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Enantioselective intramolecular α-amidoalkylation reaction in the synthesis of pyrrolo[2,1-*a*]isoquinolines

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ABSTRACT

BINOL-derived chiral Brønsted acids are capable of carrying out the intramolecular α-amidoalkylation of a tertiary N-acyliminium ions when a methoxylated benzene ring is used as internal π nucleophile. The reaction can be applied to the synthesis of pyrrolo[2,1-*a*]isoquinolines and use of the sterically congested acid **3e** is determinant to obtain good levels of enantioselection.

Enantiomerically pure nitrogen heterocycles are ubiquitous structures in natural products and pharmaceuticals. In this context, the enantioselective construction of the isoquinoline unit continues to be an intensely investigated field.[1] The asymmetric intramolecular α-amidoalkylation reaction of aromatics and heteroaromatics has become a powerful approach for the synthesis of substituted and fused isoquinoline systems.[2] Since these reactions are highly diastereoselective,[3] many efficient synthesis have been reported to date based either in the use chiral substrates or chiral auxiliaries. In this context, our group has also demonstrated the synthetic application of highly stereoselective intramolecular α-amidoalkylation reactions of α-hydroxylactams derived from N-phenethylimides for the synthesis of enantiopure 5,10b-disubstituted tetrahydropyrrolo[2,1-*a*]isoquinolines or 10b*R*-substituted 5,6-dihydrotetrahydropyrrolo[2,1-*a*]isoquinolines. In the first case, the stereochemical control was achieved starting form imides derived form L-DOPA,[4] while in the second approach the strategy implied the use of a 2-*exo*-hydroxy-10-bornylsulfinyl group as a chiral auxiliary.[5] Therefore, our next goal was to perform the reactions in an enantioselective fashion. Herein we describe our preliminary results in an enantioselective Friedel–Crafts reaction of α-hydroxylactams **2** derived form N-phenethylimides **1**, catalyzed by chiral phosphoric acids **3**, obtaining optically active pyrroloisoquinolines **4** substituted in the α position to the nitrogen atom (Scheme 1).

The first enantioselective versions of α-amidoalkylation reactions were carried out using copper-based catalysts,[6] though a significant progress in this area has been marked by the development of organocatalytic approaches, using chiral Brønsted acids (mainly BINOL derived phosphoric acids)[7] and hydrogen bond donors (mainly ureas and thioureas).[8] Thus, examples of intermolecular α-amidoalkylation of heteroaromatic systems with N-acyliminium ions formed in situ from cyclic hydroxylactams to form tertiary[9] or quaternary stereogenic centers have been reported.[10] However, despite the excellent enantioselectivity achieved, some limitations remain. Most importantly, the intramolecular α-amidoalkylation reactions are still limited to a few examples and specifically with electron-rich heteroaromatic rings. Enantioselective tertiary N-acyliminium ion cyclization under BINOL derived phosphoric acids catalysis has been reported, starting from tryptamines and enol lactones or ketoesters and keto acids.[11] The scope of the reaction has been shown to be broad, allowing the synthesis of fused β-carboline skeletons in good overall yields and excellent enantioselectivities.[12]

The intramolecular reaction using chiral proton donors (thioureas) also provides excellent yields and enantioselectivities, but requires electron rich heteroaromatic systems, as indoles or pyrroles.[13] This procedure has failed when N-acyliminium ions tethered to electron rich methoxy substituted aromatic rings (*N*-phenethyl hydroxylactams) were used, obtaining pyrroloisoquinolines with low conversions (0–40%) and 0% ee.

We reasoned that chiral BINOL derived phosphoric acids could be more active in the case of using benzene derivatives as internal π-nucleophiles, thus allowing higher conversions. Therefore, we began our investigation on α-amidoalkylation reaction selecting three different imides **1a–c**. MeLi addition to these imides leads to the N-phenethyl hydroxylactams **2a–c**, that can be efficiently cyclized to the corresponding fused isoquinolines upon treatment

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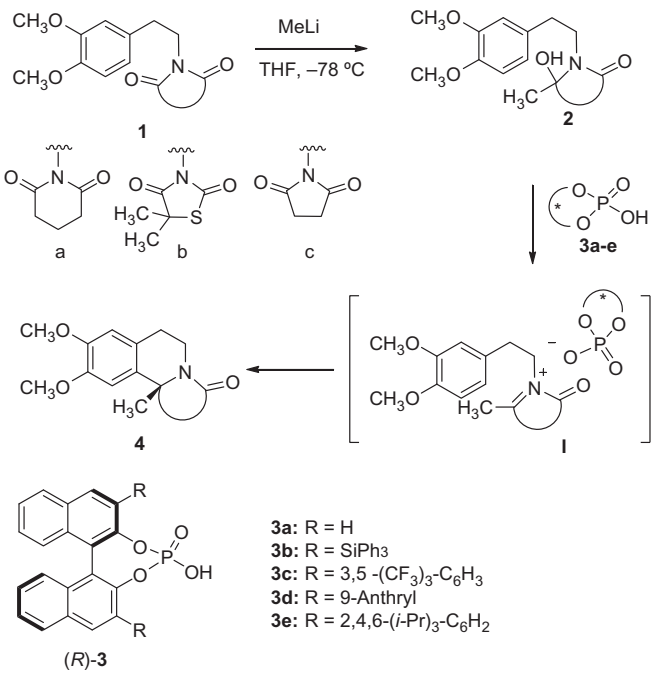


Scheme 1. Brønsted acid catalyzed intramolecular α-amidoalkylation.

with a Brønsted acid as TFA.[14] The use of a chiral phosphoric acid would lead to enantioenriched isoquinolines **4** through the formation of an N-acyliminium intermediate/chiral conjugate base ion pair as **I** (Scheme 1).

Our initial survey using phosphoric acid **3a** (10 mol %) as catalyst identified 5-hydroxy-5-methylpyrrolidin-2-one **2c** as a promising lead. Thus, treatment of hydroxylactams **2a,b** with 10 mol % of **3a** in toluene at reflux produces the formation of the N-acyliminium intermediate, but no cyclization occurs, isolating the corresponding enamide after work-up (Table 1, entries 1,2). However, cyclization took place efficiently with hyroxylactam **2c**, obtaining pyrroloisoquinoline **4c**, though with a poor enantioselectivity (12% ee, Table 1, entry 3). The use of higher catalyst loading (20 mol %, entry 4) enhanced the reaction rate, which was completed within 6 h, with similar ee. The reactions were considerably slower at room temperature with no improvement of enantioselectivity (Table 1, entry 5).

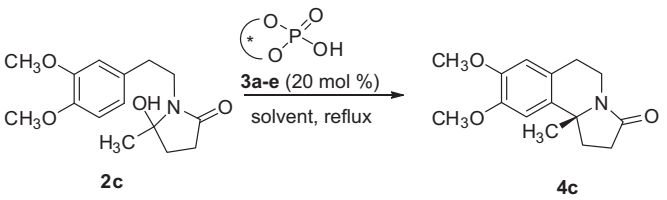
The reaction conditions were optimized using various solvents and temperatures, using 20 mol % of catalyst **3a**, for shorter reaction times (Table 2). The reaction yields improved significantly using more polar solvents as dichloromethane acetonitrile, or acetonitrile/water (10%) though **4c** was obtained almost in racemic form in all cases (Table 2, entries 1, 3, 4). No significant improvement of enantioselectivity was observed at room temperature (entries 2, 5). The reaction did not proceed at all in THF (entry 6), and

Table 1
Preliminary evaluation of lactams **2a–c**

Entry	Substrate	**3a** (mol %)	T	**4** Yield[a] (%)	ee[b] (%)
1	**2a**	10	Reflux[c]	[f]	—
2	**2b**	10	Reflux[c]	[f]	—
3	**2c**	10	Reflux[c]	64	12
4	**2c**	20	Reflux[d]	65	10
5	**2c**	20	50 °C[e]	34	8

[a] Yield of isolated product.
[b] Determined by CSP HPLC.
[c] Reaction time: 24 h.
[d] Reaction time: 6 h.
[e] Reaction time: 5 days.
[f] The corresponding enamide was isolated.

Table 2
Optimization of reaction conditions for **2c**



Entry	Solvent	Catalyst **3** (20 mol %)	Time	**4c** Yield[a] (%)	ee[b] (%)
1	CH_3CN	**3a**	6 h	72	2
2	CH_3CN	**3a**	24 h[c]	48	4
3	CH_3CN/H_2O	**3a**	5 h	93	<1
4	CH_2Cl_2	**3a**	6 h	76	6
5	CH_2Cl_2	**3a**	24 h[c]	68	4
6	THF	**3a**	2 days	—	—
7	EtOH	**3a**	6 h	35	<1
8	CH_3CN	**3b**	6 days	49	2
9	CH_3CN/H_2O	**3b**	24 h	56	2
10	CH_2Cl_2	**3b**	6 days	—	—
11	Toluene	**3b**	6 days	—	—
12	CH_3CN	**3c**	5 h	84	<1
13	CH_3CN/H_2O	**3c**	5 h	73	<1
14	CH_2Cl_2	**3c**	5 h	67	<1
15	Toluene	**3c**	5 h	64	26
16	CH_3CN	**3d**	3 days	46	6
17	CH_3CN/H_2O	**3d**	24 h	56	< 1
18	CH_2Cl_2	**3d**	4 days	10	50
19	Toluene	**3d**	4 days	37	50
20	CH_3CN	**3e**	2 days	80	16
21	CH_2Cl_2	**3e**	2 days	—	—
22	Toluene	**3e**	4 days	23	74
23	Toluene	**3e**[d]	4 days	10	76
24	Toluene	**3e**[e]	4 days	31	74

[a] Yield of isolated product.
[b] Determined by CSP HPLC.
[c] The reaction was carried out at room temperature.
[d] 10 mol % of **3e** was used.
[e] 30 mol % of **3e** was used.

no enantioselection was observed using EtOH (entry 7). Under similar conditions, catalyst **3b** proved to be less reactive (entries 8–11), observing no reaction in toluene or dichloromethane even after 6 days. On the other hand, catalyst **3c** was the most active, producing pyrroloisoquinoline **4c** in good yields in just 5 h, but almost racemic (entries 12–15). Only a small improvement of the ee was observed using toluene as solvent (entry 15, 26% ee). The sterically congested catalyst **3d** was less reactive in all solvents, though a significant increase of enantioselectivity to 50% ee was observed using toluene, with a moderate yield (entry 19). Finally, the best enantioselectivity (74% ee) was obtained with 20 mol % of catalyst **3e** in toluene.

The absolute configuration of **4c** was assigned as *R* by correlation with related pyrroloisoquinoline structures previously prepared in enantiomerically pure form by our group[5] and others.[15]

As has been shown, there is a strong influence of the structure of the phosphoric acid on the rate, and most importantly, on the enantioselectivity of the reaction. Thus, the substituents on positions 3 and 3' modulate the chiral environment in which the reaction takes place, through the formation of an N-acyliminium intermediate/chiral conjugate base ion pair as **I** (Scheme 1).[7] This concept has been invoked to explain the enantioselection in both inter- and intramolecular N-acyliminium reactions,[7,16] The related enantioselective alkylation of imines and acylimines catalyzed by BINOL-phosphoric acids has been studied quite extensively,[7] and

a model to explain the stereochemical outcome of these reactions has been reported recently.[17]

In summary, it has been shown that BINOL-derived chiral Brønsted acids are capable of carrying out the intramolecular α-amidoalkylation of a tertiary N-acyliminium ions derived from an 5-hydroxy-5-methylpyrrolidin-2-one, when an methoxylated benzene ring is used as internal π nucleophile.[18] These preliminary results are interesting because, as indicated above, this procedure failed when thiourea catalysts were used, and required electron rich heteroaromatic systems, as indoles or pyrroles.[13] In our case, the use of the sterically congested acid **3e** is determinant to obtain good levels of enantioselection, and contrasts with the results obtained by Dixon[11,12] with β-carbolines, where the best results were obtained with **3b**, the less reactive acid for this system. These results illustrate the subtle balance of interactions in an intermediate such as **I** that control both the enantioselectivity and the reactivity itself. Work along these lines is in progress.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.02.057. These data include MOL files and InChiKeys of the most important compounds described in this article.

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18. (***R***)**-(+)-8,9-dimethoxy-10b-methyl-1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-3[2*H*]-one (4c)**: To a solution of the succinimide **1c** (48.4 mg, 0.18 mmol) in dry THF (5 mL), MeLi (0.42 mL of a 0.97 M solution, 0.40 mmol) was added at −78 °C. The resulting mixture was stirred at this temperature for 6 h, and was quenched by the addition of saturated aqueous NH_4Cl solution (5 mL). The mixture was and allowed to warm to rt, and the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to afford hydroxy lactam **2c**.[14] Without further purification, **2c** was dissolved in dry toluene (25 mL), and acid **3e** (26 mg, 0.03 mmol) was added. The resulting mixture was refluxed for 4 days. The solvent was removed, and the pyrroloisoquinoline **4c** was obtained after chromatographic purification (alumina, AcOEt) (11 mg, 23%): $[\alpha]_D^{20}$: +130.1 (c = 0.5, $CHCl_3$); The enantiomeric excess was determined by HPLC to be 74%. [Chiralcel OD, 5% hexane: 2-propanol, 1 mL/min, t_r (R) = 49.6 min (87%), t_r (S) = 57.1 min (13%)]; IR (film) 1685 cm^{-1}; ^1H NMR ($CDCl_3$); 1.50 (s, 3H), 2.04–2.10 (m, 1H), 2.32-2.44 (m, 2H), 2.57–2.67 (m, 2H), 2.84–2.91 (m, 1H), 3.29 (td, J = 13.0, 4.5 Hz, 1H), 3.84 (s, 3H), 3.86 (s, 3H), 4.28 (ddd, J = 12.2, 6.2, 1.8 Hz, 1H), 6.56 (s, 1H), 6.63 (s, 1H); ^{13}C NMR ($CDCl_3$). 27.0, 27.6, 30.0, 34.4, 36.0, 55.2, 55.9, 64.6, 107.9, 116.8, 125.5, 133.3, 147.7, 147.9, 175.7; MS (EI) m/z (rel. intensity) 261 (M^+, 8), 246 (100), 230 (14), 202 (9), 185 (4), 172 (4), 123 (6), 117 (4), 91 (5), 77 (8). Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94, H, 7.33, N, 5.36. Found: C, 69.14, H, 7.09, N, 5.07.