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Direct Synthesis of Dihydropyrrolo[2,1-*a*]isoquinolines through $FeCl_3$ Promoted Oxidative Aromatization

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Abstract. We have developed a straightforward $FeCl_3$ promoted synthesis of dihydropyrrolo[2,1-*a*]isoquinolines through formal (3 + 2) cycloaddition/oxidative aromatization cascade of dihydroisoquinoline with Morita–Baylis–Hillman carbonates (up to 96% yield). Further modifications of the obtained products were successful through simple chemical transformations providing a diverse range of natural product-like molecules (12 examples).

Keywords: Pyrroloisoquinoline; Oxidative aromatization; Morita–Baylis–Hillman carbonates; Dihydroisoquinoline; Iron Chloride

Introduction

Pyrroloisoquinoline as a privileged framework can be found in a large number of biologically active molecules and functional materials (Figure 1).[1] For example, the lamellarin family has shown a wide range of biological activities such as cytotoxicity and antitumor activity. Accordingly, the efficient construction of pyrroloisoquinoline deriveatives has attracted much attention. Various elegant strategies and methodologies have been established for the assembly of this important scaffold, such as multistep synthesis[2], 1,3-dipolar cyclization[3], multicomponent reaction[4], photocatalytic reaction[5], electrocyclization[6] and other approches[7]. Inspired by previous reports, we have recently developed electrocyclization-based synthesis of nitrogen-containing heterocycles.[8] By the formation of 1,n-dipolars as key intermediates, a range of structurally diversified novel pyrroloisoquinoline and other isoquinoline-containing derivatives have been synthesized from easily accessible materials.[9]

Previous successful constructions of pyrroloisoquinolines always undergo the oxidative aromatization step and thus require additional stoichiometric amount of oxidants. For instance, Xiao[5a], Rueping[3d] and Zhao[5b] have independently reported excellent photocatalytic dipolar cyclization and they utilized NBS as additional oxidant in their studies; Wang[3c], Basavaiah[6a] and Shankaraiah[3f] have also achieved impressive [3 + 2] cycloadditions and they employed THBP as oxidant respectively for the oxidation step. Additionally, in the attractive metal-free methods of Gao[3a] and Ito[3e], the presences of H_2O_2 and O_2 were required respectively in the oxidative aromatization step. In addition, the use of expensive and toxic metal catalysts may also be necessary in many reports. To avoid the use of expensive, toxic catalyst and reduce waste generated from multistep manipulations, the development of direct and catalytic way accessing structurally diversified molecules of significant importance using inexpensive and nontoxic catalysts is in great demand.

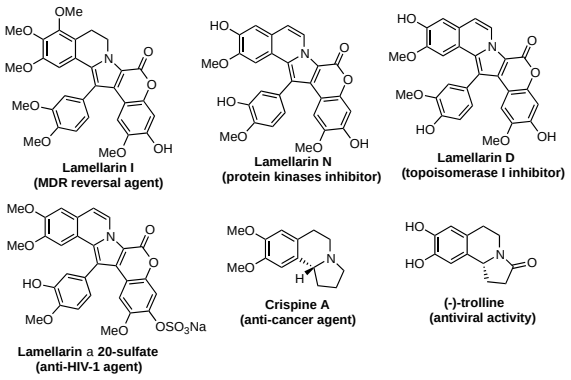


Figure 1. Representative Pyrroloisoquinoline Deriveatives.

Iron salts are suitable catalysts for organic synthesis, since they are abundant, inexpensive and nontoxic.[10] Thus Iron salts have been applied recently in a wide range of organic reactions, such as oxidative coupling reactions[11], Lewis acid catalysis[12], aerobic oxidations,[13] photocatalysis[14]

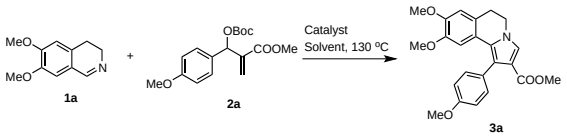
and other reactions[15], for the construction of structurally complex heterocycles. However, compared with the wide utilization of other metal catalysts, iron salts were used in a relatively narrow scope in organic synthesis. As our ongoing efforts on the synthesis of heterocycles from simple starting material, we are interested in employing iron salts as promotor in preparing nitrogen-containing molecules through cascade reactions. Here, we report our development of $FeCl_3$ promoted synthesis of dihydropyrrolo[2,1-*a*]isoquinolines through formal (3 + 2) cycloadditions/oxidative aromatization of dihydroisoquinoline with Morita–Baylis–Hillman (MBH) carbonates.[16]

Results and Discussion

Initially, the reaction of dihydroisoquinoline **1a** and MBH carbonate **2a** was selected as the model reaction to test the efficiency of catalysts at 130 °C. As shown in Table 1, a range of metal catalysts including iron, palladium and copper salts have been screened (entries 1-7). Only iron chloride was found to give a promising yield (45% yield). Further screening of solvents identified DMSO as the best solvent (entries 8-12). Complicated byproducts can be detected by TLC and ^{1}H NMR, indicating iron salts catalyzed oxidative cross-coupling reactions or further oxidations may likely be involved in this process. Thus we tested the reactions at lower reaction temperature (entries 13 and 14). However, the yields were dramatically decreased to 16% and less than 10% respectively. It suggests that the reaction temperature plays an important role in this process. A lower catalyst loading gave an improved yield (entry 15, 83%). Higher concentration resulted in slightly improvement on reaction yield (entry 16, 91% NMR yield and 88% isolated yield). Lower catalyst loading gave decreased yields with prolonged reaction time (entries 17 and 18, 67% and 65% yields respectively). Other iron salts, such as $Fe_2(SO_4)_3$, $FePO_4$, $Fe(OTf)_3$, $Fe(OTf)_2$ and $FeCl_2$ were not as effective as $FeCl_3$, giving relatively lower yields (entries 19-23, 11-46%).

Next, the reaction substrate scope and limitations were investigated as shown in Scheme 1. MBH carbonates derived from aromatic aldehydes bearing electron-donating groups gave desired dihydropyrrolo[2,1-*a*]isoquinolines in good yields (**3a-3d,** 67-88%). The change of ester group was successful as compounds **3e-3g** could be readily prepared under the current catalytic system (58-90% yields). Then various MBH carbonates possessing electron-deficient groups were submitted to this system, affording corresponding dihydropyrrolo[2,1-*a*]isoquinolines in acceptable to excellent yields (36-96% yields). Generally, MBH carbonates bearing substituents at *o*-position provided lower reaction yields than that with substituents at *m*- and *p*-position, suggesting that steric effect has significant impact on reaction yield. Naphthyl and thienyl moieties can be easily incorporated into dihydropyrrolo[2,1-*a*]isoquinoline by using corresponding MBH carbonates (**3s** and **3t,** 60% and 56% yields). In the case of compound **3m,** the yield decreased to 77% when performing at 1 mmol scale. Treatment of cinnamyl aldehyde derived MBH carbonate in this process led to 17% yield of desired product bearing styryl group. The use of alkylated MBH carbonate gave trace amount of product, likely due to the instability of the generated intermediate. By changing MBH carbonate, cyano group can be successfully installed into dihydropyrroloisoquinoline in good yield (**3w,** 82%). The employment of cyclopropen-1-one derived MBH carbonate failed to deliver compound **3x.** While MBH bearing amide moiety successfully afforded compound **3y** in 37% yield. Relative configuration of compound **3p** was confirmed by X-ray analysis and others were assigned by analogy (See ESI).[17]

Table 1. Optimization of reaction conditions.



Entry	Cat	mol %	Solvent	t (h)	Yield [%]
1	$FeCl_3$	50	DMF	3	45
2	$Pd(OAc)_2$	50	DMF	3	<10
3	$CuCl_2$	50	DMF	3	<10
4	$Cu(OTf)_2$	50	DMF	3	<10
5	$Cu(OAc)_2$	50	DMF	3	<10
6	CuI	50	DMF	3	<10
7	$Cu(OTf)_2$	50	NMP	3	<10
8	$FeCl_3$	50	DMF	3	41
9	$FeCl_3$	50	PhCl	3	17
10	$FeCl_3$	50	*m*-xylene	3	16
11	$FeCl_3$	50	Glycol	3	13
12	$FeCl_3$	50	DMSO	3	72
13[c]	$FeCl_3$	50	DMSO	6	16
14[d]	$FeCl_3$	50	DMSO	24	<10
15[e]	$FeCl_3$	25	DMSO	3	83
16[f]	$FeCl_3$	25	DMSO	4	91 (88)[g]
17	$FeCl_3$	5	DMSO	6	67
18	$FeCl_3$	10	DMSO	6	65
19	$Fe_2(SO_4)_3$	50	DMSO	3	25
20	$FePO_4$	50	DMSO	3	18
21	$Fe(OTf)_3$	50	DMSO	3	11
22	$Fe(OTf)_2$	50	DMSO	3	25
23	$FeCl_2$	50	DMSO	3	46

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), catalyst and solvent (0.2 M) at 130 °C. [b] The yield was determined by ^{1}H NMR using CH_2Br_2 as internal standard. [c] At 100 °C. [d] At 50 °C. [e] Performed at 0.2 mmol scale with 25 mol% of catalyst (0.2 M). [f] 0.4 M. [g] Isolated yield.

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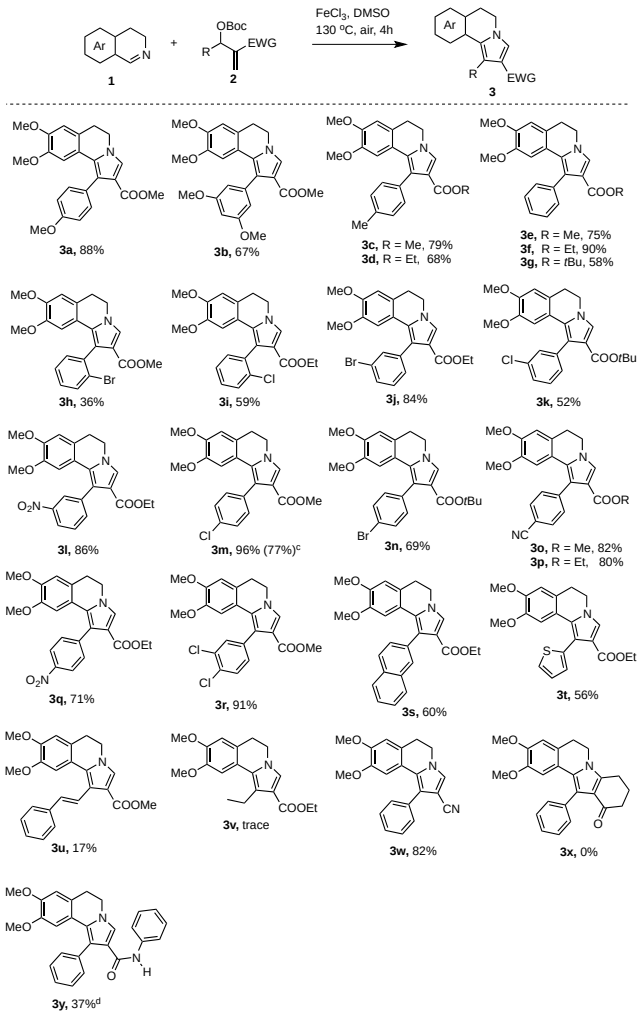
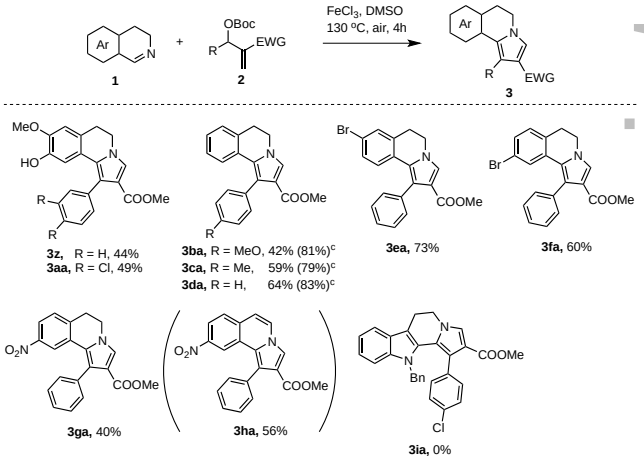
We then turned our attention to the substrate scope examination of imines (Scheme 2). Pleasingly, the reaction of dihydroisoquinoline bearing free phenolic hydroxy group proceeded smoothly affording the desired azacycles in moderate yields regardless of the nature of substituents on MBH carbonate (**3z** and **3aa**). The use of 3,4-dihydroisoquinoline delivered compounds **3ba, 3ca** and **3da** in moderate to good yields (42-64%). As inseparable over-oxidized product were detected in the cases of **3ca** and **3da,** excess amount of imines (1.5 equiv) were used instead in the cases of **3ba, 3ca** and **3da.** Generally, significant improvements were observed in these cases. Both 6-bromo-3,4-dihydroisoquinoline and 7-bromo-3,4-dihydroisoquinoline were suitable candidates for this reaction, yielding compounds **3ea** and **3fa** in good yields.[18] Interestingly, in the case of 7-nitro-3,4-dihydroisoquinoline, beside of the desired product **3ga,** over-oxidized product **3ha** was isolated in 56% yield. It indicates that the electronic nature of the dihydroisoquinoline ring plays an important role on the further aromatization of dihydroisoquinoline ring. Unfortunately, the employment of dihydrocarboline imine failed to give compound **3ia.** In this case, complicated mixture containing formal (3 + 2) cycloaddition product without further aromatization was observed.



Scheme 1. Substrate Scope of MBH Carbonates.[a-d] [a] Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), $FeCl_3$ (25 mol%) and DMSO (0.5 mL) at 130 °C in air. [b] Isolated yield. [c] Performed at 1 mmol scale for 8 h. [d] At 130 °C for 3 h.

To our delight, the gram-scale reaction was successful, albeit with decreased yield and prolonged reaction time compared with 0.2 mmol scale reaction. As shown in Scheme 3, 1.7 g of compound **3m** could be obtained in 71% yield using 1.2 equivalent of MBH carbonate **2m.**



Scheme 2. Substrate Scope of Imines.[a-c] [a] Reaction conditions: **1** (0.2 mmol, 1.0 equiv), **2** (0.3 mmol, 1.5 equiv), $FeCl_3$ (0.25 equiv) and DMSO (0.5 mL) at 130 °C in air. [b] Isolated yield. [c] Reaction conditions: **1** (0.3 mmol, 1.5 equiv), **2** (0.2 mmol, 1.0 equiv), $FeCl_3$ (0.25 equiv) and DMSO (0.5 mL) at 130 °C in air.

To show the utilization of the obtained products, further transformations and modifications have been conducted as shown in Scheme 4. A variety of highly functionalized dihydropyrroloisoquinolines could be prepared through simple chemical transformations. Treatment of compound **3p** with NBS at room temperature afforded compound **4a** in 70% yield. Suzuki coupling of compound **4a** yielded compound **4b** and **4c** in 52% and 63% yields respectively. Hydrolysis of compound **3m** in a mixed solvent of water and DMSO at 130 °C provided acid **4d** successfully in 86% yield. Further amidation of compound **4d** delivered highly functionalized amides **4e, 4f** and **4g** in moderate to good yields (50-85%). Sulfonylation of compound **3z** afforded compound **4h** in 50% yield. Vilsmeier–Haack reaction of compound **3p** produced aldehyde **4i** in 71% yield. A further oxidative coupling reaction in the presence of iron chloride (3 equivalent) led to the formation of dimeric dihydropyrroloisoquinoline **4j** in 82% yield. Suzuki reaction and oxidative Heck coupling reaction of compound **3da** with 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine yielded highly substituted heterocycle **4k** in 61% yield. Mannich reaction of

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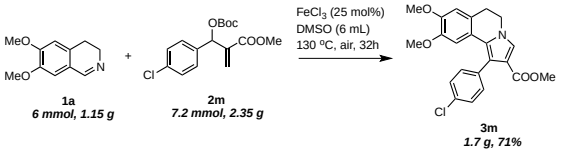
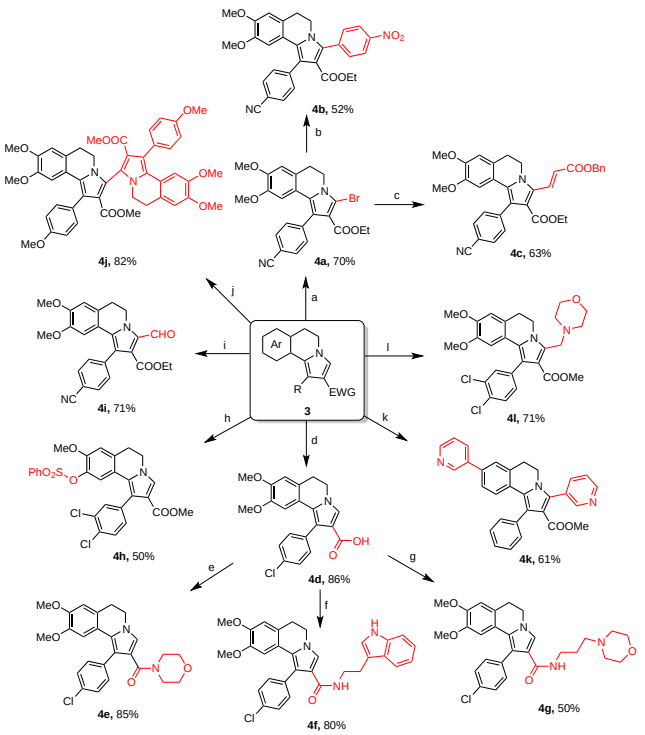
compound **3r** generated multifunctionalized tertiary amine **4l** in 71% yield.

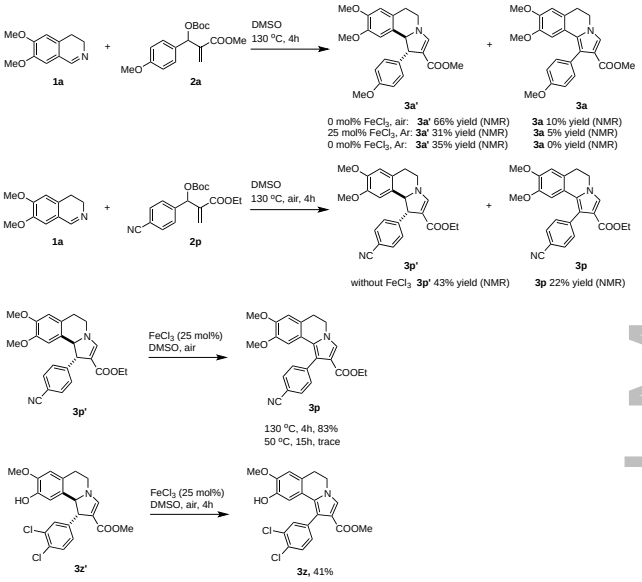


Scheme 3. Gram-scale reaction.

To get more evidence for mechanism study, control experiments have been conducted (Scheme 5). When the reaction was performed in air in the absence of $FeCl_3$, the desired product **3a** could be detected in 10% NMR yield, while the intermediate **3a'** could be detected in 66% NMR yield. When conducted in the presence of $FeCl_3$ and under Ar atmosphere, formal (3 + 2) cycloaddition **3a**' can be observed in 31% yield and oxidation product **3a** was observed in 5% yield. No oxidation product **3a** can be detected when the reaction was carried out without catalyst under Ar. It indicates that both $FeCl_3$ and air are essential for the formation of final product. In the presence of $FeCl_3$, the intermediate **3p**' can be readily oxidized to final product **3p** at 130 °C in good yield (83%). Trace product was observed at 50°C even with prolonged reaction time, suggesting the reaction temperature plays an important role in the oxidative aromatization step. While the intermediates **3p**' and **3aa**' could be easily prepared in the absence of iron chloride following a modified procedure according to our previous report (See ESI). It demonstrates that $FeCl_3$ has no significant influence on the formal (3 + 2) cycloaddition.



Scheme 4. Transformations of Dihydropyrrolo-isoquinolines.[a-l] [a] NBS (1.1 equiv), DCM, rt. [b] $Pd(PPh_3)_4$ (10 mol%), 4,4,5,5-tetramethyl-2-(4-nitrophenyl)-1,3,2-dioxaborolane (2.0 equiv), Na_2CO_3 (2.0 equiv), H_2O/DMF, 130 °C. [c] $Pd(PPh_3)_4$ (10 mol%), Benzyl acrylate (5.0 equiv), DIPEA (2.0 equiv), DMF, 130 °C. [d] LiOH (10 equiv), H_2O/DMSO, 130 °C. [e] EDCI (2.0 equiv), morpholine (1.2 equiv), DCM, rt. [f] EDCI (2.0 equiv), tryptamine (1.2 equiv), DMAP, DCE, 50 °C. [g] EDCI (2.0 equiv), N-(3-Aminopropyl)morpholine (1.2 equiv), DCM, rt. [h] $PhSO_2Cl$ (1.2 equiv), Et_3N (1.5 equiv), DCM, rt. [i] $POCl_3$ (3.0 equiv), DMF, rt. [j] $FeCl_3$ (3.0 equiv), DCM, rt. [l] $Pd(PPh_3)_4$ (10 mol%), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (2.0 equiv), Na_2CO_3 (2.0 equiv), H_2O/DMF, 130 °C. [l] Morpholine (1.2 equiv), paraformaldehyde (5 equiv), AcOH, MeCN, 50 °C. DIPEA: N,N-Diisopropylethylamine. EDCI: 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride.



Scheme 5. Control Experiments.

On the basis of our results and previous reports, a plausible mechanism was proposed as shown in Scheme 6. Firstly, nucleophilic attack of imine **1** to MBH carbonate **2** generates intermediate **A.** The following deprotonation yields zwitterion **B** which would be in equilibrium with intermediate **C**. 1,5-Electrocyclization of intermediate **C** leads to the formation of compound **3'.** Finally, $FeCl_3$ promoted oxidative aromatization as key step for this process, affords the final product **3.** Further oxidative aromatization would be possible and it depends on the electronic nature of the dihydroisoquinoline moiety.

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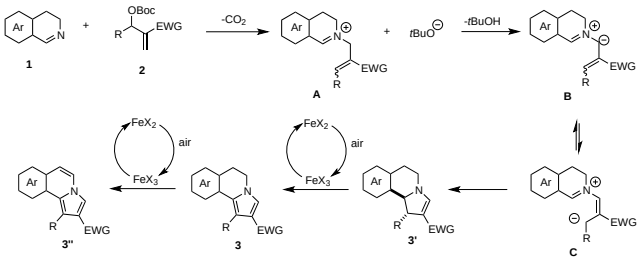

Scheme 6. Plausible Mechanism.

Conclusion

In conclusion, we have developed a straightforward $FeCl_3$ promoted synthesis of dihydropyrrolo[2,1-*a*]isoquinolines through formal (3 + 2) cycloaddition/oxidative aromatization cascade of dihydroisoquinoline with MBH carbonates. Various dihydropyrrolo[2,1-*a*]isoquinolines can be prepared from easily accessible material (up to 96% yield). Further modification of the obtained dihydropyrrolo[2,1-*a*]isoquinolines were successful through simple chemical transformations providing a diverse range of natural product-like molecules. Notably, the gram-scale reaction can be performed successfully in good yield.

Experimental Section

General procedure for the synthesis of compounds 3:

A mixture of dihydroisoquinoline imine **1** (0.2 mmol, 1.0 equiv), MBH carbonate **2** (0.3 mmol, 1.5 equiv) and $FeCl_3$ (0.05 mmol, 0.25 equiv) in DMSO (0.5 mL) was stirred at 130 °C for 4 h under air atmosphere. The mixture was cooled to room temperature and diluted with DCM (3 mL). The resulting solution was washed with water (1.0 mL x 3) and dried with Na_2SO_4, then purified directly by a silica gel flash chromatography (hexane/EtOAc) to afford compound **3**.

Acknowledgements

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[17] CCDC 1918552 (**3p**) and CCDC 1918550 (**3aa'**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_ request/cif.

[18] Over-oxidized product of **3da** on the dihydroisoquinoline ring could also be detected by HRMS (ESI-HRMS: calcd. for $C_{20}H_{15}BrNO_2^+$ (M+H) 380.0281, found 380.0289).

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FULL PAPER

Direct Synthesis of Dihydropyrrolo[2,1-*a*]isoquinolines through $FeCl_3$ Promoted Oxidative Aromatization

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