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Phenolic Activation in Chiral Brønsted Acid-Catalyzed Intramolecular α-Amidoalkylation Reactions for the Synthesis of Fused Isoquinolines

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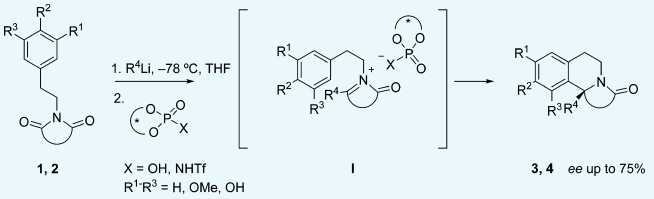
Supporting Information

ABSTRACT: An organolithium addition−intramolecular α-amidoalkylation sequence on *N*-phenethylimides has been developed for the synthesis of fused tetrahydroisoquinoline systems using 1,1′-bi-2-naphthol (binol)-derived Brønsted acids. This transformation is the first in which activated benzene derivatives are used as internal nucleophiles, instead of electron-rich heteroaromatics, generating a quaternary stereocenter. Phenolic substitution on the aromatic ring of the phenethylamino moiety and the use of binol-derived *N*-triflylphosphoramides as catalysts are determinants to achieve reasonable levels of enantioselection, that is, up to 75% enantiomeric excess, in the α-amidoalkylation step. The procedure is complementary to the intermolecular α-amidoalkylation process, as opposite enantiomers are formed, and to the Pictet−Spengler cyclization, which allows the formation of tertiary stereocenters.



INTRODUCTION

Small-molecule chiral hydrogen-bond donors, such as ureas/thioureas[1] and chiral Brønsted acids,[2] are useful and versatile catalysts for many asymmetric transformations because of their ability to activate an electrophilic substrate toward nucleophilic addition. In this context, the development of bifunctional thiourea catalysts has pushed forward *N*-acyliminium ion chemistry,[3] especially the enantioselective catalytic variant of intramolecular α-amidoalkylation reactions,[3e,f,4] which are formally asymmetric organocatalytic intramolecular Friedel−Crafts reactions.[5] In 2004, Jacobsen[6] demonstrated for the first time the ability of these catalysts to activate an acyclic *N*-acyliminium ion in the enantioselective acyl-Pictet−Spengler reaction[7] for indole alkaloid synthesis. Subsequently, the intramolecular α-amidoalkylation reaction of indole and pyrrole-tethered α-hydroxylactams catalyzed by a chiral bifunctional thiourea was reported.[8] Reactivity patterns in these reactions were found to be consistent with a first-order nucleophilic substitution-type mechanism, involving the formation of a chiral *N*-acyliminium/chloride thiourea anion pair. This anion-binding concept in thiourea-catalyzed reactions has also led to the development of related cascade reactions for the construction of polycyclic frameworks.[9] However, this mode of activation failed when the *N*-phenylethylamine counterparts, required for dihydropyrroloisoquinoline synthesis, were used.[8b] As the reactivity of thioureas is limited because of their weak acidity and therefore their activation capacity, chiral Brønsted acids, in particular, sterically demanding 1,1′-bi-2-naphthol (binol)-derived chiral phosphoric acids (CPAs), independently introduced in 2004 by Akiyama[10] and Terada,[11] have proven to be highly efficient catalysts for Mannich-type and related reactions. Key aspects for their success include their capacity to form stable ion pairs, their bifunctional character, and the facile chiral modulation of their backbone, very close to the acidic moiety.[2,12] Several research groups have demonstrated that CPAs could promote enantioselective Pictet−Spengler cyclization reactions, providing β-carboline derivatives in good to excellent yields and enantioselectivities.[13] Analogous Pictet−Spengler reactions via sulfeniminium ion intermediates have become an effective means of preparing not only enantiopure β-carbolines[14] but also tetrahydroisoquinolines, with a tertiary stereocenter at C-1.[15] In the latter case, the substitution pattern of the aromatic ring in the *N*-phenethylamine starting material and the ancillary substituent on the nitrogen atom are crucial for achieving good reactions. Iminium ion stabilization by the sulfenyl substituent was proposed to favor Pictet−Spengler cyclization over undesired enamine formation.[14] However, the successful application of CPA catalysis to intramolecular α-amidoalkylation reactions was again limited to the use of electron-rich heteroaromatics (indoles and pyrroles) as internal nucleophiles. Thus, Dixon reported a direct enantio- and diastereoselective *N*-acyliminium cyclization cascade through binol-derived phosphoric acid-catalyzed condensation of tryptamines with enol lactones[16] (or the corresponding γ- and δ-ketoacid derivatives)[17] to provide architecturally complex β-carboline derivatives, with control of the stereochemistry of up to two contiguous stereogenic centers. On the other hand, related cascade reactions via cooperative transition metal/CPA

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catalysis have also been designed for the synthesis of enantioenriched tetrahydro-β-carbolines in a highly efficient manner.[18]

Despite these breakthroughs in enantioselective *N*-acyliminium ion cyclizations, their application for the construction of optically active tetrahydroisoquinolines,[19] which are important structural motifs in biologically active compounds, still remains a major challenge. Tetrahydroisoquinolines, having a stereocenter at the C-1 carbon, are important scaffolds widely distributed in natural alkaloids and pharmaceuticals and are also commonly used as key intermediates in organic synthesis and medicinal chemistry (Figure 1).[20] For example, phenolic

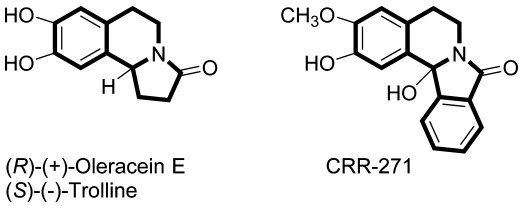


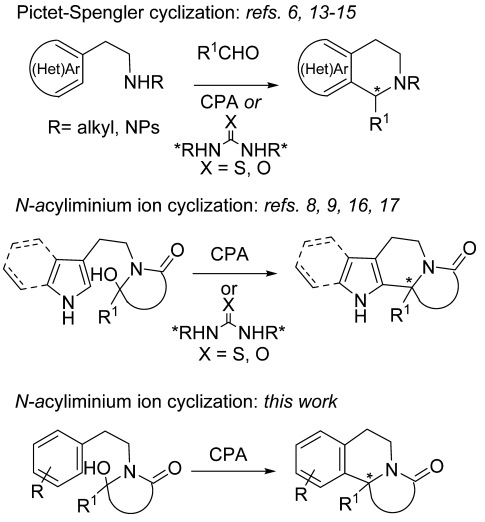
Figure 1. Selected bioactive compounds that contain fused tetrahydroisoquinoline frameworks.

pyrrolo[2,1-*a*]tetrahydroisoquinolines[21] as (−)-trolline show antibacterial activity against respiratory bacteria and antiviral activity against influenza viruses A and B,[22] whereas (+)-oleracein E exhibits potent antioxidant properties;[23] thus, it may serve as a neuroprotectant in the prevention and treatment of Parkinson's disease.[24] Alkaloids with the isoindolo[2,1-*a*]isoquinoline skeleton,[25] such as natural products hirsutine, jamtine, and nuevamine or the synthetic derivative CRR-271, also display significant pharmacological activity, that is, anti-inflammatory properties.[26] Therefore, significant attention remains focused on the development of new synthetic methods for the asymmetric synthesis of these heterocycles.

Our research group has maintained an interest in the α-amidoalkylation reactions of *N*-phenethylhydroxylactams in both the inter- and intramolecular variants for the synthesis of tetrahydroisoquinoline derivatives.[27] In a preliminary communication, we demonstrated that a sterically demanding CPA catalyzed the intramolecular α-amidoalkylation of tertiary *N*-acyliminium ions with the methoxylated benzene ring as internal π-nucleophiles to give pyrrolo[2,1-*a*]isoquinolines, with promising enantioselectivity (up to 74%), but in low yield (23%), due to low conversion.[28] Therefore, we decided to get further insight into the enantioselective intramolecular α-amidoalkylation reaction of cyclic α-hydroxylactams derived from *N*-phenethylimides using chiral Brønsted acids as catalysts to construct the tetrahydroisoquinoline framework of fused isoquinoline derivatives generating a quaternary stereocenter (Scheme 1).

Because binol-derived phosphoric acids could not be reactive enough for the activation of these challenging substrates, *N*-triflylphosphoramides (NTPAs) would also be used. The introduction of the triflylamide into well-known CPAs leads to a significant decrease in pK_a and to the formation of tighter ion pairs.[29] On the other hand, a general strategy for enhancing the reactivity of aromatic rings toward S_EAr (including Pictet−Spengler and *N*-acyliminium ion cyclizations) involves the introduction of strong electron-donating groups, in particular hydroxyl groups.[15] Besides, in some cases the formation of a hydrogen bond between the phenolic OH and the basic site of

Scheme 1. Enantioselective Synthetic Approaches to Isoquinoline Frameworks



the CPA could be crucial for the enantioselection.[30] In a related approach, we have also studied the enantioselective intramolecular α-amidoalkylation with bicyclic α-hydroxylactams for the preparation of 12b-substituted isoindoloisoquinolines using binol-derived Brønsted acids. In these cases, hydrogen-bonding interactions between the phosphate ion-paired intermediate and the N−H group in the nucleophile (indoles[31] or enamides[32]) were invoked to explain the stereochemical outcome. Therefore, we decided to study the effect of the activation of the aromatic rings (methoxyl vs hydroxyl substitutents) on the reactivity and the enantioselectivity of intramolecular α-amidoalkylation reactions of *N*-phenethylhydroxylactams using both binol-derived phosphoric acids and *N*-triflamides as catalysts. We disclose here the full details of our investigations that had led to the synthesis of enantioenriched fused isoquinoline derivatives, through the generation of tertiary and quaternary stereocenters.

RESULTS AND DISCUSSION

For this study, we selected succinimides **1** that had previously given the best results in terms of enantioselectivity.[28] In addition, we selected phthalimides **2**, which would lead to the formation of 12b-substituted isoindolo[1,2-*a*]isoquinolines (Scheme 2). The addition of an organolithium to the imide would afford the corresponding hydroxylactam, which upon treatment with a chiral Brønsted acid would be transformed into an *N*-acyliminium ion, generating chiral ion pair **I**. The *N*-acyliminium ion would be trapped by the aromatic ring, and the cyclization reaction would afford the corresponding fused isoquinolines with a new stereocenter. As stated above, we have previously developed the enantioselective synthesis of 12b-substituted isoindoloisoquinolines through a Parham cyclization−Brønsted acid-catalyzed intermolecular α-amidoalkylation sequence.[31,32] If an analogous working model to explain the stereochemical outcome is assumed,[12b] in this case, it would be expected that the intramolecular attack of the aromatic ring would lead to the opposite stereochemistry on the new stereogenic center. Thus, these strategies would constitute enantiodivergent approaches to fused isoquinoline alkaloids.

We started our study using succinimides as substrates. In our preliminary communication,[28] we had reported that methyl-

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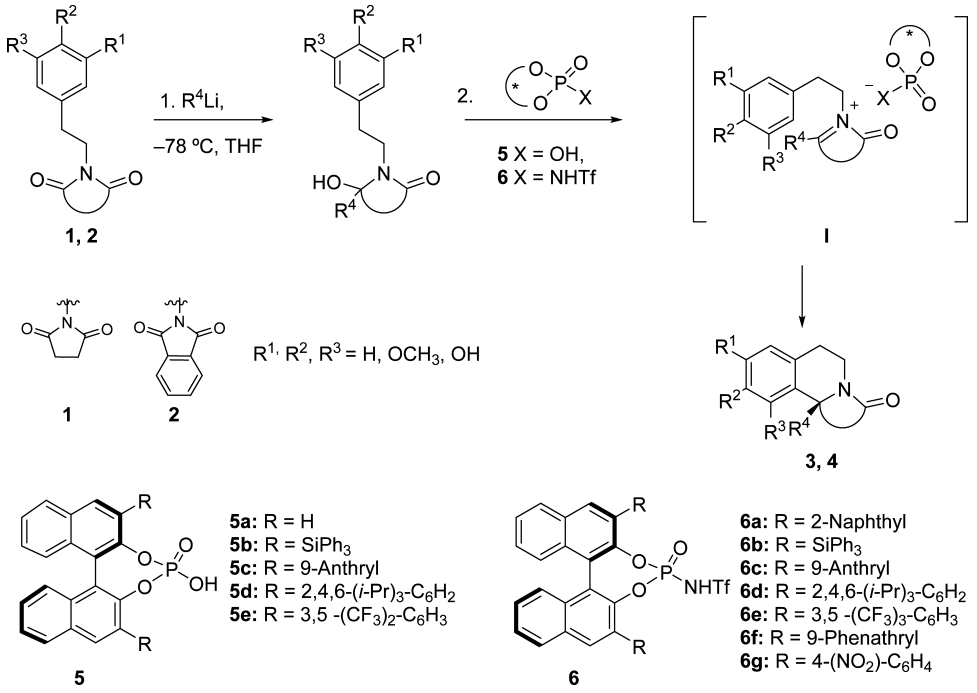
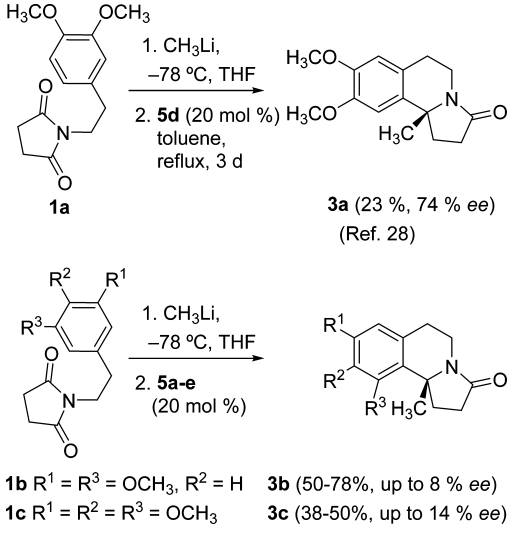
Scheme 2. Organolithium Addition/*N*-Acyliminium Cyclization Sequence



lithium (MeLi) addition to *N*-phenethylsuccinimide **1a** led to the corresponding *N*-phenethylhydroxylactam, which could be cyclized to the corresponding fused isoquinoline upon treatment with a Brønsted acid. Different CPAs and a wide range of organic solvents were tested. The reaction yields improved significantly upon using more polar solvents, although pyrroloisoquinoline **3a** was obtained almost in racemic form in all cases. The use of sterically congested acid **5d** was a determinant to obtain good levels of enantioselection, and up to 74% enantiomeric excess (ee) could be obtained using **5d** (20 mol %) in toluene, although with a low yield (Scheme 3). In view of these results, we tested more activated imides **1b** and **1c**. Addition of MeLi under the standard conditions afforded the corresponding hydroxylactams, whose purity was checked by ^{1}H NMR to make sure that there were no byproducts that could interfere in the subsequent cyclizations. However, they were not further purified or fully characterized, as hydroxylactams are not stable under chromatographic conditions and may lead to dehydrated products or tautomeric ketoamides,[27a] so they were immediately subjected to cyclization reactions. As expected, both hydroxylactams derived from imides **1b** and **1c** showed higher reactivity than that of **1a**, obtaining moderate yields in shorter reaction times. However, when the best conditions reported for **1a** were used (catalyst **5d** in toluene), the yields of pyrroloisoquinolines were moderate (59% for **3b** in 16 h; 38% for **3c** in 64 h), but no enantioselectivity was observed (8% ee for **3b**, 7% ee for **3c**). Phosphoric acid **5d** promoted the cyclization in various solvents (tetrahydrofuran (THF), CH_2Cl_2, dimethylformamide, CH_3CN, EtOH, and dioxane), even at room temperature (rt), obtaining moderate to good yields but poor enantioselection (14% ee in CH_2Cl_2). The use of **5a**–**c** or **5e** did not improve the results (see Table S1 in the Supporting Information (SI)). Thus, although the use of more activated rings enhanced the reactivity, the enantioselectivity was lost.

Scheme 3. Cyclization of Succinimides 1a–c



In view of these poor results, we decided to test phthalimides **2**, expecting that the corresponding hydroxylactams would be more stable than those derived from succinimides **1**, and would also lead to more stable *N*-acyliminium intermediates, which could interact more efficiently with the CPA, as has been shown for related structures in the intermolecular version.[31,32]

First, the reduction of imide **2a** was performed to test the *N*-acyliminium ion cyclization for the formation of a tertiary stereocenter (Table 1). Indeed, cyclization of the corresponding hydroxylactam afforded isoindoloisoquinoline **4a**, in the presence of catalyst **5a**, in toluene and acetonitrile in moderate yield but low enantioselectivity (Table 1, entries 1 and 2). High temperatures (reflux) were required to carry out the reaction in reasonable reaction times with catalyst **5a**, as at rt only low conversions were achieved (entries 3 and 4). Once again, the best results were attained with catalyst **5d** in toluene, obtaining

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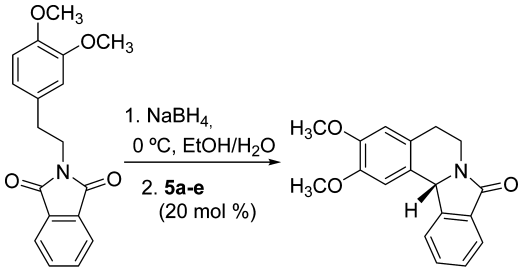
Table 1. Reduction/α-Amidoalkylation of 2a



2a 4aa

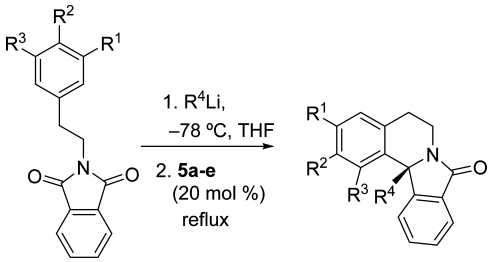
entry	catalyst	solvent	time (h)	T	yield (%)[a]	ee (%)[b]
1	**5a**	toluene	3	reflux	53	15
2	**5a**	CH_3CN	2	reflux	66	4
3	**5a**	toluene	192	rt	7	[c]
4	**5a**	CH_3CN	144	rt	46	[c]
5	**5b**	toluene	3	reflux	50	14
6	**5c**	toluene	16	reflux	79	3
7	**5d**	toluene	2	reflux	74	25
8	**5e**	toluene	2	reflux	58	11

[a]Yield of isolated product. [b]Determined by chiral stationary phase high-performance liquid chromatography (HPLC). [c]Racemic.

a good yield and the highest enantioselectivity (25% ee, entry 7). Thus, although the reactivity was enhanced, efficient control of the enantioselectivity could not be achieved with **5a−e**.

We then studied the generation of a quaternary stereocenter. Thus, addition of MeLi to imides **2a−c** in THF at −78 °C gave the corresponding hydroxylactams that, after workup, were treated with corresponding CPA **5** without further purification. As shown in Table 2, the hydroxylactam derived from imide **2a** did not cyclize when treated with **5a** and **5c** in refluxing toluene (Table 2, entries 1 and 2), and only the formation of the corresponding enamide resulting from water elimination could be observed by ^{1}H NMR. Reaction conditions were optimized using the more reactive hydroxylactam derived from imide **2b**. Acids **5b** and **5c** did not show any catalytic activity in toluene (entries 5 and 6), and again **5d** gave the best enantioselectivity (entry 7), although still low. Very low reactivity was shown at rt (entry 4). With more polar solvents, the reactivity was enhanced, obtaining good yields in shorter reaction times (entries 9 and 10), but with no enantioselection. An increase of the steric bulk on the *N*-acyliminium intermediate (R^4 = *n*-Bu, *t*-Bu) precluded cyclizations (entries 11 and 12). Hydroxylactam derived from imide **2c** was not reactive in toluene and gave similar low enantioselectivities in more polar solvents (entries 13−15). Thus, although CPAs **5a−e** have shown different catalytic activities, the substitution pattern had almost no influence on the stereoselection. To improve the results, stronger Brønsted acids, such as NTPAs **6a−g**, were tested, reasoning that an increased acidity may lead to a closer ion pair and increase the enantioselectivity. Therefore, we selected imide **2b** for the MeLi addition/intramolecular α-amidoalkylation sequence in toluene, as it had given the best results in

Table 2. Synthesis of 12b-Substituted Isoindoloisoquinolines 4



2a $R^1 = R^2 = OCH_3$, R^3 = H
2b $R^1 = R^3 = OCH_3$, R^2 = H
2c $R^1 = R^2 = R^3 = OCH_3$

4ab $R^4 = CH_3$
4bb $R^4 = CH_3$
4bc R^4 = *n*-Bu
4bd R^4 = *t*-Bu
4cb $R^4 = CH_3$

entry	substrate	solvent	catalyst	time (h)	R^4	product **4**	yield (%)[a]	ee (%)[b]
1	**2a**	toluene	**5a**	12	CH_3			
2	**2a**	toluene	**5c**	18	CH_3			
3	**2b**	toluene	**5a**	18	CH_3	**4bb**	52	4
4	**2b**	toluene[c]	**5a**	192	CH_3	**4bb**	7	[d]
5	**2b**	toluene	**5b**	72	CH_3			
6	**2b**	toluene	**5c**	72	CH_3			
7	**2b**	toluene	**5d**	36	CH_3	**4bb**	33	27
8	**2b**	toluene	**5e**	36	CH_3	**4bb**	74	4
9	**2b**	CH_3CN	**5d**	16	CH_3	**4bb**	66	2
10	**2b**	EtOH	**5d**	16	CH_3	**4bb**	80	[d]
11	**2b**	toluene	**5d**	36	*n*-Bu	**4bc**	30	7
12	**2b**	toluene	**5d**	36	*t*-Bu	**4bd**	10	16
13	**2c**	toluene	**5d**	96	CH_3			
14	**2c**	CH_3CN	**5d**	16	CH_3	**4cb**	64	[c]
15	**2c**	CH_3CN	**5e**	16	CH_3	**4cb**	63	11

[a]Yield of isolated product. [b]Determined by chiral stationary phase HPLC. [c]The reaction was performed at rt. [d]Racemic.

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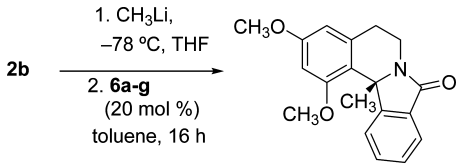
terms of enantioselection. As shown in Table 3, NTPAs **6a–g** were significantly more active catalysts than the corresponding

Table 3. Use of Triflamides 6a–g as Catalysts



4bb

entry	catalyst	*T*	yield (%)[a]	ee (%)[b]
1	**6a**	reflux	80	3
2	**6a**	rt	98	22
3	**6a**	−78 °C	56	15
4	**6b**	rt	78	8
5	**6c**	rt	95	11
6	**6d**	rt	60	9
7	**6e**	rt	87	20
8[c]	**6e**	rt	93	3
9	**6f**	rt	99	17
10	**6g**	rt	86	[d]

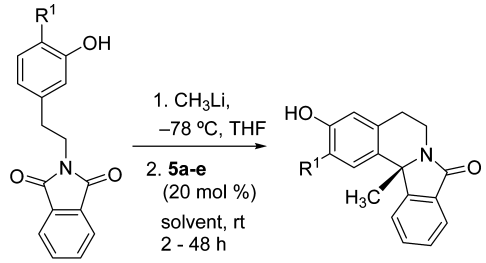
[a]Yield of isolated product. [b]Determined by chiral stationary phase HPLC. [c]THF was used as solvent. [d]Racemic.

phosphoric acids, affording **4bb** in good to excellent yields even at low temperature. The best results were obtained at rt with catalysts **6a** and **6e** (entries 2 and 7), but the ee could not be improved at lower temperatures (entry 3).

These results show that although the reactivity could be efficiently enhanced using the adequate substitution patterns in both the hydroxylactam and the CPA the simple ion pairing was not effective enough to afford good enantioselectivities, and additional interaction of the nucleophile with the CPA would be required, as has been shown for intermolecular reactions.[12b,31,32] For that purpose, we decided to test phenolic imides **2d** and **2e** (Tables 4 and 5). With these phenolic imides, four equivalents of the organolithium reagent were required to afford the corresponding hydroxylactam with full conversion. Then, the cyclization was studied using CPAs **5a–e** as catalysts in different solvents (Table 4). As shown, phenolic hydroxylactams derived from **2d** and **2e** were in fact much more reactive than the corresponding methoxylated derivatives and cyclization took place in various solvents (toluene, dichloromethane, THF, acetonitrile) at rt in high yield using catalyst **5a**. However, no enantioselection was achieved (Table 4, entries 1–6). Phosphoric acids **5b–e** also efficiently promoted the cyclization in toluene at rt, and once again, the substitution pattern did not have a significant impact on the enantioselectivity, which remained low (entries 7–14). The best results were obtained in THF at rt with catalyst **5c** providing isoindoloisoquinoline **4db** with 28% ee (entry 15). A similar enantioselection was observed at a lower temperature (entry 16).

Once again, NTPAs **6** were much more efficient than binol-derived phosphoric acids **5** both in reactivity and enantioselectivity, so the reactions could be performed in THF at −20 °C (Table 5). In this case, although NTPAs **6a–f** promoted the cyclization of the hydroxylactam derived from **2d** in high yield, significant differences in the enantioselection were observed (Table 5, entries 1–7). Thus, using catalyst **6c** in THF at −20 °C, up to 63% ee for **4db** was achieved, which could be

Table 4. Cyclization of 2d and 2e with Phosphoric Acids 5a–e[a]



2d R^1 = OH
2e R^1 = H

4db R^1 = OH
4eb R^1 = H

entry	substrate	catalyst	solvent	time (h)	product	yield (%)[b]	ee (%)[c]
1	**2d**	**5a**	CH_2Cl_2	2	**4db**	57	[d]
2	**2d**	**5a**	THF	16	**4db**	88	[d]
3	**2e**	**5a**	THF	16	**4eb**	56	[d]
4	**2d**	**5a**	toluene	16	**4db**	75	[d]
5	**2e**	**5a**	toluene	48	**4eb**	50	7
6	**2d**	**5a**	CH_3CN	16	**4db**	87	4
7	**2d**	**5b**	toluene	16	**4db**	85	6
8	**2e**	**5b**	toluene	48	**4eb**	43	9
9	**2d**	**5c**	toluene	24	**4db**	80	8
10	**2e**	**5c**	toluene	48	**4eb**	34	26
11	**2d**	**5d**	toluene	24	**4db**	70	5
12	**2e**	**5d**	toluene	48	**4eb**	26	15
13	**2d**	**5e**	toluene	24	**4db**	80	5
14	**2e**	**5e**	toluene	48	**4eb**	66	9
15	**2d**	**5c**	THF	24	**4db**	48	28
16	**2d**	**5c**	THF[e]	48	**4db**	40	26
17	**2d**	**5c**	dioxane	24	**4db**	80	21

[a]Optimization of reaction conditions. [b]Yield of isolated product. [c]Determined by chiral stationary phase HPLC. [d]Racemic. [e]The reaction was carried out at −4 °C.

improved to 75% ee after a single crystallization from dichloromethane. A further optimization of the reaction conditions using phosphoramide **6c** in different solvents and temperatures was also attempted, but the enantioselectivity was not improved. In addition, other related catalysts, such as binol-derived disulfonamide and TADDOL or VAPOL-derived phosphoric acids, were also tested, leading to racemic compounds (see Tables S2 and S3 in the SI). Different substituents (R^2 = *n*-Bu, Ph) could be introduced at C-12b just by changing the organolithium reagent used in the formation of the hydroxylactam, with similar levels of enantioselection (Table 5, entries 8 and 10), although the introduction of a bulky group (R^2 = *t*-Bu) precluded cyclization even at higher temperatures (entry 9). The reaction could also be extended to imide **2e**, showing that the removal of one phenolic group has an effect on the reactivity, obtaining **4eb** in moderate yield, but with the same level of enantioselectivity (60% ee, entry 11).

The absolute configuration was unambiguously assigned by single-crystal X-ray analysis of **4db** as *S* (Figure 2, Cambridge Crystallographic Data Center (CCDC) 1510852 contains the supplementary crystallographic data for **4db**; see SI). The configuration of the other pyrrolo- and isoindoloisoquinolines was assigned assuming a uniform mechanism. This result is in consonance with the sense of induction reported in other CPA-catalyzed intramolecular α-amidoalkylation reactions with tryptamine derivatives,[16,17] through the formation of an *N*-

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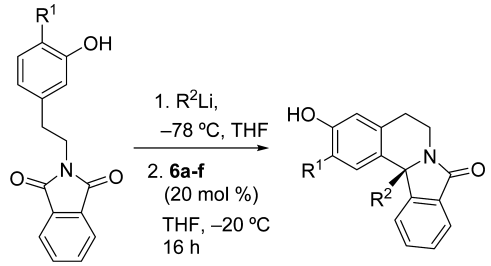
Table 5. Use of Triflamides 6[a]



2d R^1 = OH
2e R^1 = H

4db R^1 = OH, R^2= CH_3
4dc R^1 = OH, R^2= *n*-Bu
4dd R^1 = OH, R^2= *t*-Bu
4de R^1 = OH, R^2= Ph
4eb R^1 = H, R^2= CH_3

entry	substrate	catalyst	R^1	R^2	product	yield (%)[b]	ee (%)[c]
1	**2d**	**6a**	OH	CH_3	**4db**	86	18
2	**2d**[d]	**6a**	OH	CH_3	**4db**	56	10
3	**2d**	**6b**	OH	CH_3	**4db**	54	45
4	**2d**	**6c**	OH	CH_3	**4db**	78	63 (75)
5	**2d**	**6d**	OH	CH_3	**4db**	79	13
6	**2d**	**6e**	OH	CH_3	**4db**	98	1
7	**2d**	**6f**	OH	CH_3	**4db**	66	57
8	**2d**	**6c**	OH	*n*-Bu	**4dc**	70	67
9	**2d**[e]	**6c**	OH	*t*-Bu	**4dd**	20	21
10	**2d**[e]	**6c**	OH	Ph	**4de**	52	52
11	**2e**	**6c**	H	CH_3	**4eb**	40	60

[a]Synthesis of phenolic 12b-substituted isoindoloisoquinolines **4**. [b]Yield of isolated product. [c]Determined by chiral stationary phase HPLC. Figure in brackets indicates % ee after crystallization. [d]The reaction was carried out at −78 °C. [e]The reaction was carried out in CH_2Cl_2 at reflux.

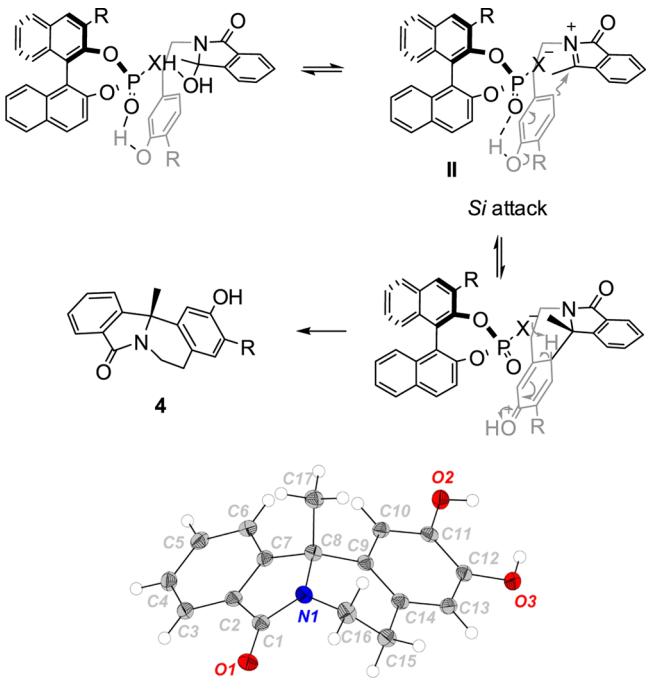


Figure 2. Proposed working model for the intramolecular α-amidoalkylation and X-ray structure of **4db**.

acyliminium intermediate/chiral conjugate base ion pair as **II** (Figure 2). It would be also consistent with the related model proposed for the intermolecular reactions, in which the coordination of the nucleophile with the catalyst through hydrogen bonding plays a crucial role.[12b,31,32] Thus, the acid would generate the chiral ion pair by protonation of the hydroxylactam. The *N*-acyliminium intermediate would be oriented in such a way to avoid the steric interactions with catalyst 3 and 3′R substituents, so the bulkiest substituent (the activated aromatic ring) would be directed toward the empty side of the catalyst oxygen and the attack of the nucleophile, in this case the internal activated aromatic ring, would occur from the Si face. In addition, in the case of phenolic hydroxylactams **2d** and **2e**, a dual activation of the substrate by the catalyst could be proposed through ion pairing and hydrogen bonding of the phenolic hydroxyl group and the oxygen of the phosphate (**II**, Figure 2). Afterward, a 6-endo-trig cyclization reaction with loss of aromaticity of the phenolic aryl ring and subsequent hydrogen elimination would lead to isoindoloisoquinoline **4**. This type of phenol activation has been proposed in related intermolecular reactions.[7d,33] The crucial role of the hydrogen-bonding activation in the stereochemical outcome of the reaction is shown in the α-amidoalkylation reaction of hydroxylactam **2b** (Table 3). In this case, the cyclization position is highly activated by two methoxyl groups; however, the directing effect of the hydrogen bonding of the phenolic hydroxyl group with the catalyst is no longer possible, resulting in high yields but with much lower enantioselectivity.

In conclusion, it has been shown that activated electron-rich aromatic rings can be efficient internal nucleophiles in the *N*-acyliminium cyclization of cyclic α-hydroxylactams derived from *N*-phenethylimides, using binol-derived phosphoric acids as catalysts. Thus, access to fused isoquinoline systems is possible, generating a new quaternary stereocenter. However, stable hydroxylactams, such as those derived from imides **2a−d**, are required to obtain good reactivity. In addition, binol-derived triflylphosphoramides **6** have been shown to be substantially more reactive than the corresponding binol-derived phosphoric acids **5**. Phenolic substitution on the aromatic ring is a determinant to achieve reasonable levels of enantioselection. Thus, a *N*-acyliminium chiral ion pair is proposed to be involved, in which the phenolic internal nucleophile would be activated through hydrogen bonding. This dual activation has been shown to be decisive for the enantioselectivity, as in the absence of phenolic groups, although the reaction proceeds with high yields, the enantioselectivity is lost. This way, C-12b-substituted phenolic isoindoloisoquinolines can be obtained in good yields and enantioselectivities up to 75%. The procedure is complementary to the intermolecular α-amidoalkylation process, as opposite enantiomers are formed, and to the Pictet−Spengler cyclization, which allows the formation of only tertiary stereocenters, and provides further evidence on the importance of dual activation between the catalyst and the substrate for these reactions.

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 or using an attenuated total reflection (ATR). 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

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resonances are supported by distortionless enhancement by polarization transfer experiments and two-dimensional correlation experiments (COSY, HSQCed, or HMBC). Mass spectra were recorded under chemical ionization (CI) at 230 eV or with an electrospray ionization (ESI^+) source. The exact mass was obtained using a time-of-flight (TOF) detector. Crystal **4db** was measured at 100 K using a Cu single-crystal diffractometer (omega scan mode) using a charge-coupled device detector. The structure was solved using SIR92 and refined with standard methods using SHELXL9 with anisotropic parameters for the nonhydrogen atoms. All hydrogens were located on the residual density map and were refined with the SHELXL97 riding model. Analysis of the absolute structure using likelihood methods was performed using PLATON (see SI for details). Thin-layer chromatography 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). Chiral stationary phase HPLC was performed using CHIRALCEL OD3, IC, ADH, or OC columns (0.46 cm × 25 cm) in isocratic elution mode, as indicated in each case. All solvents used in the reactions were anhydrous and purified according to standard procedures.[34] Organolithiums were titrated with diphenylacetic acid or *N*-benzylbenzamide periodically prior to use. Imides **1b−c**,[25e] **2a**,[27a] and **2b−e**[35] were prepared according to literature procedures. Phosphoric acids (*R*)-**5a−e** were used from commercial sources with the following purities: **5a**: 98+%; **5b**: 95%; **5c**: 95%; **5d**: >97.5%; and **5e**: 95%. Phosphoramides **6a−g** were prepared from the corresponding (*R*)-binols according to literature procedures.[29] All air- or moisture-sensitive reactions were performed under argon; the glassware was dried (130 °C) and purged with argon.

Synthesis of Racemic 3b−c and 4aa−eb. *2,3-Dimethoxy-5,12b-dihydroisoindolo[1,2-a]isoquinolin-8(6H)-one (**4aa**).* To a solution of **2a** (96.9 mg, 0.31 mmol) in EtOH/H_2O 10% (5 mL), $NaBH_4$ (84.2 mg, 2.25 mmol) was added at 0 °C. pH 9 was maintained by the addition of HCl (1 M), and the reaction mixture was stirred for 50 min. The reaction was quenched with HCl (1 M, 2 mL). The reaction mixture was extracted with dichloromethane (3 × 10 mL), and the organic phase was washed with $NaHCO_3$ (sat., 2 mL) and NaCl (sat., 2 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The obtained hydroxylactam was used in the next step without further purification. The obtained reaction crude was dissolved in dichloromethane (15 mL), and trifluoroacetyl (TFA) (0.08 mL, 1.02 mmol) was added at rt and stirred for 16 h. The reaction mixture was quenched with $NaHCO_3$ (sat., 2 mL), and the aqueous phase was extracted with dichloromethane (3 × 15 mL). The combined organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The reaction crude was purified by column chromatography (silica gel, hexane/AcOEt 4:6) to provide **4aa** (40 mg, 55%), whose characterization data are consistent with those reported:[36] IR (film) 1680 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.68−2.78 (m, 1H), 2.90−3.02 (m, 1H), 3.31−3.42 (m, 1H), 3.81 (s, 3H), 3.90 (s, 3H), 4.33−4.50 (m, 1H), 5.57 (s, 1H), 6.66 (s, 1H), 7.12 (s, 1H), 7.49 (t, J = 7.3 Hz, 1H), 7.57 (t, J = 7.3 Hz, 1H), 7.81−7.89 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 29.1, 38.2, 55.9, 56.2, 58.9, 108.4, 112.0, 123.0, 123.9, 126.0, 126.9, 128.4, 131.5, 132.7, 144.6, 147.8, 148.3, 167.9; mass spectrometry (MS) (CI) m/z (relative intensity): 296 (MH^+, 3), 295 (M^+, 23), 294 (100), 278 (10), 250 (10); high-resolution mass spectrometry (HRMS) (CI-TOF): calcd for $C_{18}H_{18}NO_3$ $[MH]^+$, 296.1287; found, 296.1281.

General Procedure for the Addition/α-Amidoalkylation Reaction: Synthesis of 3b−c and 4ab−eb. To a solution of the corresponding imide **1** or **2** (1 mmol) in dry THF (10 mL) at −78 °C, RLi (2.2 or 4 mmol) was added. The reaction mixture was stirred at −78 °C under argon for 6 h. After that, it was quenched with NH_4Cl (sat., 2 mL) and allowed to warm to rt. The aqueous phase was extracted with dichloromethane (3 × 15 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The corresponding hydroxylactam was used in the next step without further purification. To a solution of the crude solid in CH_2Cl_2 (10 mL), TFA (3 mmol) was added at rt and stirred for 16 h. The reaction mixture was quenched with $NaHCO_3$ (sat., 2 mL), and the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The reaction crude was purified by flash column chromatography to provide the pure products.

*8,10-Dimethoxy-10b-methyl-1,5,6,10b-tetrahydropyrrolo-[2,1-a]isoquinolin-3(2H)-one (**3b**).* According to the general procedure, **1b** (0.11 g, 0.42 mmol) was treated with MeLi (0.83 mL from a 1.11 M solution in Et_2O, 0.92 mmol) and then with TFA (0.1 mL, 1.23 mmol), affording pyrrolo[2,1-*a*]isoquinoline **3b** (52.4 mg, 51%) after purification by column chromatography (silica gel, hexane/EtOAc 3:7): mp (CH_2Cl_2) 109−111 °C; IR (ATR) 1687 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.49 (s, 3H), 1.92−2.04 (m, 1H), 2.29−2.38 (m, 1H), 2.47−2.7 (m, 3H), 2.82−3.03 (m, 2H), 3.76 (s, 3H), 3.79 (s, 3H), 4.24−4.3 (m, 1H), 6.21 (d, J = 0.9 Hz, 1H), 6.33 (d, J = 0.9 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 23.7, 29.3, 30.3, 33.4, 33.7, 55.1, 55.2, 60.5, 97.5, 104.6, 123.5, 134.8, 157.3, 158.9, 172.1; MS (CI) m/z (relative intensity): 262 (MH^+, 100), 261 (M^+, 1), 246 (20); HRMS (CI-TOF): calcd for $C_{15}H_{20}NO_3$ $[MH]^+$, 262.1443; found, 262.1439.

*8,9,10-Trimethoxy-10b-methyl-1,5,6,10b-tetrahydropyrrolo[2,1-a]isoquinolin-3(2H)-one (**3c**).* According to the general procedure, **1c** (0.16 g, 0.55 mmol) was treated with MeLi (1.1 mL from a 1.12 M solution in Et_2O, 1.21 mmol) and then with TFA (0.13 mL, 1.65 mmol), affording pyrrolo[2,1-*a*]isoquinoline **3c** (80.1 mg, 50%) after purification by column chromatography (silica gel, hexane/EtOAc 3:7): mp (CH_3OH) 104−106 °C; IR (ATR) 1687 cm^{-1}; ^1H NMR: ($CDCl_3$): δ 1.49 (s, 3H), 2.02−2.05 (m, 1H), 2.32−2.43 (m, 1H), 2.52−2.66 (m, 3H), 2.78−3.02 (m, 2H), 3.80 (s, 6H), 3.93 (s, 3H), 4.23−4.29 (m, 1H), 6.35 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 24.7, 28.8, 30.3, 33.4, 34.2, 55.8, 60.4, 60.5, 60.6, 107.1, 128.0, 128.2, 140.6, 150.6, 152.2, 171.9; MS (CI) m/z (relative intensity): 292 (MH^+, 100), 291 (M^+, 3), 276 (20); HRMS (CI-TOF): calcd for $C_{16}H_{22}NO_4$ $[MH]^+$, 292.1549; found, 292.1536.

*2,3-Dimethoxy-12b-methyl-5,12b-dihydroisoindolo[1,2-a]isoquinolin-8(6H)-one (**4ab**).* According to the general procedure, **2a** (0.1 g, 0.32 mmol) was treated with MeLi (0.99 mL from a 0.73 M solution in Et_2O, 0.7 mmol) and then with TFA (0.12 mL, 0.90 mmol), affording isoindolo[1,2-*a*]isoquinoline **4ab** after purification by column chromatography (silica gel, hexane/EtOAc 4:6) (65.2 mg, 63%), whose characterization data are consistent with those reported:[37] mp (hexane/EtOAc) 184−186 °C; IR (film): 1715 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.81 (s, 3H), 2.72 (dd, J = 16.1, 4.3 Hz, 1H), 2.97−3.13 (m, 1H), 3.37 (td, J = 12.1, 4.3 Hz, 1H), 3.82 (s, 3H), 3.94

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(s, 3H), 4.59−4.66 (m, 1H), 6.57 (s, 1H), 7.12 (s, 1H), 7.46 (t, J = 7.5 Hz, 1H), 7.61 (td, J = 7.5, 1.1 Hz, 1H), 7.82−7.86 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 28.9, 29.2, 35.0, 55.8, 56.2, 63.5, 109.3, 111.9, 122.0, 123.9, 125.9, 128.2, 131.0, 131.2, 131.8, 147.6, 148.2, 150.7, 167.4; MS (CI) m/z (relative intensity): 310 (MH^+, 100), 309 (M^+, 22), 295 (14), 294 (69); HRMS (CI-TOF): calcd for $C_{19}H_{20}NO_3$ $[MH]^+$, 310.1443; found, 310.1444.

*1,3-Dimethoxy-12b-methyl-5,12b-dihydroisoindolo[1,2-a]isoquinolin-8(6H)-one (**4bb**).* According to the general procedure, **2b** (0.09 g, 0.29 mmol) was treated with MeLi (0.53 mL from a 1.11 M solution in Et_2O, 0.58 mmol) and then with TFA (0.07 mL, 0.87 mmol), affording the isoindolo[1,2-*a*]isoquinoline **4bb** (47.3 mg, 53%) as an oil after purification by column chromatography (silica gel, hexane/EtOAc 3:7): IR (ATR) 1681 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.89 (s, 3H), 2.68 (dd, J = 15.6, 3.3 Hz, 1H), 3.03−3.04 (m, 1H), 3.24 (td, J = 12.6, 3.3 Hz, 1H), 3.74 (s, 3H), 3.92 (s, 3H), 4.55 (dd, J = 12.6, 5.5 Hz, 1H), 6.25 (d, J = 1.9 Hz, 1H), 6.38 (d, J = 1.9 Hz, 1H), 7.37−7.42 (m, 1H), 7.48−7.54 (m, 1H), 7.81 (d, J = 7.5 Hz, 1H), 8.18 (d, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 25.2, 31.1, 34.8, 54.9, 55.2, 64.8, 97.7, 105.5, 119.9, 123.1, 125.2, 127.9, 131.4, 131.5, 137.1, 151.1, 158.3, 158.9, 167.5; MS (CI) m/z (relative intensity): 310 (MH^+, 100), 194 (80); HRMS (CI-TOF): calcd for $C_{19}H_{20}NO_3$ $[MH]^+$, 310.1443; found, 310.1428.

*12b-Butyl-1,3-dimethoxy-5,12b-dihydroisoindolo[1,2-a]-isoquinolin-8(6H)-one (**4bc**).* According to the general procedure, imide **2b** (152 mg, 0.49 mmol) was treated with *n*-BuLi (0.8 mL from a 1.24 M solution in hexanes, 0.98 mmol) and then with TFA (0.11 mL, 1.47 mmol), affording **4bc** (90 mg, 53%) after purification by flash column chromatography (silica gel, hexane/EtOAc 3:7): mp (CH_2Cl_2) 117−119 °C; IR (ATR) 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.56−0.64 (m, 1H), 0.74 (t, J = 7.3 Hz, 3H), 0.85−0.96 (m, 1H), 1.10−1.20 (m, 2H), 1.97−2.10 (m, 1H), 2.63−2.68 (m, 1H), 2.85 (m, 1H), 3.04−3.23 (m, 2H), 3.73 (s, 3H), 3.94 (s, 3H), 4.55−4.61 (m, 1H), 6.25 (d, J = 2.3 Hz, 1H), 6.37 (d, J = 2.3 Hz, 1H), 7.39 (t, J = 7.4 Hz, 1H), 7.50 (t, J = 7.4, 1H), 7.81 (d, J = 7.4 Hz, 1H), 8.12 (d, J = 7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 13.9, 22.6, 25.3, 31.1, 34.8, 35.6, 54.9, 55.2, 68.1, 97.8, 105.7, 120.6, 123.0, 125.6, 127.9, 131.2, 132.7, 137.1, 148.9, 158.4, 158.9, 168.1; MS (CI) m/z (relative intensity): 352 (MH^+, 85), 351 (M^+, 1), 295 (21); HRMS (CI-TOF): calcd for $C_{22}H_{26}NO_3$ $[MH]^+$, 352.1913; found, 352.1908.

*12b-t-Butyl-1,3-dimethoxy-5,12b-dihydroisoindolo[1,2-a]-isoquinolin-8(6H)-one (**4bd**).* According to the general procedure, imide **2b** (169 mg, 0.54 mmol) was treated with *t*-BuLi (1.1 mL from a 0.9 M solution in pentane, 1.02 mmol) and then with TFA (0.12 mL, 1.63 mmol). The reaction crude was purified by column chromatography (silica gel, hexane/EtOAc 3:7) to afford **4bd** as an oil (94 mg, 50%): IR (ATR) 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.04 (s, 9H), 2.83 (dd, J = 16.5, 5.0 Hz, 1H), 3.01−3.08 (m, 1H), 3.42−3.51 (m, 1H), 3.74 (s, 3H), 3.90 (s, 3H), 4.70−4.76 (m, 1H), 6.26 (d, J = 2.1 Hz, 1H), 6.35 (d, J = 2.1 Hz, 1H), 7.32−7.52 (m, 2H), 7.80 (d, J = 6.6 Hz, 1H), 8.21 (d, J = 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 29.7, 30.5, 35.7, 41.4, 54.3, 55.2, 73.9, 97.4, 105.9, 118.9, 122.9, 127.8, 128.7, 130.2, 132.6, 138.2, 147.3, 158.4, 158.9, 167.3; MS (CI) m/z (relative intensity): 352 (MH^+, 48), 296 (41), 295 (39), 294 (100); HRMS (CI-TOF): calcd for $C_{22}H_{26}NO_3$ $[MH]^+$, 352.1913; found, 352.1909.

*1,2,3-Trimethoxy-12b-methyl-5,12b-dihydroisoindolo[1,2-a]isoquinolin-8(6H)-one (**4cb**).* According to the general procedure, **2c** (68.2 mg, 0.19 mmol) was treated with MeLi (0.17 mL from a 1.11 M solution in Et_2O, 0.7 mmol) and then with TFA (0.03 mL, 0.57 mmol). The reaction crude was purified by column chromatography (silica gel, hexane/EtOAc 2:8) to afford **4cb** (25.7 mg, 40%): mp (hexane/EtOAc) 187−189 °C; IR (ATR) 1685 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.90 (s, 3H), 2.64 (dd, J = 15.7, 3.5 Hz, 1H), 3.02−3.07 (m, 1H), 3.22 (td, J = 12.7, 3.5 Hz, 1H), 3.80 (s, 3H), 3.81 (s, 3H), 4.09 (s, 3H), 4.59 (dd, J = 12.7, 5.7 Hz, 1H), 6.38 (s, 1H), 7.38−7.43 (m, 1H), 7.49−7.55 (m, 1H), 7.79 (d, J = 7.5 Hz, 1H), 8.33 (d, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ 26.7, 30.8, 35.1, 55.8, 60.6, 60.7, 64.8, 107.8, 123.1, 124.6, 125.4, 128.1, 130.5, 131.4, 131.8, 140.7, 151.4, 152.4, 152.4, 167.6; MS (CI) m/z (relative intensity): 340 (MH^+, 100), 339 (M^+, 9), 325 (10), 324 (61); HRMS (CI-TOF): calcd for $C_{20}H_{22}NO_4$ $[MH]^+$, 340.1549; found, 340.1537.

*2,3-Dihydroxy-12b-methyl-5,12b-dihydroisoindolo[1,2-a]-isoquinolin-8(6H)-one (**4db**).* According to the general procedure, **2d** (0.12 g, 0.43 mmol) was treated with MeLi (1.5 mL from a 1.13 M solution in Et_2O, 1.7 mmol) at −78 °C for 2 h and then with TFA (0.09 mL, 1.29 mmol). The reaction crude was purified by column chromatography (silica gel, hexane/EtOAc 2:8) to afford **4db** as an oil (77.3 mg, 63%): IR (ATR) 3299, 1637 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD): δ 1.74 (s, 3H), 2.65 (dd, J = 15.8, 3.4 Hz, 1H), 2.76−2.93 (m, 1H), 3.40 (td, J = 12.6, 3.4 Hz, 1H), 4.43 (dd, J = 12.6, 6.2 Hz, 1H), 6.51 (s, 1H), 7.19 (s, 1H), 7.46 (t, J = 7.5 Hz, 1H), 7.63 (t, J = 7.5 Hz, 1H), 7.74 (d, J = 7.5 Hz, 1H), 7.97 (d, J = 7.5 Hz, 1H); ^{13}C NMR (75.5 MHz, CD_3OD) 27.8, 28.5, 35.6, 64.2, 112.7, 115.3, 122.6, 122.9, 123.2, 128.0, 129.6, 130.1, 132.1, 143.9, 144.4, 151.4, 168.1; MS (CI) m/z (relative intensity): 282 (MH^+, 94), 281 (M^+, 13), 267 (18), 266 (100); HRMS (CI-TOF): calcd for $C_{17}H_{16}NO_3$ $[MH]^+$, 282.1130; found, 282.1137.

*12b-Butyl-2,3-dihydroxy-5,12b-dihydroisoindolo[1,2-a]-isoquinolin-8(6H)-one (**4dc**).* According to the general procedure, **2d** (0.22 g, 0.78 mmol) was treated with *n*-BuLi (1.7 mL from a 1.8 M solution in hexanes, 3.1 mmol) at −78 °C for 2 h and then with TFA (0.18 mL, 2.3 mmol). The reaction crude was purified by column chromatography (silica gel, hexane/EtOAc 2:8) to afford **4dc** (0.18 g, 71%): mp (CH_3OH) 238−240 °C; IR (ATR) 2934, 1662 cm^{-1}; ^{1}H NMR (CD_3OD): δ 0.45−0.53 (m, 1H), 0.68 (t, J = 7.3 Hz, 3H), 0.78−0.87 (m, 1H), 1.04−1.14 (m, 2H), 2.03−2.27 (m, 2H), 2.64 (dd, J = 16.1, 3.2 Hz, 1H), 2.78−2.90 (m, 1H), 3.23−3.33 (m, 1H), 4.38−4.45 (m, 1H), 6.53 (s, 1H), 7.19 (s, 1H), 7.41 (t, J = 7.5 Hz, 1H), 7.57 (t, J = 7.5 Hz, 1H), 7.73 (d, J = 7.5 Hz, 1H), 7.88 (d, J = 7.5 Hz, 1H); ^{13}C NMR (CD_3OD): δ 11.8, 20.5, 23.7, 26.9, 33.4, 38.3, 65.7, 111.2, 113.8, 121.2, 121.3, 122.1, 126.5, 128.6, 129.8, 130.5, 142.3, 142.8, 147.9, 167.2; MS (ESI^+) m/z (relative intensity): 325 (18), 324 (MH^+, 100), 323 (M^+, 1), 267 (18), 266 (100); HRMS (ESI^+-TOF): calcd for $C_{20}H_{22}NO_3$ $[MH]^+$, 324.1600; found, 324.1602.

*12b-t-Butyl-2,3-dihydroxy-5,12b-dihydroisoindolo[1,2-a]-isoquinolin-8(6H)-one (**4dd**).* According to the general procedure, **2d** (73.6 mg, 0.24 mmol) was treated with *t*-BuLi (0.95 mL from a 1.09 M solution in pentane, 0.96 mmol) at −78 °C for 2 h and then with TFA (0.05 mL, 0.72 mmol). The reaction crude was purified by column chromatography (silica gel, hexane/EtOAc 4:6) to afford **4dd** (35.8 mg, 42%): mp (CH_3OH) 265−266 °C; IR (ATR) 2944, 1672 cm^{-1}; ^{1}H NMR

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(CD_3OD): δ 0.99 (s, 9H), 2.82−2.87 (m, 2H), 3.64−3.72 (m, 1H), 4.58−4.66 (m, 1H), 6.56 (s, 1H), 7.43 (s, 1H), 7.49 (t, J = 7.5 Hz, 1H), 7.62 (t, J = 7.5 Hz, 1H), 7.76 (d, J = 7.5 Hz, 1H), 8.06 (d, J = 7.5 Hz, 1H); ^{13}C NMR (CD_3OD): δ 26.8, 27.3, 36.2, 40.7, 71.9, 114.4, 115.2, 122.6, 125.4, 125.7, 126.0, 127.8, 130.9, 131.9, 142.9, 144.4, 148.4, 168.9; MS (ESI$^+$) m/z (relative intensity): 325 (19), 324 (MH^+, 100), 323 (M^+, 1); HRMS (ESI$^+$-TOF): calcd for $C_{20}H_{22}NO_3$ $[MH]^+$, 324.1600; found, 324.1601.

*2,3-Dihydroxy-12b-phenyl-5,12b-dihydroisoindolo[1,2-a]-isoquinolin-8(6H)-one (**4de**).* To a solution of **2d** (0.12 g, 0.42 mmol) in dry THF (10 mL), NaH (32 mg, 0.84 mmol) and phenyllithium (1.4 mL from a 0.9 M solution in Bu_2O, 1.26 mmol) were added at −78 °C under an argon atmosphere. The reaction mixture was stirred at that temperature for 2 h. The reaction mixture was quenched with NH_4Cl (sat., 2 mL) and allowed to warm to rt. The aqueous phase was extracted with dichloromethane (3 × 15 mL), and the combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The corresponding hydroxylactam was treated with TFA (0.07 mL, 0.84 mmol) according to the general procedure. After workup, the reaction crude was purified by flash column chromatography (silica gel, hexane/EtOAc 4:6) to afford **4de** (90 mg, 67%): mp (CH_3OH) 297−298 °C; IR (ATR): 2930, 1662 cm^{-1}; ^{1}H NMR (CD_3OD): δ 2.54−2.63 (m, 1H), 2.82−2.89 (m, 1H), 3.32−3.37 (m, 1H), 4.02−4.11 (m, 1H), 4.80 (b s, 2H), 6.68 (s, 1H), 6.96−6.99 (m, 2H), 7.09 (s, 1H), 7.24−7.26 (m, 3H), 7.51−7.64 (m, 3H), 7.83 (d, J = 7.5 Hz, 1H); ^{13}C NMR (CD_3OD): δ 27.1, 36.3, 70.4, 114.1, 115.4, 123.1, 124.4, 125.9, 126.6, 127.3, 127.6, 128.2, 128.3, 130.7, 131.9, 141.5, 143.4, 144.9, 150.3, 168.7; MS (ESI$^+$) m/z (relative intensity): 345 (20), 344 (MH^+, 100), 343 (M^+, 1); HRMS (ESI$^+$-TOF): calcd for $C_{22}H_{18}NO_3$ $[MH]^+$, 344.1287; found, 344.1289.

*3-Hydroxy-12b-methyl-5,12b-dihydroisoindolo[1,2-a]-isoquinolin-8(6H)-one (**4eb**).* According to the general procedure, **2e** (99.6 mg, 0.42 mmol) was treated with MeLi (1.6 mL from a 1.1 M solution in Et_2O, 1.68 mmol) for 2 h and then with TFA (0.10 mL, 1.26 mmol). The reaction crude was purified by flash column chromatography (silica gel, hexane/EtOAc 1:9) to afford **4eb** (18.4 mg, 60%): mp (hexane) 237−239 °C; IR (ATR) 3236, 1663 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.76 (s, 3H), 2.67 (dd, J = 16.4, 3.1 Hz, 1H), 2.91−2.98 (m, 1H), 3.27−3.48 (m, 1H), 4.52−4.56 (m, 1H), 6.35 (bs, 1H), 6.61 (d, J = 2.0 Hz, 1H), 6.81 (dd, J = 8.4, 2.0 Hz, 1H), 7.42 (t, J = 7.5 Hz, 1H), 7.51 (d, J = 8.4 Hz, 1H), 7.58 (t, J = 7.5 Hz, 1H), 7.82−7.84 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 29.0, 29.9, 35.1, 64.2, 114.5, 115.9, 122.4, 123.9, 127.1, 128.3, 130.1, 130.6, 132.1, 134.5, 151.1, 155.7, 168.1; MS (CI) m/z (relative intensity): 266 (MH^+, 100), 265 (M^+, 2), 251 (13), 250 (95); HRMS (CI-TOF): calcd for $C_{17}H_{16}NO_2$ $[MH]^+$, 266.1181; found, 266.1177.

Synthesis of Enantioenriched 3b−c, 4aa−eb. *(R)-8,10-Dimethoxy-10b-methyl-1,5,6,10b-tetrahydropyrrolo[2,1-a]-isoquinolin-3(2H)-one (**3b**).* To a solution of **1b** (0.06 g, 0.23 mmol) in dry THF, MeLi (0.40 mL from a 1.13 M solution in Et_2O, 0.46 mmol) was added at −78 °C. The reaction was stirred at the same temperature for 6 h under argon. NH_4Cl (sat., 2 mL) was added and the reaction mixture was warmed to rt. The aqueous phase was extracted with dichloromethane (3 × 15 mL), and the combined organic phase was dried over Na_2SO_4 and concentrated in vacuo. The crude solid was dissolved in toluene (5 mL), and phosphoric acid **5d** (35 mg, 0.046 mmol, 20 mol %) was added at rt. The reaction mixture was stirred for 16 h at reflux, and the reaction mixture was quenched with $NaHCO_3$ (sat., 2 mL), and the aqueous phase was extracted with dichloromethane (3 × 15 mL). The combined organic phase was dried over Na_2SO_4 and concentrated under vacuum. The reaction crude was purified by column chromatography (silica gel, hexane/EtOAc 3:7) to afford **3b** (35 mg, 59%): $[\alpha]_D^{20}$ = +10.2 (c 0.62, $CHCl_3$). The enantiomeric excess was determined by HPLC to be 8% (Table S1, entry 4) [CHIRALCEL OD3, 5% hexane/2-propanol, 1 mL/min, t_R (R) = 19.2 min (53.87%), t_R (S) = 23.1 min (46.13%)].

*(R)-8,9,10-Trimethoxy-10b-methyl-1,5,6,10b-tetrahydropyrrolo[2,1-a]isoquinolin-3(2H)-one (**3c**).* To a solution of **1c** (0.06 g, 0.20 mmol) in dry THF, MeLi (0.36 mL from a 1.13 M solution in Et_2O, 0.41 mmol) was added at −78 °C. The reaction was stirred at the same temperature for 6 h under argon. NH_4Cl (sat., 2 mL) was added, and the reaction mixture was warmed to rt. The aqueous phase was extracted with dichloromethane (3 × 15 mL), and the organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude solid was dissolved in dichloromethane (5 mL), and phosphoric acid **5d** (31 mg, 0.04 mmol, 20 mol %) was added at rt. The reaction mixture was heated to reflux and stirred for 72 h at the same temperature. The reaction mixture was quenched with $NaHCO_3$ (sat., 2 mL), and the aqueous phase was extracted with dichloromethane (3 × 15 mL). The combined organic phase was dried over Na_2SO_4 and concentrated under vacuum. The reaction crude was purified by column chromatography (silica gel, hexane/EtOAc 3:7) to afford **3c** (41.3 mg, 50%): $[\alpha]_D^{20}$ = −39.4 (c 0.45, $CHCl_3$). The enantiomeric excess was determined by HPLC to be 14% (Table S1, entry 14) [CHIRALCEL OD3, 5% hexane/2-propanol, 1 mL/min, t_R (S) = 23.4 min (43.08%), t_R (R) = 25.6 min (56.92%)].

*(S)-2,3-Dimethoxy-5,12b-dihydroisoindolo[1,2-a]-isoquinolin-8(6H)-one (**4aa**).* To a solution of **2a** (32.5 mg, 0.11 mmol) in EtOH/H_2O, 10% (5 mL) $NaBH_4$ (32.1 mg, 0.73 mmol) was added at 0 °C. pH 9 was maintained by the addition of HCl (1 M) and the reaction mixture was stirred for 50 min. The reaction was quenched with HCl 1 M (2 mL). The reaction mixture was extracted with dichloromethane (3 × 10 mL), and the organic phase was washed with $NaHCO_3$ (sat., 2 mL) and NaCl (sat., 2 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The obtained hydroxylactam was used in the next step without further purification. The obtained reaction crude was dissolved in toluene (10 mL), and **5d** (14.3 mg, 0.02 mmol) was added at rt and stirred for 2 h at reflux. The reaction mixture was quenched with $NaHCO_3$ (sat., 2 mL), and the aqueous phase was extracted with dichloromethane (3 × 15 mL). The combined organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The reaction crude was purified by column chromatography (silica gel, hexane/AcOEt 4:6) to provide **4aa** (28.6 g, 74%): $[\alpha]_D^{20}$ = −15.3 (c 0.5, $CHCl_3$). The enantiomeric excess was determined by HPLC to be 25% (Table 1, entry 7) [CHIRALCEL OC, 10% hexane/2-propanol, 1 mL/min, t_R (S) = 46.3 min (62.29%), t_R (R) = 79.8 min (37.71%)].

*(R)-1,3-Dimethoxy-12b-methyl-5,12b-dihydroisoindolo-[1,2-a]isoquinolin-8(6H)-one (**4bb**).* To a solution of **2b** (0.1 g, 0.32 mmol) in dry THF, MeLi (0.56 mL from a 1.13 M solution in Et_2O, 0.64 mmol) was added at −78 °C. The reaction was stirred at the same temperature for 6 h under argon. NH_4Cl (sat., 2 mL) was added, and the reaction mixture

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was warmed to rt. The aqueous phase was extracted with dichloromethane (3 × 15 mL), and the organic phase was dried over Na_2SO_4 and concentrated in vacuo. The crude solid was dissolved in toluene (7 mL), and phosphoric acid **5d** (51 mg, 0.06 mmol, 20 mol %) was added at rt. The reaction mixture was heated to reflux and stirred for 36 h at same temperature. The reaction mixture was quenched with $NaHCO_3$ (sat., 2 mL), and the aqueous phase was extracted with dichloromethane (3 × 15 mL). The combined organic phase was dried over Na_2SO_4 and concentrated under vacuum. The reaction crude was purified by column chromatography (silica gel, hexane/EtOAc 3:7) to afford **4bb** (32.6 mg, 33%): $[\alpha]_D^{20}$ = +44.1 (*c* 1, $CHCl_3$). The enantiomeric excess was determined by HPLC to be 27% (Table 2, entry 7) [CHIRALCEL OD3, 5% hexane/2-propanol, 1 mL/min, t_R (*R*) = 15.5 min (63.56%), t_R (*S*) = 20.6 min (36.44%)].

*(R)-12b-Butyl-2,3-dimethoxy-5,12b-dihydroisoindolo[1,2-a]isoquinolin-8(6H)-one (**4bc**).* To a solution of **2b** (0.1 g, 0.32 mmol) in dry THF, BuLi (0.49 mL from a 1.24 M solution in hexanes, 0.64 mmol) was added at −78 °C. The reaction was stirred at the same temperature for 6 h under argon. NH_4Cl (sat., 2 mL) was added, and the reaction mixture was warmed to rt. The aqueous phase was extracted with dichloromethane (3 × 15 mL), and the organic phase was dried over Na_2SO_4 and concentrated in vacuo. The crude solid was dissolved in toluene (7 mL), and phosphoric acid **5d** (49 mg, 0.06 mmol, 20 mol %) was added at rt. The reaction mixture was heated to reflux and stirred for 36 h at the same temperature. The reaction mixture was quenched with $NaHCO_3$ (sat., 2 mL), and the aqueous phase was extracted with dichloromethane (3 × 15 mL). The combined organic phase was dried over Na_2SO_4 and concentrated under vacuum. The reaction crude was purified by column chromatography (silica gel, hexane/EtOAc 3:7) to afford **4bc** (34 mg, 30%): $[\alpha]_D^{20}$ = +2.4 (*c* 0.5, $CHCl_3$). The enantiomeric excess was determined by HPLC to be 7% (Table 2, entry 11) [CHIRALCEL OD3, 5% hexane/2-propanol, 1 mL/min, t_R (*R*) = 11.0 min (53.62%), t_R (*S*) = 13.9 min (46.38%)].

*(R)-12b-t-Butyl-1,3-dimethoxy-5,12b-dihydroisoindolo-[1,2-a]isoquinolin-8(6H)-one (**4bd**).* To a solution of **2b** (0.1 g, 0.32 mmol) in dry THF, *t*-BuLi (0.67 mL from a 0.96 M solution in pentane, 0.64 mmol) was added at −78 °C. The reaction was stirred at the same temperature for 6 h under argon. NH_4Cl (sat., 2 mL) was added, and the reaction mixture was warmed to rt. The aqueous phase was extracted with dichloromethane (3 × 15 mL), the combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude solid was dissolved in toluene (7 mL), and phosphoric acid **5d** (49 mg, 0.06 mmol, 20 mol %) was added at rt. The reaction mixture was heated to reflux and stirred for 36 h at the same temperature. The reaction mixture was quenched with $NaHCO_3$ (sat., 2 mL), and the aqueous phase was extracted with dichloromethane (3 × 15 mL), and the combined organic phase was dried over Na_2SO_4 and concentrated under pressure. The reaction crude was purified by column chromatography (silica gel, hexane/EtOAc 3:7) to afford **4bd** (12 mg, 10%): $[\alpha]_D^{20}$ = −7.6 (*c* 0.5, $CHCl_3$). The enantiomeric excess was determined by HPLC to be 16% (Table 2, entry 12) [CHIRALCEL OD3, 5% hexane/2-propanol, 1 mL/min, t_R (*R*) = 12.4 min (58.05%), t_R (*S*) = 22.8 min (41.95%)].

*(R)-1,2,3-Trimethoxy-12b-methyl-5,12b-dihydroisoindolo-[1,2-a]isoquinolin-8(6H)-one (**4cb**).* To a solution of **2c** (78.4 mg, 0.23 mmol) in dry THF (10 mL), MeLi (0.41 mL from a 1.13 M solution in Et_2O, 0.46 mmol) was added at −78 °C. The reaction was stirred at the same temperature for 6 h under argon. NH_4Cl (sat., 2 mL) was added, and the reaction mixture was warmed to rt. The aqueous phase was extracted with dichloromethane (3 × 15 mL), and the organic phase was dried over Na_2SO_4 and concentrated in vacuo. The crude solid was dissolved in acetonitrile (7 mL), and phosphoric acid **5e** (36 mg, 0.04 mmol, 20 mol %) was added at rt. The reaction mixture was heated to reflux, stirred for 16 h at same temperature. The reaction mixture was quenched with $NaHCO_3$ (sat., 2 mL), and the aqueous phase was extracted with dichloromethane (3 × 15 mL). The combined organic phase was dried over Na_2SO_4 and concentrated under vacuum. The reaction crude was purified by column chromatography (silica gel, hexane/EtOAc 2:8) to afford **4cb** (49 mg, 63%): $[\alpha]_D^{20}$ = −6.8 (*c* 0.8, $CHCl_3$). The enantiomeric excess was determined by HPLC to be 11% (Table 2, entry 15) [CHIRALCEL OD3, 5% hexane/2-propanol, 1 mL/min, t_R (*S*) = 22.3 min (44.44%), t_R (*R*) = 28.2 min (55.56%)].

*(S)-2,3-Dihydroxy-12b-methyl-5,12b-dihydroisoindolo-[1,2-a]isoquinolin-8(6H)-one (**4db**).* To a solution of **2d** (0.06 g, 0.21 mmol) in dry THF (10 mL), MeLi (0.74 mL from a 1.13 M solution in Et_2O, 0.84 mmol) was added at −78 °C. The reaction was stirred at the same temperature for 2 h under argon. NH_4Cl (sat., 2 mL) was added, and the reaction mixture was warmed to rt. The aqueous phase was extracted with dichloromethane (3 × 15 mL), and the organic phase was dried over Na_2SO_4 and concentrated in vacuo. The crude solid was dissolved in THF (5 mL), and NTPA **6c** (35 mg, 0.042 mmol, 20 mol %) was added at −20 °C. The reaction mixture was stirred for 16 h at the same temperature. The reaction mixture was quenched with $NaHCO_3$ (sat., 2 mL), and the aqueous phase was extracted with dichloromethane (3 × 15 mL). The combined organic phase was dried over Na_2SO_4 and concentrated under pressure. The reaction crude was purified by column chromatography (silica gel, hexane/EtOAc 2:8) to afford **4db** as an oil (46 mg, 78%): $[\alpha]_D^{20}$ = +123.3 (*c* 0.49, CH_3OH). The enantiomeric excess was determined by HPLC to be 63% (Table 5, entry 4) [CHIRALCEL IC, 10% hexane/2-propanol, 1 mL/min, t_R (*S*) = 58.3 min (81.63%), t_R (*R*) = 74.4 min (18.37%)]. The ee improved to 75% after recrystallization from CH_2Cl_2.

*(S)-12b-Butyl-2,3-dihydroxy-5,12b-dihydroisoindolo[1,2-a]isoquinolin-8(6H)-one (**4dc**).* To a solution of **2d** (56 g, 0.19 mmol) in dry THF (10 mL), *n*-BuLi (0.42 mL from a 1.8 M solution in pentane, 0.76 mmol) was added at −78 °C. The reaction was stirred at the same temperature for 2 h under argon. The reaction mixture was quenched with NH_4Cl (sat., 2 mL) and was allowed to warm to rt. The aqueous phase was extracted with dichloromethane (3 × 15 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The crude solid was dissolved in THF (5 mL), and NTPA **6c** (31.6 mg, 0.038 mmol, 20 mol %) was added at −20 °C. The reaction mixture was stirred for 16 h at the same temperature. The reaction mixture was quenched with $NaHCO_3$ (sat., 2 mL), and the aqueous phase was extracted with dichloromethane (3 × 15 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The reaction crude was purified by column chromatography (silica gel, hexane/EtOAc 2:8) to afford **4dc** as a solid (42 mg, 70%): $[\alpha]_D^{20}$ = −62.7 (*c* 0.35, CH_3OH). The enantiomeric excess was determined by HPLC to be 67% (Table 5, entry 8) [CHIRALCEL IC, 10% hexane/2-propanol,

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1 mL/min, t_R (*S*) = 49.3 min (83.30%), t_R (*R*) = 57.2 min (16.70%)].

*(S)-t-Butyl-2,3-dihydroxy-5,12b-dihydroisoindolo[1,2-a]-isoquinolin-8(6H)-one (**4dd**).* To a solution of **2d** (60 mg, 0.2 mmol) in dry THF (10 mL), *t*-BuLi (0.45 mL from a 1.8 M solution in pentane, 0.81 mmol) was added at −78 °C. The reaction was stirred at the same temperature for 2 h under argon. The reaction mixture was quenched with NH_4Cl (sat., 2 mL), and allowed to warm to rt. The aqueous phase was extracted with dichloromethane (3 × 15 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The crude solid was dissolved in CH_2Cl_2 (5 mL), and NTPA **6c** (31.6 mg, 0.038 mmol, 20 mol %) was added at rt. The reaction mixture was stirred for 48 h at reflux. The reaction mixture was quenched with $NaHCO_3$ (sat., 2 mL), and the aqueous phase was extracted with dichloromethane (3 × 15 mL), and the combined organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The reaction crude was purified by column chromatography (silica gel, hexane/EtOAc 2:8) to afford **4dd** as a solid (13 mg, 20%): $[\alpha]_D^{20}$ = −10.9 (*c* 0.45, CH_3OH). The enantiomeric excess was determined by HPLC to be 21% (Table 5, entry 9) [CHIRALCEL ADH, 10% hexane/2-propanol, 1 mL/min, t_R (*S*) = 43.7 min (60.42%), t_R (*R*) = 181.4 min (39.58%)].

*(S)-2,3-Dihydroxy-12b-phenyl-5,12b-dihydroisoindolo[1,2-a]isoquinolin-8(6H)-one (**4de**).* To a solution of **2d** (62 g, 0.22 mmol) in dry THF (10 mL), NaH (16 mg, 0.44 mmol) and phenyllithium (0.97 mL from a 0.9 M solution in Bu_2O, 0.88 mmol) were added at −78 °C under an argon atmosphere. The reaction mixture was stirred at that temperature for 2 h. Then, the reaction mixture was quenched with NH_4Cl (sat., 2 mL) and allowed to warm to rt. The aqueous phase was extracted with dichloromethane (3 × 15 mL), and the combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The corresponding hydroxylactam was used in the next step without further purification. The crude solid was dissolved in CH_2Cl_2 (5 mL), and NTPA **6c** (36.6 mg, 0.044 mmol, 20 mol %) was added at rt. The reaction mixture was heated to reflux and stirred for 24 h. After that time, the reaction was quenched with $NaHCO_3$ (sat., 2 mL), the aqueous phase was extracted with dichloromethane (3 × 15 mL), and the combined organic phase was dried over Na_2SO_4 and concentrated in vacuo. The reaction crude was purified by flash column chromatography (silica gel, hexane/EtOAc 4:6) to afford **4de** as a solid (39.2 mg, 52%): $[\alpha]_D^{20}$ = +36.5 (*c* 0.22, CH_2Cl_2). The enantiomeric excess was determined by HPLC to be 52% (Table 5, entry 10) [CHIRALCEL IC, 10% hexane/2-propanol, 1 mL/min, t_R (*S*) = 53.7 min (76.17%), t_R (*R*) = 70.1 min (23.83%)].

*(S)-3-Hydroxy-12b-methyl-5,12b-dihydroisoindolo[1,2-a]-isoquinolin-8(6H)-one (**4eb**).* To a solution of imide **2e** (63 mg, 0.24 mmol) in dry THF (5 mL), MeLi (0.86 mL from a 1.1 M solution in Et_2O, 0.95 mmol) was added dropwise at −78 °C. The reaction was stirred at the same temperature for 2 h. The reaction was quenched by addition of NH_4Cl (sat., 2 mL) and the reaction mixture was allowed to warm to rt. The aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The crude solid was dissolved in THF (5 mL), and NTPA **6c** (39.8 mg, 0.048 mmol, 20 mol %) was added at rt. The reaction mixture was stirred for 48 h at the same temperature. The reaction mixture was quenched with $NaHCO_3$ (sat., 2 mL), and the aqueous phase was extracted with dichloromethane (3 × 15 mL). The combined organic phase was dried over Na_2SO_4 and concentrated under vacuum. The reaction crude was purified by flash column chromatography (silica gel, hexane/EtOAc 2:8) to afford **4eb** as a solid (25.2 mg, 40%): $[\alpha]_D^{20}$ = −40.3 (*c* 0.6, CH_2Cl_2). The enantiomeric excess was determined by HPLC to be 60% (Table 5, entry 11) [CHIRALCEL IC, 10% hexane/2-propanol, 1 mL/min, t_R (*S*) = 37.8 min (79.75%), t_R (*R*) = 53.4 min (20.25%)].

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.7b00170.

Additional details on the cyclization reactions of **1b** and **1c**; additional optimization of reaction conditions for **2d**; chiral stationary phase HPLC chromatograms; X-ray structure determination of **4db** (CCDC 1510852); copies of ^1H and ^{13}C NMR spectra of compounds **3** and **4** (PDF)

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

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Takemoto, Y. Development of chiral thiourea catalysts and its application to asymmetric catalytic reactions. *Chem. Pharm. Bull.* **2010**, *58*, 593−601. (b) Siau, W.-Y.; Wang, J. Asymmetric organocatalytic reactions by bifunctional amine-thioureas. *Catal. Sci. Technol.* **2011**, *1*, 1298−1310. (c) Marqués-López, E.; Herrera, R. P. Hydrogen Bonds as an Alternative Activation. In *New Strategies in Chemical Synthesis and Catalysis*; Pignataro, B., Ed.; Wiley-VCH: Weinheim, 2012; pp 175−199. (d) Jakab, G.; Schreiner, P. R. Brønsted Acids: Chiral (Thio)urea Derivatives. In *Comprehensive Enantioselective Organocatalysis*; Dalko, P. I., Ed.; Wiley-VCH: Weinheim, 2013; Vol. *2*, pp 315−341. (e) Narayanaperumal, S.; Rivera, D. G.; Silva, R. C.; Paixão, M. W. Terpene-derived bifunctional thioureas in asymmetric organocatalysis. *ChemCatChem* **2013**, *5*, 2756−2773. (f) Serdyuk, O. V.; Heckel, C. M.; Tsogoeva, S. B. Bifunctional primary amine-thioureas in asymmetric organocatalysis. *Org. Biomol. Chem.* **2013**, *11*, 7051−7071.

(2) (a) Kampen, D.; Reisinger, C. M.; List, B. Chiral Brønsted acids for asymmetric organocatalysis. *Top. Curr. Chem.* **2010**, *291*, 395−456. (b) Zamfir, A.; Schenker, S.; Freund, M.; Tsogoeva, S. B. Chiral BINOL-derived phosphoric acids: privileged Brønsted acid organocatalysts for C−C bond formation reactions. *Org. Biomol. Chem.* **2010**, *8*, 5262−5276. (c) Mori, K.; Akiyama, T. Brønsted Acids: Chiral Phosphoric Acid Catalysts in Asymmetric Synthesis. In *Comprehensive*

DOI: 10.1021/acsomega.7b00170
ACS Omega 2017, 2, 2706−2718

Enantioselective Organocatalysis; Dalko, P. I., Ed.; Wiley-VCH: Weinheim, 2013; Vol. 2, pp 289−314. (d) Terada, M.; Momiyama, N. Phosphoric Acid Catalysis of Reactions not Involving Imines. In *Science of Synthesis, Asymmetric Organocatalysis*; List, B., Maruoka, K., Eds.; Thieme: Stuttgart, 2012; Vol. 2, pp 219−278. (e) Zhao, R.; Shi, L. Promising combination for asymmetric organocatalysis: Brønsted acid-assisted chiral phosphoric acid catalysis. *ChemCatChem* **2014**, *6*, 3309−3311. (f) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. Complete field guide to asymmetric BINOL-phosphate derived Brønsted acid and metal catalysis: history and classification by mode of activation; Brønsted acidity, hydrogen bonding, ion pairing, and metal phosphates. *Chem. Rev.* **2014**, *114*, 9047−9153.

(3) (a) Speckamp, W. N.; Hiemstra, H. Intramolecular reactions of *N*-acyliminium intermediates. *Tetrahedron* **1985**, *41*, 4367−4416. (b) Speckamp, W. N.; Moolenaar, M. J. New developments in the chemistry of *N*-acyliminium ions and related intermediates. *Tetrahedron* **2000**, *56*, 3817−3856. (c) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. Cyclizations of *N*-acyliminium ions. *Chem. Rev.* **2004**, *104*, 1431−1628. (d) Yazici, A.; Pyne, S. G. Intermolecular addition reactions of *N*-acyliminium ions (Part II). *Synthesis* **2009**, 513−541. (e) Martínez-Estibalez, U.; Gómez-SanJuan, A.; García-Calvo, O.; Aranzamendi, E.; Lete, E.; Sotomayor, N. Strategies based on aryllithium and *N*-acyliminium ion cyclizations for the stereocontrolled synthesis of alkaloids and related systems. *Eur. J. Org. Chem.* **2011**, 3610−3633. (f) Mazurkiewicz, R.; Pazdzierniok-Holewa, A.; Adamek, J.; Zielinska, K. α-Amidoalkylating agents: structure, synthesis, reactivity and application. *Adv. Heterocycl. Chem.* **2014**, *111*, 43−94.

(4) (a) Lee, Y. S.; Alam, M.; Keri, R. S. Enantioselective reactions of *N*-acyliminium ions using chiral organocatalysts. *Chem. − Asian J.* **2013**, *8*, 2906−2919. (b) Kataja, A. O.; Masson, G. Imine and iminium precursors as versatile intermediates in enantioselective organocatalysis. *Tetrahedron* **2014**, *70*, 8783−8815. (c) Huang, Y.-Y.; Cai, C.; Yang, X.; Lv, Z.-C.; Schneider, U. Catalytic asymmetric reactions with *N*,*O*-aminals. *ACS Catal.* **2016**, *6*, 5747−5763.

(5) (a) . Bandini, M., Umani-Ronchi, A., Eds. *Catalytic Asymmetric Friedel−Crafts Alkylations*; Wiley-VCH: Weinheim, 2009. (b) You, S.-L.; Cai, Q.; Zeng, M. Chiral Brønsted acid catalyzed Friedel−Crafts alkylation reactions. *Chem. Soc. Rev.* **2009**, *38*, 2190−2201. (c) Terrasson, V.; de Figueiredo, R. M.; Campagne, J. M. Organocatalyzed asymmetric Friedel−Crafts reactions. *Eur. J. Org. Chem.* **2010**, 2635−2655. (d) Zeng, M.; You, S.-L. Asymmetric Friedel−Crafts alkylation of indoles. The control of enantio- and regioselectivity. *Synlett* **2010**, 1289−1301. (e) de Figueiredo, R. M.; Campagne, J. M. Organocatalyzed Asymmetric Arylation and Heteroarylation Reactions. In *Comprehensive Enantioselective Organocatalysis*; Dalko, P. I., Ed.; Wiley-VCH: Weinheim, 2013; Vol. 3, pp 1043−1066. (f) Beletskaya, I. P.; Averin, A. D. Asymmetric Friedel−Crafts reactions of indole and its derivatives. *Curr. Organocatal.* **2015**, *3*, 60−83.

(6) (a) Taylor, M. S.; Jacobsen, E. N. Highly enantioselective catalytic acyl-Pictet-Spengler reactions. *J. Am. Chem. Soc.* **2004**, *126*, 10558−10559. (b) Klausen, R. S.; Jacobsen, E. N. Weak Brønsted acid-thiourea co-catalysis: enantioselective, catalytic protio-Pictet-Spengler reactions. *Org. Lett.* **2009**, *11*, 887−890. (c) Lee, Y.; Klausen, R. S.; Jacobsen, E. N. Thiourea-catalyzed enantioselective iso-Pictet-Spengler reactions. *Org. Lett.* **2011**, *13*, 5564−5567.

(7) (a) Pulka, K. Pictet-Spengler reactions for the synthesis of pharmaceutically relevant heterocycles. *Curr. Opin. Drug Discovery Dev.* **2010**, *13*, 669−684. (b) Stöckigt, J.; Antonchick, A. P.; Wu, F.; Waldmann, H. The Pictet-Spengler reaction in nature and in organic chemistry. *Angew. Chem., Int. Ed.* **2011**, *50*, 8538−8564. (c) Ingallina, C.; D'Acquarica, I.; Delle Monache, G.; Ghirga, F.; Quaglio, D.; Ghirga, P.; Berardozzi, S.; Markovic, V.; Botta, B. The Pictet Spengler reaction still on stage. *Curr. Pharm. Des.* **2016**, *22*, 1808−1850. (d) Das, S.; Liu, L.; Zheng, Y.; Alachraf, M. W.; Thiel, W.; De, C. K.; List, B. Nitrated confined imidodiphosphates enable a catalytic asymmetric oxa-Pictet-Spengler reaction. *J. Am. Chem. Soc.* **2016**, *138*, 9429−9432.

(8) (a) Raheem, I. T.; Thiara, P. S.; Peterson, E. A.; Jacobsen, E. N. Enantioselective Pictet-Spengler-type cyclizations of hydroxylactams: H-bond donor catalysis by anion binding. *J. Am. Chem. Soc.* **2007**, *129*, 13404−13405. (b) Raheem, I. T.; Thiara, P. S.; Jacobsen, E. N. Regio- and enantioselective catalytic cyclization of pyrroles onto *N*-acyliminium ions. *Org. Lett.* **2008**, *10*, 1577−1580.

(9) Knowels, R. R.; Lin, S.; Jacobsen, E. N. Enantioselective thiourea-catalyzed cationic polycyclizations. *J. Am. Chem. Soc.* **2010**, *132*, 5030−5032.

(10) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. Enantioselective Mannich-type reaction catalyzed by a chiral Brønsted acid. *Angew. Chem., Int. Ed.* **2004**, *43*, 1566−1568.

(11) Uraguchi, D.; Terada, M. Chiral Brønsted acid-catalyzed direct Mannich reactions via electrophilic activation. *J. Am. Chem. Soc.* **2004**, *126*, 5356−5357.

(12) (a) Sunoj, R. B. Transition State Models for Understanding the Origin of Chiral Induction in Asymmetric Catalysis. *Acc. Chem. Res.* **2016**, *49*, 1019−1028. (b) Reid, J. P.; Simón, L.; Goodman, J. M. A practical guide for predicting the stereochemistry of bifunctional phosphoric acid catalyzed reactions of imines. *Acc. Chem. Res.* **2016**, *49*, 1029−1041.

(13) (a) Seayad, J.; Seayad, A. M.; List, B. Catalytic asymmetric Pictet-Spengler reaction. *J. Am. Chem. Soc.* **2006**, *128*, 1086−1087. (b) Sewgobind, N. V.; Wanner, M. J.; Ingemann, S.; de Gelder, R.; van Maarseveen, J. H.; Hiemstra, H. Enantioselective BINOL-phosphoric acid catalyzed Pictet-Spengler reactions of *N*-benzyltryptamine. *J. Org. Chem.* **2008**, *73*, 6405−6408. (c) Wanner, M. J.; Boots, R. N. A.; Eradus, B.; de Gelder, R.; van Maarseveen, J. H.; Hiemstra, H. Organocatalytic enantioselective total synthesis of (−)-arboricine. *Org. Lett.* **2009**, *11*, 2579−2581. (d) Wanner, M. J.; Claveau, E.; van Maarseveen, J. H.; Hiemstra, H. Enantioselective syntheses of *Corynanthe* alkaloids by chiral Bronsted acid and palladium catalysis. *Chem. − Eur. J.* **2011**, *17*, 13680−13683. (e) Badillo, J. J.; Silva-García, A.; Shupe, B. H.; Fettinger, J. C.; Franz, A. K. Enantioselective Pictet-Spengler reactions of isatins for the synthesis of spiroindolones. *Tetrahedron Lett.* **2011**, *52*, 5550.

(14) Wanner, M. J.; van der Haas, R. N. S.; de Cuba, K. R.; van Maarseveen, J. H.; Hiemstra, H. Catalytic asymmetric Pictet-Spengler reactions via sulfenyliminium ions. *Angew. Chem., Int. Ed.* **2007**, *46*, 7485−7487.

(15) (a) Mons, E.; Wanner, M. J.; Ingemann, S.; van Maarseveen, J. H.; Hiemstra, H. Organocatalytic enantioselective Pictet-Spengler reactions for the syntheses of 1-substituted 1,2,3,4-tetrahydroisoquinolines. *J. Org. Chem.* **2014**, *79*, 7380−7390. (b) Ruiz-Olalla, A.; Würdemann, M. A.; Wanner, M. J.; Ingemann, S.; van Maarseveen, J. H.; Hiemstra, H. Organocatalytic enantioselective Pictet-Spengler approach to biologically relevant 1-benzyl-1,2,3,4-tetrahydroisoquinoline alkaloids. *J. Org. Chem.* **2015**, *80*, 5125−5132. (c) Kayhan, J.; Wanner, M. J.; Ingemann, S.; van Maarseveen, J. H.; Hiemstra, H. Consecutive Pictet-Spengler condensations toward bioactive 8-benzylprotoberberines: Highly selective total syntheses of (+)-Javaberine A, (+)-Javaberine B, and (−)-Latifolian A. *Eur. J. Org. Chem.* **2016**, 3705−3708.

(16) Muratore, M. E.; Holloway, C. A.; Pilling, A. W.; Storer, R. I.; Trevitt, G.; Dixon, D. J. Enantioselective Brønsted acid-catalyzed *N*-acyliminium cyclization cascades. *J. Am. Chem. Soc.* **2009**, *131*, 10796−10797.

(17) Holloway, C. A.; Muratore, M. E.; Storer, R. I.; Dixon, D. J. Direct enantioselective Brønsted Acid catalyzed *N*-acyliminium cyclization cascades of tryptamines and ketoacids. *Org. Lett.* **2010**, *12*, 4720−4723.

(18) (a) Cai, Q.; Liang, X.-W.; Wang, S.-G.; Zhang, J.-W.; Zhang, X.; You, S.-L. Ring-closing metathesis/isomerization/Pictet−Spengler cascade via ruthenium/chiral phosphoric acid sequential catalysis. *Org. Lett.* **2012**, *14*, 5022−5025. (b) Gregory, A. W.; Jakubec, P.; Turner, P.; Dixon, D. J. Gold and BINOL-phosphoric acid catalyzed enantioselective hydroamination/*N*-sulfonyliminium cyclization cascade. *Org. Lett.* **2013**, *15*, 4330−4333.

DOI: 10.1021/acsomega.7b00170
ACS Omega 2017, 2, 2706−2718

(19) (a) Chrzanowska, M.; Rozwadowska, M. D. Asymmetric synthesis of isoquinoline alkaloids. *Chem. Rev.* **2004**, *104*, 3341−3370. (b) Chrzanowska, M.; Grajewska, A.; Rozwadowska, M. D. Asymmetric synthesis of isoquinoline alkaloids: 2004−2015. *Chem. Rev.* **2016**, *116*, 12369−12465.
(20) (a) Scott, J. D.; Williams, R. M. Chemistry and biology of the tetrahydroisoquinoline antitumor antibiotics. *Chem. Rev.* **2002**, *102*, 1669−1730. (b) Bentley, K. W. *β*-Phenylethylamines and the isoquinoline alkaloids. *Nat. Prod. Rep.* **2006**, *23*, 444−463. (c) . Antkiewicz-Michaluk, L., Rommelspacher, H., Eds. *Isoquinolines and β-Carbolines as Neurotoxins and Neuroprotectants: New Vistas in Parkinson's Disease Therapy, Current Topics in Neurotoxicity*; Springer: New York, 2012. (d) Singh, I. P.; Shah, P. Tetrahydroisoquinolines in therapeutics: a patent review (2010−2015). *Expert Opin. Ther. Pat.* **2017**, *27*, 17−36.
(21) Pässler, U.; Knöller, H. J. The pyrrolo[2,1-*a*]isoquinoline alkaloids. In *The Alkaloids: Chemistry and Biology*; Knöller, H. J., Ed.; Elsevier: San Diego, CA, 2011; Vol. *70*, pp 79−151.
(22) Wang, R. F.; Yang, X. W.; Ma, C. M.; Cai, S. Q.; Li, J. N.; Shoyama, Y. A bioactive alkaloid from the flowers of *Trollius chinensis*. *Heterocycles* **2004**, *63*, 1443−1448.
(23) Yang, Z.; Liu, C.; Xiang, L.; Zheng, Y. Phenolic alkaloids as a new class of antioxidants in *Portulaca oleracea*. *Phytother. Res.* **2009**, *23*, 1032−1035.
(24) Sun, H.; He, X.; Liu, C.; Li, L.; Zhou, R.; Jin, T.; Yue, S.; Feng, D.; Gong, J.; Sun, J.; Ji, J.; Xiang, L. Effect of Oleracein E, a neuroprotective tetrahydroisoquinoline, on rotenone-induced Parkinson's disease cell and animal models. *ACS Chem. Neurosci.* **2017**, *8*, 155−164.
(25) (a) Padwa, A.; Danca, M. D.; Hardcastle, K. I.; McClure, M. S. A short diastereoselective synthesis of the putative alkaloid Jamtine, using a tandem Pummerer/Mannich cyclization sequence. *J. Org. Chem.* **2003**, *68*, 929−941. (b) Osante, I.; Lete, E.; Sotomayor, N. Tandem Parham cyclisation−−*α*-amidoalkylation reaction in the synthesis of the isoindolo[1,2-*a*]isoquinoline skeleton of Nuevamine-type alkaloids. *Tetrahedron Lett.* **2004**, *45*, 1253−1256. (c) Moreau, A.; Couture, A.; Deniau, E.; Grandclaudon, P. Construction of the six- and five-membered aza-heterocyclic units of the isoindoloisoquinolone nucleus by Parham-type cyclization sequences−Total synthesis of Nuevamine. *Eur. J. Org. Chem.* **2005**, 3437−3442. (d) Min, J.-Y.; Kim, G. Conversion of oxazolidinediones to isoindoloisoquinolinones via intramolecular Friedel−Crafts reaction. *J. Org. Chem.* **2014**, *79*, 1444−1448. (e) Selvakumar, J.; Rao, R. S.; Srinivasapriyan, V.; Marutheeswaran, S.; Ramanathan, C. R. Synthesis of condensed tetrahydroisoquinoline class of alkaloids by employing TfOH-mediated imide carbonyl activation. *Eur. J. Org. Chem.* **2015**, 2175−2188.
(26) Suyavaran, A.; Ramamurthy, C.; Mareeswaran, R.; Shanthi, Y. V.; Selvakumar, J.; Mangalaraj, S.; Kumar, M. S.; Ramanathan, C. R.; Thirunavukkarasu, C. Synthesis and biological evaluation of isoindoloisoquinolinone, pyroloisoquinolinone and benzoquinazolinone derivatives as poly(ADP-ribose) polymerase-1 inhibitors. *Bioorg. Med. Chem.* **2015**, *23*, 488−498.
(27) (a) Collado, M. I.; Manteca, I.; Sotomayor, N.; Villa, M. J.; Lete, E. Metalation vs. nucleophilic addition in the reactions of *N*-phenethylimides with organolithium reagents. Ready access to isoquinoline derivatives via *N*-acyliminium ions and Parham-type cyclizations. *J. Org. Chem.* **1997**, *62*, 2080−2092. (b) Osante, I.; Collado, M. I.; Lete, E.; Sotomayor, N. Stereodivergent synthesis of hetero-fused isoquinolines by acyliminium and metallation methods. *Eur. J. Org. Chem.* **2001**, 1267−1277. (c) González-Temprano, I.; Osante, I.; Lete, E.; Sotomayor, N. Enantiodivergent Synthesis of pyrrolo[2,1-a]isoquinolines based on diastereoselective Parham cyclization and *α*-amidoalkylation reactions. *J. Org. Chem.* **2004**, *69*, 3875−3895. (d) García, E.; Arrasate, S.; Lete, E.; Sotomayor, N. Diastereoselective intramolecular *α*-amidoalkylation reactions of L-DOPA derivatives. Asymmetric synthesis of pyrrolo[2,1-*a*]-isoquinolines. *J. Org. Chem.* **2005**, *70*, 10368−10374.
(28) Gómez-SanJuan, A.; Sotomayor, N.; Lete, E. Enantioselective intramolecular *α*-amidoalkylation reaction in the synthesis of pyrrolo-[2,1-*a*]isoquinolines. *Tetrahedron Lett.* **2012**, *53*, 2157.
(29) (a) Akiyama, T. Stronger Brønsted acids. *Chem. Rev.* **2007**, *107*, 5744−5758. (b) Akiyama, T.; Mori, K. Stronger Brønsted Acids: Recent Progress. *Chem. Rev.* **2015**, *115*, 9277−9306.
(30) (a) Chauhan, P.; Chimni, S. S. Aromatic hydroxyl group—a hydrogen bonding activator in bifunctional asymmetric organocatalysis. *RSC Adv.* **2012**, *2*, 737−758. (b) Zhou, D.; Huang, Z.; Yu, X.; Wang, Y.; Li, J.; Wang, W.; Xie, H. A quinine-squaramide catalyzed enantioselective aza-Friedel−Crafts reaction of cyclic trifluoromethyl ketimines with naphthols and electron-rich phenols. *Org. Lett.* **2015**, *17*, 5554−5557. (c) Montesinos-Magraner, M.; Vila, C.; Cantón, R.; Blay, G.; Fernández, I.; Muñoz, M. C.; Pedro, J. R. Organocatalytic asymmetric addition of naphthols and electron-rich phenols to isatin-derived ketimines: highly enantioselective construction of tetrasubstituted stereocenters. *Angew. Chem., Int. Ed.* **2015**, *54*, 6320−6324.
(31) Aranzamendi, E.; Sotomayor, N.; Lete, E. Bronsted acid catalyzed enantioselective *α*-amidoalkylation in the synthesis of isoindoloisoquinolines. *J. Org. Chem.* **2012**, *77*, 2986−2991.
(32) Aranzamendi, E.; Arrasate, S.; Sotomayor, N.; González-Díaz, H.; Lete, E. Chiral Bronsted acid-catalyzed enantioselective *α*-amidoalkylation reactions: A joint experimental and predictive study. *ChemistryOpen* **2016**, *5*, 540−549.
(33) Zhang, H.-H.; Wang, Y.-M.; Xie, Y.-W.; Zhu, Z.-Q.; Shi, F.; Tu, S.-J. Organocatalytic chemo-, (*E*/*Z*)- and enantioselective formal alkenylation of indole-derived hydroxylactams using *o*-hydroxystyrenes as a source of alkenyl group. *J. Org. Chem.* **2014**, *79*, 7141−7151.
(34) (a) Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; Pergamon Press: Oxford, 1997. (b) Bradley, D.; Williams, G.; Lawton, M. Drying of organic solvents: quantitative evaluation of the efficiency of several desiccants. *J. Org. Chem.* **2010**, *75*, 8351−8354.
(35) Selvakumar, J.; Makriyannis, A.; Ramanathan, C. R. An unusual reactivity of BBr_3: accessing tetrahydroisoquinoline units from *N*-phenethylimides. *Org. Biomol. Chem.* **2010**, *8*, 4056−4058.
(36) Katritzky, A. R.; Mehta, S.; He, H.-Y. Syntheses of pyrrolo- and indoloisoquinolinones by intramolecular cyclizations of 1-(2-arylethyl)-5-benzotriazolylpyrrolidin-2-ones and 3-benzotriazolyl-2-(2-arylethyl)-1-isoindolinones. *J. Org. Chem.* **2001**, *66*, 148−152.
(37) (a) Hamon, M.; Dickinson, N.; Devineau, A.; Bolien, D.; Tranchant, M.-J.; Taillier, C.; Jabin, I.; Harrowven, D. C.; Whitby, R. J.; Ganesan, A.; Dalla, V. Intra- and intermolecular alkylation of *N*,*O*-acetals and *π*-activated alcohols catalyzed by in situ generated acid. *J. Org. Chem.* **2014**, *79*, 1900−1902. (b) Heaney, H.; Simcox, M. T.; Slawin, A. M. Z.; Giles, R. G. Lanthanide triflate catalysed reactions of acetals with primary amines and cascade cyclisation reactions. *Synlett* **1998**, 640−642.

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ACS Omega 2017, 2, 2706−2718