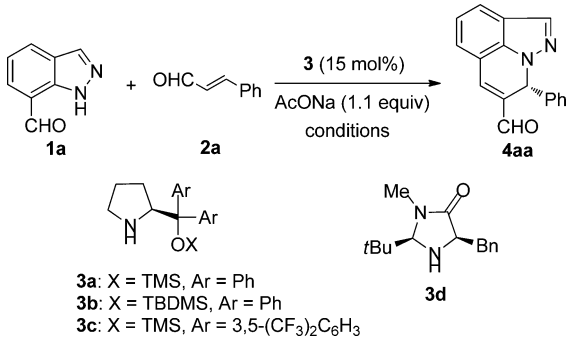


Figure 1. Selected examples of biorelevant *N*-substituted indazoles.

The study started with the optimization of the reaction conditions using 1*H*-indazole-7-carbaldehyde **1a** and *trans*-cinnamaldehyde **2a** as substrates. The reaction was promoted by an aminocatalyst **3** and a base which are known to be a good combination to promote aza-Michael addition (Table 1).[5d]

Table 1. Optimization of Reaction Conditions[a]



entry	3	solvent	time, *T* °C	yield (%)	*ee* (%)[b]
1	**3a**	$CHCl_3$	24 h, 55 °C	90	82
2	**3a**	$CHCl_3$	40 h, 55 °C	98	80
3	**3a**	$CHCl_3$	88 h, RT	55	77
4	**3a**	MeCN	24 h, 55 °C	55	54
5	**3a**	1,2-DCE	24 h, 55 °C	94	86
6	**3b**	1,2-DCE	24 h, 55 °C	85	86
7	**3c**	1,2-DCE	24 h, 55 °C	n.r.	n.d.
8[c]	**3d**	1,2-DCE	24 h, 55 °C	54	−7
9[d]	**3a**	1,2-DCE	24 h, 55 °C	78	61
10[e]	**3a**	1,2-DCE	24 h, 55 °C	94	72

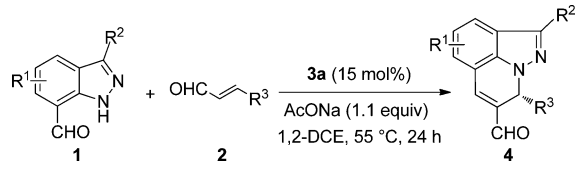
[a]Reactions were performed on a 0.2 mmol scale using 1 equiv of **1a**, 1.5 equiv of **2a**, 1.1 equiv of AcONa, 15 mol % of **3**, unless otherwise noted. n.r., no reaction; n.d., not determined. [b]Enantiomeric excesses were measured by chiral HPLC. [c]In this case, the reaction was performed with 20 mol % of **3d** and 20 mol % of HCl added in the reaction mixture from a hydrogen chloride solution 4 N in dioxane. [d]15 mol % of benzoic acid was used instead of 1.1 equiv of AcONa. [e]No AcONa was added to the reaction mixture.

The reaction of 1*H*-indazole-7-carbaldehyde **1a** with *trans*-cinnamaldehyde **2a** in the presence of the aminocatalyst **3a** led to the product **4aa** in 90% yield and 82% *ee* determined by chiral HPLC (Table 1, entry 1).[18] Extending the reaction time to 40 h slightly improved the yield of **4aa** (98%) while the enantiomeric excess was 80% (entry 2). We surmised that decreasing the reaction temperature could improve the enantioselectivity (entry 3). Nevertheless, the desired compound **4aa** was obtained in 55% yield and 77% *ee* by performing the reaction at room temperature for 88 h. Switching from chloroform to acetonitrile as a reaction solvent resulted in a dramatic decrease of both the yield and the enantioselection (entry 4). Better results were obtained by running the reaction in 1,2-dichloroethane (entry 5). Under these conditions, the product **4aa** was produced in 94% yield and 86% *ee*. The influence of the aminocatalyst structure was then investigated (entries 6−8). The use of the catalyst **3b** possessing a bulkier silyl group led to the desired product **4aa** with the same enantiomeric excess as with **3a** but a lower yield (85%, entry 6). No reaction occurred by using the $(CF_3)_2C_6H_3$-derived catalyst **3c**, and a low enantiomeric excess was obtained for **4aa** using the MacMillan imidazolidinone organocatalyst **3d** (entries 7 and 8). The influence of sodium acetate was studied by performing the reaction under acidic and neutral conditions (entries 9 and 10). The use of 15 mol % of benzoic acid in conjunction with 15 mol % of **3a** had a negative impact on the level of the enantioselection (61% *ee*, entry 9 compared to 86% *ee*, entry 5). The reaction carried out without sodium acetate followed the same trend by producing **4aa** in 94% yield but 72% *ee* (entry 10).

Having established the best reaction conditions (entry 5, Table 1), the scope and limitations of the methodology were then explored on various 1*H*-indazole-7-carbaldehyde analogues **1** and α,β-unsaturated aldehydes **2** (Table 2).

The influence of the aromatic substitution pattern of the aldehydes **2** on the levels of yields and enantiomeric excesses was first investigated (Table 2, entries 1−12). The reaction works well regardless of the introduction of electron-donating or electron-withdrawing substituents on the aromatic ring of the α,β-unsaturated aldehydes **2**. The opposite enantiomeric

Table 2. Scope and Limitations[a]



entry	R^1, R^2	R^3	4	yield (%)	*ee* (%)[b]
1	H, H (**1a**)	Ph (**2a**)	**4aa**	94	86
2	H, H (**1a**)	4-MeC_6H_4 (**2b**)	**4ab**	96	79
3	H, H (**1a**)	4-ClC_6H_4 (**2c**)	**4ac**	91	69
4	H, H (**1a**)	3-ClC_6H_4 (**2d**)	**4ad**	93	60
5	H, H (**1a**)	4-$MeOC_6H_4$ (**2e**)	**4ae**	90	73
6	H, H (**1a**)	3-$MeOC_6H_4$ (**2f**)	**4af**	90	84
7	H, H (**1a**)	2-$MeOC_6H_4$ (**2g**)	**4ag**	62	71
8	H, H (**1a**)	4-$NO_2C_6H_4$ (**2h**)	**4ah**	78	88
9	H, H (**1a**)	2-$NO_2C_6H_4$ (**2i**)	**4ai**	92	79
10	H, H (**1a**)	2-naphthyl (**2j**)	**4aj**	99	59
11	H, H (**1a**)	2-thienyl (**2k**)	**4ak**	88	55
12	H, H (**1a**)	Me (**2l**)	**4al**	33	55
13	H, I (**1b**)	Ph (**2a**)	**4ba**	88	60
14	5-Cl, H (**1c**)	Ph (**2a**)	**4ca**	84	60
15	4-Me, H (**1d**)	Ph (**2a**)	**4da**	82	79
16	4-Me, H (**1d**)	4-ClC_6H_4 (**2c**)	**4dc**	80	62

[a]Reactions were performed on a 0.2 mmol scale using 1 equiv of **1**, 1.5 equiv of **2**, 1.1 equiv of AcONa, 15 mol % of **3a** at 55 °C for 24 h in 1,2-dichloroethane. [b]Enantiomeric excesses were measured by chiral HPLC.

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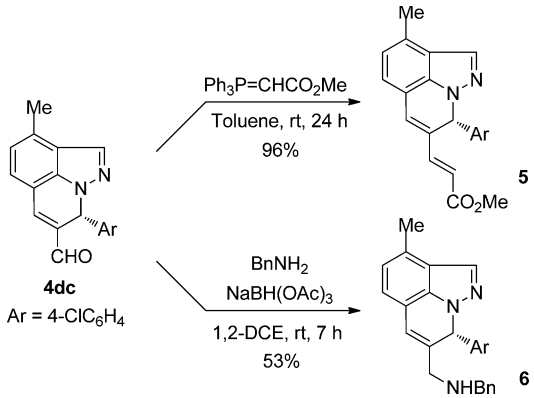
form of **4** can be obtained starting from the catalyst *ent*-**3a** with an *R* configuration. For instance, the reaction of **1a** with the aldehyde **2c** catalyzed by *ent*-**3a** produced the product *ent*-**4ac** in 80% yield and 69% *ee*. The use of crotonaldehyde **2l** had a negative impact on the yield, and **4al** was produced in 33% yield and 55% *ee* (entry 12). It is also important to demonstrate the scope of the methodology by testing diversely substituted 1*H*-indazole-7-carbaldehyde analogues **1** (entries 13−16). Good results were obtained regardless of the substituents introduced on the aromatic indazole ring. At this stage, a crystallographic structure for **4ba** was obtained, confirming the structure of the final product.[19]

The fused polycyclic indazoles **4** contain an aldehydic function which could undergo various synthetic transformations, paving the way toward new analogues. For instance, the reaction of **4dc** with methyl (triphenylphosphoranylidene)-acetate in toluene produced the ester **5** in 96% yield, while the reductive amination of **4dc** in the presence of benzylamine and $NaBH(OAc)_3$ produced the amine-derived compound **6** in 53% yield (Scheme 2)

Scheme 2. Transformations of the Product 4dc



Like their indole cousins,[5d] the fused tricyclic indazoles **4** exhibit fluorescent properties (Figure 2). For example, the compound **4dc** presents a maximum of absorption at 396 nm and the fluorescence spectrum recorded at this wavelength exhibits a maximum at 474 nm.

On the basis of previous works and the above results,[5d] a plausible catalytic cycle is depicted in Scheme 3 to explain the asymmetric synthesis of fused polycyclic indazoles **4**.

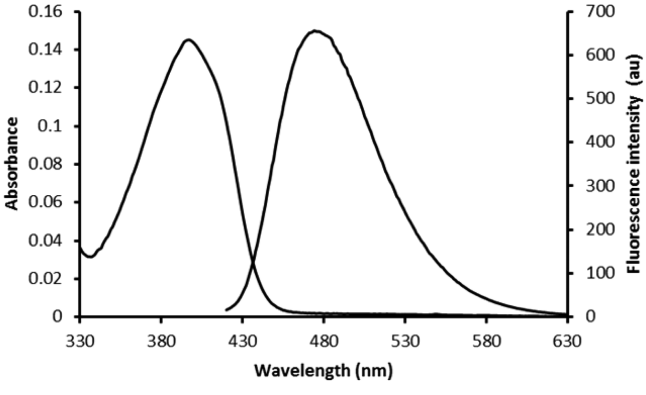


Figure 2. Absorption and fluorescence spectra of **4dc** in $CHCl_3$ (1×10^{-5} M).

The enal **2** would react with the aminocatalyst **3a** to produce the iminium **A**. Aza-Michael addition of the indazole **1** onto this intermediate from the less hindered top face would afford the intermediate **B**. It is worthwhile noting that no reaction takes place by reacting the indazoles **1** with α,β-unsaturated aldehydes **2** in the presence of AcONa for 24 h at 55 °C. Therefore, the iminium activated species **A** is required to ensure the smooth formation of **4**. The intermediate **B** would then undergo a deprotonation reaction in the presence of a base (HO^- or AcO^-) to produce the *N*-alkylated indazole **C**. The intramolecular cyclization of **C** would afford **D** through an aldol reaction. The hydrolysis of **D** would release the catalyst **3a** and the aldol product **E**, which would then undergo a dehydration reaction to give rise to the desired target **4**.

In summary, we have reported a novel approach for the asymmetric organocatalyzed *N*-alkylation of 1*H*-indazole derivatives with α,β-unsaturated aldehydes. Starting from readily available 1*H*-indazole-7-carbaldehyde substrates, an iminium−enamine cascade process enables the enantioselective formation of fused tricyclic indazole derivatives through an aza-Michael addition/intramolecular cyclization. α,β-Unsaturated aldehydes bearing aromatic, heteroaromatic, or alkyl groups and variations on the indazole framework were tolerated, giving rise to 16 examples of 1,7-annulated indazoles with *ee*'s of up to 88% and moderate-to-excellent yields. Besides fluorescent characteristics, the products can undergo synthetic transformations to form new analogues.

EXPERIMENTAL SECTION

General Experimental Methods. ^{1}H NMR (200 or 300 MHz) and ^{13}C (50 or 75 MHz) spectra were recorded with 200 or 300 MHz spectrometers in chloroform-*d* or DMSO-d6 with the residual solvent peak as an internal standard. Chemical shifts (δ) are given in parts per million, and coupling constants are given as absolute values expressed in hertz. Electrospray ionization (ESI) mass spectra were collected using a Q-TOF instrument. Samples (solubilized in MeOH at 1 mg/mL and then diluted by 1000) were introduced into the MS via an UHPLC system while a Leucine Enkephalin solution was coinjected via a micro pump. Infrared spectra were recorded with an FT spectrometer. Optical rotation values were measured at room temperature with a polarimeter. The absorption spectra were recorded on a spectrometer, while the fluorescence spectra were recorded on a spectrophotometer. Thin-layer chromatography (TLC) was carried out on aluminum sheets precoated with silica gel 60 F254. Column chromatography separations were performed using silica gel (0.040−0.060 mm). HPLC analyses were performed with a machine equipped with a UV/vis detector at 30 °C employing chiral columns. HPLC grade heptane and isopropyl alcohol were used as the eluting solvents. HPLC traces were compared to racemic samples prepared by mixture of two enantiomeric final products obtained using (*S*) and (*R*) catalysts.

General Procedure to Prepare 1*H*-Indazole-7-carbaldehyde 1 through a Four-Step Sequence: Methylation/Indazole Formation/Reduction/Oxidation. *Methylation − General Procedure.* 2-Amino-3-methylbenzoic acid derivative (1 equiv) was dissolved in DMF (3 mL/mmol of acid). K_2CO_3 (2 equiv) was added, and the mixture was stirred for 30 min at rt. MeI (1 equiv) was added, and the resulting mixture was stirred for 24 h at rt. The mixture was partitioned between water and EtOAc. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine, dried over $MgSO_4$, and then evaporated, yielding the desired methyl ester without further purification.

Methyl 2-Amino-3-methylbenzoate. According to the general procedure, 33 mmol of 2-amino-3-methylbenzoic acid (5 g) afforded 5.235 g of a brown oil (95%). Data were in accordance with those found in the literature.[20]

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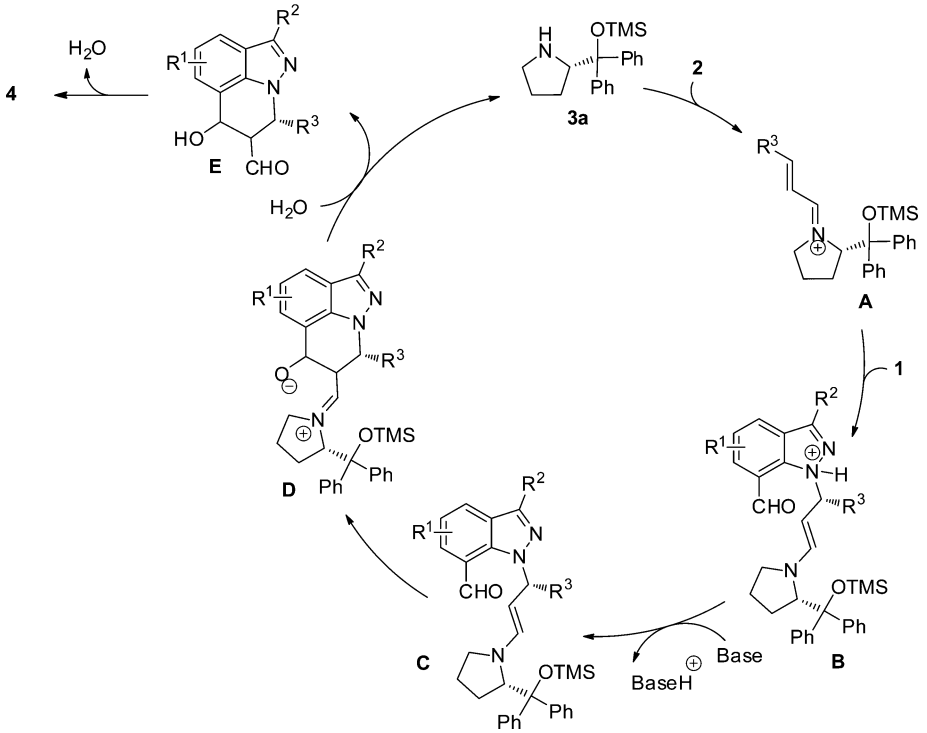
Scheme 3. Proposed Reaction Mechanism



Methyl 2-Amino-5-chloro-3-methylbenzoate. According to the general procedure, 22 mmol of 2-amino-5-chloro-3-methylbenzoic acid (4 g) afforded 4.198 g of a brown solid (97%). M.p.: 33−35 °C. R_f: 0.75 (petroleum ether:ethyl acetate 75:25). IR (neat): 3490 cm^{-1}, 3364, 1692, 1561, 1467, 1435, 1228, 1198, 1086, 790. ^1H NMR (300 MHz, $CDCl_3$) δ 7.73 ppm (d, J = 2.5 Hz, 1H), 7.15 (d, J = 2.5 Hz, 1H), 5.84 (s, 2H), 3.86 (s, 3H), 2.14 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.2 ppm, 147.7, 134.6, 128.3, 125.1, 120.1, 111.0, 51.9, 17.4. HRMS (ESI) calcd for $C_9H_{11}NO_2Cl$ $[M + H]^+$: 200.0478, found: 200.0484.

Methyl 2-Amino-3,4-dimethylbenzoate. According to the general procedure, 24 mmol of 2-amino-3,4-dimethylbenzoic acid (4 g) afforded 3.578 g of a pale brown solid (82%). M.p.: 69−71 °C. R_f: 0.72 (petroleum ether:ethyl acetate 75:25). IR (neat): 3474 cm^{-1}, 3367, 2946, 1683, 1595, 1436, 1236, 1199, 1080, 774. ^1H NMR (300 MHz, $CDCl_3$) δ 7.68 ppm (d, J = 8.2 Hz, 1H), 6.52 (d, J = 8.2 Hz, 1H), 5.88 (s, 2H), 3.88 (s, 3H), 2.29 (s, 3H), 2.06 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2 ppm, 149.1, 142.4, 128.3, 120.9, 118.5, 108.6, 51.5, 21.2, 12.6. HRMS (ESI) calcd for $C_{10}H_{14}NO_2$ $[M + H]^+$: 180.1025, found: 180.1028.

Indazole Formation − Typical Procedure. A $NaNO_2$ (2.14 g, 31 mmol, 1 equiv) solution in water (3.9 mL) was slowly added to a solution of methyl 2-amino-3-methylbenzoate (5.1 g, 31 mmol, 1 equiv) in aqueous HBF_4 (50% w/w in water, 13.5 mL, 2.5 equiv) at 0 °C. The mixture was stirred for 1 h at 0 °C, and then filtered. The obtained solid was then added to a stirred suspension of KOAc (6.09 g, 62 mmol, 2 equiv) and 18-crown-6 (125 mg, 0.5 mmol, 0.016 equiv) in $CHCl_3$ (51 mL). The resulting mixture was stirred for 1 h at rt and then filtered. The filtrate was dried over $MgSO_4$ and evaporated. The crude compound was purified by column chromatography on silica gel using a mixture of petroleum ether:ethyl acetate 7:3 as eluent, yielding the desired indazole.

Methyl 1H-Indazole-7-carboxylate. According to the typical procedure, 31 mmol of methyl 2-amino-3-methylbenzoate (5.1 g) afforded 2.98 g of the desired indazole as a white solid (55%) after purification by chromatography on silica gel (petroleum ether:ethyl acetate, 7:3). Data were in accordance with those found in the literature.[20]

Methyl 5-Chloro-1H-indazole-7-carboxylate. According to the typical procedure [a slight modification was carried out by preparing the solution of 2-amino-5-chloro-3-methylbenzoate in methanol (2 mL) and HBF_4 (50% w/w in water, 6.6 mL, 2.5 equiv)], 15.3 mmol of methyl 2-amino-5-chloro-3-methylbenzoate (3.05 g) afforded 1.4 g of the desired indazole as a white solid (44%) after purification by chromatography on silica gel (petroleum ether:ethyl acetate, 7:3). M.p.: 172−174 °C. R_f: 0.36 (petroleum ether:ethyl acetate, 75:25). IR (neat): 3148 cm^{-1}, 3082, 1716, 1327, 1242, 1195, 1169, 897, 854, 774. ^1H NMR (300 MHz, $CDCl_3$) δ 10.16 ppm (s, 1H), 8.13 (s, 1H), 8.04 (s, 1H), 7.96 (s, 1H), 4.05 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9 ppm, 129.6 (2C), 126.3 (2C), 126.0 (2C), 113.6, 52.8. HRMS (ESI) calcd for $C_9H_8N_2O_2Cl$ $[M + H]^+$: 211.0274, found: 211.0273.

Methyl 4-Methyl-1H-indazole-7-carboxylate. According to the typical procedure [a slight modification was carried out by preparing the solution of methyl 2-amino-3,4-dimethylbenzoate in methanol (10 mL) and HBF_4 (50% w/w in water, 8.6 mL, 2.5 equiv)], 20 mmol of methyl 2-amino-3,4-dimethylbenzoate (3.58 g) afforded 1.34 g of the desired indazole as a white solid (35%) after purification by chromatography on silica gel (petroleum ether:ethyl acetate, 7:3). M.p.: 145−147 °C. R_f: 0.23 (petroleum ether:ethyl acetate, 75:25). IR (neat): 3322 cm^{-1}, 1701, 1599, 1437, 1304, 1287, 1268, 1201, 1130, 780. ^1H NMR (300 MHz, $CDCl_3$) δ 10.97 ppm (s, 1H), 8.18 (s, 1H), 7.98 (d, J = 7.5 Hz, 1H), 7.00 (d, J = 7.5 Hz, 1H), 4.02 (s, 3H), 2.67 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9 ppm, 138.7, 130.3, 129.9, 127.4, 123.9, 121.0, 110.4, 52.3, 19.3. HRMS (ESI) calcd for $C_{10}H_{11}N_2O_2$ $[M + H]^+$: 191.0821, found: 191.0826.

Reduction − General Procedure. Methyl ester (10 mmol, 1 equiv) was placed in a flask under argon. Dry THF (120 mL) was added, and the resulting solution was cooled down to 0 °C. $LiAlH_4$ (790 mg, 21 mmol, 2.1 equiv) was carefully added. The mixture was stirred for 30 min at 0 °C, then quenched by successive addition of water (2 mL), 5 N $NaOH_{aq}$. (2 mL), and water (6 mL). The mixture was diluted with THF (120 mL), and $MgSO_4$ was added. The mixture was stirred for 10 min at rt and then filtered over a pad of Celite. The filtrate was evaporated, yielding clean alcohol without further purification.

(1H-Indazol-7-yl)methanol. According to the general procedure, methyl 1*H*-indazole-7-carboxylate (1.7 g) afforded 1.3 g of a beige solid (86%). Data were in accordance with those in the literature.[20]

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(5-Chloro-1H-indazol-7-yl)methanol. According to the general procedure, methyl 5-chloro-1*H*-indazole-7-carboxylate (1.9 g) afforded 1.5 g of a beige solid (90%). M.p.: 217−219 °C. R_f: 0.55 (dichloromethane:methanol, 9:1). IR (neat): 3127 cm^{-1}, 2850, 1074, 1010, 944, 870, 760, 712, 654, 608. ^1H NMR (300 MHz, DMSO-d6) δ 13.27 ppm (s, 1H), 8.08 (d, J = 1.1 Hz, 1H), 7.71 (d, J = 1.1 Hz, 1H), 7.32 (d, J = 1.1 Hz, 1H), 5.48 (t, J = 5.7 Hz, 1H), 4.83 (d, J = 5.7 Hz, 2H). ^{13}C NMR (75 MHz, DMSO-d6) δ 136.4 ppm, 133.3, 127.2, 124.7, 123.8, 123.0, 117.9, 59.3. HRMS (ESI) calcd for $C_8H_8N_2OCl$ $[M + H]^+$: 183.0325, found: 183.0331.

(4-Methyl-1H-indazol-7-yl)methanol. According to the general procedure, methyl 4-methyl-1*H*-indazole-7-carboxylate (1.3 g) afforded 1.1 g of a beige solid (95%). M.p.: 250−252 °C. R_f: 0.15 (petroleum ether:ethyl acetate,75:25). IR (neat): 3121 cm^{-1}, 2848, 1374, 1016, 938, 921, 855, 814, 775, 574. ^1H NMR (300 MHz, DMSO-d6) δ 12.99 ppm (s, 1H), 8.10 (s, 1H), 7.18 (d, J = 7.0 Hz, 1H), 6.84 (d, J = 7.0 Hz, 1H), 5.20 (t, J = 5.7 Hz, 1H), 4.77 (d, J = 5.7 Hz, 2H), 2.52 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d6) δ 137.9 ppm, 132.5, 128.7, 123.4 (2C), 122.4, 119.9, 59.9, 18.3. HRMS (ESI) calcd for $C_9H_{10}N_2ONa$ $[M + Na]^+$: 185.0691, found: 185.0682

Oxidation − General Procedure. Alcohol (8 mmol, 1 equiv) was placed in a flask under argon. Dry DCM (320 mL) and DMF (80 mL) were introduced. Activated MnO_2 (6.9 g, 80 mmol, 10 equiv) was added, and the resulting mixture was stirred overnight at rt. The mixture was filtered over Celite, the filter cake was rinsed with DCM (300 mL), and the DCM was evaporated. Compound was taken up in EtOAc (80 mL) and washed with brine (7 × 100 mL). The organic layer was dried over $MgSO_4$ and evaporated, affording the desired aldehyde **1** without further purification.

*1H-Indazole-7-carbaldehyde (**1a**).* According to the general procedure, (1*H*-indazol-7-yl)methanol (1.2 g) afforded 640 mg of a yellow solid (55%). Data were in accordance with those found in the literature.[20]

*5-Chloro-1H-indazole-7-carbaldehyde (**1c**).* According to the general procedure, (5-chloro-1*H*-indazol-7-yl)methanol (1.5 g) afforded 990 mg of a yellow solid (67%). M.p.: 213-215 °C. R_f: 0.50 (petroleum ether:ethyl acetate, 75:25). IR (neat): 3383 cm^{-1}, 1671, 1085, 1064, 947, 874, 763, 750, 693, 604. ^1H NMR (300 MHz, DMSO-d6) δ 10.15 ppm (s, 1H), 8.22 (m, 2H), 8.06 (d, J = 1.3 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d6) δ 191.5 ppm, 134.2, 133.9, 132.5, 127.0, 125.7, 124.4, 121.1. HRMS (ESI) calcd for $C_8H_6N_2OCl$ $[M + H]^+$: 181.0169, found: 181.0160.

*4-Methyl-1H-indazole-7-carbaldehyde (**1d**).* According to the general procedure, (4-methyl-1*H*-indazol-7-yl)methanol (1.1 g) afforded 900 mg of a brown solid (84%). M.p.: 89−91 °C. R_f: 0.38 (petroleum ether:ethyl acetate, 75:25). IR: 3376 cm^{-1}, 2803, 1664, 1596, 1041, 939, 773, 769, 710, 615. ^1H NMR (300 MHz, $CDCl_3$) δ 10.09 ppm (s, 1H), 8.20 (s, 1H), 7.73 (d, J = 7.3 Hz, 1H), 7.07 (br d, 1H), 2.69 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.9 ppm, 140.8, 136.8, 133.8 (2C), 124.9, 121.2, 118.8, 19.5. HRMS (ESI) calcd for $C_9H_9N_2O$ $[M + H]^+$: 161.0715, found: 161.0714.

*3-Iodo-1H-indazole-7-carbaldehyde (**1b**).* Indazole **1a** (184 mg, 1.26 mmol, 1 equiv) was dissolved in DMF (3.6 mL). KOH (177 mg, 3.15 mmol, 2.5 equiv), followed by I_2 (638 mg, 2.52 mmol, 2 equiv), were added. The mixture was stirred for 1 h at rt. The reaction was poured into 90 mL of water and 10 mL of an aqueous saturated solution of $Na_2S_2O_3$. The mixture was filtered and the solid was dried under vacuum, affording the desired compound without purification as a beige solid (300 mg, 88% yield). M.p.: 200−202 °C. R_f: 0.13 (petroleum ether:ethyl acetate, 75:25). IR (neat): 3288 cm^{-1}, 1668, 1591, 1170, 1079, 970, 787, 696, 621, 607. ^1H NMR (300 MHz, DMSO-d6) δ 10.16 ppm (s, 1H), 8.13 (d, J = 7.6 Hz, 1H), 7.82 (d, J = 7.6 Hz, 1H), 7.43 (t, J = 7.6 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d6) δ 192.0 ppm, 136.4, 134.4, 128.5, 127.9, 121.2, 120.8, 95.4. HRMS (ESI) calcd for $C_8H_6N_2OI$ $[M + H]^+$: 272.9525, found: 272.9520.

General Procedure for the Organocatalytic Sequence. Indazole **1** (0.2 mmol, 1 equiv), aldehyde **2** (0.3 mmol, 1.5 equiv), catalyst **3a** (9.8 mg, 0.03 mmol, 0.15 equiv), AcONa (18 mg, 0.22 mmol, 1.1 equiv), and 1,2-DCE (1 mL) were introduced in a capped flask. The mixture was stirred for 24 h at 55 °C. The solvent was removed under reduced pressure. The crude compound **4** was purified by column chromatography on silica gel.

*(R)-8-Phenyl-8H-pyrazolo[4,5,1-ij]quinoline-7-carbaldehyde (**4aa**).* Purification using a mixture of petroleum ether:ethyl acetate, 75:25, as eluent yielded 49 mg of a yellow solid (94%). M.p.: 145−147 °C. R_f: 0.45 (petroleum ether:ethyl acetate, 75:25). $[\alpha]_{578}^{20}$ = −457 (c = 1.05 in $CHCl_3$) for 86% *ee*. IR (neat): 2832 cm^{-1}, 1670, 1697, 1364, 1151, 1069, 748, 698, 595, 515. ^1H NMR (300 MHz, $CDCl_3$) δ 9.64 ppm (s, 1H), 8.01 (s, 1H), 7.75 (d, J = 8.2 Hz, 1H), 7.65 (s, 1H), 7.41 (d, J = 7.0 Hz, 1H), 7.33−7.10 (m, 6H), 6.85 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.0 ppm, 140.8, 139.8, 139.4, 137.8, 135.2, 128.9 (2C), 128.7, 127.2 (2C), 125.4, 125.3, 122.4, 121.1, 116.6, 61.1. HRMS (ESI) calcd for $C_{17}H_{13}N_2O$ $[M + H]^+$: 261.1028, found: 261.1031.

*(R)-8-(4-Tolyl)-8H-pyrazolo[4,5,1-ij]quinoline-7-carbaldehyde (**4ab**).* Purification using a mixture of petroleum ether:ethyl acetate, 8:2, yielded a yellow solid (53 mg, 96%). M.p.: 144−146 °C. R_f: 0.57 (petroleum ether:ethyl acetate, 75:25). $[\alpha]_{578}^{20}$ = −372 (c = 1.07 in $CHCl_3$) for 79% *ee*. IR (neat): 2835 cm^{-1}, 1668, 1597, 1571, 1143, 1067, 885, 745, 729, 512. ^1H NMR (300 MHz, $CDCl_3$) δ 9.62 ppm (s, 1H), 7.98 (s, 1H), 7.72 (d, J = 8.2 Hz, 1H), 7.62 (s, 1H), 7.38 (d, J = 7.0 Hz, 1H), 7.21−7.00 (m, 5H), 6.79 (s, 1H), 2.26 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.1 ppm, 139.7, 139.5, 138.5, 138.1, 137.7, 135.1, 129.6 (2C), 127.0 (2C), 125.3, 125.2, 122.3, 121.1, 116.6, 60.8, 21.3. HRMS (ESI) calcd for $C_{18}H_{15}N_2O$ $[M + H]^+$: 275.1184, found: 275.1177.

*(R)-8-(4-Chlorophenyl)-8H-pyrazolo[4,5,1-ij]quinoline-7-carbaldehyde (**4ac**).* Purification using a mixture of petroleum ether:ethyl acetate, 75:25, yielded a yellow solid (54 mg, 91%). M.p.: 150−152 °C. R_f: 0.39 (petroleum ether:ethyl acetate 75:25). $[\alpha]_{578}^{20}$ = −355 (c = 1.02 in $CHCl_3$) for 69% *ee*. IR (neat): 2832 cm^{-1}, 1665, 1594, 1569, 1150, 1067, 880, 744, 595, 527. ^1H NMR (300 MHz, $CDCl_3$) δ 9.68 ppm (s, 1H), 8.05 (s, 1H), 7.80 (d, J = 8.2 Hz, 1H), 7.70 (s, 1H), 7.46 (d, J = 7.0 Hz, 1H), 7.36−7.25 (m, 2H), 7.27−7.19 (m, 3H), 6.86 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.9 ppm, 140.1, 139.3, 138.9, 137.7, 135.4, 134.5, 129.1 (2C), 128.6 (2C), 125.6, 125.5, 122.5, 121.1, 116.3, 60.4. HRMS (ESI) calcd for $C_{17}H_{12}N_2OCl$ $[M + H]^+$: 295.0638, found: 295.0637.

*(R)-8-(3-Chlorophenyl)-8H-pyrazolo[4,5,1-ij]quinoline-7-carbaldehyde (**4ad**).* Purification using a mixture of petroleum ether:ethyl acetate, 75:25, yielded a yellow solid (55 mg, 93%). M.p.: 144−146 °C. R_f: 0.49 (petroleum ether:ethyl acetate, 75:25). $[\alpha]_{578}^{20}$ = −387 (c = 1.00 in $CHCl_3$) for 60% *ee*. IR (neat): 2832 cm^{-1}, 1671, 1597, 1571, 1142, 1068, 906, 748, 727, 689. ^1H NMR (300 MHz, $CDCl_3$) δ 9.62 ppm (s, 1H), 8.00 (s, 1H), 7.74 (d, J = 8.2 Hz, 1H), 7.65 (s, 1H), 7.41 (d, J = 7.0 Hz, 1H), 7.24−7.12 (m, 5H), 6.79 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.8 ppm, 142.5, 140.3, 138.5, 137.6, 135.4, 134.7, 130.1, 128.9, 127.3, 125.6, 125.6 (3C), 121.1, 116.2, 60.5. HRMS (ESI) calcd for $C_{17}H_{12}N_2OCl$ $[M + H]^+$: 295.0638, found: 295.0639.

*(R)-8-(4-Methoxyphenyl)-8H-pyrazolo[4,5,1-ij]quinoline-7-carbaldehyde (**4ae**).* Purification using a mixture of petroleum ether:ethyl acetate, 75:25, yielded a yellow solid (52 mg, 90%). M.p.: 167−169 °C. R_f: 0.3 (petroleum ether:ethyl acetate, 75:25). $[\alpha]_{578}^{20}$ = −334 (c = 1.04 in $CHCl_3$) for 73% *ee*. IR (neat): 2832 cm^{-1}, 1666, 1512, 1243, 1177, 1146, 883, 807, 745, 589. ^1H NMR (300 MHz, $CDCl_3$) δ 9.60 ppm (s, 1H), 7.98 (s, 1H), 7.71 (d, J = 8.2 Hz, 1H), 7.61 (d, J = 1.6 Hz, 1H), 7.36 (d, J = 6.3 Hz, 1H), 7.19−7.10 (m, 3H), 6.82−6.72 (m, 3H), 3.71 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.1 ppm, 159.6, 139.5, 139.4, 137.6, 135.1, 133.4, 128.3 (2C), 125.2, 125.1, 122.3, 121.0, 116.5, 114.1 (2C), 60.4, 55.2. HRMS (ESI) calcd for $C_{18}H_{15}N_2O_2$ $[M + H]^+$: 291.1134, found: 291.1139.

*(R)-8-(3-Methoxyphenyl)-8H-pyrazolo[4,5,1-ij]quinoline-7-carbaldehyde (**4af**).* Purification using a mixture of petroleum ether:ethyl acetate, 75:25, yielded a yellow solid (52 mg, 90%). M.p.: 178−180 °C. R_f: 0.39 (petroleum ether:ethyl acetate, 75:25). $[\alpha]_{578}^{20}$ = −294 (c = 0.98 in $CHCl_3$) for 84% *ee*. IR (neat): 2832 cm^{-1}, 1674, 1599, 1572, 1259, 1141, 1069, 1042, 751, 695. ^1H NMR (300 MHz, $CDCl_3$) δ 9.62 ppm (s, 1H), 7.99 (s, 1H), 7.72 (d, J = 8.2 Hz, 1H), 7.61 (s, 1H), 7.38 (d, J = 7.0 Hz, 1H), 7.22−7.10 (m, 2H), 6.78 (m, 4H), 3.72 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.0 ppm, 159.9, 142.2, 139.8, 139.2,

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J. Org. Chem. 2016, 81, 6855−6861

137.8, 135.2, 129.9, 125.4, 125.3, 122.4, 121.1, 119.5, 116.5, 113.8, 113.2, 60.9, 55.3. HRMS (ESI) calcd for $C_{18}H_{15}N_2O_2$ $[M + H]^+$: 291.1134, found: 291.1128.

*(R)-8-(2-Methoxyphenyl)-8H-pyrazolo[4,5,1-ij]quinoline-7-carbaldehyde (**4ag**).* Purification using a mixture of toluene:acetonitrile, 9:1, yielded a yellow solid (36 mg, 62%). M.p.: 191−193 °C. R_f: 0.39 (petroleum ether:ethyl acetate, 75:25). $[\alpha]_{578}^{20}$ = −314 (*c* = 1.09 in $CHCl_3$) for 71% *ee*. IR (neat): 2832 cm^{-1}, 1673, 1598, 1492, 1252, 1144, 907, 884, 747, 723. ^1H NMR (300 MHz, $CDCl_3$) δ 9.77 ppm (s, 1H), 8.12 (s, 1H), 7.92−7.79 (m, 2H), 7.59−7.49 (m, 1H), 7.46−7.26 (m, 4H), 7.10−6.97 (m, 2H), 3.83 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.1 ppm, 157.3, 140.1, 139.1, 138.1, 134.6, 130.0, 129.5, 129.1, 125.0, 124.6, 121.9, 120.9, 120.7, 117.0, 111.9, 56.5, 56.0. HRMS (ESI) calcd for $C_{18}H_{15}N_2O_2$ $[M + H]^+$: 291.1134, found: 291.1130.

*(R)-8-(4-Nitrophenyl)-8H-pyrazolo[4,5,1-ij]quinoline-7-carbaldehyde (**4ah**).* Purification using a mixture of petroleum ether:ethyl acetate, 7:3, yielded a yellow solid (48 mg, 78%). M.p.: 196−198 °C. R_f: 0.47 (petroleum ether:ethyl acetate 75:25). $[\alpha]_{578}^{20}$ = −463 (*c* = 1.01 in $CHCl_3$) for 88% *ee*. IR (neat): 2832 cm^{-1}, 1673, 1599, 1571, 1520, 1350, 1144, 746, 696, 668. ^1H NMR (300 MHz, $CDCl_3$) δ 9.63 ppm (s, 1H), 8.12 (d, *J* = 8.7 Hz, 2H), 8.01 (s, 1H), 7.88−7.69 (m, 2H), 7.42 (m, 3H), 7.23 (m, 1H), 6.94 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.8 ppm, 147.9, 146.9, 140.9, 138.0, 137.8, 135.8, 128.3 (2C), 126.0 (2C), 124.2 (2C), 122.8, 121.2, 116.0, 60.3.HRMS (ESI) calcd for $C_{17}H_{12}N_3O_3$ $[M + H]^+$: 306.0879, found: 306.0881.

*(R)-8-(2-Nitrophenyl)-8H-pyrazolo[4,5,1-ij]quinoline-7-carbaldehyde (**4ai**).* Purification using a mixture of petroleum ether:ethyl acetate, 75:25, yielded a yellow solid (56 mg, 92%). M.p.: 165−167 °C. R_f: 0.31 (petroleum ether:ethyl acetate, 75:25). $[\alpha]_{578}^{20}$ = −399 (*c* = 1.05 in $CHCl_3$) for 79% *ee*. IR (neat): 2832 cm^{-1}, 1671, 1599, 1527, 1350, 1147, 908, 887, 727, 684. ^1H NMR (300 MHz, $CDCl_3$) δ 9.54 ppm (s, 1H), 8.00 (s, 1H), 7.97−7.87 (m, 1H), 7.78−7.71 (m, 2H), 7.69 (s, 1H), 7.45−7.33 (m, 3H), 7.18 (t, *J* = 7.6 Hz, 1H), 7.07 (dd, *J* = 6.8, 2.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.7 ppm, 148.2, 140.7, 138.5, 137.8, 135.6, 134.6, 133.4, 129.6, 129.3, 125.8, 125.7, 124.8, 122.7, 121.0, 115.9, 55.5. HRMS (ESI) calcd for$C_{17}H_{12}N_3O_3$ $[M + H]^+$: 306.0879, found: 306.0879.

*(R)-8-(Naphthalen-2-yl)-8H-pyrazolo[4,5,1-ij]quinoline-7-carbaldehyde (**4aj**).* Purification using a mixture of petroleum ether:ethyl acetate, 8:2, yielded a yellow solid (62 mg, 99%). M.p.: 162−164 °C. R_f: 0.44 (petroleum ether:ethyl acetate, 75:25). $[\alpha]_{578}^{20}$ = −498 (*c* = 1.06 in $CHCl_3$) for 59% *ee*. IR (neat): 3056 cm^{-1}, 2816, 1672, 1597, 1570, 1141, 1069, 904, 727, 478. ^1H NMR (300 MHz, $CDCl_3$) δ 9.61 ppm (s, 1H), 7.97 (s, 1H), 7.82−7.60 (m, 6H), 7.46−7.36 (m, 3H), 7.27−7.12 (m, 2H), 6.99 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.0 ppm, 139.9, 139.1, 137.9, 137.7, 135.2, 133.3, 133.2, 128.9, 128.5, 127.7, 126.6, 126.4, 126.3, 125.4, 125.3, 124.5, 122.4, 121.1, 116.5, 61.2. HRMS (ESI) calcd for $C_{21}H_{15}N_2O$ $[M + H]^+$: 311.1184, found: 311.1182.

*(R)-8-(Thiophen-2-yl)-8H-pyrazolo[4,5,1-ij]quinoline-7-carbaldehyde (**4ak**).* Purification using a mixture of petroleum ether:ethyl acetate, 8:2, yielded a yellow solid (47 mg, 88%). M.p.: 115−117 °C. R_f: 0.47 (petroleum ether:ethyl acetate, 75:25). $[\alpha]_{578}^{20}$ = −194 (*c* = 0.94 in $CHCl_3$) for 55% *ee*. IR (neat): 2819 cm^{-1}, 2360, 1669, 1598, 1570, 1141, 1119, 1066, 725, 699. ^1H NMR (300 MHz, $CDCl_3$) δ 9.69 ppm (s, 1H), 8.04 (s, 1H), 7.74 (d, *J* = 8.2 Hz, 1H), 7.65 (s, 1H), 7.41 (d, *J* = 7.0 Hz, 1H), 7.20−7.13 (m, 3H), 7.03 (d, *J* = 3.4 Hz, 1H), 6.88 (dd, *J* = 5.0, 3.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.8 ppm, 143.7, 139.7, 138.3, 137.3, 135.5, 127.0, 126.0, 125.9, 125.6, 125.5, 122.5, 121.4, 116.2, 55.6. HRMS (ESI) calcd for $C_{15}H_9N_2OS$ $[M - H]^+$: 265.0436, found: 265.0432.

*(R)-8-Methyl-8H-pyrazolo[4,5,1-ij]quinoline-7-carbaldehyde (**4al**).* Purification using a mixture of petroleum ether:ethyl acetate, 75:25, yielded a yellow solid (13 mg, 33%). M.p.: 48−50 °C. R_f: 0.6 (petroleum ether:ethyl acetate, 75:25). $[\alpha]_{578}^{20}$ = −289 (*c* = 1.15 in $CHCl_3$) for 55% *ee*. IR (neat): 2924 cm^{-1}, 1673, 1599, 1573, 1372, 1148, 1094, 1070, 880, 748. ^1H NMR (300 MHz, $CDCl_3$) δ 9.44 ppm (s, 1H), 7.78 (s, 1H), 7.45 (d, *J* = 8.2 Hz, 1H), 7.03 (t, *J* = 3.5 Hz, 2H), 6.93−6.78 (m, 1H), 5.64 (q, *J* = 6.5 Hz, 1H), 1.44 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.7 ppm, 141.0, 140.9, 137.4, 134.3, 125.0, 124.6, 122.2, 121.1, 116.9, 53.8, 23.5. HRMS (ESI) calcd for $C_{12}H_{11}N_2O$ $[M + H]^+$: 199.0871, found: 199.0865.

*(R)-2-Iodo-8-phenyl-8H-pyrazolo[4,5,1-ij]quinoline-7-carbaldehyde (**4ba**).* Purification using a mixture of petroleum ether:ethyl acetate, 75:25, yielded a yellow solid (68 mg, 88%). M.p.: 161−163 °C. R_f: 0.63 (petroleum ether:ethyl acetate, 75:25). $[\alpha]_{578}^{20}$ = −296 (*c* = 098 in $CHCl_3$) for 60% *ee*. IR (neat): 2832 cm^{-1}, 1676, 1596, 1144, 1068, 922, 748, 698, 601, 518. ^1H NMR (300 MHz, $CDCl_3$) δ 9.59 ppm (s, 1H), 7.58 (s, 1H), 7.44 (t, *J* = 8.4 Hz, 2H), 7.31−7.15 (m, 6H), 6.81 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.7 ppm, 140.4, 139.6, 138.8, 138.4, 128.9 (2C), 128.8, 127.2 (2C), 126.1, 126.1, 125.2, 123.0, 116.7, 92.8, 61.4. HRMS (ESI) calcd for $C_{17}H_{12}N_2OI$ $[M + H]^+$: 386.9994, found: 386.9997.

*(R)-4-Chloro-8-phenyl-8H-pyrazolo[4,5,1-ij]quinoline-7-carbaldehyde (**4ca**).* Purification using a mixture of petroleum ether:ethyl acetate, 85:15, yielded a yellow solid (49 mg, 84%). M.p.: 196−198 °C. R_f: 0.56 (petroleum ether:ethyl acetate 75:25). $[\alpha]_{578}^{20}$ = −309 (*c* = 1.02 in $CHCl_3$) for 60% *ee*. IR (neat): 2923 cm^{-1}, 1676, 1573, 1339, 1144, 1084, 904, 771, 731, 698. ^1H NMR (300 MHz, $CDCl_3$) δ 9.64 ppm (s, 1H), 7.93 (s, 1H), 7.70 (s, 1H), 7.57 (s, 1H), 7.38 (s, 1H), 7.27−7.24 (m, 3H), 7.20−7.16 (m, 2H), 6.80 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.7 ppm, 140.6, 140.3, 138.1, 136.2, 134.6, 129.0, 128.9 (2C), 127.9, 127.1 (2C), 125.4, 124.0, 121.6, 117.4, 61.1. HRMS (ESI) calcd for $C_{17}H_{12}N_2OCl$ $[M + H]^+$: 295.0638, found: 295.0641.

*(R)-3-Methyl-8-phenyl-8H-pyrazolo[4,5,1-ij]quinoline-7-carbaldehyde (**4da**).* Purification using a mixture of petroleum ether:ethyl acetate, 8:2, yielded a yellow solid (45 mg, 82%). M.p.: 211−213 °C. R_f: 0.55 (petroleum ether:ethyl acetate, 75:25). $[\alpha]_{578}^{20}$ = −435 (*c* = 0.96 in $CHCl_3$) for 79% *ee*. IR (neat): 2841 cm^{-1}, 1673, 1598, 1142, 810, 747, 694, 630, 519, 433. ^1H NMR (300 MHz, $CDCl_3$) δ 9.63 ppm (s, 1H), 8.03 (s, 1H), 7.64 (s, 1H), 7.37−7.20 (m, 6H), 6.97 (d, *J* = 7.1 Hz, 1H), 6.85 (s, 1H), 2.64 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.9 ppm, 141.0, 140.1, 138.3, 137.8, 137.5, 134.3, 128.8 (2C), 128.6, 127.1 (2C), 125.8, 122.5, 121.8, 114.3, 61.1, 19.5. HRMS (ESI) calcd for $C_{18}H_{15}N_2O$ $[M + H]^+$: 275.1184, found: 275.1179.

*(R)-8-(4-Chlorophenyl)-3-methyl-8H-pyrazolo[4,5,1-ij]quinoline-7-carbaldehyde (**4dc**).* Purification using a mixture of petroleum ether:ethyl acetate, 75:25, yielded a yellow solid (49 mg, 80%). M.p.: 179−181 °C. R_f: 0.34 (petroleum ether:ethyl acetate, 75:25). $[\alpha]_{578}^{20}$ = −490 (*c* = 1.13 in $CHCl_3$) for 62% *ee*. IR (neat): 2822 cm^{-1}, 1669, 1598, 1565, 1139, 1089, 1057, 907, 807, 727. ^1H NMR (300 MHz, $CDCl_3$) δ 9.58 ppm (s, 1H), 8.00 (s, 1H), 7.59 (dd, *J* = 2.9, 0.8 Hz, 1H), 7.30 (d, *J* = 7.1 Hz, 1H), 7.24−7.18 (m, 2H), 7.18−7.11 (m, 2H), 6.94 (dd, *J* = 7.1, 0.8 Hz, 1H), 6.77 (s, 1H), 2.60 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.8 ppm, 140.3, 139.4, 137.7 (2C), 137.6, 134.4, 134.4, 129.0 (2C), 128.5 (2C), 126.0, 122.6, 121.8, 114.0, 60.3, 19.4. HRMS (ESI) calcd for $C_{18}H_{14}N_2OCl$ $[M + H]^+$: 309.0795, found: 309.0803.

*(E)-Methyl 3-(8-(4-Chlorophenyl)-3-methyl-8H-pyrazolo[4,5,1-ij]-quinolin-7-yl)acrylate (**5**).* The aldehyde **4dc** (31 mg, 0.1 mmol, 1 equiv) was introduced in a flask under argon. Dry toluene (1 mL) was added, followed by methyl (triphenylphosphoranylidene)acetate (43 mg, 0.12 mmol, 1.2 equiv). The mixture was stirred for 24 h at rt, and then the toluene was removed under reduced pressure. The crude compound was purified by preparative chromatography on silica gel using a mixture of dichloromethane:diethyl ether, 9:1, as eluent, yielding the desired compound **5** as a yellow solid (35 mg, 96%). M.p.: 178−180 °C. R_f: 0.47 (petroleum ether:ethyl acetate, 75:25). $[\alpha]_{578}^{20}$ = −490 (*c* = 1.13 in $CHCl_3$) for 62% *ee*. IR (neat): 2942 cm^{-1}, 1702, 1595, 1316, 1273, 1192, 1089, 907, 854, 728. ^1H NMR (300 MHz, $CDCl_3$) δ 7.92 ppm (s, 1H), 7.46 (d, *J* = 16.0 Hz, 1H), 7.36−7.30 (m, 2H), 7.30−7.20 (m, 3H), 7.14 (d, *J* = 7.1 Hz, 1H), 6.86 (dd, *J* = 7.1, 0.7 Hz, 1H), 6.64 (s, 1H), 5.79 (d, *J* = 16.0 Hz, 1H), 3.72 (s, 3H), 2.55 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1 ppm, 143.2, 138.7, 136.2, 134.9, 134.7, 134.2, 132.9, 131.3, 129.4 (2C), 128.9 (2C), 124.0, 122.4, 121.5, 118.5, 115.4, 62.2, 51.8, 19.2. HRMS (ESI) calcd for $C_{21}H_{18}N_2O_2Cl$ $[M + H]^+$: 365.1057, found: 365.1063.

*N-Benzyl-1-(8-(4-chlorophenyl)-3-methyl-8H-pyrazolo[4,5,1-ij]-quinolin-7-yl)methanamine (**6**).* Benzylamine (21 μL, 0.2 mmol, 2

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J. Org. Chem. 2016, 81, 6855−6861

equiv) and benzoic acid (61 mg, 0.5 mmol, 5 equiv) were suspended in 1,2-DCE (0.5 mL). The suspension was cooled down to 0 °C. Aldehyde **4dc** (36.5 mg, 0.1 mmol, 1 equiv) and then $NaBH(OAc)_3$ (42.4 mg, 0.2 mmol, 2 equiv) were added. The mixture was stirred for 7 h, being allowed to come back to rt. The reaction was quenched upon addition of saturated $NaHCO_3$ (15 mL). The mixture was diluted with ethyl acetate (20 mL). The organic layer was washed with brine (15 mL), dried over $MgSO_4$, and evaporated. The crude compound was purified by preparative chromatography on silica gel using a mixture of petroleum ether:ethyl acetate 6:4 as eluent, yielding 21 mg of **6** as a viscous yellow oil (53%). R_f: 0.32 (petroleum ether:ethyl acetate 75:25). IR (neat): ν 2907 cm^{-1}, 1488, 1088, 1014, 907, 880, 906, 728, 697, 579. ^1H NMR (300 MHz, $CDCl_3$) δ 7.90 ppm (d, J = 8.3 Hz, 1H), 7.35−7.22 (m, 8H), 7.12 (d, J = 7.7 Hz, 2H), 6.95 (d, J = 6.9 Hz, 1H), 6.79 (d, J = 6.9 Hz, 1H), 6.78 (s, 1H), 6.56 (s, 1H), 3.83 (d, J = 13.3 Hz, 1H), 3.69 (d, J = 13.3 Hz, 1H), 3.26 (d, J = 14.2 Hz, 1H), 3.18 (d, J = 14.2 Hz, 1H), 2.53 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.7 ppm, 139.5, 137.7, 136.9, 134.3, 133.7, 131.8, 129.2 (2C), 128.9 (2C), 128.6 (2C), 128.4 (2C), 127.3, 121.8, 121.3, 121.0, 120.3, 116.0, 63.7, 53.1, 51.7, 19.0. HRMS (ESI) calcd for $C_{25}H_{23}N_3Cl$ $[M + H]^+$: 400.1581, found: 400.1578.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01201.

Crystallographic data for **4ba** (CIF)

Copies of ^1H, ^{13}C NMR, HPLC traces and crystallographic data for **4ba** (PDF)

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Notes

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