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Synthesis of 3,4-Dihydroisoquinolin-1-ones from *N*-Boc-(β-Arylethyl)-carbamates via Isocyanate Intermediates

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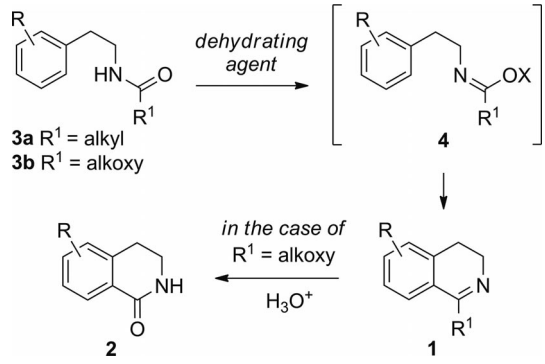
Mild reaction conditions for the regioselective synthesis of isoquinolin-1-ones and related fused-ring heterocycles from *N*-Boc-protected (β-arylethyl)carbamates are described. The reactions involved the use of Tf_2O and 2-chloropyridine and isocyanates are likely to be key intermediates. The method was extended to substrates bearing less nucleophilic aryl moieties by using Lewis acid additives, such as $BF_3{\cdot}Et_2O$, to enhance the Friedel–Crafts-type cyclization of the isocyanate intermediates. This method allowed the synthesis of various substituted isoquinolin-1-ones, β-carbolines, thiophene-fused ring systems and tetrahydrobenzoazepin-1-ones in good yields and with high regioselectivities.

Introduction

The Bischler–Napieralski reaction is an intramolecular aromatic substitution reaction that leads to the formation of 3,4-dihydroisoquinolines **1** and 3,4-dihydroisoquinolin-1-ones **2** from (β-arylethyl)amides **3a** and (β-arylethyl)carbamates **3b**, respectively (Scheme 1).[1] This reaction involves the cyclodehydration of the carbonyl groups in **3** via an imidate intermediate **4**. Historically, the classic Bischler–Napieralski reaction has required the use of harsh conditions, such as high temperatures and aggressive dehydrating agents ($POCl_3$ and P_2O_5). Consequently, a number of milder and more effective reaction conditions have been developed. In this regard, Banwell et al. reported the use of a combination of Tf_2O and DMAP (5:3 molar ratio) in the cyclocondensation of both *N*-(β-arylethyl)amides and (β-arylethyl)carbamates at or below room temperature.[2] This reagent combination has been widely used, especially in the synthesis of *Amaryllidaceae* alkaloids.[3]

To achieve the total synthesis of (+)-*trans*-dihydronarciclasine, we needed to convert *N*-Boc-protected (β-arylethyl)carbamate **5** into 3,4-dihydroisoquinolin-1-one **6** (Scheme 2).[4] Although Banwell's modified Bischler–Napieralski reaction has been reported to only be effective for primary alkyl carbamate substrates,[3] we employed these reaction conditions for the cyclization reaction. Our attempt, which lacked any certainty of success, was not entirely futile. We were able to obtain the desired product **6** along with the regioisomer **7** from the *N*-Boc-carbamate **5**. However, the chemical yield was much lower than that achieved[5] when Banwell's conditions were applied to the corresponding methoxycarbonyl (Moc) compound **8** (38 vs. 82%). Interestingly, the regioselectivity was considerably higher in the reaction of **5** than in the reaction of the corresponding *N*-Moc carbamate **8** (11.5:1 vs. up to 3.6:1), which implies that the two substrates undergo cycloaddition via different intermediates.



Scheme 1. General Bischler–Napieralski reaction.

After careful monitoring of the reaction of **5** under Banwell's conditions, we identified isocyanate **9** as an intermediate.[6] This observation led us to believe that the *N*-Boc-carbamate of **5** was first converted into an isocyanate under Banwell's acidic reaction conditions, presumably via imino triflate **10**. This isocyanate then underwent an in situ Friedel–Crafts-type cyclization. We speculated that the enhanced regioselectivity achieved with the *N*-Boc-carbamate

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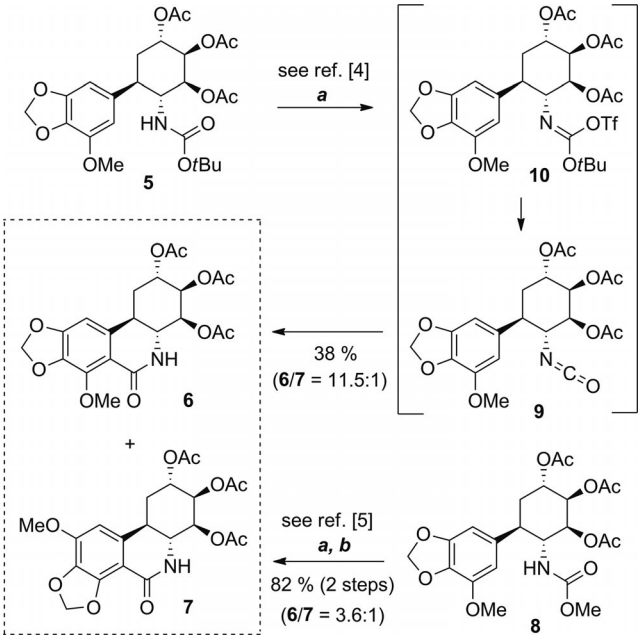
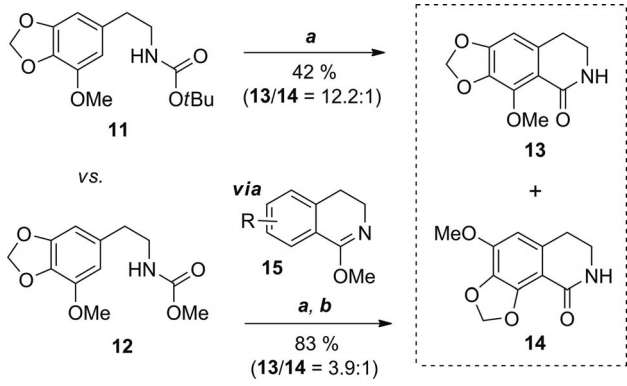


Scheme 2. B-ring construction under Banwell's reaction conditions. Reagents and conditions: a) Tf_2O, DMAP, CH_2Cl_2, 0 °C to room temp., 20 h; b) 3 M HCl, THF, 4 h.

substrate **5** was due to the involvement of the sterically less demanding isocyanate intermediate. With these considerations in mind, we could finally determine the optimal reaction conditions to regioselectively produce **6** in high yield (76%).[4] Herein, we wish to report our detailed study of the in situ Friedel–Crafts-type cyclization of the *N*-Boc-carbamate via an isocyanate intermediate and disclose the scope and efficiency of this transformation, which is a useful complement to Banwell's variant of the Bischler–Napieralski reaction.

Results and Discussion

Although there have been several reports of isocyanates being used in Friedel–Crafts-type cyclization reactions,[7] no examples of intramolecular Friedel–Crafts capture of an isocyanate intermediate generated from *N*-Boc-carbamates have been reported.[8] Isocyanates can be prepared by several methods, such as from an amine by treatment with phosgene[7a] or an equivalent including $(Boc)_2O$/DMAP,[7b] from an acid or amide by a Curtius or Hoffmann rearrangement,[7c,7d] or from a carbamate by treatment with dehydrating reagents.[9] In principle, the *N*-Boc-carbamate can be converted into an isocyanate function through the loss of its acid-labile *tert*-butyl group and dehydration. However, only a few examples of the direct conversion of *N*-Boc-carbamates into isocyanates have been reported.[9a,9b] Recently, Schofield and co-workers suggested the possibility that the reagent combination of Tf_2O and an amine base such as Et_3N or a pyridine is effective for such conversions.[10] Based on these observation and our initial results using Banwell's reaction conditions, we started our study of the Friedel–Crafts-type reactions of *N*-Boc-carbamate substrates via isocyanate intermediates by using the reagent combination of Tf_2O and base. *N*-Boc-carbamate **11** (Scheme 3) was chosen as an initial model substrate.



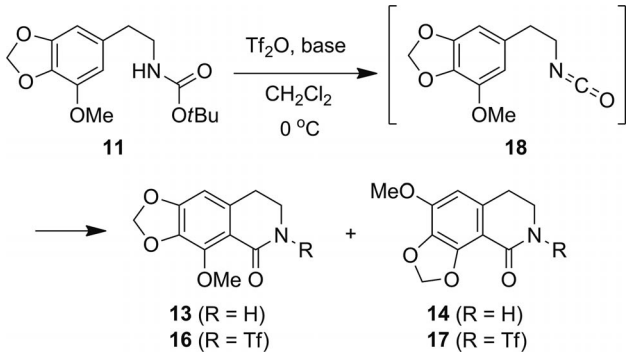
Scheme 3. B-ring construction under Banwell's reaction conditions. Reagents and conditions are identical those applied in the reactions of compounds **5** and **8** in Scheme 2.

Before identifying the optimal reaction conditions for our purposes, we first examined the differences in the chemical behavior of *N*-Boc-carbamate substrate **11** and the corresponding *N*-Moc substrate **12** under Banwell's modified Bischler–Napieralski reaction conditions (Scheme 3). Under Banwell's conditions, the *N*-Boc-substrate **11** provided dihydroisoquinolinone **13** along with the minor regioisomeric product **14** in 42% combined yield and 12.2:1 regioselectivity. On the other hand, the *N*-Moc substrate **12** provided methyl imidate **15**, which upon hydrolysis with 3 M HCl afforded **13** and **14** in a higher combined yield (83%) but with much lower regioselectivity (3.9:1). These results are very similar to those observed for the more complex substrates **5** and **8**.

When the DMAP i**13** and **14** as well as the corresponding *N*-triflated derivatives **16** and **17** (Table 1, entries 2 and 3). The combined yield of cyclized products increased and the high regioselectivity was maintained (entries 2 and 3 vs. entry 1). To avoid the *N*-triflation caused by excess Tf_2O,[12] the amount of Tf_2O was reduced to 1.5 equiv. In this case, isocyanate **18** was rapidly formed (within 20 min) as the only detectable reaction product and exhibited prolonged stability without conversion into dihydroisoquinolinones (entry 4). The identification of isocyanate **18** strengthened our belief that an *N*-Boc-carbamate could be transformed into a dihydroisoquinolinone via an isocyanate intermediate. The addition of excess Lewis acid (10 equiv.) to the reaction mixture containing isocyanate **18** led to the formation of dihydroisoquinolinones **13** and **14** without the formation of the *N*-triflated derivatives (entries 5–7). The yield from this stepwise process was much improved compared with that obtained under Banwell's conditions (85–90 vs. 42%), although the degree of regioselectivity was slightly lower (8.5:1–9.7:1 vs. 12.2:1). The above results indicate that

the reaction process is greatly influenced by the amount of base present and the acidity of the reaction medium.

Table 1. Optimization of the Friedel–Crafts-type cyclization reaction.[a]



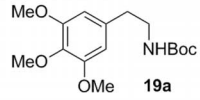
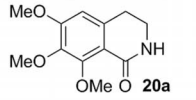
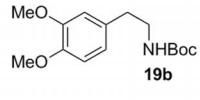
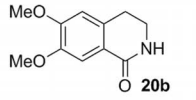
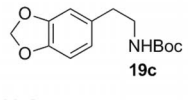
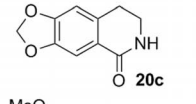
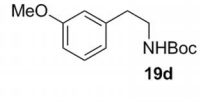
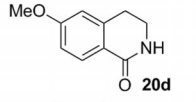
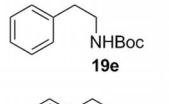
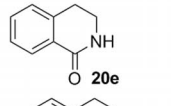
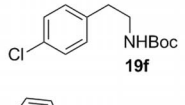
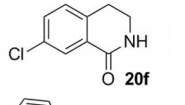
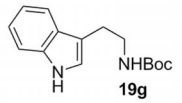
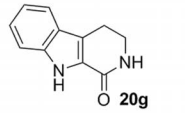
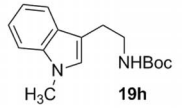
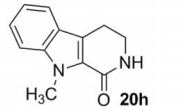
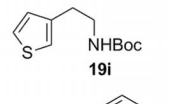
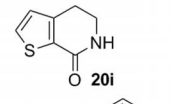
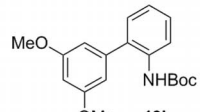
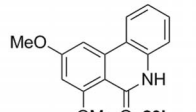
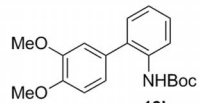
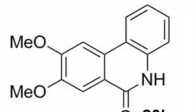
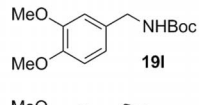
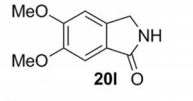
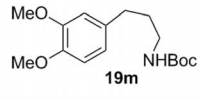
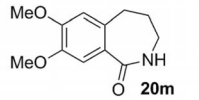
Entry	Tf_2O [equiv.]	Base (Amount [equiv.])	Lewis acid	*t* [h]	Yield [%][b]	(**13**+**16**)/(**14**+**17**)[c]
1	5.0	DMAP (3.0)	–	20	42	12.2:1
2	5.0	Py (3.0)	–	20	21+(45)	12.1:1
3	5.0	2-ClPy (3.0)	–	20	44+(40)	12.4:1
4	1.5	2-ClPy (3.0)	–	20	–	–
5[d]	1.5	2-ClPy (3.0)	$BF_3{\cdot}Et_2O$	2	86	8.5:1
6[d]	1.5	2-ClPy (3.0)	MsOH	0.5	90	8.5:1
7[d]	1.5	2-ClPy (3.0)	TfOH	0.5	85	9.7:1
8[e]	1.1	2-ClPy (1.5)	–	20	82	12.3:1

[a] Reagents and conditions: **11** (0.3 mmol), Tf_2O, base, CH_2Cl_2 (10 mL), 0 °C for 0.5 h and then room temp. [b] Isolated yield of the mixture of **13** and **14**. The values in parentheses are the isolated yields of the mixture of **16** and **17**. [c] Determined by ^1H NMR analysis. [d] Lewis acid was added after the formation of the isocyanate. [e] The reaction was conducted at –78 °C for 0.5 h and then at 35 °C for 20 h.

By further changing the molar ratios of Tf_2O and 2-chloropyridine, we finally determined the optimal reaction conditions for the reaction of **11** to be 1.1 equiv. of Tf_2O, 1.5 equiv. of 2-chloropyridine and heating at 35 °C for 20 h. Under these conditions, *N*-triflation was minimized and the product **13** was obtained in high yield and with high regioselectivity (entry 8).

By using the optimized reaction conditions with or without an acid additive, we next investigated the substrate scope of the reaction (Table 2). All the substrates were first subjected to the reaction conditions in the absence of the acid additive [Method A: Tf_2O (1.1 equiv.), 2-ClPy (1.5 equiv.), –78 °C to room temp.]. If method A gave unsatisfactory results, a Lewis acid was added after the formation of the isocyanate to facilitate the Friedel–Crafts reaction [Method B: Tf_2O (1.1 equiv.), 2-ClPy (1.5 equiv.), then $BF_3{\cdot}Et_2O$ (5.0 equiv.), –78 °C to room temp.]. The results are summarized in Table 2. Remarkably, the cyclization reactions of all compounds bearing electron-rich aryl rings proceeded in high yields and with high or exclusive regioselectivities.

Table 2. Substrate scope of the reactions.

Entry	*N*-Boc carbamate **19**	Product **20**	Method[a]	Yield[b] (%)
1	 **19a**	 **20a**	A	71
2	 **19b**	 **20b**	A	87
3	 **19c**	 **20c**	B	86
4	 **19d**	 **20d**	B	83[c]
5	 **19e**	 **20e**	A or B	–[d]
6	 **19f**	 **20f**	A or B	–[d]
7	 **19g**	 **20g**	A	70
8	 **19h**	 **20h**	A	92
9	 **19i**	 **20i**	B	79
10	 **19j**	 **20j**	A	81
11	 **19k**	 **20k**	B	70
12	 **19l**	 **20l**	A or B	–[d]
13	 **19m**	 **20m**	B	83[e]

[a] Method A: Tf_2O (1.1 equiv.), 2-ClPy (1.5 equiv.), CH_2Cl_2, –78 °C to room temp. Method B: Tf_2O (1.1 equiv.), 2-ClPy (1.5 equiv.), $BF_3{\cdot}Et_2O$ (5.0 equiv.), CH_2Cl_2, –78 °C to room temp. [b] Isolated yield. [c] Regioisomeric mixture (18:1). [d] The lactam product was not detected, instead, the corresponding isocyanate was obtained. [e] TfOH was used instead of $BF_3{\cdot}Et_2O$.

The *N*-Boc-carbamate **19a** bearing a trimethoxy-substituted benzene ring as the nucleophilic moiety was easily transformed into 3,4-dihydroisoquinolin-1-one **20a** in 71% yield by using method A (entry 1). The 3,4-dimethoxy-substituted substrate **19b** also afforded the cyclized product **20b** in high yield (87%) with very high regioselectivity (>20:1; entry 2) by using method A. However, substrates **19c** and **19d** required the addition of $BF_3{\cdot}Et_2O$ to obtain the cyclization products **20c** and **20d** (entries 3 and 4), which, under these conditions, were also obtained in high yields and regioselectivities. The requirement of the Lewis acid for these substrates might be due to the lower nucleophilicity of their aryl rings compared with those of the electron-rich substrates **19a** and **19b**.[13] Substrates with electron-neutral or deficient groups at the aryl moiety, **19e** and **19f**, did not undergo the cyclization reaction under either set of reaction conditions, yielding only the corresponding isocyanates (entries 5 and 6).

The phenyl rings could also be replaced by heteroarene units. Electron-rich heterocycles, such as indole and *N*-methylindole, showed good cyclization efficiency to afford tetrahydro-β-carbolin-1-ones **20g** and **20h** in good yields (70 and 92%, respectively; entries 7 and 8). With the aid of an acid additive, thiophene substrate **19i** also produced the cyclized product **20i** in 79% yield (entry 9).

Substrates in which the *N*-Boc-carbamate group is bonded directly to an aromatic ring also provided the cyclized product (entries 10 and 11). The 3,5-dimethoxy-substituted substrate **19j** readily afforded phenanthridone **20j** in high yield (81%) by using method A. However, the 3,4-dimethoxy-substituted substrate **19k** required the addition of the Lewis acid for cyclization and provided phenanthridone **20k** in a slightly lower yield (70%).

We also explored the feasibility of forming a five- or seven-membered-ring lactams by using these methods. Attempts to generate the dihydroisoindolone **20l** from the reaction of substrate **19l** under the above conditions produced complex unidentified mixtures (entry 12).[14] However, under acid-induced conditions, γ-arylpropylcarbamate **19m** was transformed into the benzo[*c*]azepin-1-one **20m** in 83% yield (entry 13).

Conclusions

The in situ Friedel–Crafts-type cyclization of *N*-Boc-carbamates via isocyanate intermediates has been developed as a versatile alternative to the original Bischler–Napieralski reaction for synthesizing 3,4-dihydroisoquinolin-1-ones and related heterocyclic compounds. The reaction conditions are milder than those of other modified Bischler–Napieralski reactions, including Banwell's conditions. Moreover, the regioselectivity of the cyclization of unsymmetrical aryl substrates was superior to previous methods. The cyclization efficiency was enhanced by the addition of a Lewis acid, which is useful for substrates with less nucleophilic aryl groups. Other approaches to the nucleophilic capture of an isocyanate intermediate are under investigation by our group.

Experimental Section

General Methods: All chemicals were of reagent grade and used as received. All reactions were performed under dry nitrogen using distilled, dry solvents. The reactions were monitored by TLC (Merck®, Silica gel 60 F_{254}). Flash column chromatography was performed on silica gel (230–400 mesh). ^1H (300 or 400 MHz) and ^{13}C NMR (75 or 100 MHz) spectra were recorded. Chemical shifts (δ) are reported in ppm relative to the non-deuteriated solvent as internal reference; coupling constants (J) are given in Hz. Multiplicities are denoted as follows: s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. The ^1H NMR spectra are presented as follows: chemical shift (multiplicity, coupling constant, integration). IR spectra were recorded with a Fourier Transform Infrared spectrometer. Melting points were measured with a Büchi B-540 melting-point apparatus. HRMS were recorded by using fast atom bombardment (FAB). Previously reported compounds (**19b**–**19h**, **19j**, **20a**–**20d**, **20g**–**20k**, and **20m**) were confirmed by comparison of their spectroscopic data (^1H NMR, HRMS, and melting points) with those of references.

Representative Procedure for the Preparation of *N*-Boc-Carbamates. *tert*-Butyl [2-(7-Methoxybenzo[*d*][1,3]dioxol-5-yl)ethyl]carbamate (11): NEt_3 (2.9 mL, 20.5 mmol, 2.0 equiv.), DMAP (125 mg, 1.03 mmol, 0.1 equiv.), and $(Boc)_2O$ (2.5 g, 11.3 mmol, 1.1 equiv.) were added to a solution of 2-(7-methoxybenzo[*d*][1,3]dioxol-5-yl) ethanamine[15] (2.0 g, 10.3 mmol, 1.0 equiv.) in CH_2Cl_2 (52 mL) at 0 °C. After stirring for 3 h at room temperature, the reaction was quenched by the addition of brine at 0 °C. The mixture was then extracted twice with CH_2Cl_2. The combined organic layers were washed with a saturated NH_4Cl solution and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (hexane/EtOAc, 2:1) to give *N*-Boc-carbamate **11** (2.8 g, 93%) as a white solid, m.p. 78.0–79.2 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.40 (s, 9 H), 2.66 (t, J = 6.9 Hz, 2 H), 3.23–3.33 (m, 2 H), 3.85 (s, 3 H), 4.57 (br. s, 1 H), 5.89 (s, 2 H), 6.31 (s, 1 H), 6.33 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.36 (3 C), 36.22, 41.87, 56.48, 79.22, 101.26, 102.75, 107.83, 133.44, 133.67, 143.52, 148.86, 155.80 ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3404, 3360, 2974, 2936, 1709, 1510 cm^{-1}. HRMS (FAB): calcd. for $C_{15}H_{22}NO_5$ $[M + H]^+$ 296.3389; found 296.3396.

The amines required for the preparation of carbamate compounds **19a**–**19g**, **19i**, **19l**, and **19m** are commercially available. Carbamate **19h** were prepared from **19g** by simple *N*-methylation.[16] The amines required for **19j** and **19k** were prepared by a previously developed procedure.[17]

***tert*-Butyl (3,4,5-Trimethoxyphenethyl)carbamate (19a):** White solid, m.p. 79.2–80.3 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.42 (s, 9 H), 2.72 (t, J = 6.9 Hz, 2 H), 3.30–3.39 (m, 2 H), 3.81 (s, 3 H), 3.83 (s, 6 H), 4.54 (br. s, 1 H), 6.38 (s, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.37 (3 C), 36.54, 41.72, 56.03 (2 C), 60.78, 79.21, 105.62 (2 C), 134.62, 136.50, 153.21 (2 C), 155.82 ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3371, 2974, 2937, 1711 cm^{-1}. HRMS (FAB): calcd. for $C_{16}H_{26}NO_5$ $[M + H]^+$ 312.1811; found 312.1820.

***tert*-Butyl (3,4-Dimethoxyphenethyl)carbamate (19b):**[18] White solid, m.p. 59.5–60.5 °C (lit.: 61–62 °C). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.41 (s, 9 H), 2.71 (t, J = 7.1 Hz, 2 H), 3.28–3.35 (m, 2 H), 3.83 (s, 3 H), 3.85 (s, 3 H), 4.51 (br. s, 1 H), 6.65–6.80 (m, 3 H) ppm. HRMS (FAB): calcd. for $C_{15}H_{24}NO_4$ $[M + H]^+$ 282.1705; found 282.1709.

***tert*-Butyl [2-(Benzo[*d*][1,3]dioxol-5-yl)ethyl]carbamate (19c):**[19] White solid, m.p. 61.5–62.5 °C (lit.: 60 °C). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.42 (s, 9 H), 2.69 (t, J = 7.0 Hz, 2 H), 3.27–3.35 (m,

2 H), 4.51 (br. s, 1 H), 5.91 (s, 2 H), 6.60–6.66 (m, 2 H), 6.72 (d, *J* = 7.9 Hz, 1 H) ppm. HRMS (FAB): calcd. for $C_{14}H_{20}NO_4$ [M + H]$^+$ 266.1392; found 266.1395.

***tert*-Butyl (3-Methoxyphenethyl)carbamate (19d):**[20] Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (s, 9 H), 2.75 (t, *J* = 7.0 Hz, 2 H), 3.33–3.37 (m, 2 H), 3.78 (s, 3 H), 4.52 (br. s, 1 H), 6.72–6.77 (m, 3 H), 7.20 (t, *J* = 7.8 Hz, 1 H) ppm. HRMS (FAB): calcd. for $C_{14}H_{22}NO_3$ [M + H]$^+$ 252.1600; found 252.1603.

***tert*-Butyl Phenethylcarbamate (19e):**[21] White solid, m.p. 56.4–57.2 °C (lit.: 56.1–56.4 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.45 (s, 9 H), 2.83 (t, *J* = 7.3 Hz, 2 H), 3.35–3.45 (m, 2 H), 4.57 (br. s, 1 H), 7.16–7.38 (m, 5 H) ppm. HRMS (FAB): calcd. for $C_{13}H_{20}NO_2$ [M + H]$^+$ 222.1494; found 222.1490.

***tert*-Butyl (4-Chlorophenethyl)carbamate (19f):** White solid, m.p. 61.2–62.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 (s, 9 H), 2.72 (t, *J* = 6.9 Hz, 2 H), 3.23–3.36 (m, 2 H), 4.63 (br. s, 1 H), 7.08 (d, *J* = 8.3 Hz, 2 H), 7.20–7.25 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.28 (3 C), 35.47, 41.56, 79.14, 128.52 (2 C), 130.05 (2 C), 132.05, 137.39, 155.73 ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3348, 2976, 2932, 2869, 1689 cm^{-1}. HRMS (FAB): calcd. for $C_{13}H_{19}ClNO_2$ [M + H]$^+$ 256.1104; found 256.1109.

***tert*-Butyl [2-(1*H*-Indol-3-yl)ethyl]carbamate (19g):**[22] White solid, m.p. 89.5–90.5 °C (lit.: 88–90 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (s, 9 H), 2.94 (t, *J* = 6.8 Hz, 2 H), 3.38–3.51 (m, 2 H), 4.60 (br. s, 1 H), 6.98–7.13 (m, 1 H), 7.10 (dt, *J* = 1.0, 7.4 Hz, 1 H), 7.19 (dt, *J* = 1.2, 7.6 Hz, 1 H), 7.35 (d, *J* = 8.0 Hz, 1 H), 7.59 (d, *J* = 7.7 Hz, 1 H), 8.07 (br. s, 1 H) ppm. HRMS (FAB): calcd. for $C_{15}H_{21}N_2O_2$ [M + H]$^+$ 261.1603; found 261.1608.

***tert*-Butyl [2-(1-Methyl-1*H*-indol-3-yl)ethyl]carbamate (19h):**[16] White solid, m.p. 64.3–65.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (s, 9 H), 2.93 (t, *J* = 6.8 Hz, 2 H), 3.42 (br. s, 2 H), 3.74 (s, 3 H), 4.57 (br. s, 1 H), 6.87 (s, 1 H), 7.07–7.11 (m, 1 H), 7.19–7.30 (m, 2 H), 7.57 (d, *J* = 7.7 Hz, 1 H) ppm. HRMS (FAB): calcd. for $C_{16}H_{23}N_2O_2$ [M + H]$^+$ 275.1760; found 275.1765.

***tert*-Butyl [2-(Thiophen-3-yl)ethyl]carbamate (19i):** White solid, m.p. 49.5–50.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (s, 9 H), 2.80 (t, *J* = 6.9 Hz, 2 H), 3.30–3.41 (m, 2 H), 4.54 (br. s, 1 H), 6.92–6.98 (m, 2 H), 7.25–7.27 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.35 (3 C), 30.65, 40.99, 79.21, 121.25, 125.75, 128.05, 139.23, 155.80 ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3350, 2977, 2931, 1694 cm^{-1}. HRMS (FAB): calcd. for $C_{11}H_{18}NO_2S$ [M + H]$^+$ 228.1058; found 228.1063.

***tert*-Butyl (3′,5′-Dimethoxy-1,1′-biphenyl-2-yl)carbamate (19j):**[23] White solid, m.p. 88.5–89.6 °C (lit.: 88.0–88.8 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.45 (s, 9 H), 3.80 (s, 6 H), 6.48 (s, 3 H), 6.60 (br. s, 1 H), 7.06 (dt, *J* = 1.2, 7.5 Hz, 1 H), 7.20 (dd, *J* = 1.7, 7.5 Hz, 1 H), 7.32 (dt, *J* = 1.7, 8.4 Hz, 1 H), 8.10 (d, *J* = 8.3 Hz, 1 H) ppm. HRMS (FAB): calcd. for $C_{19}H_{24}NO_4$ 330.1705; found 330.1709.

***tert*-Butyl (3′,4′-Dimethoxy-1,1′-biphenyl-2-yl)carbamate (19k):** Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.45 (s, 9 H), 3.88 (s, 3 H), 3.93 (s, 3 H), 6.54 (br. s, 1 H), 6.85–6.98 (m, 3 H), 7.06 (dt, *J* = 1.2, 7.5 Hz, 1 H), 7.20 (dd, *J* = 1.7, 7.5 Hz, 1 H), 7.30 (dt, *J* = 1.4, 7.1 Hz, 1 H), 8.10 (d, *J* = 8.3 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.30 (3 C), 55.88, 55.91, 80.40, 111.51, 112.30, 119.55, 121.46, 122.87, 128.15, 130.05, 130.70, 130.97, 135.34, 148.53, 149.09, 152.84 ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3345, 2977, 2934, 1730 cm^{-1}. HRMS (FAB): calcd. for $C_{19}H_{24}NO_4$ [M + H]$^+$ 330.1705; found 330.1704.

***tert*-Butyl (3,4-Dimethoxybenzyl)carbamate (19l):** White solid, m.p. 65.0–66.5 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.48 (s, 9 H), 3.84 (s, 6 H), 4.21 (d, *J* = 5.3 Hz, 2 H), 4.79 (br. s, 1 H), 6.74–6.83 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.31 (3 C), 44.42, 55.72, 55.83, 79.27, 110.79, 111.09, 119.55, 131.56, 148.20, 148.99, 155.77 ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3352, 2975, 2934, 1725 cm^{-1}. HRMS (FAB): calcd. for $C_{14}H_{22}NO_4$ [M + H]$^+$ 268.1549; found 268.1553.

***tert*-Butyl [3-(3,4-Dimethoxyphenyl)propyl]carbamate (19m):** White solid, m.p. 69.5–72.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (s, 9 H), 1.77 (quint., *J* = 7.4 Hz, 2 H), 2.57 (t, *J* = 7.8 Hz, 2 H), 3.05–3.20 (m, 2 H), 3.83 (s, 3 H), 3.85 (s, 3 H), 4.50 (br. s, 1 H), 6.68–6.78 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.39 (3 C), 31.92, 32.68, 40.19, 55.81, 55.92, 79.11, 111.31, 111.74, 120.13, 134.19, 147.27, 148.89, 155.95 ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3374, 2974, 2935, 1709 cm^{-1}. HRMS (FAB): calcd. for $C_{16}H_{26}NO_4$ [M + H]$^+$ 296.1862; found 296.1862.

Synthesis of Methyl [2-(7-Methoxybenzo[*d*][1,3]dioxol-5-yl)ethyl]-carbamate (12): NEt_3 (2.9 mL, 20.5 mmol, 2.0 equiv.), DMAP (125 mg, 1.03 mmol, 0.1 equiv.), and methyl chloroformate (0.9 mL, 11.3 mmol, 1.1 equiv.) were added to a solution of 2-(7-methoxybenzo[*d*][1,3]dioxol-5-yl)ethanamine[15] (2.0 g, 10.3 mmol, 1.0 equiv.) in CH_2Cl_2 (52 mL) at 0 °C. After stirring for 3 h at room temperature, the reaction was quenched by the addition of brine at 0 °C. The mixture was then extracted twice with CH_2Cl_2. The combined organic layers were washed with a saturated NH_4Cl solution and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (hexane/EtOAc, 2:1) to give methyl carbamate **12** (2.5 g, 95%) as a pale-yellow solid, m.p. 100.2–101.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.69 (t, *J* = 6.8 Hz, 2 H), 3.33–3.42 (m, 2 H), 3.64 (s, 3 H), 3.86 (s, 3 H), 4.69 (br. s, 1 H), 5.91 (s, 2 H), 6.31 (s, 1 H), 6.34 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 36.18, 42.28, 52.03, 56.53, 101.29, 102.64, 107.90, 133.19, 133.75, 143.56, 148.93, 156.91 ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3340, 2942, 2890, 2843, 1697 cm^{-1}. HRMS (FAB): calcd. for $C_{12}H_{16}NO_5$ [M + H]$^+$ 254.1028; found 254.1025.

General Procedure for the Optimization of the Friedel–Crafts-Type Cyclization Reaction (Table 1): The specified amount of base (DMAP, pyridine, or 2-chloropyridine) and triflic anhydride (1.0 M in CH_2Cl_2) was added to a stirred solution of *N*-Boc-carbamate **11** (89 mg, 0.30 mmol, 1.0 equiv.) in CH_2Cl_2 (10 mL) at the specified temperature (0 or –78 °C). After 30 min, the reaction mixture was warmed to room temperature and stirred for the indicated duration. (In the case of entries 5–7 of Table 1, a Lewis acid was added after 20 min, stirred for another 10 min, and then warmed to room temperature.) Then the reaction was quenched by the addition of a saturated $NaHCO_3$ solution at 0 °C. This solution was diluted with CH_2Cl_2, washed with brine, dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 20:1) to give the cyclized products **13** and **14** as a white solid. [When DMAP was replaced by the less basic pyridine or 2-chloropyridine (Table 1, entries 2 and 3), *N*-triflated derivatives **16** and **17** were also generated.] Isocyanate **18** could be obtained by quenching the reaction mixture with aqueous $NaHCO_3$ solution before the addition of the Lewis acid.

4-Methoxy-7,8-dihydro-[1,3]dioxolo[4,5-*g*]isoquinolin-5(6*H*)-one (13): White solid, m.p. 163.0–165.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.79 (t, *J* = 6.4 Hz, 2 H), 3.37 (dt, *J* = 3.6, 6.3 Hz, 2 H), 4.03 (s, 3 H), 5.94 (s, 2 H), 6.38 (s, 1 H), 6.51 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.38, 39.69, 60.76, 101.37, 102.29, 115.68, 134.50, 137.04, 144.74, 151.26, 164.68 ppm. IR

($CHCl_3$): $\tilde{\nu}_{max}$ = 3406, 3221, 2929, 1664 cm^{-1}. HRMS (FAB): calcd. for $C_{11}H_{12}NO_4$ $[M + H]^+$ 222.0766; found 222.0761.

4-Methoxy-7,8-dihydro-[1,3]dioxolo[4,5-*h*]isoquinolin-9(6*H*)-one (14): White solid, m.p. 206.0–207.5 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.86 (t, J = 6.4 Hz, 2 H), 3.47 (dt, J = 2.9, 6.4 Hz, 2 H), 3.91 (s, 3 H), 6.10 (s, 2 H), 6.33 (s, 1 H), 6.44 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.89, 40.43, 56.58, 102.79, 105.90, 106.72, 133.86, 134.99, 145.95, 149.20, 164.44 ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3179, 2991, 2903, 1657, 1636 cm^{-1}. HRMS (FAB): calcd. for $C_{11}H_{12}NO_4$ $[M + H]^+$ 222.0766; found 222.0768.

4-Methoxy-6-[(trifluoromethyl)sulfonyl]-7,8-dihydro-[1,3]dioxolo-[4,5-*g*]isoquinolin-5(6*H*)-one (16):[24] White solid, m.p. 200.5–202.0 °C. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.97 (t, J = 6.0 Hz, 2 H), 4.03 (t, J = 5.9 Hz, 2 H), 4.05 (s, 3 H), 6.01 (s, 2 H), 6.40 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.22, 46.45, 60.64, 102.09, 102.29, 113.09, 119.57 (q, J = 321 Hz, 1 C), 137.26, 137.51, 146.04, 153.72, 159.88 ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3008, 2956, 2905, 1700, 1608 cm^{-1}. HRMS (FAB): calcd. for $C_{12}H_{11}F_3NO_6S$ $[M + H]^+$ 354.0259; found 354.0268.

4-Methoxy-8-[(trifluoromethyl)sulfonyl]-7,8-dihydro-[1,3]dioxolo-[4,5-*h*]isoquinolin-9(6*H*)-one (17):[24] ^1H NMR (400 MHz, $CDCl_3$): δ = 3.05 (t, J = 6.0 Hz, 2 H), 3.96 (s, 3 H), 4.11 (t, J = 5.8 Hz, 2 H), 6.14 (s, 2 H), 6.36 (s, 1 H) ppm.

6-(2-Isocyanatoethyl)-4-methoxybenzo[*d*][1,3]dioxole (18): Colorless oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.79 (t, J = 6.8 Hz, 2 H), 3.46 (t, J = 6.8 Hz, 2 H), 3.88 (s, 3 H), 5.96 (s, 2 H), 6.36 (d, J = 1.5 Hz, 1 H), 6.38 (d, J = 1.6 Hz, 1 H) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 2943, 2892, 2274, 1634, 1512 cm^{-1}.

Final Optimized Procedure for the Friedel–Crafts-Type Cyclization Reaction (Table 2)

Method A: 2-Chloropyridine (0.45 mmol, 1.5 equiv.) and triflic anhydride (0.33 mmol, 1.1 equiv.) were added to a stirred solution of *N*-Boc-carbamate **19** (0.30 mmol, 1.0 equiv.) in CH_2Cl_2 (6 mL) at –78 °C. After 30 min, the reaction mixture was warmed to room temperature and stirred for 20 h. Next, the reaction was quenched by the addition of a saturated $NaHCO_3$ solution at 0 °C, diluted with CH_2Cl_2, washed with brine, dried with $MgSO_4$, filtered, and concentrated in vacuo. This residue was purified by column chromatography on silica gel using an appropriate CH_2Cl_2/MeOH mixture as eluent to yield the cyclized product **20**.

Method B: Identical to method A except for the addition of $BF_3{\cdot}Et_2O$ (5.0 equiv.) 20 min after the addition of Tf_2O. In this case, the reaction was completed within 2 h.

6,7,8-Trimethoxy-3,4-dihydroisoquinolin-1(2*H*)-one (20a):[25] White solid, m.p. 139.0–141.0 °C (lit.: 138 °C). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.86 (t, J = 6.3 Hz, 2 H), 3.40–3.44 (m, 2 H), 3.85 (s, 3 H), 3.87 (s, 3 H), 3.93 (s, 3 H), 6.01 (br. s, 1 H), 6.48 (s, 1 H) ppm. HRMS (FAB): calcd. for $C_{12}H_{16}NO_4$ $[M + H]^+$ 238.1079; found 238.1083.

6,7-Dimethoxy-3,4-dihydroisoquinolin-1(2*H*)-one (20b):[7c] White solid, m.p. 164.5–166.5 °C (lit.: 174–177 °C). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.91 (t, J = 6.8 Hz, 2 H), 3.53 (dt, J = 2.8, 6.4 Hz, 2 H), 3.91 (s, 6 H), 6.01 (br. s, 1 H), 6.65 (s, 1 H), 7.55 (s, 1 H) ppm. HRMS (FAB): calcd. for $C_{11}H_{14}NO_3$ $[M + H]^+$ 208.0974; found 208.0979.

7,8-Dihydro-[1,3]dioxolo[4,5-*g*]isoquinolin-5(6*H*)-one (20c):[7c] White solid, m.p. 184.5–186.0 °C (lit.: 185–187 °C). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.86 (t, J = 6.6 Hz, 2 H), 3.49 (t, J = 6.6 Hz, 2 H), 5.97 (s, 2 H), 6.62 (s, 1 H), 6.80 (br. s, 1 H), 7.47 (s, 1 H) ppm. HRMS (FAB): calcd. for $C_{10}H_{10}NO_3$ $[M + H]^+$ 192.0661; found 192.0657.

6-Methoxy-3,4-dihydroisoquinolin-1(2*H*)-one (20d):[26] White solid, m.p. 130.0–132.0 °C (lit.: 136–138 °C). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.94 (t, J = 6.5 Hz, 2 H), 3.52 (dt, J = 2.7, 6.5 Hz, 2 H), 3.83 (s, 3 H), 6.11 (br. s, 1 H), 6.68 (s, 1 H), 6.83 (dd, J = 2.1, 8.6 Hz, 1 H), 8.00 (d, J = 8.6 Hz, 1 H) ppm. HRMS (FAB): calcd. for $C_{10}H_{12}NO_2$ $[M + H]^+$ 178.0868; found 178.0873.

2,3,4,9-Tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-one (20g):[7c] White solid, m.p. 185.5–187.0 °C (lit.: 186–188 °C). ^1H NMR (400 MHz, $CDCl_3$): δ = 3.05 (t, J = 7.0 Hz, 2 H), 3.71 (dt, J = 2.0, 6.9 Hz, 2 H), 6.25 (br. s, 1 H), 7.12 (t, J = 7.5 Hz, 1 H), 7.28 (t, J = 7.6 Hz, 1 H), 7.47 (d, J = 8.3 Hz, 1 H), 7.58 (d, J = 8.0 Hz, 1 H), 9.96 (br. s, 1 H) ppm. HRMS (FAB): calcd. for $C_{11}H_{11}N_2O$ $[M + H]^+$ 187.0871; found 187.0876.

9-Methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-one (20h):[7c] White solid, m.p. 157.5–160.0 °C (lit.: 160–162 °C). ^1H NMR (400 MHz, $CDCl_3$): δ = 3.04 (t, J = 6.9 Hz, 2 H), 3.64 (dt, J = 2.7, 6.8 Hz, 2 H), 4.10 (s, 3 H), 5.57 (br. s, 1 H), 7.14 (dt, J = 1.1, 7.5 Hz, 1 H), 7.32–7.38 (m, 2 H), 7.58 (d, J = 8.0 Hz, 1 H) ppm. HRMS (FAB): calcd. for $C_{12}H_{13}N_2O$ $[M + H]^+$ 201.1028; found 201.1025.

5,6-Dihydrothieno[2,3-*c*]pyridin-7(4*H*)-one (20i):[27] White solid, m.p. 113.5–115.5 °C (lit.: 123.5–125.0 °C). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.90 (t, J = 6.9 Hz, 2 H), 3.60 (dt, J = 2.2, 6.8 Hz, 2 H), 6.48 (br. s, 1 H), 6.92 (d, J = 4.8 Hz, 1 H), 7.47 (d, J = 4.8 Hz, 1 H) ppm. HRMS (FAB): calcd. for C_7H_8NOS $[M + H]^+$ 154.0327; found 154.0328.

7,9-Dimethoxyphenanthridin-6(5*H*)-one (20j):[28] White solid, m.p. 260.0–261.5 °C. ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 3.85 (s, 3 H), 3.97 (s, 3 H), 6.70 (d, J = 1.7 Hz, 1 H), 7.16 (t, J = 7.6 Hz, 1 H), 7.24 (d, J = 8.1 Hz, 1 H), 7.41–7.48 (m, 2 H), 8.32 (d, J = 8.1 Hz, 1 H) ppm. HRMS (FAB): calcd. for $C_{15}H_{14}NO_3$ $[M + H]^+$ 256.0974; found 256.0979.

8,9-Dimethoxyphenanthridin-6(5*H*)-one (20k):[29] White solid, m.p. 305.0–307.0 °C (lit.: 314–319 °C). ^1H NMR (400 MHz, [D$_6$]-DMSO): δ = 3.90 (s, 3 H), 4.02 (s, 3 H), 7.23 (t, J = 7.5 Hz, 1 H), 7.33 (d, J = 8.0 Hz, 1 H), 7.43 (t, J = 7.6 Hz, 1 H), 7.71 (s, 1 H), 7.88 (s, 1 H), 8.38 (d, J = 8.0 Hz, 1 H), 11.56 (s, 1 H) ppm. HRMS (FAB): calcd. for $C_{15}H_{14}NO_3$ $[M + H]^+$ 256.0974; found 256.0978.

7,8-Dimethoxy-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-1-one (20m):[30] White solid, m.p. 183.0–184.2 °C (lit.: 182–183 °C). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.99 (quint., J = 6.8 Hz, 2 H), 2.80 (t, J = 7.1 Hz, 2 H), 3.12 (q, J = 6.4 Hz, 2 H), 3.89 (s, 3 H), 3.90 (s, 3 H), 6.22 (br. s, 1 H), 6.65 (s, 1 H), 7.24 (s, 1 H) ppm. HRMS (FAB): calcd. for $C_{12}H_{16}NO_3$ $[M + H]^+$ 222.1130; found 222.1134.

Supporting Information (see footnote on the first page of this article): ^1H NMR spectra of compounds **11**–**14**, **16**, mixture of **16** and **17**, **18**, **19a**–**19m**, **20a**–**20d**, **20g**–**20k**, **20m**, ^{13}C NMR spectra of compounds **11**–**14**, **16**, **19a**, **19f**, **19i**, **19k**, **19l**, **19m**, and IR spectrum of compound **18**.

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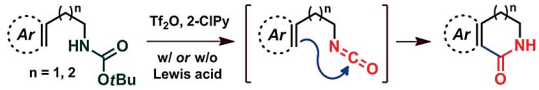
Friedel–Crafts-Type Cyclization



Isoquinolin-1-ones and related fused-ring heterocycles have been prepared from *N*-Boc-protected (β-arylethyl)carbamates. The *N*-Boc-carbamates were first converted into isocyanates by using the reagents Tf_2O and 2-chloropyridine. These isocyanates were then subjected to in situ intramolecular Friedel–Crafts-type reaction to give the products in good yields and with high regioselectivities.

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Synthesis of 3,4-Dihydroisoquinolin-1-ones from *N*-Boc-(β-Arylethyl)carbamates via Isocyanate Intermediates

Keywords: Synthetic methods / Cyclization / Fused-ring systems / Nitrogen heterocycles / Isocyanates

