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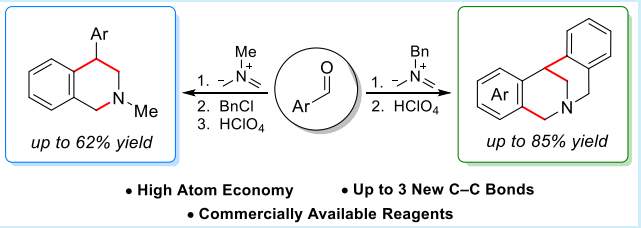
Synthesis of 6,12-Methanodibenzo[*c*,*f*]azocines and 4-Aryltetrahydroisoquinolines from Aromatic Aldehydes

Evgeny M. Buev, Maxim A. Stepanov, Vladimir S. Moshkin,* and Vyacheslav Y. Sosnovskikh

Institute of Natural Sciences and Mathematics, Ural Federal University, 620000 Ekaterinburg, Russian Federation

Supporting Information

ABSTRACT: A methodology for the synthesis of 7,12-dihydro-5*H*-6,12-methanodibenzo[*c*,*f*]azocines from aromatic aldehydes and *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)-benzylamine using catalysis by trifluoroacetic and perchloric acids is described. The developed protocol was applied for the synthesis of *N*-unsubstituted and *N*-methyl-4-aryltetrahydroisoquinolines.



Tetrahydroisoquinoline is a well-known core structure of a wide range of alkaloids and pharmaceuticals.[1] A subgroup of these alkaloids is represented by 4-aryl-1,2,3,4-tetrahydroisoquinolines.[2] For instance, *Amaryllidaceae* alkaloids such as (−)-cherylline (**I**) have been isolated from *Crinum latifolium* and other *Crinum* species (Figure 1).[3] Structurally close to the latter is the synthetic drug nomifensine (**II**), a monoamine reuptake inhibitor possessing dual inhibition activity to norepinephrine and dopamine, which was marketed as an antidepressant in the 1970s−1980s.[4] Considerable efforts were made for the synthesis of drugs based on the nomifensine structure.[5] (−)-Amurensinine **III** found in *Papaver* species is an alkaloid of the isopavine family that was investigated for the treatment of Parkinson's and Alzheimer's diseases.[6] Alkaloid **III** also represents a constrained 4-aryltetrahydroisoquinoline bearing the methylene link between C-1 and the veratryl group. Another natural product bearing a different bridge between nitrogen and the partially hydrogenated 4-aryl moiety is *Amaryllidaceae* alkaloid (−)-montanine **IV** exhibiting anticancer activity and an affinity to serotonin transporter.[7]

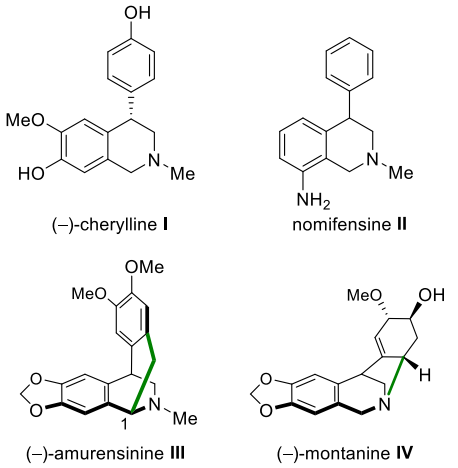
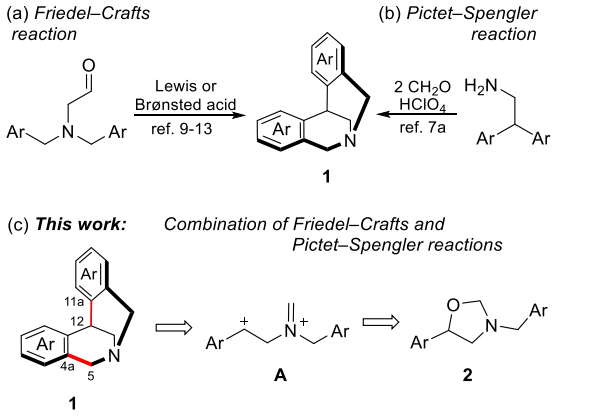


Figure 1. Selected 4-aryltetrahydroisoquinolines and related molecules.

In addition to natural bridged 4-aryltetrahydroisoquinolines **III** and **IV**, similar dihydro-6,12-methanodibenzo[*c*,*f*]azocines **1** have garnered much interest in the scientific society (Scheme 1).[8] Azocines **1** possess a bridging methylene link between the 4-aryl moiety and isoquinoline nitrogen that forms a strained skeleton of tetracyclic structure resembling isopavine alkaloids. Moreover, a number of works applied dibenzo[*c*,*f*]azocines **1** as scaffolds in the syntheses of isopavines via Stevens rearrangement[9] and (−)-cherylline via a Polonovski-type reaction.[10]

Scheme 1. Synthetic Pathways to 6,12-Methanodibenzo[*c*,*f*]azocines



Among the articles dedicated to the synthesis of methanodibenzo[*c*,*f*]azocines **1**, the majority of rely on intramolecular Friedel−Crafts double cyclization of *N*,*N*-

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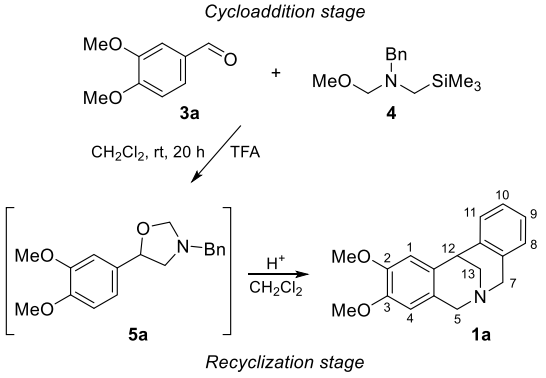
dibenzyl aminoacetaldehydes[8a,9,11] (Scheme 1a), their dialkylacetals,[12] related ketones,[13] and rarely *N*-benzyltetrahydroisoquinolines.[14] There is also a single example of an opposite approach to this synthesis via double Pictet–Spengler cyclization of 2,2-diarylethan-1-amine (Scheme 1b).[7a] Upon an examination of the azocine **1** structure, we envisioned another possible retrosynthetic direction. This is the cleavage of C(4a)–C(5) and C(11a)–C(12) bonds that leads to synthon **A** bearing both iminium and benzylic carbocations (Scheme 1c). In light of simple modification of synthon **A** by an oxygen atom, 5-aryl-3-benzyloxazolidine **2** seems to be the most appropriate synthetic equivalent for the synthesis of dibenzo[*c*,*f*]azocines **1**. To the best of our knowledge, this type of transformation has never been explored.

We commenced our study with the [3 + 2]-cycloaddition reaction of *N*-benzylazomethine ylide derived from *N*-(methoxymethyl)-*N*-(trimethylsilylmethyl)benzylamine (**4**) in the presence of trifluoroacetic acid with veratraldehyde (**3a**), which was selected as a model substrate to facilitate further Pictet–Spengler reaction and to increase the stability of the formed benzylic carbocation (Table 1). To our delight, readily obtained *N*-benzyloxazolidine **5a** was smoothly recyclized into 2,3-dimethoxy-6,12-methanodibenzo[*c*,*f*]azocine **1a** in 32% yield by treatment with sulfuric acid (96%) at room temperature for 2 h (Table 1, entry 1). The use of perchloric acid (70%) led to an improvement in the reaction efficiency, and azocine **1a** was isolated in 44% yield (entry 5). After an optimization of the recyclization conditions (entries 1–6), we examined the possibility of a combination of cycloaddition and recyclization stages in one experimentally simple process that consisted of sequential catalysis by two acids without an isolation of intermediate oxazolidine **5a** (entries 7 and 8). Thus, optimal conditions were treatment of the mixture of veratraldehyde (**3a**) and azomethine ylide precursor **4** with TFA (5 mol %) for 20 h and then with excess $HClO_4$ (70%) for 3 h. These allowed us to synthesize the target 6,12-methanodibenzo[*c*,*f*]azocine **1a** in 57% yield (entry 8). It should be noted that catalysis of the observed domino-process with only perchloric acid failed, apparently, due to the sensitivity of azomethine ylides to strong acids and oxidizers (entry 9). Despite that $AlCl_3$ and $FeCl_3$ were known to catalyze Friedel–Crafts cyclization in the construction of dibenzoazocines **1** (Scheme 1a),[9,12d] they did not cause the recyclization of oxazolidine **5a** (entries 10 and 11).

Encouraged by this operationally convenient methodology for the synthesis of 6,12-methanodibenzo[*c*,*f*]azocines **1**, we examined benzaldehyde under the optimized conditions found for veratraldehyde; however, the intermediate 3-benzyl-5-phenyloxazolidine was obtained. This result forced us to increase the temperature of the recyclization stage. Thus, treating the mixture with excess perchloric acid at 80 °C for 3 h led to 7,12-dihydro-5*H*-6,12-methanodibenzo[*c*,*f*]azocine (**1b**) in 85% yield (Scheme 2). Under these conditions, 3-methylazocine **1c** was obtained from *p*-tolualdehyde, while *p*-isopropylbenzaldehyde provided the related 3-isopropylazocine **1d**. The reaction of 3-bromobenzaldehyde resulted in the formation of 2-bromoazocine **1e** along with 4-bromoazocine **1e′** which were separated by column chromatography in 50 and 19% yields, respectively. In the case of 3-methoxybenzaldehyde, performing the recyclization at room temperature did not lead to the complete conversion of intermediate oxazolidine **5f** into azocine **1f** (the NMR ratio of the resulting mixture **5f**:**1f** was 30:70 correspondingly). This fact indicates

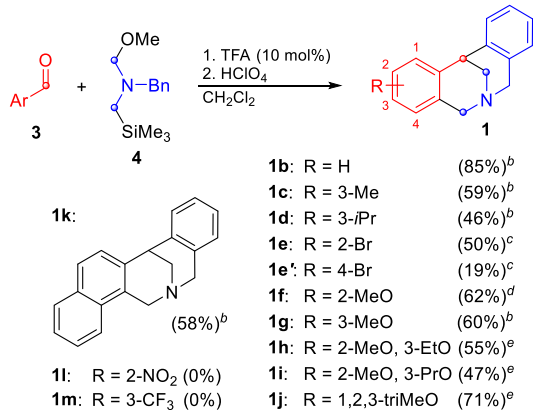
Table 1. Optimization of the One-Pot Synthesis of 6,12-Methanodibenzo[*c*,*f*]azocines



entry	reaction conditions	yield **1a**[a] (%)
1	**5a**, H_2SO_4 (96%), CH_2Cl_2, rt, 2 h[b]	32
2	**5a**, H_2SO_4 (80%), CH_2Cl_2, rt, 2 h[b]	33
3	**5a**, PPA, 90 °C, 1.5 h[b]	0
4	**5a**, $HClO_4$ (65%), CH_2Cl_2, rt, 24 h[b]	24
5	**5a**, $HClO_4$ (70%), CH_2Cl_2, rt, 3 h[b]	44
6	**5a**, $HClO_4$ (70%), CH_2Cl_2, rt, 24 h[b]	43
7	**3a** (1.0 mmol), **4** (1.1 mmol), TFA (5 mol %), CH_2Cl_2, rt, 20 h, then 70% $HClO_4$ (2 mL), rt, 4 h[c]	52
8	**3a** (1.0 mmol), **4** (1.5 mmol), TFA (10 mol %), CH_2Cl_2, rt, 20 h, then 70% $HClO_4$ (2 mL), rt, 3 h[c]	57
9	**3a** (1.0 mmol), **4** (1.1 mmol), $HClO_4$ (3 mol %), CH_2Cl_2, rt, 20 h, then 70% $HClO_4$ (2 mL), rt, 3 h[c]	*d*
10	**5a**, $AlCl_3$ (4.0 mmol), CH_2Cl_2, 40 °C, 4 h[b]	*d*
11	**5a**, $FeCl_3$ (4.0 mmol), CH_2Cl_2, 40 °C, 3 h[b]	*e*

[a]Reactions were performed on 1.0 mmol of **3a**. Isolated yields based on a starting veratraldehyde (**3a**) are depicted. [b]Crude oxazolidine **5a** was obtained using **3a** (1.0 mmol), **4** (1.07 mmol), and TFA (5 mol %) and was used further without purification. [c]$HClO_4$ (2 mL) was added to the reaction mixture after 20 h. [d]Complex mixture. [e]Complex mixture with an admixture of oxazolidine **5a**.

Scheme 2. Synthesis of 6,12-Methanodibenzo[*c*,*f*]azocines[a]



[a]Reaction conditions: **3** (1.0 mmol), **4** (1.5 mmol), TFA (10 mol %), CH_2Cl_2, rt, 20 h, then 70% $HClO_4$ (2 mL/1 mmol of aldehyde **3**), rt or 80 °C, 3 h. [b]$HClO_4$, 80 °C for 3 h. [c]$HClO_4$, 80 °C for 3 h, then at rt for 120 h. Azocines **1e** and **1e′** were obtained from 3-bromobenzaldehyde as a mixture and were separated by column chromatography. [d]$HClO_4$, 80 °C for 70 min. [e]$HClO_4$, rt for 3 h.

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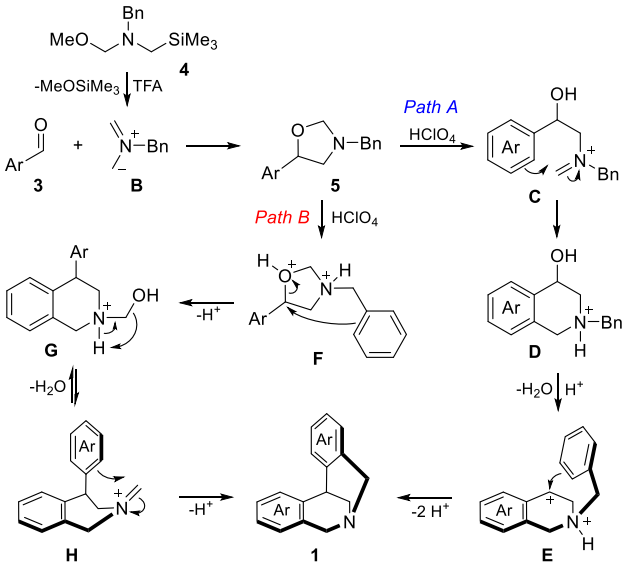
the insufficiency of one electron-donating group in the starting substrate for completing the process under mild conditions (rt, 3 h). An improved result was obtained upon heating the reaction mixture at 80 °C for 70 min, which provided 2-methoxymethanodibenzo[*c*,*f*]azocine **1f** as a single regioisomer in 62% yield. Considering the above, we performed the reaction of *p*-anisaldehyde under heating conditions (70% $HClO_4$, 80 °C, 3 h) that allowed us to isolate 3-methoxyazocine **1g** in 60% yield. Electron-rich aldehydes such as alkylated vanillins and 2,3,4-trimethoxybenzaldehyde readily afforded products **1h**–**j** at room temperature in 47–71% yields. 2-Naphthaldehyde was also successfully transformed into the pentacyclic piperidine **1k** in 58% yield as a single regioisomer under heating conditions. 3-Nitro- and 4-(trifluoromethyl)benzaldehydes, containing electron-withdrawing substituents, failed to give azocines **1l** and **1m** at 80 °C, while intermediate *N*-benzyloxazolidines **5** and 2-(benzylamino)-1-arylethanols were the general products.

A proposed mechanism of the reaction is depicted in Scheme 3. Initially, we assumed that acid-catalyzed ring-

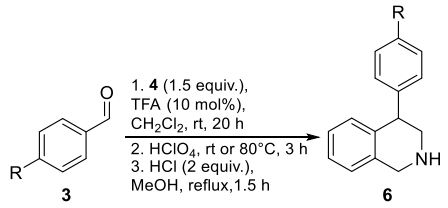
Scheme 3. Proposed Mechanism for the Acid-Promoted Domino-Reaction of *N*-Benzyloxazolidines



opening of oxazolidine **5** and the formation of iminium cation **C** lead to Pictet–Spengler cyclization into tetrahydroisoquinolin-4-ol **D** (Scheme 3, path A). Subsequent intramolecular Friedel–Crafts reaction of the formed benzylic carbocation **E** with the *N*-benzylic moiety results in the desired azocine **1**. However, the reaction of 5-(3-methoxyphenyl)-3-benzyloxazolidine did not proceed well at room temperature despite the favorable position of the electron-donating group that should promote Pictet–Spengler cyclization into azocine **1f**. In comparison, 5-(3-methoxyphenyl)-3-methyloxazolidine was readily recyclized into *N*-methyltetrahydroisoquinolin-4-ol of type **D** under the treatment with HCl.[15] This fact prompted us to consider an alternative mechanism of the observed reaction (path B). Apparently, in perchloric acid, in contrast to HCl, the double protonation of oxazolidine **5** occurs (intermediate **F**, Scheme 3). The formation of a benzylic carbocation and intramolecular Friedel–Crafts reaction give 4-aryltetrahydroisoquinoline **G** bearing a hemiaminal group. The elimination of water and the Pictet–Spengler reaction of the formed iminium cation **H** ultimately result in dibenzoazocine **1**.

Upon a closer investigation of the developed methodology, we examined the reaction of *p*-anisaldehyde at room temperature ($HClO_4$, rt, 3 h, Scheme 4). Surprisingly, the

Scheme 4. Reaction of 4-Substituted Benzaldehydes[a]



[a]Reaction conditions: **3** (1.0 mmol), **4** (1.5 mmol), TFA (0.1 mmol), CH_2Cl_2, rt, 20 h, then 70% $HClO_4$ (2 mL/1 mmol of aldehyde **3**), rt or 80 °C, 3 h, then 37% HCl (2 mmol), MeOH, reflux, 1.5 h. [b]$HClO_4$, rt for 3 h. [c]$HClO_4$, 80 °C for 3 h.

reaction did not stop at the intermediate oxazolidine **5** but resulted in the formation of *N*-unsubstituted 4-(4-anisyl)-1,2,3,4-tetrahydroisoquinoline (**6g**) in 45% yield. Gratifyingly, 4-halogen-substituted benzaldehydes were successfully involved in the same process upon heating at the recyclization stage ($HClO_4$, 80 °C, 3 h) that gave *N*-unsubstituted tetrahydroisoquinolines **6n**–**p** in 42–59% yields. In these cases, *para*-substituents did not promote the final Pictet–Spengler cyclization and hemiaminal **G** (Scheme 3) eliminated formaldehyde to give **6** (see the detailed mechanism in the Supporting Information).

Considering that 4-aryltetrahydroisoquinolines are intermediates of the domino-transformation of *N*-benzyloxazolidines **5** into dibenzo[*c*,*f*]azocines **1**, we were intrigued to find other possibilities to stop the reaction on their formation regardless of the substituents in the starting aromatic aldehyde. In general, the solution to this problem is to prevent the final Pictet–Spengler cyclization. Given that the active intermediate of this reaction is an iminium cation, the simplest approach is to suppress its formation. This, in turn, can be achieved by depriving the nitrogen atom of the lone pair, and quaternary ammonium salts prepared on the basis of oxazolidines **5** seem to be quite suitable for this purpose.

The feasibility of this idea was first evaluated with 3-methoxybenzaldehyde (Scheme 5). Crude *N*-benzyloxazolidine **5** was obtained as usual, and then, it was treated with methyl iodide to provide quaternary ammonium salt **7**. Heating the latter in $HClO_4$ at 80 °C for 3 h led to *N*-methyl-4-(3-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (**8a**) in 28% overall yield based on a starting aldehyde **3**. Similarly, 4-chlorobenzaldehyde gave rise to tetrahydroisoquinoline **8b** in 47% overall yield.

Next, we intended to expand the variability of the developed protocol for the construction of *N*-methyltetrahydroisoquinolines **8**. Given the structure of the intermediate quaternary ammonium salt **7** bearing benzyl and methyl groups, we decided to change the order for the introduction of these moieties into the molecule. Thus, the [3 + 2]-cycloaddition reaction of 3-methoxybenzaldehyde with *N*-methylazomethine ylide derived from sarcosine and formaldehyde provided 3-methyl-5-(3-methoxyphenyl)oxazolidine (**9a**), which was read-

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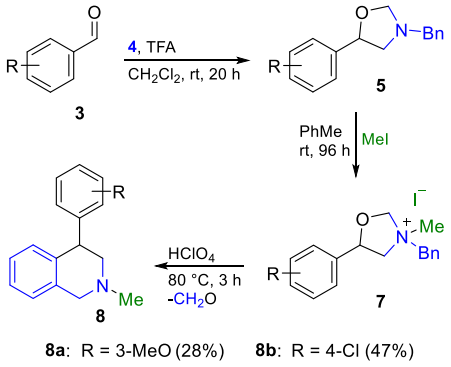
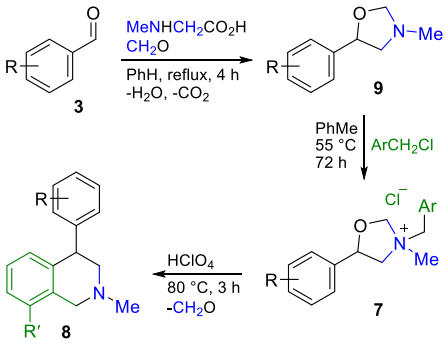
Scheme 5. One-Pot Synthesis of *N*-Methyl-4-aryl-1,2,3,4-tetrahydroisoquinolines 8 from *N*-Benzylazomethine Ylide[a]



[a]Reaction conditions: **3** (1.0 mmol), **4** (1.5 mmol), TFA (10 mol%), CH_2Cl_2, rt, 20 h, then MeI (3.0 mmol), PhMe, rt, 96 h, then 70% $HClO_4$ (2 mL/1 mmol of aldehyde **3**), 80 °C, 3 h.

ily converted to quaternary ammonium salt **7a** by treating with benzyl chloride (Scheme 6). Pleasingly, its recyclization in

Scheme 6. One-Pot Synthesis of *N*-Methyl-4-aryl-1,2,3,4-tetrahydroisoquinolines 8 from *N*-Methylazomethine Ylide[a]



[a]Reaction conditions: **3** (2.0 mmol), sarcosine (2.4 mmol), paraformaldehyde (3.6 mmol of CH_2O), PhH, 3 h, then $ArCH_2Cl$ (2.2 mmol), PhMe, 55 °C, 72 h, then 70% $HClO_4$ (2 mL/1 mmol of aldehyde **3**), 80 °C, 3 h. Overall yields based on starting aromatic aldehydes **3** are depicted.

perchloric acid for 3 h provided isoquinoline **8a** in 24% overall yield. It is noteworthy that the use of the most inexpensive reagents for the generation of azomethine ylides makes this approach a powerful tool for the construction of 4-aryltetrahydroisoquinolines, which attracted significant attention in the search of pharmaceuticals.[5,16]

We also examined benzaldehyde in the same one-pot reaction, and 4-phenyltetrahydroisoquinoline **8c** was isolated in 57% yield. To demonstrate the possibility for the modification of substituents in both aromatic moieties of **8**, we carried out the aforementioned process using 4-methylbenzaldehyde. The desired 2,8-dimethyl-4-(4-tolyl)-tetrahydroisoquinoline **8d** was formed in 27% overall yield utilizing 2-methylbenzyl chloride as an alkylating reagent (Scheme 6). We also synthesized the patented 4-(4-bromophenyl)tetrahydroisoquinoline **8e**, possessing antidepressant and antiulcer activities,[17] from 4-bromobenzaldehyde in 43% overall yield. Related anisyl derivatives **8f** and **8g** were obtained in 50 and 62% overall yields correspondingly. Unexpectedly, *o*-ethoxybenzaldehyde gave 4-(2-hydroxyphenyl)tetrahydroisoquinoline **8h** in 17% overall yield instead of the ethoxy-substituted product. This apparently indicates an unfavorable effect of the bulky *o*-substituent on the cyclization that causes a decrease in its rate and hydrolysis of the EtO group to phenolic OH (see the detailed mechanism in the Supporting Information).

In conclusion, we developed a straightforward and flexible approach to the construction of aza-polycycles from aromatic aldehydes that consisted of the sequential [3 + 2]-cycloaddition of nonstabilized azomethine ylides and acid-catalyzed recyclization of intermediate 5-aryloxazolidines. This new method is of great value owing to its desirable features including a rapid increase in molecular complexity, atom-economy, and readily available materials, and it is expected to find widespread use in the synthesis of 4-aryltetrahydroisoquinolines as well as their constrained analogues—6,12-methanodibenzo[*c*,*f*]azocines.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04401.

Detailed experimental procedures and compound characterization data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: mvslc@mail.ru.

ORCID

Vladimir S. Moshkin: 0000-0001-7673-1852

Notes

The authors declare no competing financial interest.

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