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HCl-mediated cascade cyclocondensation of oxygenated arylacetic acids with arylaldehydes: one-pot synthesis of 1-arylisoquinolines†

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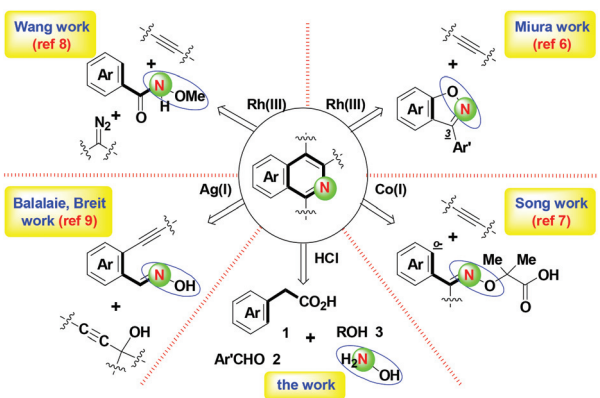
In this paper, a concise, open-vessel synthesis of 1-arylisoquinolines is described *via* HCl-mediated intermolecular cyclocondensation of oxygenated arylacetic acids with arylaldehydes in the presence of NH_2OH and alcoholic solvents under mild and one-pot reaction conditions. A plausible mechanism is proposed and discussed herein. In the overall reaction process, only water was generated as the byproduct. Various environmentally friendly reaction conditions are investigated for convenient transformation *via* the (4C + 1C + 1N) annulation. This protocol provides a highly effective ring closure *via* the formations of one carbon–carbon (C–C) bond, two carbon–nitrogen (C–N) bonds and one carbon–oxygen (C–O) bond.

Introduction

The core structure of isoquinoline is frequently found in natural products, bioactive molecules, functionalized materials and synthetic intermediates.[1–3] However, traditional approaches (*e.g.* Bischler–Napieralski reaction, Pomeranz–Fritsch reaction and Pictet–Spengler reaction) often result in poor functional group tolerance and harsh reaction conditions.[4,5] Therefore, it is highly desirable to explore a facile-operational, efficient synthetic route that possesses simple and mild reaction conditions, less expensive reagents and uncomplicated starting substrates.

Among the previous studies on the synthesis of isoquinoline, most methods adopted an amine group (a N atom) as the source of the nitrogen atom, while only a few reports were documented for the nitrogen atom that originated from a hydroxylamine synthon (a labile N–O linkage). As shown in Scheme 1, by using Cp*Rh(III) as the catalyst, Miura *et al.* demonstrated the facile synthesis of 1-arylisoquinoline through annulative cross-coupling of 3-aryl-1,2-benzisoxazole bearing a N–O bond source with symmetric acetylene.[6] Song *et al.* investigated the preparation of isoquinoline *via* a Cp*-free Co(II)-catalyzed *ortho* C–H promoting activation of a traceless aryloxime derivative followed by annulation with alkynes.[7]

By changing the transition metal from Co(II) to Rh(III), Wang *et al.* converted the three-component reaction including Weinreb amide, α-diazoester and alkyne into various isoquinolines smoothly.[8] Besides the difference of the catalyst, the Song[7] and Wang[8] teams focused on similar starting substrates, benzamide oxime and alkyne respectively. Furthermore, Balalaie and Breit reported Ag(I)-promoted one-pot tandem annulation of *o*-alkynylbenzaldoxime (a conjugation of alkyne and benzamide oxime) with propargylic alcohol.[9] On the basis of the recent examples of the N–O bond cleavage-mediated synthesis of the isoquinoline core, we herein present an efficient synthetic route towards diverse 1-arylisoquinolines *via* HCl-mediated cascade cyclocondensation of oxygenated arylacetic acids **1** with arylaldehydes **2** in the presence of NH_2OH and alcoholic solvents. In the intermolecular multicomponent



Scheme 1 Labile N–O bond activation synthetic routes toward functionalized isoquinolines.

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†Electronic supplementary information (ESI) available: Scanned photocopies of NMR spectral data for all compounds and X-ray analysis data of **4r**, **4x** and **6e**. CCDC 2000637–2000639. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0ob02431g

(4C + 1C + 1N) annulation process, water is the only by-product obtained. This experiment is based on clean and environmentally friendly reaction conditions that provide valuable isoquinoline products. In contrast to the above-discussed benzamide or oxime, NH_2OH-HCl is a simple synthon that can provide a nitrogen atom for the formation of isoquinoline. To the best of our knowledge, no similar report has been published regarding the generation of functionalized isoquinoline by combining carboxylic acid, aldehyde, alcohol and hydroxylamine.

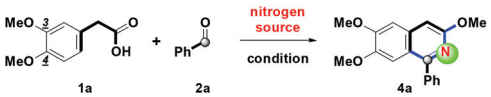
Results and discussion

According to the previous studies on the synthetic applications of oxygenated arylacetic acids and the ongoing efforts to emphasize the synthesis of benzofused molecules,[10] the initial research began by including an NH_2OH-HCl (a nitrogen source)-promoted reaction of model homoveratric acid (**1a**, Ar = 3,4-$(MeO)_2C_6H_3$, 1.0 mmol) and benzaldehyde (**2a**, Ar′ = Ph, 1.0 equiv.) in different solvents (10 mL). First, by the addition of NH_2OH-HCl (1.1 equiv.) and MeOH (**3a**), **4a** was obtained in a 21% yield at 25 °C after 5 h *via* intermolecular cascade annulation (Table 1, entry 1). On the basis of the results, we examined the optimal annulation conditions in the next step. By using 1.1 equivalent of NH_2OH-HCl as a nitrogen synthon and 10 mL of methanol as the reaction solvent, we surveyed the parameters associated with the reaction temperature and time which could affect the benzannulation process. However, a slightly higher yield (58%) of **4a** was observed at reflux temperature (65 °C, entry 2). To increase the isolated yield, four elongated times (10, 15, 20 and 25 h) were checked (entries 3–6). The results showed that 10 h and 15 h provided lower yields of 74% and 88% respectively as compared to 20 h where 92% yield was obtained. When the time was changed to 25 h (an additional 5 h), the yield was slightly decreased to 90%. As indicated, a longer reaction time did not improve the yield outcome.

Two commercially available nitrogen sources with the N–O bonding were tested at 65 °C and 20 h (entries 7 and 8). After changing the nitrogen source from NH_2OH-HCl to NH_2OMe-HCl and NH_2OBn-HCl, neither of them resulted in higher yields, which were only 72% and 58% respectively of **4a**. Furthermore, a stoichiometric amount of NH_2OH-HCl was studied. When the amount of NH_2OH-HCl was increased to 1.5 and 2.0 equivalents, lower yields of 78% and 68%, respectively, were provided (entries 9 and 10). From these observations, we concluded that 1.1 equivalent of NH_2OH-HCl provided an optimal condition for the generation of **4a** (for entry 5) *via* the intermolecular cyclocondensation of **1a** with **2a** in MeOH. Encouraged by the above-mentioned reaction conditions (entries 1–10), after replacing NH_2OH-HCl with 50% aqueous NH_2OH, the desired **4a** was obtained in trace amounts (10%) along with a 66% yield of benzaldehyde oxime with a mixture of *E*- and *Z*-isomers (entry 11). However, after the use of $HCl_{(aq)}$ (37%, 0.1 mL), a 72% yield of **4a** was observed (entry 12). The results suggested that HCl played a key role during the annulation process. By maintaining the nitrogen source as NH_2OH-HCl, two solvents were screened (entries 13 and 14). By changing the solvent to MeCN, no reaction process was detected as MeCN consumed NH_2OH-HCl such that **4a** could not be isolated under the reflux (82 °C) condition. Additionally, it was observed that $MeNO_2$ provided complex and unidentified mixtures as the major products. The reason for this could be that the *in situ* formed intermediate was unstable under the refluxing $MeNO_2$ (101 °C) condition. In particular, NH_2NH_2-2HCl could also provide **4a** in an 80% yield (entry 15). From the experimental data, it is obvious that NH_2OH-HCl provided better results than NH_2NH_2-2HCl. On the basis of the above-mentioned results, we can conclude that entry 5 provided the optimal conditions for the formation of **4a** (92%) *via* an intermolecular benzannulation of **1a** with **2a** in MeOH.

On the basis of the results, the plausible reaction mechanism of **4a** is illustrated in Scheme 2. Initially, coupling of **2a** with NH_2OH-HCl yielded oxime **A** and water *via* a condensation reaction. With the use of **1a**, a lone pair of nitrogen atoms on **A** promoted the acylation to lead to **B** with an ammonium ion. Following the Pictet–Spengler-type intramolecular ring closure, the C3-methoxy group on the benzene ring triggered the *p*-carbon to attack oximium, thereby generating **C**. After chloride-mediated dehydrogenative aromatization, **D** could be formed spontaneously. By the use of *in situ* generated HCl, both dehydration of **D** and protonation of **E** could give **F** having a conjugated cyclohexdienyl system. Sequentially, the addition reaction of **F** with MeOH resulted in **G**. Finally, proton exchange from **G** to **H** occurred and aromatizative dehydration of **H** took place; **4a** could be obtained along with the

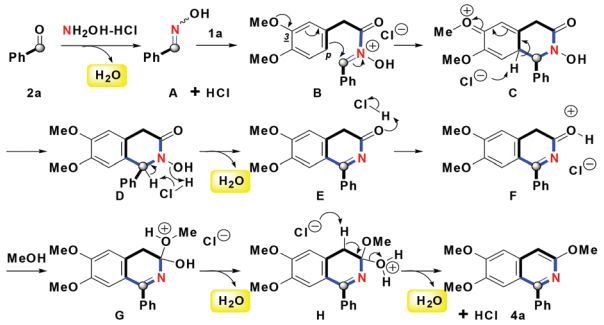
Table 1 Reaction conditions[a]



1a 2a 4a

Entry	Nitrogen source	Solvent	Temperature (°C)	Time (h)	4a[b] (%)
1	NH_2OH-HCl	MeOH	25	5	21
2	NH_2OH-HCl	MeOH	65	5	58
3	NH_2OH-HCl	MeOH	65	10	74
4	NH_2OH-HCl	MeOH	65	15	88
5	NH_2OH-HCl	MeOH	65	20	92
6	NH_2OH-HCl	MeOH	65	25	90
7	NH_2OMe-HCl	MeOH	65	20	72
8	NH_2OBn-HCl	MeOH	65	20	58
9	NH_2OH-HCl[c]	MeOH	65	20	78
10	NH_2OH-HCl[d]	MeOH	65	20	68
11	NH_2OH	MeOH	65	20	<10[e]
12	NH_2OH[f]	MeOH	65	20	72
13	NH_2OH-HCl	MeCN	82	20	—[g]
14	NH_2OH-HCl	$MeNO_2$	101	20	—[h]
15	NH_2NH_2-2HCl	MeOH	65	20	80

[a] Reaction conditions: **1a** (196 mg, 1.0 mmol), **2a** (106 mg, 1.0 equiv.), solvent (10 mL), and NH_2OH-HCl (75 mg, 1.1 equiv.). [b] Isolated yields. [c] 1.5 equiv. [d] 2.0 equiv. [e] Benzaldehyde oxime (66%) was isolated. [f] $HCl_{(aq)}$ (37%, 0.1 mL) was added. [g] No reaction. [h] A complex and unidentified mixture was detected.



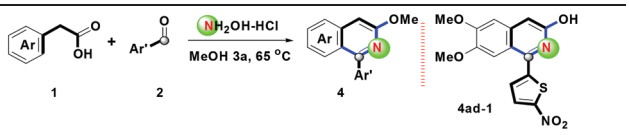
Scheme 2 Plausible mechanism.

formation of water and HCl was recovered. In the overall cyclocondensation process, four equivalents of water were generated.

To explore the substrate scope and limitations of this facile HCl-mediated synthetic route, homoveratric acid (**1a**) and the related derivatives of **1b–1e** were reacted with diverse arylbenzaldehydes **2a–2ad** to afford functionalized 1-arylisoquinolines **4a–4am** in the presence of NH_2OH and MeOH **3a**, as shown in Table 2. On the basis of the established optimal conditions (Table 1, entry 5) and a plausible mechanism (Scheme 2), we found that this route allowed a direct (4C + 1N + 1C) annulation process under easily-operational and environmentally friendly conditions with moderate to good yields (75%–93%). For entries 1–16, efficient formations of **4a–4p** showed that the Ar group with mono-substituent halogens, electron-donating methoxy groups, electron-withdrawing nitro, cyano and trifluoromethyl groups, and methylthio group did not exert any influence on the isolated yields. In entries 17 and 18, bicyclic 2-naphthyl and tricyclic 9-anthryl aromatic groups provided **4q** and **4r** in yields of 83% and 80%, respectively. The molecular structure of **4r** with the anthryl-conjugated isoquinoline was determined by single-crystal X-ray analysis.[11] For the Ar group with di-substituent halogen and oxygen-rich groups, entries 19–23 showed that the yields of **4s–4w** were in the range of 80%–90%. Adjusting the Ar group to combine one nitro group and one oxygenated or methyl group, a similar yield distribution (84%–90%) was observed in the formation of **4x–4aa** (entries 24–27). The structure of **4x** was determined by single-crystal X-ray analysis.[11]

The tri-substituted oxygenated Ar group produced **4ab** and **4ac** in slightly lower yields (79% and 82%, entries 28 and 29, respectively). In particular, entry 30 showed that **4ad** with a heterocyclic nitrothienyl group was afforded in an 83% yield, along with ~5% yield of **4ad-1**. One possible reason for this is that trace amounts of H_2O in MeOH produced the side product **4ad-1**. By changing homoveratric acid (**1a**) to 2,3-methylenedioxyphenylacetic acid (**1b**), **4ae–4aj** were obtained in similar yields (75%–90%, entries 31–36). After elongating the carbon chain from dimethoxy to di-*n*-propoxy on the Ar group (for **1c**), however, the yield of **4ak** was maintained at 80% (entry 37). Additionally, 3,4,5-trimethoxyphenylacetic acid (**1d**) provided **4al** in a slightly lower yield (78%, entry 38).

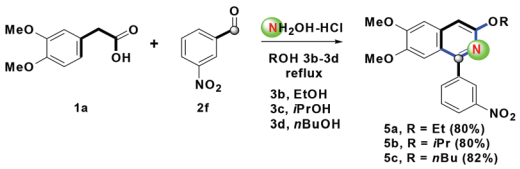
Table 2 Synthesis of **4a–4am** [a]



Entry	**1a**, Ar =	**2**, Ar′ =	**4** [b] (%)
1	**1a**, 3,4-$(MeO)_2C_6H_3$	**2a**, Ph	**4a**, 92
2	**1a**, 3,4-$(MeO)_2C_6H_3$	**2b**, 2-BrC_6H_4	**4b**, 90
3	**1a**, 3,4-$(MeO)_2C_6H_3$	**2c**, 2-$NO_2C_6H_4$	**4c**, 86
4	**1a**, 3,4-$(MeO)_2C_6H_3$	**2d**, 2-FC_6H_4	**4d**, 88
5	**1a**, 3,4-$(MeO)_2C_6H_3$	**2e**, 3-$MeOC_6H_4$	**4e**, 90
6	**1a**, 3,4-$(MeO)_2C_6H_3$	**2f**, 3-$NO_2C_6H_4$	**4f**, 90
7	**1a**, 3,4-$(MeO)_2C_6H_3$	**2g**, 3-$CF_3C_6H_4$	**4g**, 93
8	**1a**, 3,4-$(MeO)_2C_6H_3$	**2h**, 4-FC_6H_4	**4h**, 89
9	**1a**, 3,4-$(MeO)_2C_6H_3$	**2i**, 4-ClC_6H_4	**4i**, 87
10	**1a**, 3,4-$(MeO)_2C_6H_3$	**2j**, 4-$MeSC_6H_4$	**4j**, 90
11	**1a**, 3,4-$(MeO)_2C_6H_3$	**2k**, 4-MeC_6H_4	**4k**, 85
12	**1a**, 3,4-$(MeO)_2C_6H_3$	**2l**, 4-$MeOC_6H_4$	**4l**, 88
13	**1a**, 3,4-$(MeO)_2C_6H_3$	**2m**, 4-$NO_2C_6H_4$	**4m**, 86
14	**1a**, 3,4-$(MeO)_2C_6H_3$	**2n**, 4-$CF_3C_6H_4$	**4n**, 90
15	**1a**, 3,4-$(MeO)_2C_6H_3$	**2o**, 4-NCC_6H_4	**4o**, 93
16	**1a**, 3,4-$(MeO)_2C_6H_3$	**2p**, 4-PhC_6H_4	**4p**, 90
17	**1a**, 3,4-$(MeO)_2C_6H_3$	**2q**, 2-naphthyl	**4q**, 83
18	**1a**, 3,4-$(MeO)_2C_6H_3$	**2r**, 9-anthryl	**4r**, 80
19	**1a**, 3,4-$(MeO)_2C_6H_3$	**2s**, 3,4-$Cl_2C_6H_3$	**4s**, 83
20	**1a**, 3,4-$(MeO)_2C_6H_3$	**2t**, 3,4-$F_2C_6H_3$	**4t**, 90
21	**1a**, 3,4-$(MeO)_2C_6H_3$	**2u**, 2-F-6-ClC_6H_3	**4u**, 89
22	**1a**, 3,4-$(MeO)_2C_6H_3$	**2v**, 3,4-$(MeO)_2C_6H_3$	**4v**, 82
23	**1a**, 3,4-$(MeO)_2C_6H_3$	**2w**, 3,4-$CH_2O_2C_6H_3$	**4w**, 80
24	**1a**, 3,4-$(MeO)_2C_6H_3$	**2x**, 3-NO_2-6-$MeOC_6H_3$	**4x**, 88
25	**1a**, 3,4-$(MeO)_2C_6H_3$	**2y**, 3-NO_2-4-$MeOC_6H_3$	**4y**, 86
26	**1a**, 3,4-$(MeO)_2C_6H_3$	**2z**, 3-NO_2-6-$C_5H_9OC_6H_3$	**4z**, 84
27	**1a**, 3,4-$(MeO)_2C_6H_3$	**2aa**, 3-NO_2-4-MeC_6H_3	**4aa**, 90
28	**1a**, 3,4-$(MeO)_2C_6H_3$	**2ab**, 2,3,4-$(MeO)_3C_6H_2$	**4ab**, 79
29	**1a**, 3,4-$(MeO)_2C_6H_3$	**2ac**, 3,4,5-$(MeO)_3C_6H_2$	**4ac**, 82
30	**1a**, 3,4-$(MeO)_2C_6H_3$	**2ad**, 5-NO_2-2-thienyl	**4ad**, 83[c]
31	**1b**, 3,4-$CH_2O_2C_6H_3$	**2f**, 3-$NO_2C_6H_4$	**4ae**, 90
32	**1b**, 3,4-$CH_2O_2C_6H_3$	**2m**, 4-$NO_2C_6H_4$	**4af**, 90
33	**1b**, 3,4-$CH_2O_2C_6H_3$	**2v**, 3,4-$(MeO)_2C_6H_3$	**4ag**, 80
34	**1b**, 3,4-$CH_2O_2C_6H_3$	**2w**, 3,4-$CH_2O_2C_6H_3$	**4ah**, 80
35	**1b**, 3,4-$CH_2O_2C_6H_3$	**2ab**, 2,3,4-$(MeO)_3C_6H_2$	**4ai**, 75
36	**1b**, 3,4-$CH_2O_2C_6H_3$	**2ac**, 3,4,5-$(MeO)_3C_6H_2$	**4aj**, 87
37	**1c**, 3,4-$(n$PrO$)_2C_6H_3$	**2v**, 3,4-$(MeO)_2C_6H_3$	**4ak**, 80
38	**1d**, 3,4,5-$(MeO)_3C_6H_2$	**2v**, 3,4-$(MeO)_2C_6H_3$	**4al**, 78
39	**1e**, 3-$MeOC_6H_4$	**2v**, 3,4-$(MeO)_2C_6H_3$	**4am**, 78

[a] Reaction conditions: Oxygenated arylacetic acids **1** (1.0 mmol), arylaldehydes **2** (1.0 equiv.), NH_2OH-HCl (75 mg, 1.1 equiv.), and MeOH **3a** (10 mL) for 20 h at 65 °C. [b] Isolated yields. [c] **4ad-1** (~5%) was isolated.

Regarding the association of **1e** with the 3-methoxyphenyl group, **4am** was afforded in a 78% yield (entry 39). Furthermore, NH_2OH-HCl-promoted cyclocondensation of **1a** with hexanal (an aliphatic aldehyde) in the presence of MeOH **3a** was examined. However, only hexyl oxime was detected. We observed that oxime–enamine tautomerization was easily triggered such that a desirable amount of 1-pentylisoquinoline was not generated. Although the substrate was limited to alkanals, the expeditious synthetic route sets up the 1-arylisoquinoline skeleton, including the formation of one carbon–carbon (C–C) single bond, one carbon–nitrogen (C–N) single bond and one carbon–nitrogen (C=N) double bond *via* a tandem (4C + 1C + 1N) benzannulation process.



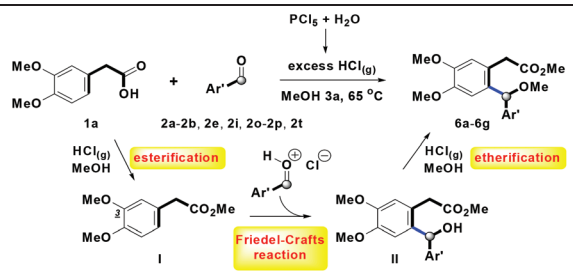
Scheme 3 Synthesis of 5a–5c.

By using the starting homoveratric acid (**1a**) and 3-nitrobenzaldehyde (**2f**) as the sources of arylacetic acid and arylaldehyde, different alcohols **3b–3e** (**3b**, EtOH; **3c**, iPrOH; **3d**, *n*BuOH) were screened next (Scheme 3). By the use of four alcoholic solvents, **5a–5c** were produced in 80%, 80% and 82% yields, respectively. From the above-mentioned observations, we concluded that the synthesis of the 1-arylisoquinoline skeleton with different 3-alkoxy (3-RO) substituents could be accomplished by using different alcoholic solvents.

Encouraged by the above experimental results, gaseous HCl-mediated reactions of homoveratric acid **1a** with arylaldehydes **2a**, **2b**, **2e**, **2i**, **2o**, **2p** and **2t** were studied next in the presence of MeOH **3a** (Table 3). By removing the nitrogen source of NH_2OH, **6a–6g** were obtained in a yield range of 70%–80%. In entries 1–7, efficient formation of **6a–6g** showed that the Ar substituent with mono- or di-halogen groups, electron-donating 3-methoxy group, electron-withdrawing 4-cyano group and biphenyl group were well tolerated. The structure of **6e** was determined by single-crystal X-ray analysis.[11] Gaseous HCl was freshly prepared from the reaction between PCl_5 and water (general equation, $PCl_5 + 4H_2O \rightarrow H_3PO_4 + 5HCl$). For the proposed mechanism, *in situ* generated HCl triggered the initial esterification of **1a** and provided **I**. Then, the C3-methoxy group on the benzene ring promoted the *p*-carbon to attack the oxocarbenium ion of **2a**, **2b**, **2e**, **2i**, **2o**, **2p** and **2t** (formed from the reaction of arylaldehydes with $HCl_{(g)}$) generating **II** *via* a Friedel–Crafts process. Finally, excess $HCl_{(g)}$-mediated etherification of **II** with MeOH **3a** provided **6a–6g**. This was an efficient transformation for preparing the skeleton of benzhydryl ether. Benzhydryl derivatives are widely used as intermediates in pharmaceuticals (including antihistamines) and other organic compounds.[12,13] They are also used as precursors to prepare modafinil,[14] benztropine[15] and diphenhydramine.[16] Furthermore, conversion from benzhydryl derivatives to 1-arylisoquinolines was examined. Under the refluxing MeOH condition, treatment of **6a** with NH_2OH-HCl could provide **4a** in a good yield (88%).

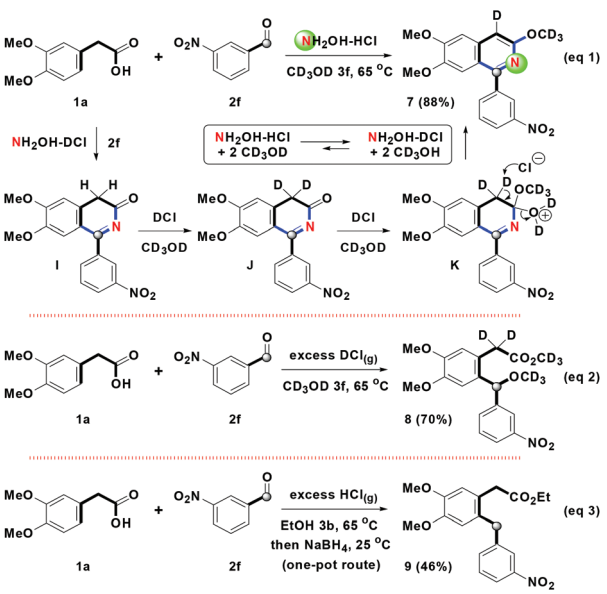
Based on the above results, **7** with one deuterium and one deuterium methyl-labelling was isolated in an 88% yield after changing MeOH **3a** to CD_3OD **3f** (Scheme 4, eqn (1)). For the one-pot formation of 1-arylisoquinoline, this important result confirmed the proposed reaction mechanism. After the reaction equilibrium was achieved, we envisioned that the reaction equation "NH_2OH-HCl + CD_3OD ⇄ NH_2OH-DCl + CD_3OH" occurred easily under reflux temperature conditions.[17,18] Similar to intermediate **E** of Scheme 2, **I** could be generated by the *in situ* formation of the NH_2OH-DCl-promoted stepwise pathway. Following that, **I** could be converted into **J** by proton exchange from two α-hydrogen to α-deuterium atoms. Furthermore, by the use of CD_3OD and DCl, the releasing chloride-mediated dehydrogenative aromatization could afford **7**. Changing the condition from NH_2OH-HCl to DCl, the reaction of **1a** with **2f** produced **8** in a 70% yield (eqn (2)). Specifically, **8** exhibited eight deuterium atoms, including one deuterium methoxy and one deuterium methyl ester group and two α-deuterium atoms. The possible reaction mechanism was similar as shown in Table 3. These steps included (1) esterification of **1a** with CD_3OD in the presence of DCl, (2) the Friedel–Crafts reaction of the resulting ester with **2a**, (3) the

Table 3 Synthesis of **6a–6g** [a]



Entry	2, Ar =	6 [b] (%)
1	**2a**, Ph	**6a**, 73
2	**2b**, 2-BrC_6H_4	**6b**, 78
3	**2e**, 3-$MeOC_6H_4$	**6c**, 74
4	**2i** 4-ClC_6H_4	**6d**, 76
5	**2o**, 4-NCC_6H_4	**6e**, 70
6	**2p**, 4-PhC_6H_4	**6f**, 80
7	**2t**, 3,4-$F_2C_6H_4$	**6g**, 73

[a] Reaction conditions: **1a** (196 mg, 1.0 mmol), **2** (1.0 equiv.), MeOH **3a** (10 mL), and excess freshly prepared gaseous HCl. [b] Isolated yields.



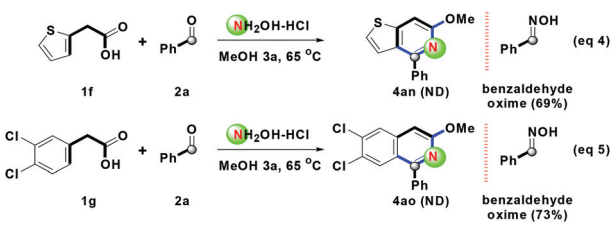
Scheme 4 Synthesis of **7**, **8** and **9**.

proton–deuterium exchange, and (4) etherification with CD_3OD. On the other hand, by the use of $NaBH_4$, the removal of the secondary alkoxy group on the benzhydryl skeleton was investigated. By using the above $HCl_{(g)}$-mediated reaction condition (eqn (3)), the reaction of **1a** with **2f** in the presence of EtOH **3b** generated the initial structure of ester **6**. Sequentially, $NaBH_4$-mediated reduction afforded **9** in a 46% yield. Compared with the ester, the reduction condition was preferred to transform benzhydryl ether into diarylmethane.

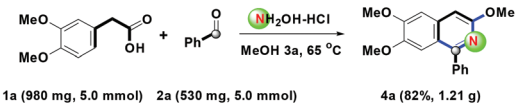
To understand the electronic influences of the aromatic ring (for Ar) on **1**, the electron-rich 2-thienyl (for **1f**) and 3,4-dichlorophenyl (for **1g**) groups were examined for the (4C + 1C + 1N) annulation (Scheme 5) under the above reaction conditions. In the presence of NH_2OH-HCl, the reaction of **1f** with **2a** provided only benzaldehyde oxime in a 69% yield and the desired product **4an** could not be isolated (eqn (4)). Next, by changing **1f** to **1g**, however, the expected **4ao** could not be obtained and only benzaldehyde oxime was yielded (73%, eqn (5)). Under the standard reaction conditions, the two results were similar. From this phenomenon, we understood that an oxygenated group could enrich the electron density of the Ar ring easily than 2-thienyl and 3,4-dichlorophenyl groups. Although substrate **1** was limited to the oxygenated aryl group, it still provided a novel and efficient synthesis of the 1-arylisoquinoline skeleton.

Because of the potential application of this protocol in the synthesis of various 1-arylisoquinolines, attempts to scale up the transformation would improve the significance of the results. Thus, the development of a gram-scale route was in high demand. As shown in Scheme 6, cyclocondensation of **1a** (980 mg, 5.0 mmol) and **2a** (530 mg, 5.0 mmol) could produce **4a** in an 82% (1.21 g) yield in the presence of NH_2OH-HCl under the refluxing MeOH **3a** condition. Compared with the 1 mmol scale (92%), 5 mmol provided a slightly lower yield (82%). Although the obtained yield was lower, the gram-scale synthetic route of 1-arylisoquinolines was well established.

In summary, we have developed a facile and environmentally friendly (4C + 1C + 1N) annulation route for the synthesis of 1-arylisoquinolines *via* HCl-mediated intermolecular cyclocondensation of oxygenated arylacetic acids with arylaldehydes in the presence of NH_2OH and alcoholic solvents. The synthesis of benzhydryl derivatives was also discussed. The structures of the key products were confirmed by X-ray crystallography. The uses of various reaction conditions and related plausible mechanisms were investigated and proposed for efficient transformation. Further investigations regarding the synthetic application of oxygenated arylacetic acids will be conducted and published in due course.



Scheme 5 Reactions of **1f** and **1g** with **2a**.



Scheme 6 Gram-scale synthesis of **4a**.

Experimental

General

All reagents and solvents were obtained from commercial sources and used without further purification. Reactions were routinely carried out under an atmosphere of dry air with magnetic stirring. Products in organic solvents were dried with anhydrous magnesium sulfate before concentration *in vacuo*. Melting points were determined with an SMP3 melting apparatus. ^1H and ^{13}C NMR spectra were recorded on a Varian INOVA-400 spectrometer operating at 400 and 100 MHz, respectively. Chemical shifts (δ) are reported in parts per million (ppm) and the coupling constants (J) are given in hertz. High resolution mass spectra (HRMS) were measured with a mass spectrometer Finnigan/Thermo Quest MAT 95XL. X-ray crystal structures were obtained with an Enraf-Nonius FR-590 diffractometer (CAD4, Kappa CCD).

The starting substrates oxygenated arylacetic acids **1a–1g** and arylaldehydes **2a–2ad** were purchased commercially and were used without further purification.

General synthetic procedure of 4a–4am

NH_2OH-HCl (75 mg, 1.1 mmol) was added to a solution of substituted arylaldehydes **2a–2ad** (1.0 mmol) in methanol **3a** (5 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 15 min. A solution of oxygenated arylacetic acids **1a–1e** (1.0 mmol) in methanol **3a** (5 mL) was added to the reaction mixture at 25 °C. The reaction mixture was stirred at reflux for 20 h. The reaction mixture was cooled to 25 °C and the solvent was concentrated. The residue was diluted with water (10 mL) and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford the crude product under reduced pressure. Purification on silica gel (hexanes/EtOAc = 8/1–4/1) afforded **4a–4am**.

3,6,7-Trimethoxy-1-phenylisoquinoline (4a). **4a** was prepared according to the general synthetic procedure from **1a** (196 mg, 1.0 mmol), **2a** (106 mg, 1.0 mmol) and MeOH **3a** (10 mL); yield = 92% (272 mg); white solid; mp = 80–82 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{18}NO_3$ 296.1287, found 296.1292; ^1H NMR (400 MHz, $CDCl_3$): δ 7.76–7.73 (m, 2H), 7.54–7.44 (m, 3H), 6.73 (s, 1H), 6.97 (s, 1H), 6.88 (s, 1H), 4.02 (s, 3H), 4.00 (s, 3H), 3.83 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 159.7, 156.1, 153.1,

148.2, 139.6, 137.7, 129.8 (2x), 128.4, 128.2 (2x), 118.4, 105.2, 103.8, 99.7, 55.9, 55.7, 54.0.

1-(2-Bromophenyl)-3,6,7-trimethoxyisoquinoline (4b). **4b** was prepared according to the general synthetic procedure from **1a** (196 mg, 1.0 mmol), **2b** (184 mg, 1.0 mmol) and MeOH **3a** (10 mL); yield = 90% (336 mg); colorless liquid; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{18}H_{17}BrNO_3$ 374.0392, found 374.0387; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, J = 8.0 Hz, 1H), 7.47–7.45 (m, 2H), 7.36–7.32 (m, 1H), 6.99 (s, 1H), 6.65 (d, J = 0.8 Hz, 1H), 6.72 (s, 1H), 4.02 (s, 3H), 4.00 (s, 3H), 3.77 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 159.6, 155.3, 153.3, 148.4, 140.1, 137.1, 132.9, 131.5, 129.8, 127.3, 123.0, 119.0, 104.9, 103.7, 100.4, 56.0, 55.8, 54.3.

3,6,7-Trimethoxy-1-(2-nitrophenyl)isoquinoline (4c). **4c** was prepared according to the general synthetic procedure from **1a** (196 mg, 1.0 mmol), **2c** (151 mg, 1.0 mmol) and MeOH **3a** (10 mL); yield = 86% (292 mg); colorless liquid; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{18}H_{17}N_2O_5$ 341.1138, found 341.1132; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (dd, J = 1.2, 8.4 Hz, 1H), 7.74 (dt, J = 1.2, 7.6 Hz, 1H), 7.67–7.61 (m, 2H), 6.99 (s, 1H), 6.93 (s, 1H), 6.83 (s, 1H), 3.93 (s, 6H), 3.78 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 159.5, 153.5, 151.7, 148.9, 137.5, 132.6, 132.1, 129.4, 124.6, 118.7, 116.9, 114.5, 104.0, 103.4, 101.0, 56.0, 55.8, 54.2.

1-(2-Fluorophenyl)-3,6,7-trimethoxyisoquinoline (4d). **4d** was prepared according to the general synthetic procedure from **1a** (196 mg, 1.0 mmol), **2d** (124 mg, 1.0 mmol) and MeOH **3a** (10 mL); yield = 88% (276 mg); white solid; mp = 113–115 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{18}H_{17}FNO_3$ 314.1193, found 314.1187; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (dt, J = 2.0, 7.6 Hz, 1H), 7.50–7.44 (m, 1H), 7.31 (dt, J = 1.2, 7.6 Hz, 1H), 7.23 (dt, J = 1.2, 7.6 Hz, 1H), 6.99 (s, 1H), 6.94 (s, 1H), 6.91 (d, J = 3.2 Hz, 1H), 4.02 (s, 3H), 4.01 (s, 3H), 3.82 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 159.9 (d, J = 247.2 Hz), 159.8, 153.4, 151.1, 148.5, 137.2, 132.2 (d, J = 3.8 Hz), 130.4 (d, J = 8.3 Hz), 127.1 (d, J = 16.0 Hz), 124.3 (d, J = 3.8 Hz), 119.5, 115.8 (d, J = 21.2 Hz), 104.9 (d, J = 3.0 Hz), 103.7, 100.5, 56.0, 55.7, 54.2.

3,6,7-Trimethoxy-1-(3-methoxyphenyl)isoquinoline (4e). **4e** was prepared according to the general synthetic procedure from **1a** (196 mg, 1.0 mmol), **2e** (136 mg, 1.0 mmol) and MeOH **3a** (10 mL); yield = 90% (293 mg); colorless liquid; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{19}H_{20}NO_4$ 326.1392, found 326.1385; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (t, J = 8.0 Hz, 1H), 7.33 (s, 1H), 7.32–7.29 (m, 2H), 7.02 (ddd, J = 0.8, 2.4, 8.0 Hz, 1H), 6.98 (s, 1H), 6.88 (s, 1H), 4.02 (s, 3H), 4.01 (s, 3H), 3.87 (s, 3H), 3.84 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 159.63, 159.57, 155.9, 153.1, 148.2, 140.9, 137.7, 129.2, 122.2, 118.5, 115.1, 114.4, 105.2, 103.8, 99.8, 55.9, 55.8, 55.3, 54.0.

3,6,7-Trimethoxy-1-(3-nitrophenyl)isoquinoline (4f). **4f** was prepared according to the general synthetic procedure from **1a** (196 mg, 1.0 mmol), **2f** (151 mg, 1.0 mmol) and MeOH **3a** (10 mL); yield = 90% (306 mg); white solid; mp = 188–190 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{18}H_{17}N_2O_5$ 341.1138, found 341.1132; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (t, J = 1.6 Hz, 1H), 8.34 (ddd, J = 0.8, 2.4, 8.0 Hz, 1H), 8.12 (dt, J = 2.4, 8.0 Hz, 1H), 7.72 (t, J = 8.0 Hz, 1H), 7.17 (s, 1H), 7.02 (s, 1H), 6.97 (s, 1H), 4.04 (s, 6H), 3.85 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 159.6, 153.6, 152.7, 149.1, 148.3, 140.8, 138.2, 135.9, 129.4, 124.9, 123.4, 118.3, 104.1, 103.9, 101.1, 56.1, 55.9, 54.3.

3,6,7-Trimethoxy-1-(3-trifluoromethylphenyl)isoquinoline (4g). **4g** was prepared according to the general synthetic procedure from **1a** (196 mg, 1.0 mmol), **2g** (174 mg, 1.0 mmol) and MeOH **3a** (10 mL); yield = 93% (338 mg); white solid; mp = 109–111 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{19}H_{17}F_3NO_3$ 364.1161, found 364.1153; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (s, 1H), 7.95 (d, J = 7.6 Hz, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.65 (t, J = 7.6 Hz, 1H), 7.20 (s, 1H), 6.99 (s, 1H), 6.91 (s, 1H), 4.03 (s, 3H), 4.02 (s, 3H), 3.83 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 159.8, 154.2, 153.2, 148.6, 140.4, 137.8, 133.1, 130.7 (q, J = 32.6 Hz), 128.8, 126.8 (q, J = 3.8 Hz), 125.1 (q, J = 3.8 Hz), 124.1 (q, J = 270.6 Hz), 118.4, 104.4, 103.9, 100.5, 56.0, 55.7, 54.0.

1-(4-Fluorophenyl)-3,6,7-trimethoxyisoquinoline (4h). **4h** was prepared according to the general synthetic procedure from **1a** (196 mg, 1.0 mmol), **2h** (124 mg, 1.0 mmol) and MeOH **3a** (10 mL); yield = 89% (279 mg); white solid; mp = 139–141 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{18}H_{17}FNO_3$ 314.1193, found 314.1186; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74–7.70 (m, 2H), 7.24–7.19 (m, 2H), 7.23 (s, 1H), 6.99 (s, 1H), 6.89 (s, 1H), 4.022 (s, 3H), 4.019 (s, 3H), 3.84 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 163.0 (d, J = 246.3 Hz), 159.6, 155.0, 153.3, 148.4, 137.8, 135.4, 131.6 (d, J = 8.4 Hz, 2x), 118.4, 115.3 (d, J = 21.2 Hz, 2x), 105.0, 103.9, 99.8, 56.0, 55.8, 54.1.

1-(4-Chlorophenyl)-3,6,7-trimethoxyisoquinoline (4i). **4i** was prepared according to the general synthetic procedure from **1a** (196 mg, 1.0 mmol), **2i** (140 mg, 1.0 mmol) and MeOH **3a** (10 mL); yield = 87% (286 mg); white solid; mp = 147–149 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{18}H_{17}ClNO_3$ 330.0897, found 330.0893; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, J = 8.4, 2H), 7.49 (d, J = 8.8 Hz, 2H), 7.21 (s, 1H), 6.97 (s, 1H), 6.88 (s, 1H), 4.009 (s, 3H), 4.006 (s, 3H), 3.84 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 159.6, 154.7, 153.2, 148.4, 138.0, 137.8, 134.5, 131.1 (2x), 128.5 (2x), 118.4, 104.7, 103.9, 100.1, 56.0, 55.8, 54.0.

3,6,7-Trimethoxy-1-(4-methylsulfanylphenyl)isoquinoline (4j). **4j** was prepared according to the general synthetic procedure from **1a** (196 mg, 1.0 mmol), **2j** (152 mg, 1.0 mmol) and MeOH **3a** (10 mL); yield = 90% (307 mg); white solid; mp = 180–182 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{19}H_{20}NO_3S$ 342.1164, found 342.1169; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, J = 8.4 Hz, 2H), 7.81 (d, J = 8.4 Hz, 2H), 7.20 (s, 1H), 7.00 (s, 1H), 6.93 (s, 1H), 4.027 (s, 3H), 4.025 (s, 3H), 3.84 (s, 3H), 2.82 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 159.5, 154.2, 153.6, 148.8, 146.0, 138.1, 130.9 (2x), 125.9, 123.7 (2x), 118.4, 104.5, 104.0, 100.5, 56.1, 55.9, 54.3, 43.9.

3,6,7-Trimethoxy-1-*p*-tolylisoquinoline (4k). **4k** was prepared according to the general synthetic procedure from **1a** (196 mg, 1.0 mmol), **2k** (120 mg, 1.0 mmol) and MeOH **3a** (10 mL);

yield = 85% (263 mg); white solid; mp = 100–102 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{19}H_{20}NO_3$ 310.1443, found 310.1436; ^1H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, J = 8.0 Hz, 2H), 7.333 (s, 1H), 7.332 (d, J = 7.6 Hz, 2H), 6.98 (s, 1H), 6.87 (s, 1H), 4.024 (s, 3H), 4.018 (s, 3H), 3.84 (s, 3H), 2.46 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 159.5, 156.1, 153.2, 148.2, 138.5, 137.8, 136.4, 129.8 (2x), 129.0 (2x), 118.5, 105.5, 103.9, 99.5, 56.0, 55.8, 54.1, 21.3.

3,6,7-Trimethoxy-1-(4-methoxyphenyl)isoquinoline (4l). 4l was prepared according to the general synthetic procedure from **1a** (196 mg, 1.0 mmol), **2l** (136 mg, 1.0 mmol) and MeOH **3a** (10 mL); yield = 88% (286 mg); white solid; mp = 97–99 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{19}H_{20}NO_4$ 326.1392, found 326.1397; ^1H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, J = 9.2 Hz, 2H), 7.33 (s, 1H), 7.05 (d, J = 8.8 Hz, 2H), 6.97 (s, 1H), 6.84 (s, 1H), 4.02 (s, 3H), 4.01 (s, 3H), 3.89 (s, 3H), 3.85 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 159.9, 159.5, 155.8, 153.1, 148.2, 137.8, 131.8, 131.1 (2x), 118.4, 113.7 (2x), 105.4, 103.9, 99.2, 55.9, 55.8, 55.3, 54.1.

3,6,7-Trimethoxy-1-(4-nitrophenyl)isoquinoline (4m). 4m was prepared according to the general synthetic procedure from **1a** (196 mg, 1.0 mmol), **2m** (151 mg, 1.0 mmol) and MeOH **3a** (10 mL); yield = 86% (292 mg); white solid; mp = 242–244 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{18}H_{17}N_2O_5$ 341.1138, found 341.1132; ^1H NMR (400 MHz, $CDCl_3$): δ 8.38 (d, J = 8.8 Hz, 2H), 7.92 (d, J = 8.4 Hz, 2H), 7.15 (s, 1H), 7.01 (s, 1H), 6.96 (s, 1H), 4.03 (s, 3H), 4.02 (s, 3H), 3.85 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 159.7, 153.4, 153.1, 149.0, 147.7, 146.0, 138.0, 130.8 (2x), 123.6 (2x), 118.4, 104.0, 103.9, 101.2, 56.1, 55.9, 54.2.

3,6,7-Trimethoxy-1-(4-trifluoromethylphenyl)isoquinoline (4n). 4n was prepared according to the general synthetic procedure from **1a** (196 mg, 1.0 mmol), **2n** (174 mg, 1.0 mmol) and MeOH **3a** (10 mL); yield = 90% (327 mg); white solid; mp = 153–155 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{19}H_{17}F_3NO_3$ 364.1161, found 364.1156; ^1H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, J = 8.0 Hz, 2H), 7.78 (d, J = 8.0 Hz, 2H), 7.19 (s, 1H), 6.97 (s, 1H), 6.91 (s, 1H), 4.01 (s, 6H), 3.83 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 159.7, 154.2, 153.2, 148.6, 143.3, 137.8, 130.3 (q, J = 32.6 Hz), 130.1 (2x), 124.2 (q, J = 269.6 Hz), 125.2 (q, J = 3.8 Hz, 2x), 118.4, 104.4, 103.9, 100.6, 55.9, 55.8, 53.9.

4-(3,6,7-Trimethoxyisoquinolin-1-yl)benzonitrile (4o). 4o was prepared according to the general synthetic procedure from **1a** (196 mg, 1.0 mmol), **2o** (131 mg, 1.0 mmol) and MeOH **3a** (10 mL); yield = 93% (298 mg); white solid; mp = 205–207 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{19}H_{17}N_2O_3$ 321.1239, found 321.1244; ^1H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, J = 8.0 Hz, 2H), 7.82 (d, J = 8.0 Hz, 2H), 7.14 (s, 1H), 7.00 (s, 1H), 6.94 (s, 1H), 4.03 (s, 3H), 4.02 (s, 3H), 3.84 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 159.7, 153.5, 153.4, 148.9, 144.0, 138.0, 132.2 (2x), 130.5 (2x), 118.7, 118.3, 112.2, 104.03, 104.01, 101.0, 56.1, 55.8, 54.2.

1-Biphenyl-4-yl-3,6,7-trimethoxyisoquinoline (4p). 4p was prepared according to the general synthetic procedure from **1a** (196 mg, 1.0 mmol), **2p** (182 mg, 1.0 mmol) and MeOH **3a** (10 mL); yield = 90% (334 mg); white solid; mp = 173–175 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{24}H_{22}NO_3$ 372.1600, found 372.1593; ^1H NMR (400 MHz, $CDCl_3$): δ 7.86–7.76 (m, 4H), 7.71–7.69 (m, 2H), 7.51–7.47 (m, 2H), 7.41–7.37 (m, 2H), 7.02 (s, 1H), 6.92 (s, 1H), 4.06 (s, 3H), 4.04 (s, 3H), 3.87 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 159.4, 155.5, 153.6, 148.6, 141.6, 140.6, 138.1, 134.5, 130.4 (2x), 128.9 (2x), 127.6, 127.2 (2x), 127.1 (2x), 118.5, 105.4, 104.0, 99.9, 56.1, 56.0, 55.9.

3,6,7-Trimethoxy-1-naphthalen-2-ylisoquinoline (4q). 4q was prepared according to the general synthetic procedure from **1a** (196 mg, 1.0 mmol), **2q** (156 mg, 1.0 mmol) and MeOH **3a** (10 mL); yield = 83% (286 mg); white solid; mp = 140–142 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{22}H_{20}NO_3$ 346.1443, found 346.1438; ^1H NMR (400 MHz, $CDCl_3$): δ 8.23 (d, J = 1.2 Hz, 1H), 8.00 (d, J = 8.4 Hz, 1H), 7.95–7.88 (m, 3H), 7.57–7.51 (m, 2H), 7.37 (s, 1H), 7.00 (s, 1H), 6.92 (s, 1H), 4.06 (s, 3H), 4.01 (s, 3H), 3.79 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 159.7, 155.9, 153.0, 148.2, 137.7, 137.0, 133.12, 133.07, 129.1, 128.3, 127.8, 127.6, 127.5, 126.4, 126.2, 118.6, 105.1, 103.8, 99.7, 55.8, 55.6, 54.0.

1-Anthracen-9-yl-3,6,7-trimethoxyisoquinoline (4r). 4r was prepared according to the general synthetic procedure from **1a** (196 mg, 1.0 mmol), **2r** (206 mg, 1.0 mmol) and MeOH **3a** (10 mL); yield = 80% (316 mg); white solid; mp = 249–251 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{26}H_{22}NO_3$ 396.1600, found 396.1595; ^1H NMR (400 MHz, $CDCl_3$): δ 8.59 (s, 1H), 8.08 (d, J = 8.4 Hz, 2H), 7.50 (dt, J = 1.2, 7.6 Hz, 2H), 7.38 (d, J = 8.8 Hz, 2H), 7.29 (dt, J = 1.2, 7.6 Hz, 2H), 7.11 (s, 1H), 7.10 (s, 1H), 6.31 (s, 1H), 4.03 (s, 3H), 3.99 (s, 3H), 3.32 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 160.0, 154.6, 153.7, 148.6, 137.3, 131.4 (3x), 130.4 (2x), 128.4 (2x), 127.8, 126.3 (2x), 125.9 (2x), 125.2 (2x), 121.4, 105.1, 103.7, 100.5, 56.0, 55.6, 54.4. Single-crystal X-ray diagram: the crystal of compound **4r** was grown by slow diffusion of EtOAc into a solution of compound **4r** in $CHCl_3$ to yield colorless prisms. The compound crystallizes in the triclinic crystal system, space group $P\bar{1}$, a = 9.82420(10) Å, b = 13.6944(2) Å, c = 17.0549(3) Å, V = 2226.41(6) Å^3, Z = 2, d_{calcd} = 1.358 g cm^{-3}, $F(000)$ = 948, 2θ range 4.08–52°, R indices (all data) $R1$ = 0.0770, w$R2$ = 0.1861.

1-(3,4-Dichlorophenyl)-3,6,7-trimethoxyisoquinoline (4s). 4s was prepared according to the general synthetic procedure from **1a** (196 mg, 1.0 mmol), **2s** (174 mg, 1.0 mmol) and MeOH **3a** (10 mL); yield = 83% (301 mg); white solid; mp = 184–186 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{18}H_{16}Cl_2NO_3$ 364.0507, found 364.0502; ^1H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, J = 1.2 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.57 (d, J = 8.4 Hz, 1H), 7.18 (s, 1H), 6.98 (s, 1H), 6.91 (s, 1H), 4.02 (s, 3H), 4.01 (s, 3H), 3.86 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 159.6, 153.4, 153.2, 148.7, 139.4, 137.9, 132.72, 132.66, 131.8, 130.3, 129.0, 118.3, 104.3, 103.9, 100.6, 56.0, 55.8, 54.1.

1-(3,4-Difluorophenyl)-3,6,7-trimethoxyisoquinoline (4t). **4t** was prepared according to the general synthetic procedure from **1a** (196 mg, 1.0 mmol), **2t** (142 mg, 1.0 mmol) and MeOH **3a** (10 mL); yield = 90% (298 mg); white solid; mp = 183–185 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{18}H_{16}F_2NO_3$ 332.1098, found 332.1104; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61–7.55 (m, 1H), 7.49–7.45 (m, 1H), 7.33–7.26 (m, 1H), 7.20 (s, 1H), 6.97 (s, 1H), 6.89 (s, 1H), 4.011 (s, 3H), 4.005 (s, 3H), 3.85 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 159.6, 153.5, 153.3, 150.5 (dd, J = 9.1, 244.8 Hz), 150.3 (dd, J = 9.1, 253.2 Hz), 148.6, 137.9, 136.6 (t, J = 5.3 Hz), 125.9 (dd, J = 3.0, 6.1 Hz), 119.0 (d, J = 17.4 Hz), 118.2, 117.1 (d, J = 17.4 Hz), 104.4, 103.9, 100.4, 56.0, 55.8, 54.0.

1-(2-Chloro-6-fluorophenyl)-3,6,7-trimethoxyisoquinoline (4u). **4u** was prepared according to the general synthetic procedure from **1a** (196 mg, 1.0 mmol), **2u** (158 mg, 1.0 mmol) and MeOH **3a** (10 mL); yield = 89% (309 mg); white solid; colorless liquid; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{18}H_{16}ClFNO_3$ 348.0803, found 348.0810; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45–7.36 (m, 2H), 7.17 (dt, J = 1.2, 8.4 Hz, 1H), 7.01 (s, 1H), 6.99 (s, 1H), 6.64 (s, 1H), 4.02 (s, 3H), 4.00 (s, 3H), 3.78 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 160.8 (d, J = 248.7 Hz), 159.7, 153.7, 148.9 (2x), 148.3, 137.2, 135.1, 130.4 (d, J = 9.1 Hz), 125.5 (d, J = 3.8 Hz), 119.9, 114.4 (d, J = 22.0 Hz), 103.84, 103.78, 101.2, 56.1, 55.8, 54.4.

1-(3,4-Dimethoxyphenyl)-3,6,7-trimethoxyisoquinoline (4v). **4v** was prepared according to the general synthetic procedure from **1a** (196 mg, 1.0 mmol), **2v** (166 mg, 1.0 mmol) and MeOH **3a** (10 mL); yield = 82% (291 mg); white solid; mp = 112–114 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{20}H_{22}NO_5$ 356.1498, found 356.1491; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (s, 1H), 7.32–7.30 (m, 2H), 7.01 (d, J = 8.8 Hz, 1H), 6.97 (s, 1H), 6.85 (s, 1H), 4.02 (s, 3H), 4.01 (s, 3H), 3.96 (s, 3H), 3.04 (s, 3H), 3.85 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 159.6, 155.9, 153.1, 149.4, 148.8, 148.1, 137.8, 132.3, 122.4, 118.4, 113.1, 110.8, 105.4, 103.9, 99.2, 56.0, 55.9 (2x), 55.8, 54.0.

1-Benzo[1,3]dioxol-5-yl-3,6,7-trimethoxyisoquinoline (4w). **4w** was prepared according to the general synthetic procedure from **1a** (196 mg, 1.0 mmol), **2w** (150 mg, 1.0 mmol) and MeOH **3a** (10 mL); yield = 80% (271 mg); white solid; mp = 167–169 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{19}H_{18}NO_5$ 340.1185, found 340.1179; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (s, 1H), 7.24–7.21 (m, 2H), 6.98 (s, 1H), 6.95 (d, J = 8.0 Hz, 1H), 6.87 (s, 1H), 6.05 (s, 2H), 4.021 (s, 3H), 4.017 (s, 3H), 3.86 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 159.1, 155.3, 153.5, 148.4, 148.2, 147.8, 138.0, 123.9 (2x), 118.4, 110.4, 108.1, 105.3, 103.9, 101.3, 99.6, 56.0, 55.9, 54.3.

3,6,7-Trimethoxy-1-(2-methoxy-5-nitrophenyl)isoquinoline (4x). **4x** was prepared according to the general synthetic procedure from **1a** (196 mg, 1.0 mmol), **2x** (181 mg, 1.0 mmol) and MeOH **3a** (10 mL); yield = 88% (326 mg); white solid; mp = 202–204 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{19}H_{19}N_2O_6$ 371.1243, found 371.1237; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (dd, J = 2.8, 8.8 Hz, 1H), 8.35 (s, 1H), 7.11 (dd, J = 1.6, 8.0 Hz, 1H), 6.99 (s, 1H), 6.94 (s, 1H), 6.68 (s, 1H), 4.01 (s, 3H), 3.98 (s, 3H), 3.83 (s, 3H), 3.76 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 161.9, 159.8, 153.4, 151.3, 148.4, 141.5, 137.1, 129.4, 127.5, 126.0, 119.4, 110.8, 104.5, 103.7, 100.7, 56.2, 56.0, 55.7, 54.2. Single-crystal X-ray diagram: the crystal of compound **4x** was grown by slow diffusion of EtOAc into a solution of compound **4x** in CH_2Cl_2 to yield colorless prisms. The compound crystallizes in the monoclinic crystal system, space group $P2_1/c$, a = 10.5325(2) Å, b = 8.1523(2) Å, c = 19.8965(4) Å, V = 1702.70(6) Å^3, Z = 4, d_{calcd} = 1.445 g cm^{-3}, F(000) = 776, 2θ range 3.88–54.028°, R indices (all data) $R1$ = 0.0440, w$R2$ = 0.0939.

3,6,7-Trimethoxy-1-(4-methoxy-3-nitrophenyl)isoquinoline (4y). **4y** was prepared according to the general synthetic procedure from **1a** (196 mg, 1.0 mmol), **2y** (181 mg, 1.0 mmol) and MeOH **3a** (10 mL); yield = 86% (318 mg); white solid; mp = 228–230 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{19}H_{19}N_2O_6$ 371.1243, found 371.1236; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (d, J = 2.0 Hz, 1H), 7.99 (dd, J = 2.0, 8.8 Hz, 1H), 7.25 (d, J = 8.8 Hz, 1H), 7.23 (s, 1H), 6.99 (s, 1H), 6.90 (s, 1H), 4.06 (s, 3H), 4.03 (s, 3H), 4.02 (s, 3H), 3.88 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 159.7, 153.4, 153.0, 152.7, 148.8, 139.4, 138.0, 135.5, 132.0, 127.1, 118.2, 113.5, 104.2, 104.1, 100.5, 56.7, 56.0, 55.9, 54.1.

1-(2-Cyclopentyloxy-5-nitrophenyl)-3,6,7-trimethoxyisoquinoline (4z). **4z** was prepared according to the general synthetic procedure from **1a** (196 mg, 1.0 mmol), **2z** (235 mg, 1.0 mmol) and MeOH **3a** (10 mL); yield = 84% (356 mg); white solid; mp = 158–160 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{23}H_{25}N_2O_6$ 425.1713, found 425.1707; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (d, J = 2.4 Hz, 1H), 8.32 (dd, J = 2.8, 9.2 Hz, 1H), 7.6 (d, J = 9.2 Hz, 1H), 6.97 (s, 1H), 6.92 (s, 1H), 6.69 (s, 1H), 4.84–4.80 (m, 1H), 4.01 (s, 3H), 3.98 (s, 3H), 3.76 (s, 3H), 1.89–1.82 (m, 1H), 1.77–1.70 (m, 1H), 1.48–1.47 (m, 2H), 1.45–1.30 (m, 4H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 160.7, 159.8, 153.1, 151.8, 148.1, 141.0, 136.9, 130.0, 127.7, 125.8, 119.4, 112.5, 104.8, 103.7, 100.5, 80.9, 55.9, 55.6, 54.2, 32.8, 32.7, 23.9, 23.8.

3,6,7-Trimethoxy-1-(4-methyl-3-nitrophenyl)isoquinoline (4aa). **4aa** was prepared according to the general synthetic procedure from **1a** (196 mg, 1.0 mmol), **2aa** (165 mg, 1.0 mmol) and MeOH **3a** (10 mL); yield = 90% (319 mg); white solid; mp = 192–194 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{19}H_{19}N_2O_5$ 355.1294, found 355.1286; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (d, J = 1.6 Hz, 1H), 7.93 (dd, J = 1.6, 8.0 Hz, 1H), 7.51 (d, J = 8.4 Hz, 1H), 7.23 (s, 1H), 7.00 (s, 1H), 6.93 (s, 1H), 4.04 (s, 3H), 4.03 (s, 3H), 3.87 (s, 3H), 2.71 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 159.7, 153.4, 152.9, 149.2, 148.9, 138.3, 138.0, 134.2, 133.7, 132.7, 126.0, 118.3, 104.1, 104.0, 100.8, 56.1, 55.9, 54.2, 20.4.

3,6,7-Trimethoxy-1-(2,3,4-trimethoxyphenyl)isoquinoline (4ab). **4ab** was prepared according to the general synthetic procedure from **1a** (196 mg, 1.0 mmol), **2ab** (196 mg, 1.0 mmol) and MeOH **3a** (10 mL); yield = 79% (304 mg); white solid; colorless liquid; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{21}H_{24}NO_6$

386.1604, found 386.1597; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14 (d, J = 8.4 Hz, 1H), 6.97 (s, 1H), 6.91 (s, 2H), 6.82 (d, J = 8.4 Hz, 1H), 4.014 (s, 3H), 4.013 (s, 3H), 3.954 (s, 3H), 3.949 (s, 3H), 3.79 (s, 3H), 3.63 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 154.3, 151.9, 148.2, 142.1, 137.3, 125.8, 125.7, 123.9, 119.7, 113.7, 107.3, 105.8, 103.6, 100.7, 99.7, 61.6, 61.1, 56.1, 56.0, 55.8, 54.5.

3,6,7-Trimethoxy-1-(3,4,5-trimethoxyphenyl)isoquinoline (4ac). **4ac** was prepared according to the general synthetic procedure from **1a** (196 mg, 1.0 mmol), **2ac** (196 mg, 1.0 mmol) and MeOH **3a** (10 mL); yield = 82% (316 mg); white solid; mp = 123–125 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{24}NO_6$ 386.1604, found 386.1610; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (s, 1H), 6.99 (s, 1H), 6.97 (s, 2H), 6.87 (d, J = 0.4 Hz, 1H), 4.02 (s, 3H), 4.01 (s, 3H), 3.93 (s, 6H), 3.90 (s, 3H), 3.85 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 159.5, 155.8, 153.2, 153.1 (2x), 148.2, 138.3, 137.8, 134.8, 118.3, 107.1 (2x), 105.2, 103.9, 99.5, 60.9, 56.2 (2x), 56.0, 55.8, 54.2.

3,6,7-Trimethoxy-1-(5-nitrothiophen-2-yl)isoquinoline (4ad). **4ad** was prepared according to the general synthetic procedure from **1a** (196 mg, 1.0 mmol), **2ad** (157 mg, 1.0 mmol) and MeOH **3a** (10 mL); yield = 83% (287 mg); red solid; mp = 233–235 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{15}N_2O_5S$ 347.0702, found 347.0698; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, J = 4.4 Hz, 1H), 7.58 (d, J = 4.0 Hz, 1H), 7.55 (s, 1H), 6.97 (s, 2H), 4.04 (s, 3H), 4.03 (s, 3H), 3.99 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 158.9, 153.6, 151.4, 150.0, 144.9, 138.6, 128.7 (2x), 125.9, 118.3, 104.2, 103.5, 103.0, 56.1, 56.0, 54.1.

6,7-Dimethoxy-1-(5-nitrothiophen-2-yl)isoquinolin-3-ol (4ad-1). **4ad-1** was prepared according to the general synthetic procedure from **1a** (196 mg, 1.0 mmol), **2ad** (157 mg, 1.0 mmol) and MeOH **3a** (10 mL); yield = 5% (16 mg); red solid; mp = 213–215 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{15}H_{13}N_2O_5S$ 333.0545, found 333.0540; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, J = 4.4 Hz, 1H), 7.73 (s, 1H), 7.58 (d, J = 4.0 Hz, 1H), 6.99 (s, 1H), 6.97 (s, 1H), 6.00 (br s, 1H), 4.07 (s, 3H), 4.04 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 158.7, 151.1, 146.1, 145.2, 138.1, 131.1, 128.7, 126.1, 118.7, 113.6, 106.3, 103.6 (2x), 56.2, 54.0.

7-Methoxy-5-(3-nitrophenyl)[1,3]dioxolo[4,5-*g*]isoquinoline (4ae). **4ae** was prepared according to the general synthetic procedure from **1b** (180 mg, 1.0 mmol), **2f** (151 mg, 1.0 mmol) and MeOH **3a** (10 mL); yield = 90% (292 mg); white solid; mp = 197–199 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{13}N_2O_5$ 325.0825, found 325.0830; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.55 (t, J = 2.0 Hz, 1H), 8.32 (ddd, J = 1.2, 2.4, 8.0 Hz, 1H), 8.01 (dt, J = 1.6, 7.6 Hz, 1H), 7.68 (t, J = 7.6 Hz, 1H), 7.12 (s, 1H), 7.01 (s, 1H), 6.92 (s, 1H), 6.05 (s, 2H), 4.01 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 159.9, 153.4, 151.2, 148.2, 147.3, 141.2, 139.5, 135.8, 129.3, 124.8, 123.2, 119.4, 102.2, 101.7, 101.6, 101.5, 54.1.

7-Methoxy-5-(4-nitrophenyl)[1,3]dioxolo[4,5-*g*]isoquinoline (4af). **4af** was prepared according to the general synthetic procedure from **1b** (180 mg, 1.0 mmol), **2m** (151 mg, 1.0 mmol) and MeOH **3a** (10 mL); yield = 90% (292 mg); white solid; mp = 188–190 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{13}N_2O_5$ 325.0825, found 325.0832; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (d, J = 8.8 Hz, 2H), 7.86 (d, J = 8.8 Hz, 2H), 7.13 (s, 1H), 7.02 (s, 1H), 6.94 (s, 1H), 6.06 (s, 2H), 4.01 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 159.8, 153.5, 151.3, 147.8, 147.4, 145.6, 139.7, 130.9 (2x), 123.5 (2x), 119.5, 102.4, 101.8, 101.68, 101.65, 54.2.

5-(3,4-Dimethoxyphenyl)-7-methoxy[1,3]dioxolo[4,5-*g*]isoquinoline (4ag). **4ag** was prepared according to the general synthetic procedure from **1b** (180 mg, 1.0 mmol), **2v** (166 mg, 1.0 mmol) and MeOH **3a** (10 mL); yield = 80% (271 mg); white solid; mp = 167–169 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{19}H_{18}NO_5$ 340.1185, found 340.1179; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 (s, 1H), 7.26 (d, J = 2.0 Hz, 1H), 7.23 (dd, J = 2.0, 8.0 Hz, 1H), 7.000 (d, J = 8.0 Hz, 1H), 6.995 (s, 1H), 6.85 (s, 1H), 6.04 (s, 2H), 4.02 (s, 3H), 3.96 (s, 3H), 3.95 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 159.6, 156.3, 151.1, 149.6, 148.9 (2x), 146.7, 139.5, 122.6, 119.7, 113.2, 110.7, 103.1, 101.6, 101.4, 100.4, 56.04, 56.00, 54.2.

5-Benzo[1,3]dioxol-5-yl-7-methoxy[1,3]dioxolo[4,5-*g*]isoquinoline (4ah). **4ah** was prepared according to the general synthetic procedure from **1b** (180 mg, 1.0 mmol), **2w** (150 mg, 1.0 mmol) and MeOH **3a** (10 mL); yield = 80% (258 mg); white solid; mp = 212–214 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{18}H_{14}NO_5$ 324.0872, found 324.0868; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (s, 1H), 7.18 (d, J = 1.6 Hz, 1H), 7.15 (dd, J = 1.6, 8.0 Hz, 1H), 6.96 (s, 1H), 6.93 (d, J = 8.4 Hz, 1H), 6.83 (s, 1H), 6.04 (s, 2H), 6.02 (s, 2H), 4.00 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 159.7, 155.9, 150.9, 147.9, 147.6, 146.6, 139.4, 133.4, 123.9, 119.5, 110.4, 108.1, 102.9, 101.5, 101.4, 101.2, 100.8, 54.0.

7-Methoxy-5-(2,3,4-trimethoxyphenyl)[1,3]dioxolo[4,5-*g*]isoquinoline (4ai). **4ai** was prepared according to the general synthetic procedure from **1b** (180 mg, 1.0 mmol), **2ab** (196 mg, 1.0 mmol) and MeOH **3a** (10 mL); yield = 75% (277 mg); white solid; mp = 168–170 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{20}NO_6$ 370.1291, found 370.1285; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.06 (d, J = 8.4 Hz, 1H), 6.96 (s, 1H), 6.89 (s, 1H), 6.87 (d, J = 0.4 Hz, 1H), 6.79 (d, J = 8.4 Hz, 1H), 5.99 (s, 2H), 3.99 (s, 3H), 3.95 (s, 3H), 3.93 (s, 3H), 3.65 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 159.7, 154.3, 154.0, 151.8, 151.1, 146.4, 142.2, 138.7, 126.4, 125.5, 121.0, 107.3, 103.2, 101.3, 101.2, 100.9, 61.5, 61.0, 56.1, 54.2.

7-Methoxy-5-(3,4,5-trimethoxyphenyl)[1,3]dioxolo[4,5-*g*]isoquinoline (4aj). **4aj** was prepared according to the general synthetic procedure from **1b** (180 mg, 1.0 mmol), **2ac** (196 mg, 1.0 mmol) and MeOH **3a** (10 mL); yield = 87% (321 mg); white solid; mp = 145–147 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{20}NO_6$ 370.1291, found 370.1286; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (s, 1H), 7.02 (s, 1H), 6.89 (s, 3H), 6.06 (s, 2H), 4.03 (s, 3H), 3.93 (s, 3H), 3.91 (s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 159.2, 153.8, 153.1 (2x), 147.1, 139.8, 119.6, 107.4, 107.2, 103.1, 102.1, 101.8, 101.7 (2x), 100.7, 99.1, 61.0, 56.3 (2x), 54.5.

1-(3,4-Dimethoxyphenyl)-3-methoxy-6,7-dipropoxyisoquinoline (4ak). 4ak was prepared according to the general synthetic procedure from **1c** (252 mg, 1.0 mmol), **2v** (166 mg, 1.0 mmol) and MeOH **3a** (10 mL); yield = 80% (329 mg); white solid; mp = 110–112 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{24}H_{30}NO_5$ 412.2124, found 412.2118; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (s, 1H), 7.31–7.29 (m, 2H), 7.01 (d, J = 8.8 Hz, 1H), 6.95 (s, 1H), 6.81 (s, 1H), 4.08 (t, J = 6.8 Hz, 2H), 4.01 (s, 3H), 3.96 (s, 3H), 3.93 (s, 3H), 3.90 (t, J = 6.4 Hz, 2H), 1.95–1.82 (m, 4H), 1.09 (t, J = 7.6 Hz, 3H), 1.03 (t, J = 7.6 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 159.4, 155.7, 153.2, 149.3, 148.7, 148.0, 137.8, 132.2, 122.5, 118.4, 113.1, 110.7, 107.1, 104.7, 98.9, 70.3, 70.1, 55.90, 55.88, 54.0, 22.3, 22.2, 10.41, 10.40.

1-(3,4-Dimethoxyphenyl)-3,6,7,8-tetramethoxyisoquinoline (4al). 4al was prepared according to the general synthetic procedure from **1d** (226 mg, 1.0 mmol), **2v** (166 mg, 1.0 mmol) and MeOH **3a** (10 mL); yield = 78% (300 mg); colorless liquid; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{21}H_{24}NO_6$ 386.1604, found 386.1598; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13–7.11 (m, 2H), 6.94 (d, J = 8.8 Hz, 1H), 6.86 (s, 1H), 6.83 (s, 1H), 4.02 (s, 3H), 4.01 (s, 3H), 3.95 (s, 3H), 3.91 (s, 3H), 3.88 (s, 3H), 3.35 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 158.9, 156.0, 150.3, 149.0, 147.6, 140.8, 140.0, 124.0, 122.1, 114.3, 113.0, 109.9, 104.1, 100.3, 99.1, 61.2, 61.0, 56.04, 55.97, 55.9, 54.7.

1-(3,4-Dimethoxyphenyl)-3,6-dimethoxyisoquinoline (4am). 4am was prepared according to the general synthetic procedure from **1e** (166 mg, 1.0 mmol), **2v** (166 mg, 1.0 mmol) and MeOH **3a** (10 mL); yield = 78% (254 mg); white solid; mp = 78–80 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{19}H_{20}NO_4$ 326.1392, found 326.1388; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, J = 9.6 Hz, 1H), 7.30 (d, J = 2.0 Hz, 1H), 7.26 (dd, J = 2.0, 8.4 Hz, 1H), 7.00 (d, J = 8.4 Hz, 1H), 6.97 (d, J = 2.8 Hz, 1H), 6.94 (dd, J = 2.4, 9.2 Hz, 1H), 6.86 (s, 1H), 4.04 (s, 3H), 3.96 (s, 3H), 3.94 (s, 3H), 3.93 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 160.8, 160.6, 158.2, 149.6, 148.8, 142.8, 131.7, 129.5, 122.9, 118.8, 117.7, 113.3, 110.6, 103.2, 99.0, 55.99, 55.96, 55.3, 54.2.

General synthetic procedure of 5a–5d

NH_2OH-HCl (75 mg, 1.1 mmol) was added to a solution of 3-nitrobenzaldehyde **2f** (151 mg, 1.0 mmol) in alcohols **3b–3e** (5 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 15 min. A solution of 3,4-dimethoxyphenylacetic acid **1a** (196 mg, 1.0 mmol) in alcohols **3b–3e** (5 mL) was added to the reaction mixture at 25 °C. The reaction mixture was stirred at reflux for 20 h. The reaction mixture was cooled to 25 °C and the solvent was concentrated. The residue was diluted with water (10 mL) and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford the crude product under reduced pressure. Purification on silica gel (hexanes/EtOAc = 8/1–4/1) afforded **5a–5d**.

3-Ethoxy-6,7-dimethoxy-1-(3-nitrophenyl)isoquinoline (5a). 5a was prepared according to the general synthetic procedure from **1a** (196 mg, 1.0 mmol), **2f** (151 mg, 1.0 mmol) and EtOH **3b** (10 mL); yield = 80% (283 mg); white solid; mp = 184–186 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{19}H_{19}N_2O_5$ 355.1294, found 355.1297; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53 (t, J = 2.0 Hz, 1H), 8.39 (ddd, J = 1.2, 2.4, 8.4 Hz, 1H), 8.11 (dt, J = 1.2, 8.0 Hz, 1H), 7.64 (t, J = 8.0 Hz, 1H), 7.56 (s, 1H), 7.26 (s, 1H), 6.86 (s, 1H), 4.06 (q, J = 7.2 Hz, 2H), 4.02 (s, 3H), 3.94 (s, 3H), 1.08 (t, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 165.2, 152.6, 149.9, 148.4, 140.8, 139.2, 134.4, 134.1, 129.7, 127.1, 123.7, 121.7, 112.3 (2x), 110.1, 61.5, 56.31, 56.30, 13.8.

3-Isopropoxy-6,7-dimethoxy-1-(3-nitrophenyl)isoquinoline (5b). 5b was prepared according to the general synthetic procedure from **1a** (196 mg, 1.0 mmol), **2f** (151 mg, 1.0 mmol) and *i*PrOH **3c** (10 mL); yield = 80% (295 mg); colorless liquid; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{20}H_{21}N_2O_5$ 369.1451, found 369.1455; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.62 (t, J = 2.0 Hz, 1H), 8.34 (ddd, J = 0.8, 2.4, 8.0 Hz, 1H), 8.10 (dt, J = 1.2, 7.6 Hz, 1H), 7.72 (t, J = 7.6 Hz, 1H), 7.15 (s, 1H), 6.99 (s, 1H), 6.93 (s, 1H), 5.29–5.23 (m, 1H), 4.04 (s, 3H), 3.84 (s, 3H), 1.42 (d, J = 6.4 Hz, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 158.5, 153.6, 152.7, 149.0, 148.2, 140.8, 138.2, 135.9, 129.4, 124.9, 123.4, 118.1, 104.0, 103.9, 102.4, 69.2, 56.1, 55.9, 22.2 (2x).

3-*n*-Butoxy-6,7-dimethoxy-1-(3-nitrophenyl)isoquinoline (5c). 5c was prepared according to the general synthetic procedure from **1a** (196 mg, 1.0 mmol), **2f** (151 mg, 1.0 mmol) and *n*BuOH **3d** (10 mL); yield = 82% (313 mg); white solid; mp = 89–91 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{21}H_{23}N_2O_5$ 383.1607, found 383.1601; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.62 (t, J = 2.0 Hz, 1H), 8.33 (ddd, J = 1.2, 2.4, 8.4 Hz, 1H), 8.10 (dt, J = 1.2, 8.0 Hz, 1H), 7.70 (t, J = 8.0 Hz, 1H), 7.15 (s, 1H), 7.00 (s, 1H), 6.94 (s, 1H), 4.33 (t, J = 6.8 Hz, 2H), 4.03 (s, 3H), 3.84 (s, 3H), 1.87–1.80 (m, 2H), 1.58–1.50 (m, 2H), 0.98 (t, J = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 159.5, 153.5, 152.9, 148.9, 148.2, 140.9, 138.1, 135.9, 129.4, 124.9, 123.3, 118.2, 104.0, 103.9, 101.1, 66.8, 56.1, 55.8, 31.3, 19.3, 13.9.

General synthetic procedure of 6a–6g

H_2O (180 mg, 10 mmol) was added to PCl_5 (2.1 g, 10 mmol) to generate gaseous HCl. Excess HCl gas was added to a solution of substituted benzaldehydes **2a**, **2b**, **2e**, **2i**, **2o**, **2p** or **2t** (1.0 mmol) in methanol **3a** (5 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 15 min. A solution of 3,4-dimethoxyphenylacetic acid **1a** (196 mg, 1.0 mmol) in methanol **3a** (5 mL) was added to the reaction mixture at 25 °C. The reaction mixture was stirred at reflux for 20 h. The reaction mixture was cooled to 25 °C and the solvent was concentrated. The residue was diluted with water (10 mL) and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford the crude product under reduced pressure. Purification on silica gel (hexanes/EtOAc = 15/1–8/1) afforded **6a–6g**.

[4,5-Dimethoxy-2-(methoxyphenylmethyl)phenyl]acetic acid methyl ester (6a). 6a was prepared according to the general synthetic procedure from **1a** (196 mg, 1.0 mmol), **2a** (106 mg,

1.0 mmol) and MeOH **3a** (10 mL); yield = 73% (241 mg); colorless liquid; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{19}H_{23}O_5$ 331.1546, found 331.1540; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32–7.21 (m, 5H), 6.92 (s, 1H), 6.74 (s, 1H), 5.43 (s, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 3.58 (s, 3H), 3.57 (s, 2H), 3.36 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 171.8, 148.0, 140.9, 132.0, 128.1 (2x), 127.3, 127.1 (3x), 124.6, 113.9, 110.8, 82.0, 56.9, 55.73, 55.72, 51.7, 37.6.

{2-[(2-Bromophenyl)methoxymethyl]-4,5-dimethoxyphenyl}-acetic acid methyl ester (6b). 6b was prepared according to the general synthetic procedure from **1a** (196 mg, 1.0 mmol), **2b** (184 mg, 1.0 mmol) and MeOH **3a** (10 mL); yield = 78% (318 mg); colorless liquid; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{19}H_{22}BrO_5$ 409.0651, found 409.0645; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (dd, J = 1.2, 8.0 Hz, 1H), 7.31–7.23 (m, 2H), 7.15 (dt, J = 2.0, 8.0 Hz, 1H), 6.80 (s, 1H), 6.78 (s, 1H), 5.74 (s, 1H), 3.88 (s, 3H), 3.77 (s, 3H), 3.60 (s, 2H), 3.59 (s, 3H), 3.42 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 171.7, 148.3, 148.0, 139.5, 133.0, 130.5, 129.3, 129.3, 127.5, 125.3, 124.7, 114.1, 110.6, 80.7, 57.6, 55.9, 55.8, 51.9, 37.9.

{4,5-Dimethoxy-2-[methoxy-(3-methoxyphenyl)methyl]-phenyl}acetic acid methyl ester (6c). 6c was prepared according to the general synthetic procedure from **1a** (196 mg, 1.0 mmol), **2e** (136 mg, 1.0 mmol) and MeOH **3a** (10 mL); yield = 74% (267 mg); colorless liquid; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{20}H_{25}O_6$ 361.1651, found 361.1648; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 (dt, J = 0.4, 8.0 Hz, 1H), 6.90 (s, 1H), 6.86–6.84 (m, 2H), 6.80–6.77 (m, 1H), 6.74 (s, 1H), 5.39 (s, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 3.76 (s, 3H), 3.61 (s, 3H), 3.58 (s, 2H), 3.36 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 171.9, 159.6, 148.2, 148.1, 142.6, 132.0, 129.2, 124.7, 119.6, 114.0, 112.8 (2x), 110.9, 81.9, 57.0, 55.83, 55.81, 55.1, 51.8, 37.7.

{2-[(4-Chlorophenyl)methoxymethyl]-4,5-dimethoxyphenyl}-acetic acid methyl ester (6d). 6d was prepared according to the general synthetic procedure from **1a** (196 mg, 1.0 mmol), **2i** (140 mg, 1.0 mmol) and MeOH **3a** (10 mL); yield = 76% (277 mg); colorless liquid; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{19}H_{22}ClO_5$ 365.1156, found 365.1150; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (d, J = 8.8 Hz, 2H), 7.21 (d, J = 8.8 Hz, 2H), 6.86 (s, 1H), 6.74 (s, 1H), 5.39 (s, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.59 (s, 3H), 3.56 (d, J = 16.0 Hz, 1H), 3.54 (d, J = 16.0 Hz, 1H), 3.35 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 171.8, 148.4, 148.3, 139.8, 133.2, 131.5, 128.6 (2x), 128.4 (2x), 124.8, 114.1, 111.0, 81.4, 57.0, 55.93, 55.89, 51.9, 37.7.

{4,5-Dimethoxy-2-[methoxy(4-cyanophenyl)methyl]phenyl}-acetic acid methyl ester (6e). 6e was prepared according to the general synthetic procedure from **1a** (196 mg, 1.0 mmol), **2o** (131 mg, 1.0 mmol) and MeOH **3a** (10 mL); yield = 70% (249 mg); white solid; mp = 123–125 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{20}H_{22}NO_5$ 356.1498, found 356.1493; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, J = 8.4 Hz, 2H), 7.40 (d, J = 8.0 Hz, 2H), 6.76 (s, 1H), 6.74 (s, 1H), 5.45 (s, 1H), 3.86 (s, 3H), 3.80 (s, 3H), 3.583 (d, J = 16.0 Hz, 1H), 3.579 (s, 3H), 3.53 (d, J = 16.0 Hz, 1H), 3.34 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 171.6, 148.6, 148.4, 146.8, 132.0 (2x), 130.6, 127.6 (2x), 125.0, 118.7, 114.1, 111.2, 111.0, 81.3, 57.0, 55.9, 55.8, 51.9, 37.6. Single-crystal X-ray diagram: the crystal of compound **6e** was grown by slow diffusion of EtOAc into a solution of compound **6e** in CH_2Cl_2 to yield colorless prisms. The compound crystallizes in the monoclinic crystal system, space group $P2_1/n$, a = 8.6565(2) Å, b = 9.9527(2) Å, c = 20.7506(5) Å, V = 1777.20(7) Å^3, Z = 4, d_{calcd} = 1.328 g cm^{-3}, F(000) = 752, 2θ range 4.54–52°, R indices (all data) $R1$ = 0.0728, w$R2$ = 0.1550.

[2-(Biphenyl-4-ylmethoxymethyl)-4,5-dimethoxyphenyl]acetic acid methyl ester (6f). 6f was prepared according to the general synthetic procedure from **1a** (196 mg, 1.0 mmol), **2p** (182 mg, 1.0 mmol) and MeOH **3a** (10 mL); yield = 80% (325 mg); colorless liquid; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{25}H_{27}O_5$ 407.1859, found 407.1862; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60–7.55 (s, 4H), 7.45–7.32 (m, 5H), 7.00 (s, 1H), 6.78 (s, 1H), 5.49 (s, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 3.62 (s, 2H), 3.61 (s, 3H), 3.41 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 171.9, 148.2, 140.7, 140.3, 140.1, 131.9, 128.7 (2x), 127.6 (2x), 127.2 (2x), 126.9 (4x), 124.6, 114.0, 110.9, 81.9, 57.0, 55.9, 55.8, 51.8, 37.7.

{2-[(3,4-Difluorophenyl)methoxymethyl]-4,5-dimethoxy-phenyl}acetic acid methyl ester (6g). 6g was prepared according to the general synthetic procedure from **1a** (196 mg, 1.0 mmol), **2t** (142 mg, 1.0 mmol) and MeOH **3a** (10 mL); yield = 73% (267 mg); colorless liquid; HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{19}H_{21}F_2O_5$ 367.1357, found 367.1362; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14–7.05 (m, 2H), 6.99–6.95 (m, 1H), 6.83 (s, 1H), 6.75 (s, 1H), 5.37 (s, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.61 (s, 3H), 3.58 (d, J = 16.0 Hz, 1H), 3.53 (d, J = 15.6 Hz, 1H), 3.34 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 171.8, 151.2 (dd, J = 12.9, 246.4 Hz), 149.5 (dd, J = 12.9, 246.4 Hz), 148.5, 148.4, 138.5 (t, J = 4.6 Hz), 131.1, 124.8, 123.1 (dd, J = 3.0, 6.0 Hz), 116.9 (d, J = 17.4 Hz), 116.2 (d, J = 18.2 Hz), 114.1, 110.9, 80.9, 57.0, 56.0, 55.9, 51.9, 37.7.

6,7-Dimethoxy-3-(methoxy-d3)-1-(3-nitrophenyl)isoquinoline-4-d (7). NH_2OH-HCl (75 mg, 1.1 mmol) was added to a solution of 3-nitrobenzaldehyde **2f** (151 mg, 1.0 mmol) in CD_3OD **3f** (5 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 15 min. A solution of 3,4-dimethoxyphenylacetic acid **1a** (196 mg, 1.0 mmol) in CD_3OD **3f** (5 mL) was added to the reaction mixture at 25 °C. The reaction mixture was stirred at reflux for 20 h. The reaction mixture was cooled to 25 °C and the solvent was concentrated. The residue was diluted with water (10 mL) and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford the crude product under reduced pressure. Purification on silica gel (hexanes/EtOAc = 8/1–4/1) afforded **7**. Yield = 88% (303 mg); white solid; mp = 189–191 °C (recrystallized from hexanes and EtOAc); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{18}H_{13}D_4N_2O_5$ 345.1385, found 3445.1379; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.63 (t, J = 2.0 Hz, 1H), 8.33 (dd, J = 1.2, 8.0 Hz, 1H), 8.11 (d, J = 7.6 Hz, 1H), 7.71 (t, J = 8.0 Hz, 1H), 7.17 (s, 1H), 7.01 (s, 1H), 4.03 (s, 3H), 3.84 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 159.7, 153.4, 152.8, 149.0, 148.3, 141.1, 138.0, 135.9, 129.4, 124.8, 123.3, 118.3, 104.0, 103.9, 100.9 (t, J = 19.6 Hz, CD), 56.0, 55.8,

55.5 (septet, J = 18.3 Hz, CD_3); ^{2}H NMR (92 MHz, CH_2Cl_2): δ 6.99 (s, 1D), 3.96 (s, 3D).

Methyl-d3 2-(4,5-dimethoxy-2-((methoxy-d3)(3-nitrophenyl)-methyl)phenyl)acetate-d2 (8). D_2O (200 mg, 10 mmol) was added to PCl_5 (2.1 g, 10 mmol) to generate gaseous DCl. Excess freshly prepared DCl gas was added to a solution of 3-nitrobenzaldehyde **2f** (151 mg, 1.0 mmol) in CD_3OD **3f** (5 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 15 min. A solution of 3,4-dimethoxyphenylacetic acid **1a** (196 mg, 1.0 mmol) in CD_3OD **3f** (5 mL) was added to the reaction mixture at 25 °C. The reaction mixture was stirred at reflux for 20 h. The reaction mixture was cooled to 25 °C and the solvent was concentrated. The residue was diluted with water (10 mL) and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford the crude product under reduced pressure. Purification on silica gel (hexanes/EtOAc = 15/1–8/1) afforded **8**. Yield = 70% (268 mg); colorless liquid; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{19}H_{14}D_8NO_7$ 384.1890, found 384.1883; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (t, J = 1.2 Hz, 1H), 8.11 (dd, J = 0.8, 7.6 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.47 (t, J = 8.0 Hz, 1H), 6.82 (s, 1H), 6.77 (s, 1H), 5.52 (s, 1H), 3.89 (s, 3H), 3.83 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.7, 148.8, 148.6, 148.3, 144.0, 133.0, 130.7, 129.1, 124.9, 122.4, 122.0, 114.1 (d, J = 3.9 Hz), 111.0, 80.8, 56.3 (septet, J = 18.3 Hz, CD_3), 56.0, 55.9, 51.3 (septet, J = 19.0 Hz, CD_3), 37.5 (quintet, J = 17.0 Hz, CD_2); ^{2}H NMR (92 MHz, CH_2Cl_2): δ 3.54 (s, 5D), 3.31 (s, 3D).

[4,5-Dimethoxy-2-(3-nitrobenzyl)phenyl]acetic acid ethyl ester (9). H_2O (180 mg, 10 mmol) was added to PCl_5 (2.1 g, 10 mmol) to generate gaseous HCl. Excess freshly prepared HCl gas was added to a solution of 3-nitrobenzaldehyde **2f** (151 mg, 1.0 mmol) in EtOH **3b** (5 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 15 min. A solution of 3,4-dimethoxyphenylacetic acid **1a** (196 mg, 1.0 mmol) in EtOH **3b** (5 mL) was added to the reaction mixture at 25 °C. The reaction mixture was stirred at reflux for 20 h. The reaction mixture was cooled to 25 °C. The reaction could be monitored by TLC. $NaBH_4$ (114 mg, 3.0 mmol) was added to the reaction mixture at 25 °C. Then, the reaction mixture was stirred at 25 °C for 5 h, and the solvent was concentrated. The residue was diluted with water (10 mL) and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford the crude product under reduced pressure. Purification on silica gel (hexanes/EtOAc = 15/1–8/1) afforded **9**. Yield = 46% (165 mg); colorless liquid; HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{19}H_{22}NO_6$ 360.1447, found 360.1440; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07–8.03 (m, 1H), 7.98 (s, 1H), 7.46–7.42 (m, 2H), 7.90 (s, 1H), 6.63 (s, 1H), 4.09 (s, 2H), 4.06 (q, J = 7.2 Hz, 2H), 3.89 (s, 3H), 3.82 (s, 3H), 3.49 (s, 2H), 1.20 (t, J = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 171.4, 148.3, 148.0, 142.8, 134.7, 129.5, 129.3, 128.3, 125.0, 123.3, 121.3, 114.1, 113.7, 60.9, 56.0, 55.9, 38.5, 38.2, 14.1.

Gram-scale synthesis of compound 4a. NH_2OH-HCl (380 mg, 5.5 mmol) was added to a solution of benzaldehyde **2a** (530 mg, 5.0 mmol) in methanol **3a** (30 mL) at 25 °C. The reaction mixture was stirred at 25 °C for 15 min. A solution of homoveratric acid **1a** (980 mg, 5.0 mmol) in methanol **3a** (30 mL) was added to the reaction mixture at 25 °C. The reaction mixture was stirred at reflux for 30 h. The reaction mixture was cooled to 25 °C and the solvent was concentrated. The residue was diluted with water (20 mL) and the mixture was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford the crude product under reduced pressure. Purification on silica gel (hexanes/EtOAc = 8/1–4/1) afforded **4a** (1.21 g, 82%).

Conflicts of interest

There are no conflicts of interest to declare.

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