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Brønsted Acid Catalyzed Enantioselective α-Amidoalkylation in the Synthesis of Isoindoloisoquinolines

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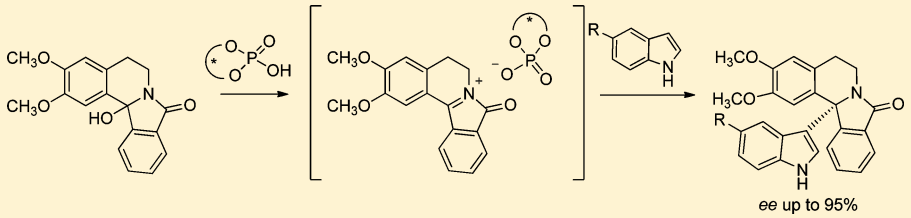
Supporting Information



ABSTRACT: The Parham cyclization−intermolecular α-amidoalkylation sequence results in the facile enantioselective synthesis of 12b-substituted isoindoloisoquinolines (ee up to 95%) using BINOL-derived Brønsted acids. α-Amidoalkylation of indole occurs through the formation of a chiral conjugate base/bicyclic quaternary *N*-acyliminium ion pair.

The α-amidoalkylation reaction of aromatic systems using *N*-acyliminium ions as electrophiles is one of the most attractive methods for C−C bond formation in heterocyclic chemistry and has found widespread application in natural products synthesis.[1] One of the goals of this chemistry in the last years has been the search for new catalysts to effect these transformations in a more efficient way. Since the first reported enantioselective versions of α-amidoalkylation reactions using metal catalysts,[2] significant progress has been marked by the development of chiral Brønsted acids (mainly BINOL derived phosphoric acids)[3−7] and hydrogen bond donors (mainly ureas and thioureas),[8,9] not only for the application of these reactions to the enantioselective synthesis of complex heterocyclic products but also for the mechanistic studies related to the interactions of the chiral inductor with the substrate.

The tetrahydroisoquinoline framework is present in many natural products and biologically active compounds,[10] and therefore, the development of new synthetic procedures for the enantioselective synthesis of these heterocycles continues to be an intensely investigated field. More precisely, the isoindolo[2,1-*a*]isoquinoline skeleton is present in natural products with interesting biological properties, such as hirsutine and jamtine, isolated from *Cocculus Hirustus*, or nuevamine, from *Berberis darwinii*.[11] The intramolecular *N*-acyliminium cyclization has been shown to be an extremely versatile route to fused or substituted tetrahydroisoquinoline systems.[1] However, the enantioselective version using chiral proton donors (thioureas) has failed when *N*-acyliminium ions tethered to electron-rich methoxy-substituted aromatic rings (*N*-phenethylhydroxylactams) were used.[12] In fact, the intramolecular cyclization on *N*-acyliminium ions requires more reactive heteroaromatic systems, such as indoles or pyrroles.[12−14] We thought that the Parham cyclization[15]−enantioselective intermolecular α-amidoalkylation sequence would offer an efficient alternative.[16]

Therefore, we decided to investigate the use of a chiral phosphoric acid to generate a conjugate base/*N*-acyliminium ion pair **I** (Scheme 1) starting from 12b-hydroxyisoindolo[1,2-*a*]isoquinolone **2**,[17] obtained by Parham cyclization of **1**. This chiral intermediate would be trapped with a (hetero)aromatic system to form the nuevamine-type alkaloids **4**, generating a quaternary stereocenter. For this study, we chose indole as the aromatic system. BINOL-derived phosphoric acids have indeed been used in *N*-acyliminium reactions,[18] and more precisely, the intermolecular α-amidoalkylation of indoles with *N*-acyliminium ions formed in situ from cyclic hydroxylactams to form tertiary[19,20] or quaternary stereogenic centers has been reported.[21,22] However, no examples of bicyclic *N*-acyliminium intermediates have been reported so far. Herein, we report significant progress toward this goal.

A preliminary evaluation of the catalyst was performed reacting hydroxylactam **2** and indole **5a** in the presence of several 3,3′-substituted binaphthyl phosphoric acids **3a−e** (Table 1). Although under these conditions sterically congested catalyst **3c** was the most active, the best ee was obtained with catalyst **3d**, which gave the 3-substituted indole **4a** with a 42% ee.

The reaction conditions were optimized using various solvents and temperatures (Table 2). The α-amidoalkylation proceeded efficiently using 20 mol % of **3d** at low temperature (Table 2, entries 1−4), obtaining the best ee (62%) in THF, although the reaction required 72 h to reach a reasonable conversion (entry 6). However, when the reaction was carried out at room temperature, **4a** was obtained in high ee (74% ee, 91% ee after crystallization) and good yield (70%, entry 7). The

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Scheme 1. Enantioselective α-Amidoalkylation

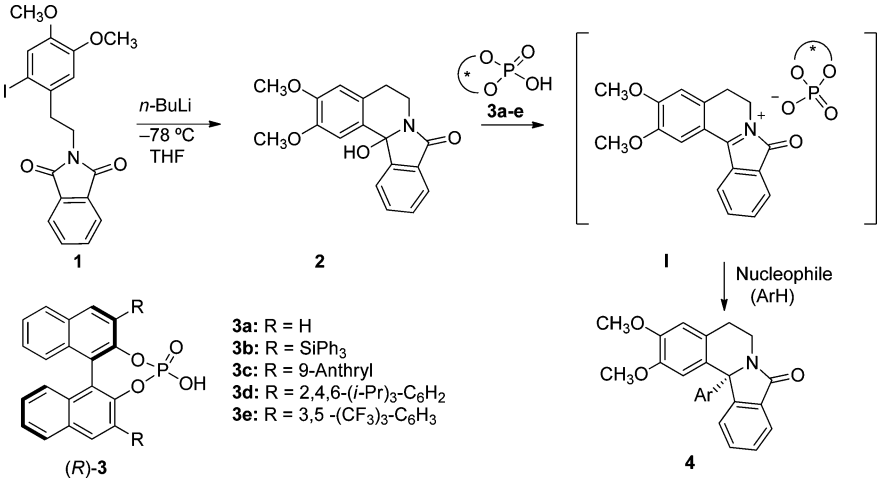
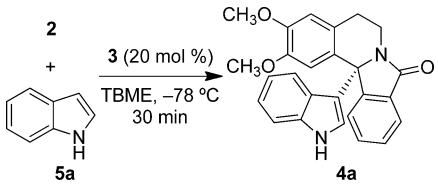


Table 1. Preliminary Evaluation of the Catalyst



entry	catalyst	yield[a] (%)	ee[b] (%)
1	**3a**	68	12
2	**3b**	53	6
3	**3c**	85	15
4	**3d**	67	42
5	**3e**	84	2

[a]Yield of isolated product. [b]Determined by chiral stationary-phase HPLC.

use of lower temperatures (−10 °C, entry 8) or the presence of additives (4 Å molecular sieve or TMSCl, entries 9, 10) caused a significant reduction of the yield or the enantioselectivity. An increase of the catalyst loading does not improve the results (entry 12), and in fact **3d** was active even in just a 2.5 mol %, though with a slight erosion of enantioselectivity (entries 13−15). As could be expected, an increase in the temperature resulted in a faster reaction, but in a low ee (entry 16). Having established THF and room temperature as the best reactions conditions with **3d**, we reinvestigated the use of phosphoric acids **3b**, **3c**, and **3e**, obtaining **4a** in good yields but significantly lower ee (entries 17−19). Finally, other polar solvents were used under these conditions, not improving the results obtained in THF (entries 20−27).

These reaction conditions were extended to 5-substituted indoles (Table 3). The introduction of a strong acceptor, such as the nitro group, completely precludes the α-amidoalkylation reaction, presumably due the lower C-3 reactivity, while the introduction of donating groups results in smooth reactions, even with low catalyst loadings, down to 2.5 mol %.

Although the enantioselectivities obtained in some cases were moderate, the optical purity of the isoindoloisoquinolines could be significantly improved after a single crystallization. The absolute configuration was unambiguously assigned by single-crystal X-ray analysis of **4c** as *R* (see the Supporting Information).[23] The configuration of **4a,d** was assigned assuming a uniform mechanism.

The course of reaction was investigated using ^{1}H NMR[24] and ESI-MS.[25] The reaction of **2** with 1 equiv of phosphoric acid **3d** in $CDCl_3$ and in THF-d_6 was monitored by ^{1}H NMR. Although protonation of the hydroxylactam **2** could be observed, the formation of the intermediate *N*-acyliminium ion pair **I** (Scheme 1) could not be confirmed by ^{1}H NMR either in $CDCl_3$ or in THF-d_6 (see the Supporting Information). ESI-MS and ESI-MS/MS experiments support the formation of a chiral ion pair as **I**. Thus, the presence of an ion m/z = 1068.49 indicates the formation of the ion pair **I** (calculated for $[\mathbf{I}\cdot Na]^+$ $C_{68}H_{72}NNaO_7P^+$ 1068.4939, found 1068.4988). Moreover, the MS/MS analysis of this peak showed the presence of the *N*-acyliminium intermediate (calculated for $C_{18}H_{16}NO_3^+$ 294.1125, found 294.1114), and the phosphoric acid catalyst (see the Supporting Information). On the other hand, when the reaction was carried out under the same reaction conditions with 1-methylindole **5e**, a significant decrease in the efficiency and an inversion of the enantioselectivity were observed (Scheme 2), indicating an important role of the NH moiety in the enantioselection.[26]

The formation of the *R* isomer in the reaction of **2** with indoles **5a,c,d** is in consonance with the sense of induction reported in other intermolecular α-amidoalkylation reactions through the formation of an *N*-acyliminium intermediate/chiral conjugate base ion pair as **I** (Scheme 1). The concept of asymmetric counteranion-directed catalysis[5,27] or chiral contact-ion-pair catalysis[6] has been invoked to explain the enantioselection in *N*-acyliminium reactions,[18] and more precisely, the intermolecular α-amidoalkylation of indoles.[19−22] The related enantioselective alkylation of imines and acylimines catalyzed by BINOL-phosphoric acids has been studied quite extensively,[3−7,28,29] and a model to explain the stereochemical outcome of these reactions has been reported recently.[30] Thus, the phosphoric acid may act as a bifunctional catalyst, interacting also with the nucleophile. When indoles are used as nucleophiles, there is experimental evidence of these interactions, as the reactions are not so effective with *N*-alkylated indoles.[31] In our case, a similar working model, in which the acid generates the chiral ion pair (**II**, Figure 1) by protonation of the hydroxylactam and forms an hydrogen bond with the indole N−H moiety, could be proposed. As compound **2** is racemic, the protonation−elimination step to form the

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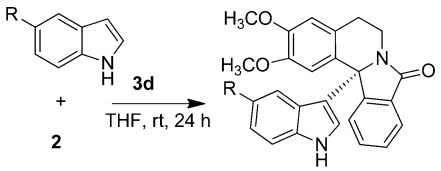
Table 2. Optimization of Reaction Conditions

entry	solvent	cat.	mol %	temp (°C)	time (h)	**4a** yield[a] (%)	ee[b] (%)
1	toluene	**3d**	20[c]	−78	0.5	56	12[c]
2	CH_2Cl_2	**3d**	20[c]	−78	0.5	73	4
3	Mesytylene:xylene	**3d**	20[c]	−78	0.5	30	18
4	CH_3CN	**3d**	20	−10	2	78	40
5	CH_3CN	**3d**	20	rt	2	74	38
6	THF	**3d**	20	−78	72	46	62
7	THF	**3d**	20	rt	24	70	74 (91)
8	THF	**3d**	20	−10	24	15	78
9	THF	**3d**	20[c]	rt	24	65	45
10	THF	**3d**	20[d]	rt	24	67	2
11	THF	**3d**	20[e]	rt	24	47	77 (87)
12	THF	**3d**	30	rt	24	70	68
13	THF	**3d**	10	rt	24	80	74 (83)
14	THF	**3d**	5	rt	24	90	79
15	THF	**3d**	2.5	rt	24	93	78
16	THF	**3d**	2.5	45	4	78	40
17	THF	**3b**	20	rt	24	77	32
18	THF	**3c**	20	rt	24	54	21
19	THF	**3e**	20	rt	24	81	10
20	DMF	**3d**	2.5	rt	24	47	60
21	DMF	**3d**	5	rt	24	39	49
22	DMF	**3d**	10	rt	24	61	44
23	DMF	**3d**	20	rt	24	77	44
24	EtOH	**3d**	20	rt	24	75	32
25	EtOH	**3d**	2.5	rt	7	78	26
26	dioxane	**3d**	20	rt	24	84	66
27	dioxane	**3d**	2.5	rt	24	48	26

[a]Yield of isolated product. [b]Determined by chiral stationary-phase HPLC. Figures in parentheses indicate ee after crystallization. [c]4 Å molecular sieves were added. [d]TMSCl was added. [e]Nondried THF was used.

Table 3. Extension to 5-Substituted Indoles



5b: R = NO_2
5c: R = Br
5d: R = OCH_3

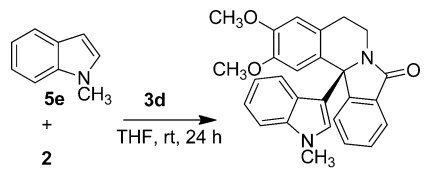
4b: R = NO_2
4c: R = Br
4d: R = OCH_3

entry	R	**3d** (mol %)	yield[a] (%)	ee[b] (%)
1	NO_2	20		
2	Br	20	74	58
3	Br	5	42	69 (95)
4	Br	2.5	44	64
5	OCH_3	20	79	74
6	OCH_3	5	50	72
7	OCH_3	2.5	49	71

[a]Yield of isolated product. [b]Determined by chiral stationary-phase HPLC Figures in parentheses indicate ee after crystallization.

acyliminium chiral ion pair should be nonselective. The steric interaction between the *N*-acyliminium ion and the congested 3,3′-substituted BINOL would determine the orientation inside the chiral pocket of the catalyst. As reported for related reactions by Simón and Goodman,[30] the interaction of the benzene ring of the indole with the catalyst would displace the indole away from the catalyst rings. On the other hand, the acyliminium intermediate would be oriented in such a way that the bulkiest substituent (the methoxylated aromatic ring) is

Scheme 2. α-Amidoalkylation of *N*-Methylindole



4e (21 %, 37 % *ee*)

directed toward the empty side of the catalyst oxygen, avoiding the steric interactions with the catalyst R substituents and, as a result, favoring the *Si* attack of the indole nucleophile, which leads preferentially to the *R* isomers. Figure 1 represents this proposal in a conventional projection (upper part) and using the projections developed by Simón and Goodman,[30] in which the two BINOL oxygen atoms and the phosphorus atom are in the plane of the paper (lower part). When the *N*-methylated indole **5e** was used, the directing effect of the hydrogen bonding of the nucleophile with the catalyst is no longer possible, resulting in a much lower selectivity. Thus, although the orientation of the acyliminium intermediate could be the same, attack of the indole could also occur from the *Re* side leading to the *S* enantiomer.

In conclusion, the Parham cyclization−enantioselective intermolecular α-amidoalkylation sequence provides an efficient alternative to the intramolecular *N*-acyliminium cyclization for the enantioselective synthesis of the tetrahydroisoquinoline core present in many natural and/or biologically active products. A sterically demanding Brønsted acid such as **3d** is required to obtain good enantioselection. On the basis of NMR and ESI-MS/MS studies, a bicyclic *N*-acyliminium chiral ion

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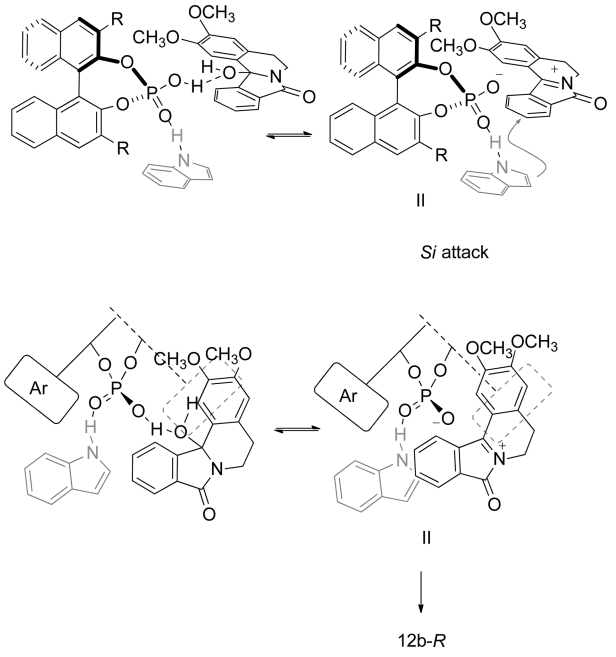

Figure 1. Proposed working model for the α-amidoalkylation of indoles.[30]

pair is proposed to be involved, creating a new quaternary stereocenter. This is the first reported example of quaternary bicyclic *N*-acyliminium intermediates in this type of enantioselective processes.

EXPERIMENTAL SECTION

General Experimental Methods. Melting points were determined in unsealed capillary tubes and are uncorrected. IR spectra were obtained in film over NaCl pellets. NMR spectra were recorded at 20–25 °C, at 300 MHz for ^{1}H and 75.5 MHz for ^{13}C, or at 500 MHz for ^{1}H and 125.7 MHz for ^{13}C in $CDCl_3$ solutions, unless otherwise stated. Assignments of individual ^{13}C and ^{1}H resonances are supported by DEPT experiments and 2D correlation experiments (COSY, HSQCed or HMBC). Mass spectra were recorded under electron impact (EI) at 70 eV or under chemical ionization (CI) at 230 eV. Exact mass was obtained using a TOF detector. TLC was carried out with 0.2 mm thick silica gel plates. Visualization was accomplished by UV light. Flash column chromatography was performed on silica gel (230–400 mesh) or on alumina (70–230 mesh). Chiral stationary-phase HPLC was performed using a Chiralcel OD column (0.46 cm × 25 cm). All solvents used in reactions were anhydrous and purified according to standard procedures.[32] *n*-Butyllithium was titrated with diphenylacetic acid or *N*-benzylbenzamide periodically prior to use. Phosphoric acids **3a**–**e** were used from commercial sources (Aldrich) with the following purities: **3a**: 98+%; **3b**: 96%; **3d**: 98%; **3e**: 95%. Purity of **3c** was not available. All air- or moisture-sensitive reactions were performed under argon; the glassware was dried (130 °C) and purged with argon.

General Procedure for the Synthesis of Racemic 12b-(1*H*-Indol-3-yl)isoindolo[1,2-*a*]isoquinolones 4a–e. $TiCl_4$ (0.12 mL, 1.08 mmol) was added dropwise to a solution of 12b-hydroxyisoindoloisoquinolone **2**[33] (170 mg, 0.54 mmol) and indole **5a**–**e** (0.54 mmol) in dry CH_2Cl_2 (20 mL) at −78 °C. After 1 h of stirring, NH_4Cl (saturated aqueous solution, 2 mL) was added, and the reaction mixture was allowed to warm to room temperature. The organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (3× 15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The crude isoindoloisoquinolines **4a**–**e** were purified by column chromatography (silica gel, hexane/ethyl acetate, 3:7).

12b-(1*H*-Indol-3-yl)-2,3-dimethoxy-5,6-dihydroisoindolo-[1,2-*a*]isoquinolin-8(12b*H*)-one (4a). According to the general procedure, **2** (71.9 mg, 0,23 mmol) was treated with indole **5a** (54 mg, 0.23 mmol) and $TiCl_4$ (0.05 mL, 0.46 mmol) to afford isoindolo[1,2-*a*]-isoquinoline **4a** (66 mg, 70%): mp (hexane/ethyl acetate) 290–292 °C; IR (film) 1663, 3379 cm^{-1}; ^{1}H NMR ($CDCl_3$) 2.72–2.77 (m, 1H), 3.14–3.22 (m, 2H), 3.85 (s, 3H), 3.88 (s, 3H), 4.37–4.41 (m, 1H), 6.40 (d, J = 8.1 Hz, 1H), 6.67 (s, 1H), 6.75 (d, J = 2.6 Hz, 1H), 6.79 (t, J = 7.6 Hz, 1H), 7.08 (t, J = 7.3 Hz, 1H), 7.25 (s, 1H), 7.31 (d, J = 8.2 Hz, 1H), 7.51–7.54 (m, 2H), 7.64–7.67 (m, 1H), 7.97–8.01 (m, 1H), 8.31 (broad s, 1H); ^{13}C NMR ($CDCl_3$) 29.7, 34.9, 55.9, 56.2, 66.1, 110.9, 111.2, 111.8, 117.7, 119.8, 120.0, 122.4, 123.9, 124.0, 124.9, 126.5, 127.3, 128.6, 129.5, 131.88, 132.0, 136.9, 147.0, 148.5, 149.8, 167.2; MS (CI) m/z (rel intensity) 411 (MH^+, 100), 410 (M^+, 48), 292 (9), 293 (13), 294 (13); HRMS (CI) calcd for $C_{26}H_{23}N_2O_3$ [MH^+] 411.1709, found 411.1716.

2,3-Dimethoxy-12b-(5-nitro-1*H*-indol-3-yl)-5,6-dihydroisoindolo[1,2-*a*]isoquinolin-8(12b*H*)-one (4b). According to the general procedure, **2** (151 mg, 0.48 mmol) was treated with indole **5b** (79 mg, 0.48 mmol) and $TiCl_4$ (0.1 mL, 0.97 mmol) to afford isoindolo[1,2-*a*]isoquinoline **4b** (69 mg, 40%): mp (hexane/ethyl acetate) 292–294 °C; IR (film) 1672, 3397 cm^{-1}; ^{1}H NMR ($CDCl_3$) 2.76–2.78 (m, 1H), 3.13–3.22 (m, 2H), 3.85 (s, 3H), 3.89 (s, 3H), 4.43–4.46 (m, 1H), 6.59 (s, 1H), 6.93 (d, J = 2.0 Hz, 1H), 7.22 (s, 1H), 7.25 (d, J = 2.0 Hz, 1H), 7.35 (d, J = 9 Hz, 1H), 7.56–7.65 (m, 2H), 7.71–7.72 (m, 1H), 8.01 (d, J = 9.0 Hz, 1H,), 8.10–8.04 (m, 1H), 8.9 (broad s, 1H); ^{13}C NMR (DMSO-d_6) 28.6, 34.9, 55.9, 56.4, 65.6, 111.7, 112.7, 113.0, 115.8, 117.2, 118.9, 123.5, 124.1, 125.3, 127.1, 128.8, 129.5, 131.4, 131.7, 133.1, 140.7, 140.8, 147.5, 148.8, 150.0, 166.5; MS (CI) m/z (rel intensity) 456 (MH^+, 100), 455 (M^+, 5), 457 (25), 123 (8); HRMS (CI) calcd for $C_{26}H_{22}N_3O_5$ [MH^+] 456.1559, found 456.1582.

12b-(5-Bromo-1*H*-indol-3-yl)-2,3-dimethoxy-5,6-dihydroisoindolo[1,2-*a*]isoquinolin-8(12b*H*)-one (4c). According to the general procedure, **2** (165 mg, 0.53 mmol) was treated with indole **5c** (104 mg, 0.53 mmol) and $TiCl_4$ (0.13 mL, 1.06 mmol) to afford isoindolo[1,2-*a*]isoquinoline **4c** (142 mg, 55%): mp (hexane/ethyl acetate) 278–280 °C; IR (film) 1672, 3341 cm^{-1}; ^{1}H NMR ($CDCl_3$) 2.70–2.90 (m, 1H), 3.09–3.24 (m, 2H), 3.84 (s, 3H), 3.87 (s, 3H), 4.34–4.43 (m, 1H), 6.45 (s, 1H), 6.66 (s, 1H), 6.77 (d, J = 2.5 Hz, 1H), 7.14–7.22 (m, 3H), 7.54–7.57 (m, 2H), 7.62–7.65 (m, 1H), 7.98–8.01 (m, 1H), 8.49 (broad s, 1H); ^{13}C NMR ($CDCl_3$) 28.6, 34.9, 55.97, 56.2, 65.8, 111.6, 111.8, 112.8, 113.4, 117.5, 122.3, 123.9, 124.0, 125.4, 126.5, 127.3, 127.7, 128.9, 129.2, 131,8, 132.1, 135.7, 147.1, 148.6, 149.4, 167.3; MS (CI) m/z (rel intensity) 491 (MH^+ + 2, 99) 490 (59), 489 (MH^+, 100), 488 (33), 293 (19), 294 (17); HRMS (CI) calcd for $C_{26}H_{22}BrN_2O_3$ [MH^+] 489.0814, found 489.0815.

2,3-Dimethoxy-12b-(5-methoxy-1*H*-indol-3-yl)-5,6-dihydroisoindolo[1,2-*a*]isoquinolin-8(12b*H*)-one (4d). According to the general procedure, **2** (172 mg, 0.55 mmol) was treated with indole **5d** (81 mg, 0.55 mmol) and $TiCl_4$ (0.14 mL, 1.09 mmol) to afford isoindolo[1,2-*a*]isoquinoline **4d** (208 mg, 85%): mp (hexane/ethyl acetate) 245–247 °C; IR (film) 1672, 3354 cm^{-1}; ^{1}H NMR ($CDCl_3$) 2.73–2.82 (m, 1H), 3.09–3.28 (m, 2H), 3.41 (s, 3H), 3.84 (s, 3H), 3.87 (s, 3H), 4.38–4.44 (m, 1H), 5.71–5.72 (m, 1H), 6.57 (s, 1H), 6.71–6.74 (m, 2H), 7.18 (d, J = 8.8 Hz, 1H), 7.26 (s, 1H), 7.50–7.59 (m, 2H), 7.69–7.71 (m, 1H), 7.98–8.01 (m, 1H), 8.32 (broad s, 1H); ^{13}C NMR ($CDCl_3$) 28.9, 35.8, 55.2, 55.9, 56.2, 66.3, 101.1, 110.9, 111.7, 112.1, 112.7, 117.0, 123.7, 124.3, 125.3, 127.2, 127.3, 128.6, 129.5, 131.9, 132.0, 132.2, 147.1, 148.5, 149.9, 153.8, 167.1; MS (CI) m/z (rel intensity) 441 (MH^+, 100), 440 (M^+, 36), 442 (29), 294 (14), 293 (13); HRMS (CI) calcd for $C_{27}H_{25}N_2O_4$ [MH^+] 441.1833, found 441.1814.

2,3-Dimethoxy-12b-(1-methyl-1*H*-indol-3-yl)-5,6-dihydroisoindolo[1,2-*a*]isoquinolin-8(12b*H*)-one (4e). According to the general procedure, **2** (165 mg, 0.53 mmol) was treated with *N*-methyl indole **5e** (0.07 mL, 0.53 mmol) and $TiCl_4$ (0.12 mL, 1.06 mmol) to afford isoindolo[1,2-*a*]isoquinoline **4e** (167 mg, 79%): mp (hexane/EtOAc) 264–266 °C. IR (film) 1672 cm^{-1}; ^{1}H NMR ($CDCl_3$) 2.72–2.82 (m, 1H), 3.09–3.27 (m, 2H), 3.69 (s, 3H), 3.86

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(s, 3H), 3.89 (s, 3H), 4.36−4.42 (m, 1H), 6.40 (d, J = 8 Hz, 1H), 6.56 (s, 1H), 6.69 (s, 1H), 6.8 (t, J = 7.5 Hz, 1H), 7.12 (t, J = 7.6 Hz, 1H), 7.22 (s, 1H), 7.26 (s, 1H), 7.51−7.54 (m, 2H), 7.65−7.69 (m, 1H), 7.97−8.00 (m, 1H); ^{13}C NMR ($CDCl_3$) 28.7, 32.8, 34.7, 55.8, 56.1, 65.9, 109.3, 110.9, 111.7, 115.9, 119.5, 119.9, 121.9, 123.8, 124.0, 125.3, 127.2, 128.5, 129.6, 130.8, 131.7, 132.0, 137.6, 146.9, 148.4, 149.8, 167.0; MS (CI) m/z (rel intensity) 425 (MH^+, 100), 424 (M^+, 23), 294 (17), 293 (12), 132 (12), 292 (6); HRMS (CI) calcd for $C_{27}H_{25}N_2O_3$ [MH^+] 425.1865, found 425.1875.

General Procedure for the Synthesis of Enantioenriched Isoindolo[1,2-*a*]isoquinolones 4a,c,d,e. A solution of 12b-hidroxyisoindoloisoquinolone **2** (60 mg, 0.2 mmol), indole **5a**, **5c**, or **5d** (0.2 mmol), and catalyst **3d** in dry THF (2 mL) was stirred during 24 h at room temperature. The solvent was evaporated under reduced pressure, and the crude reaction mixture was purified by column chromatography (alumina, hexane/ethyl acetate 3:7) to afford the enantioenriched isoindolo[1,2-*a*]isoquinolones **4a,c,d** as white solids.

(*R*)-12b-(1*H*-Indol-3-yl)-2,3-dimethoxy-5,6-dihydroisoindolo[1,2-*a*]isoquinolin-8(12b*H*)-one (4a). According to the general procedure, **2** (63 mg, 0.20 mmol) was treated with indole **5a** (24 mg, 0.20 mmol) and **3d** (30 mg, 0.04 mmol, 20 mol %) to afford isoindolo[1,2-*a*]isoquinoline **4a** (68 mg, 70%): $[\alpha]^{20}_D$ +30.61 (c = 0.36, CH_2Cl_2). The enantiomeric excess was determined by HPLC to be 74% that was improved to 91% after single crystallization from hexane. [Chiralcel OD, 15% hexane/2-propanol, 1 mL/min, t_R (S) = 23.4 min (4.53%), t_R (R) = 28.0 min (95.47%)].

(*R*)-12b-(5-Bromo-1*H*-indol-3-yl)-2,3-dimethoxy-5,6-dihydroisoindolo[1,2-*a*]isoquinolin-8(12b*H*)-one (4c). According to the general procedure, **2** (57.5 mg, 0.18 mmol) was treated with indole **5c** (36 mg, 0.18 mmol) and **3d** (7 mg, 0.009 mmol, 5 mol %) to afford isoindolo[1,2-*a*]isoquinoline **4c** (36 mg, 42%): $[\alpha]^{20}_D$ −25.71 (c = 0.62, CH_2Cl_2); The enantiomeric excess was determined by HPLC to be 69% that was improved to 95% after single crystallization from hexane. [Chiralcel OD, 15% hexane/2-propanol, 1 mL/min, t_R (S) = 24.9 min (2.36%), t_R (R) = 29.9 min (97.64%)].

(*R*)-2,3-Dimethoxy-12b-(5-methoxy-1*H*-indol-3-yl)-5,6-dihydroisoindolo[1,2-*a*]isoquinolin-8(12b*H*)-one (4d). According to the general procedure, **2** (59.5 mg, 0.19 mmol) was treated with indole **5d** (28 mg, 0.19 mmol) and **3d** (29 mg, 0.038 mmol, 20 mol %) to afford isoindolo[1,2-*a*]isoquinoline **4d** (61 mg, 79%): $[\alpha]^{20}_D$ −32.41 (c = 1.08, CH_2Cl_2). The enantiomeric excess was determined by HPLC to be 74% [Chiralcel OD, 15% hexane/2-propanol, 1 mL/min, t_R (S) = 23.8 min (12.72%), t_R (R) = 30.9 min (87.28%)].

(*S*)-2,3-Dimethoxy-12b-(1-methyl-1*H*-indol-3-yl)-5,6-dihydroisoindolo[1,2-*a*]isoquinolin-8(12b*H*)-one (4e). According to the general procedure, **2** (66 mg, 0.19 mmol) was treated with indole **5e** (0.027 mL, 0.19 mmol) and **3d** (32 mg, 0.038 mmol, 20 mol %) to afford isoindolo[1,2-*a*]isoquinoline **5e** (17 mg, 21%): $[\alpha]^{20}_D$ −10.05 (c = 0.3, CH_2Cl_2). The enantiomeric excess was determined by HPLC to be 37% [Chiralcel OD, 15% hexane/2-propanol, 1 mL/min, t_R (S) = 14.9 min (68.74%), t_r (R) = 23.5 min (31.26%)].

(*R*)-2,3-Dimethoxy-12b-(1-methyl-1*H*-indol-3-yl)-5,6-dihydroisoindolo[1,2-*a*]isoquinolin-8(12b*H*)-one (4e). (R)-**4a** (79% ee) (37 mg, 0.12 mmol) was added to a suspension of KOH (13 mg, 0.24 mmol) in DMSO (5 mL) at room temperature. After the mixture was stirred for 2 h, MeI (0.008 mL, 0.14 mmol) was added, and the reaction mixture was stirred for 2 h at room temperature. Water (2 mL) was added, and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with water (3 × 10 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on alumina (hexane/ethyl acetate, 2:8) to afford (R)-**4e** as a white solid (24 mg, 46%): $[\alpha]^{20}_D$ +161.1 (c = 0.25, CH_2Cl_2). The enantiomeric excess was determined by HPLC to be 75% [Chiralcel OD, 15% hexane/2-propanol, 1 mL/min, t_R (S) = 15.9 min (12.40%), t_R (R) = 23.1 min (87.60%)].

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Chiral stationary-phase HPLC chromatograms, X-ray structure determination of **4c** (CDC-853329), ^{1}H NMR and ESI MS studies for the detection of intermediates, and copies of ^{1}H and ^{13}C NMR spectra of compounds **4a−e**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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