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Trapping of Transient Zwitterionic Intermediates by *N*-Acylpyridinium Salts: A Palladium-Catalyzed Diastereoselective Three-Component Reaction

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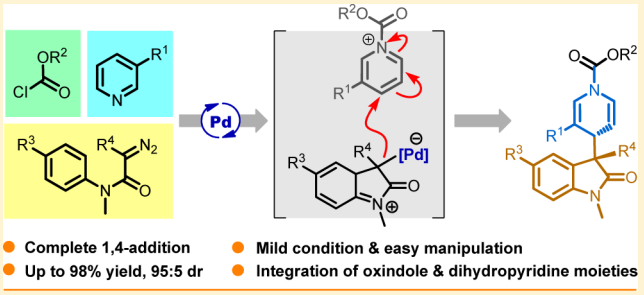
Supporting Information

ABSTRACT: We developed a palladium-catalyzed diastereoselective three-component reaction of *N*-aryl diazoamides, pyridine, and chloroformate, which proceeded through trapping of transient zwitterionic intermediates by in situ formed *N*-acylpyridinium salts in a regioselective 1,4-addition fashion. This reaction can rapidly provide a library of biologically relevant 4-(2-oxoindolin-3-yl)-1,4-dihydropyridine derivatives in high yields (up to 98%) with moderate to excellent diastereoselectivities (up to >95:5 dr) under mild reaction conditions.



Nitrogen-containing heterocycles are most prevalent in natural products and, in particular, a diverse range of pharmaceutical molecules.[1] A survey of U.S. FDA approved pharmaceuticals indicated that 59% of small molecule drugs contain nitrogen heterocycles.[2] Among all scaffolds, dihydropyridine (DHP) is a unique, privileged structural constituent in biologically and pharmaceutically important molecules.[3] For example, reduced coenzyme NADH and NADPH play a critical role in biological oxidation−reduction process, and many multisubstituted 1,4-dihydropyridine derivatives, such as nifedipine, felodipine, amlodipine, and clevidipine, are significant calcium channel blockers that are widely used to treat cardiovascular disease and others (Figure 1).[3,4] Until recently, structural modification of the 1,4-dihydropyridine core has led to more than 20 marketed drugs characterized by the suffix "-dipine" in their name. In view of their great values in pharmaceuticals, development of novel chemical approaches to structurally diverse polyfunctional dihydropyridine derivatives would greatly promote new drug discovery.

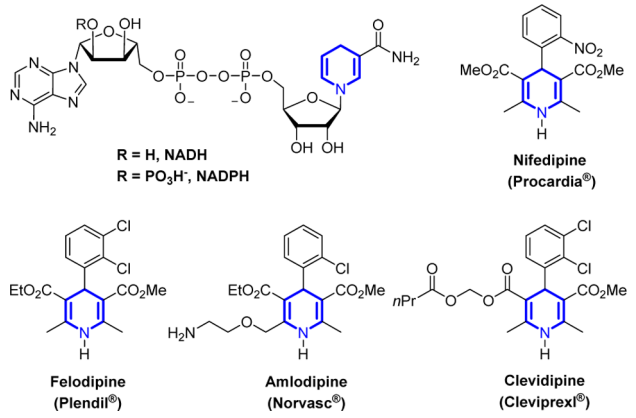


Figure 1. Natural reducing agents NADH and NADPH and selected examples of 1,4-dihydropyridine-containing pharmaceuticals.

As for the synthesis of 1,4-dihydropyridine skeleton, one straightforward strategy is dearomatization of pyridine via *N*-activation and subsequent nucleophilic addition (Scheme 1a).[5] The common protocols for *N*-activation include acylation,[6] alkylation,[7] oxidation,[8] and coordination with Lewis acid,[9] which could enable the nucleophilic addition to the inert pyridine ring. However, the existing nucleophilic additions are still limited to preformed traditional nucleophiles,[5] such as organometallic reagents, silyl enolates, trimethylsilyl cyanide (TMSCN), and alkynylcopper intermediates.[10] Thus, we became interested if in situ generated transient intermediates, such as oxonium/ammonium ylides and zwitterionic intermediates (Scheme 1b),[11] could serve as active nucleophiles for dearomatization of pyridines. In comparison with the functionalization of *N*-activated pyridines by traditional nucleophiles, this transformation would introduce a multifunctional structural moiety to dihydropyridine skeleton in a highly efficient manner. Considering the unstable nature of the transient nucleophiles, we can, however, anticipate the upcoming challenges in the chemoselectivity between nucleophilic addition and side reaction pathways. In this context, regio- and stereocontrol of the desired process might also be difficult.

The hypothetical zwitterionic intermediates, generated from transition-metal-catalyzed activation of *N*-aryl diazoamides, are transient and highly reactive intermediates in the course of C−

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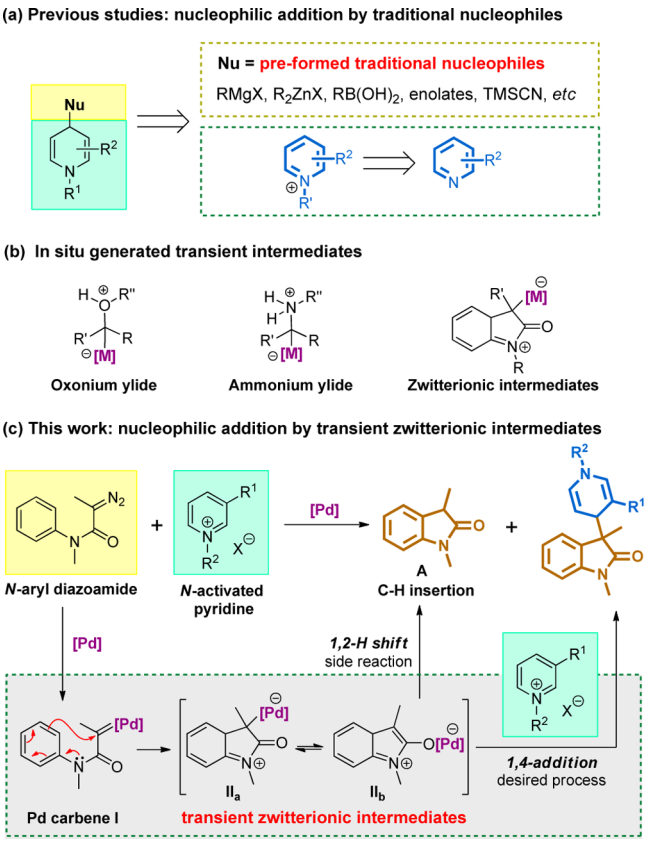
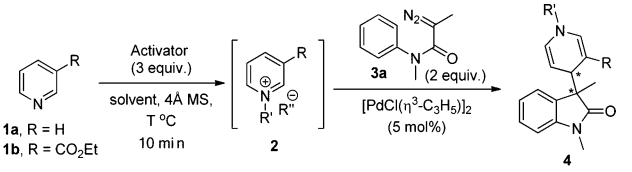
Scheme 1. Synthetic Strategies for the Functionalized Dihydropyridine from *N*-Activated Pyridines



H functionalization proposed by Doyle[12] and can be trapped by benchtop-stable electrophiles, including imines and carbonyl compounds, as reported by our group previously.[13] Trapping of these transient zwitterionic intermediates by a variety of electrophiles presents efficient approaches to structurally valuable 3,3-disubstituted oxindoles.[14] We report herein the study on trapping of transient zwitterionic intermediates by in situ prepared N-activated pyridines. It was envisioned that zwitterionic intermediates $\mathbf{II}_a$ or $\mathbf{II}_b$ (Scheme 1c) derived from *N*-aryldiazoamides under the catalysis of palladium catalyst could undergo nucleophilic attack to the preformed N-activated pyridinium salts, incorporating the biologically important dihydropyridine and oxindole moieties to make novel 4-(2-oxoindolin-3-yl)-1,4-dihydropyridine derivatives.

We first investigated the reaction of unsubstituted pyridine **1a** with *N*-aryldiazoamide **3a** under the catalysis of $[PdCl(\eta^3\text{-}C_3H_5)]_2$[15] (Table 1). Pyridine **1a** was converted to *N*-carbobenzoxy pyridinium salts **2a** in situ with benzyl chloroformate (Cbz-Cl) in CH_2Cl_2 before adding the metal catalyst and **3a**. It is worth mentioning that a slight excess of acylating agent (3.0 equiv) was utilized to avoid remaining free pyridine in reaction system that may poison the transition-metal catalyst. Unfortunately, we found that only a trace of desired product **4a** was detected (entry 1), along with dominant intramolecular C−H insertion side product **A** (Scheme 1c) from **3a**. No improvement was obtained when a more polar solvent, THF, was used (entry 2). Failure to trap transient zwitterionic intermediates II was attributed to the low reactivity and poor solubility of pyridinium salt **2a** in organic solvents. When ethyl nicotinate **1b**, which has an electron-withdrawing carbonyl group conjugated to the pyridine ring,

Table 1. Discovery and Optimization of the Addition of Zwitterionic Intermediate to Pyridiniums[a]



entry	1	activator	solvent	*T* (°C)	yield[b] (%)	dr[c]
1	**1a**	Cbz-Cl	CH_2Cl_2	20	**4a**, <5	
2	**1a**	Cbz-Cl	THF	20	**4a**, <5	
3	**1b**	Cbz-Cl	CH_2Cl_2	20	**4b**, 51	60:40
4	**1b**	Tf_2O	CH_2Cl_2	20		
5	**1b**	$BF_3{\cdot}Et_2O$	CH_2Cl_2	20		
6	**1b**	Cbz-Cl	CH_2Cl_2	−20	**4b**, 60	60:40
7	**1b**	Cbz-Cl	$CHCl_3$	−20	**4b**, 62	60:40
8	**1b**	Cbz-Cl	Toluene	−20	**4b**, 68	58:42
9	**1b**	Cbz-Cl	THF	−20	**4b**, 86	60:40

[a]Reaction conditions: **1**/activator/**3**/$[PdClC_3H_5]_2$ = 1:3:2:0.05. [b]Isolated combined yields of isomers. [c]*Syn/anti*, determined by crude ^{1}H NMR

was employed, the trapping product **4b** was obtained in acceptable yield with a regioselective C4-position selectivity and moderate diastereoselectivity (entry 3). Moreover, further optimization of reaction conditions (entries 4−9), including activating reagents, reaction temperature, and solvents, was proven to improve the yield to 86%. Thus, the optimal conditions shown in entry 9 were then applied in the substrate scope evaluations.

Having identified the optimized reaction conditions for regioselective C-4 addition of active zwitterionic intermediates to *N*-acylpyridinium salts, we then demonstrated the generality of this reaction with a variety of substrates (Scheme 2). As for chloroformates, Cbz-Cl, trichloroethyl chloroformate (Troc-Cl), 9-fluorenylmethyl chloroformate (Fmoc-Cl), and allyl chloroformate (Alloc-Cl) gave corresponding products **4b−e** in high yields (86%−96%) with complete C-4 regioselectivities and moderate diastereoselectivity, among which Alloc-Cl increased the yield to 96%. With respect to the *N*-aryldiazoamides, all substrates with methyl, methoxyl, and halides on the *para*-position of the *N*-aryl groups afforded desired products **4f−j** in equally high yields (87−95%) with similar diastereoselectivities as above, while the *ortho*-substituted diazoamides failed to produce the trapping products. 3-Acetylpyridine and nicotinonitrile as substrates were also tolerated, providing products **4k−m** in similar high yields but no improvement in diastereoselectivities, and pyridines with a 3-Br, 3-Me, 2-Br, or 2-Ac functionality are incapable of trapping the zwitterionic intermediates. Interestingly, when *N*,*N*-diethylnicotinamide was employed as the substrate, the desired product **4n** was obtained in high yield (93%) with remarkably enhanced diastereoselectivity (>95:5 dr). When assessed with substituted *N*-aryl diazoamides, the corresponding products **4o−t** were furnished with excellent results in both yields and diastereoselectivities.

The structures of products were unambiguously confirmed by single-crystal X-ray diffraction analysis of both *syn* and *anti* diastereoisomers of **4m** (Figure 2). The relative configurations of all other products, especially those derived from nicotinamide, were assigned by analogy under the assistance of ^{1}H NMR spectra.

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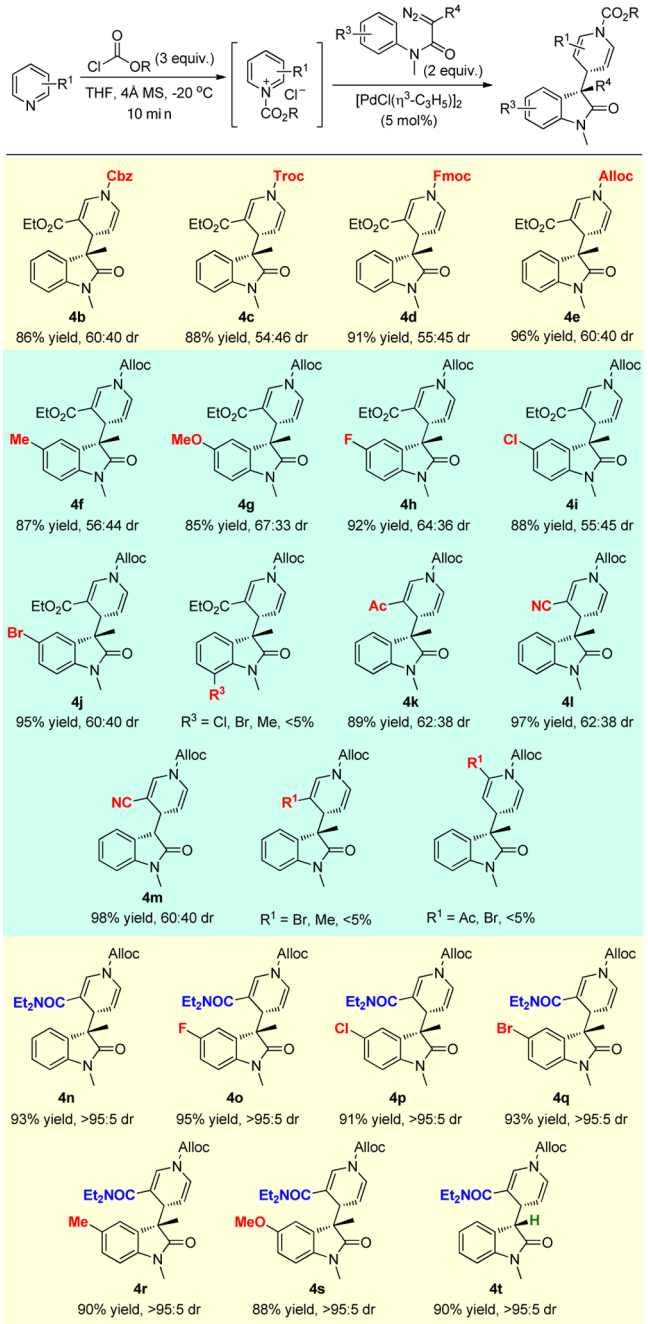
Scheme 2. Substrate Scope of the Three-Component Reaction



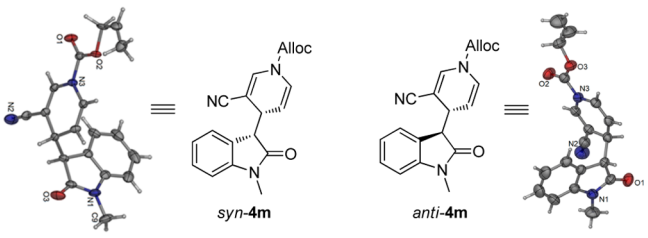


Figure 2. Single-crystal structures of *syn*-**4m** (CCDC 1469819) and *anti*-**4m** (CCDC 1469820). Ellipsoids are drawn at the 50% probability level. Hydrogen atoms are omitted for clarity.

The excellent diastereoselective outcome achieved in this trapping process can be rationalized by the following models in Scheme 3. The in situ generated zwitterionic intermediate could be considered as a racemic mixture as for the Pd-coordinated quantenary carbon, and each enantiomer could undergo nucleophilic addition onto either the *Re* or *Si* face of pyridinium, giving rise to four plausible transition states. For the *Re*-face attack on pyridinium, the approaching of (*R*)-zwitterionic intermediate may suffer more steric hindrance due to the repulsive interaction between amide and aromatic ring (**I**), while the transition state with (*S*)-isomer is much less hindered (**II**), and thus, the formation of *syn*-product is favored. On the contrary, for the case of *Si*-face attack on pyridinium, the approaching of (*R*)-isomer of zwitterionic intermediates (**III**) is more favored over its (*S*)-counterpart (**IV**), selectively providing *syn*-products. Overall, the formation of *syn* isomers can be favored by nucleophilic attack with less steric hindrance (**II** and **III**) to avoid the repulsive interactions (**I** and **IV**). In addition, the remarkable enhancement in diastereoselective control by using *N,N*-diethylnicotinamide, as opposed to ester as substrate, might be attributed to the rigid conformation of amide bond as well as relatively lower electron-withdrawing feature of amide group.

In conclusion, we report herein a palladium-catalyzed regio- and diastereoselective three-component reaction via trapping of transient zwitterionic intermediates with *N*-acylpyridinium salts containing a C-3 electron-withdrawing group. The reactions proceeded with high yields (up to 98%) and moderate to excellent diastereoselectivities (up to >95:5 dr) under mild reaction conditions. This transformation provides an efficient platform to construct a library of structurally novel heterocyclic compounds bearing 2-oxindole and 1,4-dihydropyridine moieties, which are new chemical entities for drug discovery.

EXPERIMENTAL SECTION

General Information. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a 400 MHz spectrometer at 298 K. Chemical shifts (δ) are presented in ppm and calibrated using tetramethylsilane (0.00 ppm for ^{1}H in $CDCl_3$) and $CDCl_3$ (77.0 ppm for ^{13}C) as standards. Coupling constants (J) were obtained from analysis of 1D-spectra and are given in hertz (Hz). The multiplicities are reported using abbreviations: singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublet (dd), multiplet (m), and broad (br). High-resolution mass spectrometry (HRMS) data were recorded by electrospray ionization (ESI) with a TOF mass analyzer.

General Procedure. To an oven-dried test tube with a stir bar were added pyridines (0.4 mmol) and 4 Å molecular sieves (500 mg), and the reaction vessel was then capped with a septum for injection. Anhydrous solvent (2 mL) and activator (1.2 mmol) were added sequentially, and the resulting slurry was stirred and kept at corresponding temperature shown in Table 1 for 10 min. $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (7.3 mg, 5.0 mol %) was added to the mixture, followed by adding a solution of *N*-aryldiazoamide **3** (0.8 mmol, 2.0 equiv) in 1.5 mL of solvent during 1 h via a syringe pump. Upon completion of the addition, the mixture was stirred until complete consumption of **3** (12 h at −20 °C). The mixture was filtered, and the filtrate was concentrated to give a residue, which was subjected to ^{1}H NMR spectroscopy analysis for the determination of diastereoselectivity (dr value). Purification of the crude product by flash chromatography on silica gel (eluent: EtOAc/petroleum ether = 1/50−1/1) afforded products **4**. For **4b−m**, both the *syn* and *anti* diastereoisomers can be obtained for analytical spectra by careful chromatography isolation. As for the reactions with nicotinamide, the reactions were carried out on a 0.2 mmol scale based on nicotinamide.

*1-Benzyl 3-Ethyl 4-(1,3-dimethyl-2-oxoindolin-3-yl)pyridine-1,3(4H)-dicarboxylate (**4b**).* Colorless sticky liquid (153 mg, 86%). Data for (4*R**,3′*S**)-**4b** (*syn*-**4b**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.54−7.27 (m, 5H), 7.20−7.09 (m, 2H), 6.75 (d, J = 7.8 Hz,

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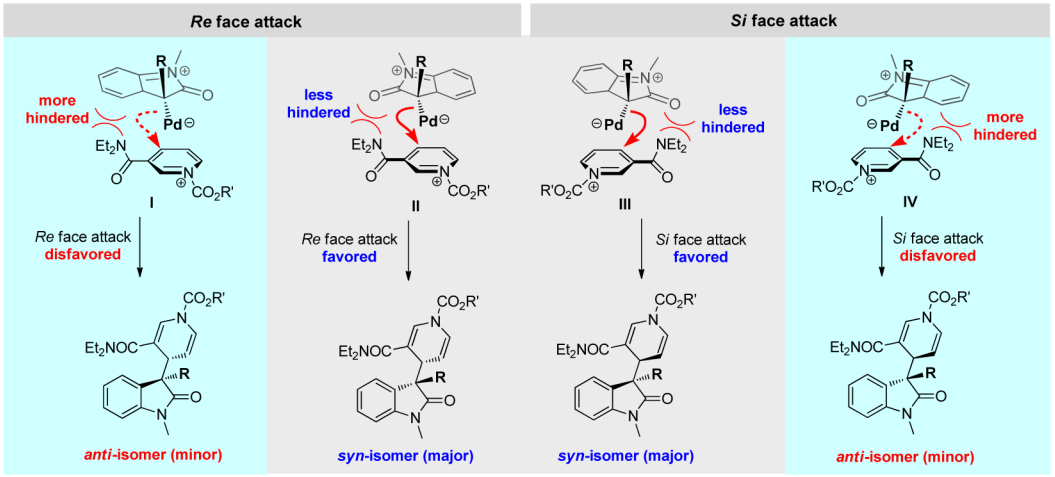
Scheme 3. Rationalization of the Diastereoselective Outcome



2H), 6.50 (s, 1H), 5.17 (d, J = 11.3 Hz, 2H), 4.92 (s, 1H), 4.28 (q, J = 7.1 Hz, 2H), 3.96 (d, J = 5.5 Hz, 1H), 3.19 (s, 3H), 1.35 (t, J = 7.2 Hz, 3H), 1.27 (s, 3H)l ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.9, 167.6, 150.5, 143.6, 135.0, 134.9, 131.4, 128.7, 128.7, 128.4, 128.0, 124.4, 123.4, 121.7, 107.5, 107.2, 68.7, 60.7, 53.6, 39.3, 26.1, 19.2, 14.3l HRMS (ESI) calcd for $C_{26}H_{26}N_2O_5Na$ (M + Na)$^+$ 469.1739, found 469.1727.

Data for (4*R**,3′*R**)-**4b** (*anti*-**4b**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.47−7.32 (m, 5H), 7.25−7.10 (m, 2H), 6.95 (s, 1H), 6.83 (t, J = 7.4 Hz, 1H), 6.75 (d, J = 7.8 Hz, 1H), 5.34−5.13 (m, 3H), 4.19−4.10 (m, 1H), 4.09−3.99 (m, 1H), 3.90 (d, J = 5.6 Hz, 1H), 3.10 (s, 3H), 1.33 (s, 3H), 1.22 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.1, 167.1, 150.8, 143.6, 135.0, 134.1, 132.1, 128.7, 128.4, 128.1, 124.3, 122.8, 121.9, 107.6, 68.9, 60.5, 52.9, 39.3, 26.0, 18.3, 14.2; HRMS (ESI) calcd for $C_{26}H_{26}N_2O_5Na$ (M + Na)$^+$ 469.1739, found 469.1740.

*3-Ethyl 1-(2,2,2-Trichloroethyl) 4-(1,3-dimethyl-2-oxoindolin-3-yl)pyridine-1,3(4H)-dicarboxylate (**4c**).* Colorless sticky liquid (171 mg, 88%). Data for (4*R**,3′*S**)-**4c** (*syn*-**4c**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.24−7.13 (m, 2H), 6.94−6.87 (m, 1H), 6.77 (d, J = 7.9 Hz, 1H), 6.54 (s, 1H), 5.01 (s, 1H), 4.87−4.67 (m, 2H), 4.29 (q, J = 7.1 Hz, 2H), 4.00 (d, J = 5.6 Hz, 1H), 3.21 (s, 3H), 1.36 (t, J = 7.1 Hz, 3H), 1.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.8, 167.3, 149.2, 143.7, 134.3, 131.3, 128.2, 123.4, 121.9, 108.4, 107.7, 94.3, 75.6, 60.9, 53.5, 39.3, 26.1, 19.4, 14.3; HRMS (ESI) calcd for $C_{21}H_{21}N_2O_5Cl_3Na$ (M + Na)$^+$ 509.0414, found 509.0412.

Data for (4*R**,3′*R**)-**4c** (*anti*-**4c**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.28−7.11 (m, 2H), 7.04−6.85 (m, 2H), 6.77 (d, J = 7.7 Hz, 1H), 5.24 (s, 1H), 5.04−4.66 (m, 2H), 4.28−3.99 (m, 2H), 3.93 (d, J = 5.6 Hz, 1H), 3.11 (s, 3H), 1.35 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.9, 166.8, 149.4, 143.6, 133.4, 132.0, 128.2, 122.8, 122.0, 108.8, 107.7, 94.4, 75.7, 60.7, 52.8, 39.3, 26.0, 18.5, 14.1; HRMS (ESI) calcd for $C_{21}H_{21}N_2O_5Cl_3Na$ (M + Na)$^+$ 509.0414, found 509.0434.

*1-((9H-Fluoren-9-yl)methyl) 3-Ethyl 4-(1,3-dimethyl-2-oxoindolin-3-yl)pyridine-1,3(4H)-dicarboxylate (**4d**).* Colorless sticky liquid (193 mg, 91%). Data for (4*R**,3′*S**)-**4d** (*syn*-**4d**): ^{1}H NMR (400 MHz, $CDCl_3$) δ8.08 (s, 1H), 7.78 (d, J = 7.1 Hz, 2H), 7.65−7.27 (m, 6H), 7.22−7.08 (m, 2H), 6.82 (s, 1H), 6.76 (d, J = 7.8 Hz, 1H), 6.50 (s, 1H), 5.04−4.90 (m, 1H), 4.56−4.44 (m, 1H), 4.31 (dd, J = 14.2, 7.1 Hz, 2H), 4.23 (dd, J = 14.1, 7.0 Hz, 2H), 4.00 (d, J = 5.5 Hz, 1H), 3.21 (s, 3H), 1.37 (t, J = 7.1 Hz, 3H), 1.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.9, 167.5, 150.5, 143.7, 143.3, 143.1, 141.4, 141.3, 134.6, 131.4, 128.2, 128.1, 128.0, 127.3, 127.2, 125.0, 124.9, 124.2, 123.5, 121.7, 120.2, 120.2, 109.4, 107.6, 107.4, 69.1, 60.8, 53.7, 46.8, 39.4, 26.1, 19.3, 14.4; HRMS (ESI) calcd for $C_{33}H_{30}N_2O_5Na$ (M + Na)$^+$ 557.2052, found 557.2045.

Data for (4*R**,3′*R**)-**4d** (*anti*-**4d**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.79 (d, J = 7.5 Hz, 2H), 7.62−7.49 (m, 2H), 7.43 (t, J = 7.4 Hz, 2H), 7.38−7.28 (m, 2H), 7.20 (t, J = 7.8 Hz, 2H), 7.03−6.79 (m, 2H), 6.76 (d, J = 7.8 Hz, 1H), 5.21 (dd, J = 7.9, 5.7 Hz, 1H), 4.65−4.36 (m, 2H), 4.29 (t, J = 7.0 Hz, 1H), 4.23−4.00 (m, 2H), 3.94 (d, J = 5.3 Hz, 1H), 3.12 (s, 3H), 1.36 (s, 3H), 1.31−1.19 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.1, 167.0, 150.70, 143.6, 143.3, 143.1, 141.4, 141.3, 133.9, 132.2, 128.2, 128.0, 127.3, 127.3, 125.1, 124.9, 124.2, 122.9, 121.9, 120.2, 109.1, 107.8, 107.6, 69.1, 60.5, 52.9, 46.8, 39.4, 26.0, 18.4, 14.3; HRMS (ESI) calcd for $C_{33}H_{30}N_2O_5Na$ (M + Na)$^+$ 557.2052, found 557.2025.

*1-Allyl 3-Ethyl 4-(1,3-dimethyl-2-oxoindolin-3-yl)pyridine-1,3(4H)-dicarboxylate (**syn-4e**).* Colorless sticky liquid (152 mg, 96%). Data for (4*R**,3′*S**)-**4e** (*syn*-**4e**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.25−7.16 (m, 2H), 6.90 (t, J = 7.5 Hz, 1H), 6.77 (d, J = 7.7 Hz, 1H), 6.63−6.45 (m, 1H), 6.03−5.76 (m, 1H), 5.38−5.20 (m, 2H), 5.02−4.86 (m, 1H), 4.74−4.58 (m, 2H), 4.28 (q, J = 7.1 Hz, 2H), 3.97 (d, J = 5.6 Hz, 1H), 3.20 (s, 3H), 1.35 (t, J = 7.1 Hz, 3H), 1.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.9, 167.7, 150.4, 143.7, 134.8, 131.5, 131.3, 128.0, 124.3, 123.5, 121.8, 119.1, 107.6, 107.1, 67.6, 60.7, 53.6, 39.3, 26.1, 19.2, 14.3; HRMS (ESI) calcd for $C_{22}H_{24}N_2O_5Na$ (M + Na)$^+$ 419.1583, found 419.1563

Data for (4*R**,3′*R**)-**4e** (*anti*-**4e**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.25−7.15 (m, 2H), 6.97−6.88 (m, 2H), 6.76 (d, J = 7.7 Hz, 1H), 5.94 (ddd, J = 22.5, 10.9, 5.7 Hz, 1H), 5.42−5.26 (m, 2H), 5.18 (dd, J = 8.0, 5.7 Hz, 1H), 4.72 (d, J = 5.5 Hz, 2H), 4.20−3.99 (m, 2H), 3.91 (d, J = 5.6 Hz, 1H), 3.11 (s, 3H), 1.34 (s, 3H), 1.23 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.1, 167.1, 150.6, 143.6, 134.1, 132.2, 131.4, 128.1, 124.3, 122.9, 121.9, 119.1, 107.6, 67.7, 60.5, 52.9, 39.3, 26.0, 18.3, 14.2; HRMS (ESI) calcd for $C_{22}H_{24}N_2O_5Na$ (M + Na)$^+$ 419.1583, found 419.1578.

*1-Allyl 3-Ethyl 4-(1,3,5-trimethyl-2-oxoindolin-3-yl)pyridine-1,3(4H)-dicarboxylate (**4f**).* Colorless sticky liquid (142 mg, 87%). Data for (4*R**,3′*S**)-**4f** (*syn*-**4f**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.03−6.96 (m, 2H), 6.65 (d, J = 8.3 Hz, 1H), 6.56−6.41 (m, 1H), 6.01−5.74 (m, 1H), 5.41−5.15 (m, 2H), 5.01−4.87 (m, 1H), 4.74−4.54 (m, 2H), 4.29 (q, J = 7.1 Hz, 2H), 3.95 (d, J = 5.7 Hz, 1H), 3.18 (s, 3H), 2.24 (s, 3H), 1.36 (t, J = 7.1 Hz, 3H), 1.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.9, 167.7, 150.4, 141.3, 134.9, 131.6, 131.3, 128.7, 128.2, 124.3, 119.1, 117.0, 107.3, 107.2, 67.6, 60.7, 53.6, 39.2, 26.1, 21.0, 19.1, 14.3; HRMS (ESI) calcd for $C_{23}H_{26}N_2O_5Na$ (M + Na)$^+$ 433.1739, found 433.1735.

Data for (4*R**,3′*R**)-**4f** (*anti*-**4f**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.07−6.98 (m, 2H), 6.94 (d, J = 7.5 Hz, 1H), 6.64 (d, J = 8.2 Hz, 1H), 5.94 (ddd, J = 22.8, 11.0, 5.8 Hz, 1H), 5.36 (d, J = 17.1 Hz, 1H), 5.30 (dd, J = 10.4, 1.0 Hz, 1H), 5.20 (dd, J = 8.0, 5.7 Hz, 1H), 4.72 (d, J = 5.7 Hz, 2H), 4.20−4.09 (m, 1H), 4.08−3.98 (m, 1H), 3.88 (d, J = 5.7 Hz, 1H), 3.09 (s, 3H), 2.26 (s, 3H), 1.32 (s, 3H), 1.24 (t, J = 5.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.0, 167.1, 150.6, 141.2, 134.1, 132.2, 131.4, 128.3, 124.3, 123.8, 119.2, 107.7,

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107.3, 67.7, 60.5, 52.9, 39.3, 26.0, 21.0, 18.2, 14.2; HRMS (ESI) calcd for $C_{23}H_{26}N_2O_5Na$ $(M + Na)^+$ 433.1739, found 433.1718.

*1-Allyl 3-Ethyl 4-(5-methoxy-1,3-dimethyl-2-oxoindolin-3-yl)-pyridine-1,3(4H)-dicarboxylate (**4g**).* Colorless sticky liquid (144 mg, 85%). Data for (4*R**,3′*S**)-**4g** (*syn*-**4g**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 6.82 (d, J = 2.5 Hz, 1H), 6.75 (dd, J = 8.4, 2.5 Hz, 1H), 6.67 (d, J = 8.4 Hz, 1H), 6.52 (br, 1H), 5.41−5.19 (m, 1H), 5.00−4.86 (m, 1H), 4.73−4.54 (m, 1H), 4.29 (q, J = 7.1 Hz, 2H), 3.97 (d, J = 5.6 Hz, 1H), 3.72 (s, 3H), 3.18 (s, 3H), 1.36 (t, J = 7.1 Hz, 3H), 1.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.6, 167.6, 155.5, 150.4, 137.2, 134.9, 132.8, 131.3, 124.3, 119.1, 107.9, 107.2, 67.7, 60.8, 55.7, 54.1, 39.2, 26.2, 19.3, 14.3; HRMS (ESI) calcd for $C_{23}H_{26}N_2O_6Na$ $(M + Na)^+$ 449.1689, found 449.1689.

Data for (4*R**,3′*R**)-**4g** (*anti*-**4g**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.00−6.91 (m, 1H), 6.81 (d, J = 2.4 Hz, 1H), 6.76 (dd, J = 8.4, 2.6 Hz, 1H), 6.66 (d, J = 8.4 Hz, 1H), 5.95 (ddd, J = 16.3, 11.0, 5.8 Hz, 1H), 5.35 (d, J = 17.3 Hz, 1H), 5.30 (dd, J = 10.4, 1.0 Hz, 1H), 5.20 (dd, J = 8.0, 5.7 Hz, 1H), 4.72 (d, J = 5.7 Hz, 2H), 4.21−4.10 (m, 1H), 4.09−4.00 (m, 1H), 3.89 (d, J = 5.6 Hz, 1H), 3.74 (s, 3H), 3.09 (s, 3H), 1.33 (s, 3H), 1.24 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.8, 167.1, 155.7, 150.6, 137.1, 134.1, 133.5, 131.4, 124.3, 119.1, 107.9, 107.6, 67.8, 60.5, 55.7, 53.3, 39.3, 26.1, 18.3, 14.2; HRMS (ESI) calcd for $C_{23}H_{26}N_2O_6Na$ $(M + Na)^+$ 449.1689, found 449.1703.

*1-Allyl 3-Ethyl 4-(5-fluoro-1,3-dimethyl-2-oxoindolin-3-yl)-pyridine-1,3(4H)-dicarboxylate (**4h**).* Colorless sticky liquid (151 mg, 92%). Data for (4*R**,3′*S**)-**4h** (*syn*-**4h**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H), 6.97−6.89 (m, 2H), 6.69 (dd, J = 8.4, 4.2 Hz, 1H), 6.56 (d, J = 7.5 Hz, 1H), 5.99−5.81 (m, 1H), 5.40−5.22 (m, 2H), 5.00−4.87 (m, 1H), 4.68 (d, J = 4.7 Hz, 2H), 4.29 (q, J = 7.1 Hz, 2H), 3.98 (d, J = 5.7 Hz, 1H), 3.19 (s, 3H), 1.36 (t, J = 7.1 Hz, 3H), 1.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.6, 167.5, 158.8 (d, J = 240.0 Hz), 150.3, 139.6 (d, J = 1.8 Hz), 135.0, 133.3 (d, J = 7.5 Hz), 131.2, 124.5, 119.2, 114.1 (d, J = 23.4 Hz), 111.6 (d, J = 25.0 Hz), 108.7, 107.9 (d, J = 8.1 Hz), 106.9, 67.8, 60.8, 54.0 (d, J = 1.7 Hz), 39.25, 26.2, 19.1, 14.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ −121.6; HRMS (ESI) calcd for $C_{22}H_{23}N_2O_5NaF$ $(M + Na)^+$ 437.1489, found 437.1504.

Data for (4*R**,3′*R**)-**4h** (*anti*-**4h**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.01−6.88 (m, 3H), 6.68 (dd, J = 8.6, 4.1 Hz, 1H), 5.95 (ddd, J = 16.3, 11.1, 5.8 Hz, 1H), 5.36 (dd, J = 17.3, 0.9 Hz, 1H), 5.33−5.29 (m, 1H), 5.20 (dd, J = 7.9, 5.7 Hz, 1H), 4.74 (d, J = 5.7 Hz, 2H), 4.19−4.11 (m, 1H), 4.11−4.04 (m, 1H), 3.91 (d, J = 5.6 Hz, 1H), 3.10 (s, 3H), 1.33 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.8, 166.9, 159.0 (d, J = 240.0 Hz), 150.5, 139.5, 134.2, 133.9 (d, J = 8.5 Hz), 131.3, 124.5, 119.2, 114.2 (d, J = 23.4 Hz), 111.1 (d, J = 24.9 Hz), 108.6, 107.9 (d, J = 8.1 Hz), 107.2, 67.9, 60.6, 53.3(d, J = 1.6 Hz), 39.3, 26.1, 18.2, 14.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ −121.4; HRMS (ESI) calcd for $C_{22}H_{23}N_2O_5NaF$ $(M + Na)^+$ 437.1489, found 437.1467.

*1-Allyl 3-Ethyl 4-(5-chloro-1,3-dimethyl-2-oxoindolin-3-yl)-pyridine-1,3(4H)-dicarboxylate (**4i**).* Colorless sticky liquid (153 mg, 88%). Data for (4*R**,3′*S**)-**4i** (*syn*-**4i**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.22−7.13 (m, 2H), 6.69 (d, J = 8.3 Hz, 1H), 6.55 (d, J = 7.4 Hz, 1H), 6.05−5.84 (m, 1H), 5.44−5.22 (m, 2H), 4.97−4.87 (m, 1H), 4.78−4.61 (m, 2H), 4.29 (q, J = 7.1 Hz, 2H), 3.96 (dd, J = 5.7, 0.7 Hz, 1H), 3.19 (s, 3H), 1.36 (t, J = 6.5 Hz, 3H), 1.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5, 167.4, 150.3, 142.3, 135.1, 133.4, 131.3, 128.0, 127.3, 124.7, 123.8, 119.3, 108.5, 106.8, 77.3, 77.2, 77.0, 76.7, 68.0, 60.8, 53.8, 39.3, 26.2, 18.9, 14.3; HRMS (ESI) calcd for $C_{22}H_{23}N_2O_5NaCl$ $(M + Na)^+$ 453.1193, found 453.1199.

Data for (4*R**,3′*R**)-**4i** (*anti*-**4i**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.34 (dd, J = 8.2, 2.0 Hz, 1H), 7.31 (d, J = 1.8 Hz, 1H), 6.65 (d, J = 8.2 Hz, 1H), 6.54 (d, J = 7.0 Hz, 1H), 6.04−5.85 (m, 1H), 5.41−5.24 (m, 2H), 4.95−4.87 (m, 1H), 4.78−4.65 (m, 2H), 4.29 (q, J = 7.1 Hz, 2H), 3.96 (d, J = 5.7 Hz, 1H), 3.19 (s, 3H), 1.36 (t, J = 7.1 Hz, 3H), 1.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.3, 167.4, 150.3, 142.8, 135.1, 133.8, 131.3, 130.9, 126.5, 124.7, 119.4, 114.5, 109.0, 106.8, 68.0, 60.9, 53.8, 39.3, 26.2, 18.9, 14.3; HRMS (ESI) calcd for $C_{22}H_{23}N_2O_5NaCl$ $(M + Na)^+$ 453.1193, found 453.1200.

*1-Allyl 3-Ethyl 4-(5-bromo-1,3-dimethyl-2-oxoindolin-3-yl)-pyridine-1,3(4H)-dicarboxylate (**4j**).* Colorless sticky liquid (180 mg, 95%). Data for (4*R**,3′*S**)-**4j** (*syn*-**4j**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.20 (dd, J = 8.2, 2.1 Hz, 1H), 7.16 (d, J = 2.0 Hz, 1H), 6.99 (d, J = 7.7 Hz, 1H), 6.68 (d, J = 8.2 Hz, 1H), 6.05−5.90 (m, 1H), 5.37 (dd, J = 17.2, 1.1 Hz, 1H), 5.31 (dd, J = 10.4, 1.1 Hz, 1H), 5.24 (dd, J = 7.9, 5.7 Hz, 1H), 4.74 (d, J = 5.8 Hz, 2H), 4.22−4.12 (m, 1H), 4.11−4.05 (m, 1H), 3.90 (d, J = 5.7 Hz, 1H), 3.10 (s, 3H), 1.33 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.6, 166.9, 150.5, 142.2, 134.3, 131.3, 128.0, 127.3, 124.7, 123.4, 119.3, 108.4, 107.2, 88.2, 68.0, 60.6, 53.1, 39.4, 26.1, 17.9, 14.2; HRMS (ESI) calcd for $C_{22}H_{23}N_2O_5NaBr$ $(M + Na)^+$ 497.0688, found 497.0677.

*Allyl 3-Acetyl-4-(1,3-dimethyl-2-oxoindolin-3-yl)pyridine-1(4H)-carboxylate (**4k**).* Colorless sticky liquid (130 mg, 89%). Data for (4*R**,3′*S**)-**4k** (*syn*-**4k**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.22 (t, J = 7.8 Hz, 1H), 7.14 (d, J = 7.2 Hz, 1H), 6.92 (t, J = 7.5 Hz, 1H), 6.78 (d, J = 7.8 Hz, 1H), 6.71−6.57 (m, 1H), 5.97−5.83 (m, 1H), 5.36−5.25 (m, 2H), 5.05 (s, 1H), 4.76−4.63 (m, 2H), 4.07 (d, J = 5.5 Hz, 1H), 3.19 (s, 3H), 2.43 (s, 3H), 1.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.8, 179.0, 150.5, 143.6, 135.1, 131.9, 131.2, 128.1, 124.4, 123.2, 121.7, 119.2, 118.8, 107.8, 107.7, 67.8, 53.0, 37.8, 26.1, 25.3, 18.7; HRMS (ESI) calcd for $C_{21}H_{22}N_2O_4Na$ $(M + Na)^+$ 389.1477, found 389.1496.

Data for (4*R**,3′*R**)-**4k** (*anti*-**4k**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (s, 1H), 7.27−7.19 (m, 2H), 6.97 (t, J = 7.5 Hz, 1H), 6.87 (d, J = 7.8 Hz, 1H), 6.76 (d, J = 7.7 Hz, 1H), 5.96 (ddd, J = 16.2, 11.0, 5.7 Hz, 1H), 5.38 (dd, J = 17.2, 1.0 Hz, 1H), 5.33 (dd, J = 10.4, 1.0 Hz, 1H), 5.04 (dd, J = 7.9, 5.6 Hz, 1H), 4.75 (d, J = 5.7 Hz, 2H), 4.08 (d, J = 5.6 Hz, 1H), 3.09 (s, 3H), 2.25 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.8, 179.1, 150.6, 143.6, 134.7, 132.5, 131.3, 128.1, 123.9, 122.8, 122.1, 119.3, 118.4, 108.2, 107.5, 67.9, 52.9, 37.9, 26.0, 25.1, 19.1; HRMS (ESI) calcd for $C_{21}H_{22}N_2O_4Na$ $(M + Na)^+$ 389.1477, found 389.1463.

*Allyl 3-Cyano-4-(1,3-dimethyl-2-oxoindolin-3-yl)pyridine-1(4H)-carboxylate (syn-**4l**).* Colorless sticky liquid (134 mg, 97%). Data for (4*R**,3′*S**)-**4l** (*syn*-**4l**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (br, 1H), 7.35−7.22 (m, 2H), 6.99 (dd, J = 7.5 Hz, 1H), 6.82 (d, J = 7.8 Hz, 1H), 6.50 (d, J = 7.1 Hz, 1H), 6.01−5.70 (m, 1H), 5.41−5.16 (m, 2H), 4.82 (dd, J = 7.8, 5.2 Hz, 1H), 4.65 (d, J = 4.8 Hz, 2H), 3.61 (d, J = 5.0 Hz, 1H), 3.21 (s, 3H), 1.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9, 149.4, 143.7, 138.7, 130.8, 130.6, 128.6, 123.8, 123.3, 122.4, 119.6, 119.3, 108.0, 105.8, 89.4, 68.1, 53.8, 41.5, 26.2, 20.1; HRMS (ESI) calcd for $C_{20}H_{19}N_3O_3Na$ $(M + Na)^+$ 372.1324, found 372.1329.

Data for (4*R**,3′*R**)-**4l** (*anti*-**4l**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.25 (m, 1H), 7.25−7.17 (m, 2H), 7.03−6.91 (m, 2H), 6.87 (d, J = 7.8 Hz, 1H), 6.01−5.77 (m, 1H), 5.43−5.26 (m, 2H), 5.23 (dd, J = 8.2, 5.0 Hz, 1H), 4.69 (d, J = 4.8 Hz, 1H), 3.65 (d, J = 4.9 Hz, 1H), 3.23 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.2, 149.5, 143.8, 137.5, 130.9, 130.9, 128.7, 124.2, 122.9, 122.4, 119.7, 118.1, 108.2, 105.7, 89.8, 68.2, 52.5, 41.1, 26.5, 19.3; HRMS (ESI) calcd for $C_{20}H_{19}N_3O_3Na$ $(M + Na)^+$ 372.1324, found 372.1306.

*Allyl 3-Cyano-4-(1-methyl-2-oxoindolin-3-yl)pyridine-1(4H)-carboxylate (**4m**).* White solid (131 mg, 98%). Data for (4*R**,3′*S**)-**4m** (*syn*-**4m**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (br, 1H), 7.37−7.28 (m, 2H), 7.04 (dd, J = 7.5, 7.5 Hz, 1H), 6.84 (d, J = 8.0 Hz, 1H), 6.70−6.44 (m, 1H), 6.03−5.77 (m, 1H), 5.48−5.17 (m, 2H), 4.69 (d, J = 5.1 Hz, 1H), 4.59 (d, J = 4.8 Hz, 1H), 4.17−3.99 (m, 1H), 3.74 (d, J = 3.6 Hz, 1H), 3.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 149.5, 144.8, 137.1, 130.8, 128.7, 125.5, 124.5, 123.8, 122.8, 119.9, 117.7, 108.2, 105.0, 91.6, 68.3, 49.3, 36.5, 26.3; HRMS (ESI) calcd for $C_{19}H_{17}N_3O_3Na$ $(M + Na)^+$ 358.1168, found 358.1165.

Data for (4*R**,3′*R**)-**4m** (*anti*-**4m**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (br, 1H), 7.37−7.24 (m, 2H), 7.03 (dd, J = 7.5 Hz, 1H), 6.95−6.77 (m, 2H), 5.92 (qd, J = 11.2, 5.9 Hz, 1H), 5.42−5.26 (m, 2H), 4.95−4.90 (m, 1H), 4.89 (d, J = 4.8 Hz, 1H), 4.71 (d, J = 5.7 Hz, 2H), 4.09−3.99 (m, 1H), 3.52 (d, J = 2.5 Hz, 1H), 3.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.6, 149.6, 145.2, 136.8, 130.9, 128.8, 125.4, 123.9, 123.6, 122.5, 119.9, 117.6, 108.4, 107.0, 90.2, 77.4, 77.2, 77.0,

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76.7, 68.3, 50.1, 36.5, 26.4; HRMS (ESI) calcd for $C_{19}H_{17}N_3O_3Na$ (M + Na)$^+$ 358.1168, found 358.1159.

(R)-Allyl 3-(Diethylcarbamoyl)-4-((S*)-1,3-dimethyl-2-oxoindolin-3-yl)pyridine-1(4H)-carboxylate (syn-**4n**).* Colorless sticky liquid (79 mg, 93%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58−7.39 (m, 1H), 7.35−7.08 (m, 2H), 6.90 (s, 1H), 6.70 (d, J = 7.8 Hz, 1H), 6.56 (d, J = 8.0 Hz, 1H), 5.94−5.73 (m, 1H), 5.38−5.07 (m, 2H), 4.90−4.77 (m, 1H), 4.65−4.44 (m, 2H), 3.92−3.58 (m, 1H), 3.55−3.17 (m, 4H), 3.11 (d, J = 1.7 Hz, 3H), 1.27 (d, J = 1.7 Hz, 3H), 1.18−1.02 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.9, 170.8, 170.4, 150.7, 150.5, 143.4, 131.5, 128.0, 127.1, 124.7, 124.4, 122.2, 119.0, 118.7, 114.0, 107.4, 105.5, 67.3, 53.5, 42.4, 39.3, 26.1, 19.7, 13.3; HRMS (ESI) calcd for $C_{24}H_{29}N_3O_4Na$ (M + Na)$^+$ 446.2056, found 446.2041.

(R)-Allyl 4-((S*)-5-Fluoro-1,3-dimethyl-2-oxoindolin-3-yl)-3-(diethylcarbamoyl)pyridine-1(4H)-carboxylate (syn-**4o**).* Colorless sticky liquid (84 mg, 95%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (br, 1H), 7.26 (s, 1H), 6.91 (td, J = 8.8, 2.6 Hz, 1H), 6.73−6.61 (m, 2H), 5.97−5.81 (m, 1H), 5.36−5.23 (m, 2H), 4.87 (dd, J = 8.0, 5.2 Hz, 1H), 4.64 (d, J = 4.3 Hz, 2H), 3.96−3.66 (m, 1H), 3.54−3.25 (m, 4H), 3.17 (s, 3H), 1.34 (s, 3H), 1.25−1.12 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5, 170.6, 160.3, 157.9, 150.5, 139.5, 132.9, 131.4, 127.3, 124.7, 119.0, 114.3, 114.0, 113.9, 113.1, 112.9, 107.7, 107.7, 105.2, 67.5, 54.2, 42.4, 39.0, 26.2, 19.7, 13.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ −120.7 (d, J = 172.3 Hz); HRMS (ESI) calcd for $C_{24}H_{28}N_3O_4NaF$ (M + Na)$^+$ 464.1962, found 464.1939.

(R)-Allyl 4-((S*)-5-Chloro-1,3-dimethyl-2-oxoindolin-3-yl)-3-(diethylcarbamoyl)pyridine-1(4H)-carboxylate (syn-**4p**).* Colorless sticky liquid (83 mg, 91%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64−7.43 (m, 1H), 7.32−7.26 (m, 1H), 7.21 (dd, J = 8.3, 2.1 Hz, 1H), 6.70 (d, J = 8.3 Hz, 1H), 6.69−6.59 (m, 1H), 6.05−5.84 (m, 1H), 5.43−5.22 (m, 2H), 4.96−4.82 (m, 1H), 4.72−4.59 (m, 2H), 3.95−3.66 (m, 1H), 3.60−3.26 (m, 4H), 3.18 (s, 3H), 1.35 (s, 3H), 1.29−1.13 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4, 170.6, 150.5, 142.1, 131.4, 128.0, 127.7, 127.5, 125.2, 125.1, 119.3, 113.8, 108.3, 105.1, 67.6, 54.0, 42.5, 39.3, 26.2, 19.4, 13.4; HRMS (ESI) calcd for $C_{24}H_{28}N_3O_4NaCl$ (M + Na)$^+$ 480.1666, found 480.1650.

(R)-Allyl 4-((S*)-5-Bromo-1,3-dimethyl-2-oxoindolin-3-yl)-3-(diethylcarbamoyl)pyridine-1(4H)-carboxylate (syn-**4q**).* Colorless sticky liquid (93 mg, 93%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (br, 1H), 7.34 (d, J = 8.2 Hz, 1H), 7.28 (s, 1H), 6.65 (d, J = 8.2 Hz, 2H), 6.03−5.84 (m, 1H), 5.29 (t, J = 14.1 Hz, 2H), 4.94−4.80 (m, 1H), 4.74−4.60 (m, 2H), 3.92−3.62 (m, 1H), 3.56−3.22 (m, 4H), 3.16 (s, 3H), 1.34 (s, 3H), 1.24−1.12 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.3, 170.3, 150.5, 142.6, 133.1, 131.5, 130.9, 127.9, 127.5, 125.0, 119.2, 114.9, 113.8, 108.8, 105.0, 67.7, 53.8, 42.5, 39.2, 26.1, 19.3, 13.3; HRMS (ESI) calcd for $C_{24}H_{28}N_3O_4BrNa$ (M + Na)$^+$ 524.1161, found 524.1154.

(R)-Allyl 3-(Diethylcarbamoyl)-4-((S*)-1,3,5-trimethyl-2-oxoindolin-3-yl)pyridine-1(4H)-carboxylate (syn-**4r**).* Colorless sticky liquid (79 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.28 (m, 1H), 7.24 (s, 1H), 7.01 (d, J = 7.8 Hz, 1H), 6.65 (d, J = 7.8 Hz, 1H), 6.63 (d, J = 7.6 Hz, 1H), 6.00−5.79 (m, 1H), 5.41−5.17 (m, 2H), 4.97−4.86 (m, 1H), 4.63 (d, J = 5.4 Hz, 2H), 3.77 (d, J = 48.5 Hz, 1H), 3.62−3.21 (m, 1H), 3.16 (s, 3H), 2.28 (s, 3H), 1.34 (s, 3H), 1.17 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.8, 170.9, 150.7, 141.1, 131.5, 129.9, 128.2, 127.2, 125.5, 124.7, 124.4, 119.3, 118.5, 114.3, 107.1, 105.6, 67.5, 53.5, 42.4, 39.3, 26.1, 21.1, 19.7, 13.5; HRMS (ESI) calcd for $C_{25}H_{31}N_3O_4Na$ (M + Na)$^+$ 460.2212, found 460.2202.

(R)-Allyl 3-(Diethylcarbamoyl)-4-((S*)-5-methoxy-1,3-dimethyl-2-oxoindolin-3-yl)pyridine-1(4H)-carboxylate (syn-**4s**).* Colorless sticky liquid (80 mg, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (s, 2H), 6.76 (dd, J = 8.4, 2.5 Hz, 1H), 6.67 (d, J = 8.4 Hz, 1H), 6.61 (d, J = 7.9 Hz, 1H), 6.00−5.74 (m, 1H), 5.37−5.16 (m, 2H), 4.88 (dd, J = 8.0, 5.3 Hz, 1H), 4.67−4.55 (m, 2H), 3.84−3.67 (m, 4H), 3.59−3.23 (m, 4H), 3.16 (s, 3H), 1.34 (s, 3H), 1.25−1.08 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5, 170.9, 155.8, 150.5, 136.9, 132.3, 131.5, 127.3, 124.5, 119.1, 118.6, 114.3, 113.8, 111.1, 107.8, 105.5, 67.4, 55.8, 54.2, 42.4, 39.1, 26.1, 19.9, 13.2; HRMS (ESI) calcd for $C_{25}H_{31}N_3O_5Na$ (M + Na)$^+$ 476.2161, found 476.2124.

(R)-Allyl 3-(Diethylcarbamoyl)-4-((S*)-1-methyl-2-oxoindolin-3-yl)pyridine-1(4H)-carboxylate (syn-**4t**).* Colorless sticky liquid (74 mg, 90%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 7.3 Hz, 1H), 7.44−7.11 (m, 2H), 7.05−6.94 (m, 1H), 6.78 (d, J = 7.8 Hz, 1H), 6.60 (d, J = 12.0 Hz, 1H), 6.02−5.78 (m, 1H), 5.42−5.16 (m, 2H), 4.74−4.52 (m, 3H), 4.09 (s, 1H), 3.69 (d, J = 26.5 Hz, 1H), 3.52−3.31 (m, 4H), 3.21 (s, 3H), 1.24−1.16 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.8, 175.7, 168.7, 150.6, 144.6, 131.5, 128.0, 126.4, 125.8, 124.8, 122.7, 118.8, 114.8, 107.5, 104.8, 67.4, 50.1, 41.2, 37.1, 26.2, 13.7; HRMS (ESI) calcd for $C_{23}H_{27}N_3O_4Na$ (M + Na)$^+$ 432.1899, found 432.1884.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00560.

^{1}H NMR and ^{13}C NMR spectra for new compounds (PDF)

Crystallographic data for *syn*-**4m** (CIF)

Crystallographic data for *anti*-**4m** (CIF)

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Notes

The authors declare no competing financial interest.

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