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Metal-Free Synthesis of *N*-Aryl-Substituted Azacycles from Cyclic Ethers using $POCl_3$

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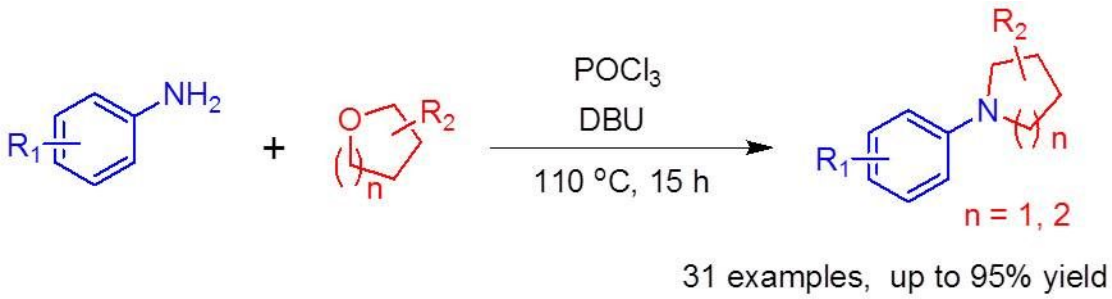
GRAPHICAL ABSTRACT



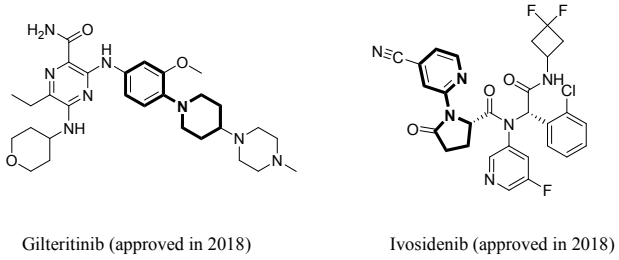
31 examples, up to 95% yield

ABSTRACT

A facile method for the synthesis of *N*-aryl substituted azacycles from arylamines and cyclic ethers has been developed. In this study, arylamines were treated with cyclic ethers in the presence of $POCl_3$ and DBU to provide five- and six-membered azacycles. Using this method, various azacycloalkanes, isoindolines, and tetrahydroisoquinolines were prepared in high yields. This synthetic method offers an efficient approach to the production of azacycles from cyclic ethers.

INTRODUCTION

The development of novel synthetic methods for *N*-substituted azacycles is an important topic in organic and medicinal chemistry; this is because these motifs possess valuable properties as building blocks for structures of complex biomolecules, and *N*-substituted azacycles are present in many pharmaceuticals as well as organic materials.[1] Thus, azacycle structures have received much attention in the drug discovery and materials industries. In particular, it was reported that several novel drugs recently approved by the FDA contain an *N*-substituted azacycle moiety (Figure 1).[2].

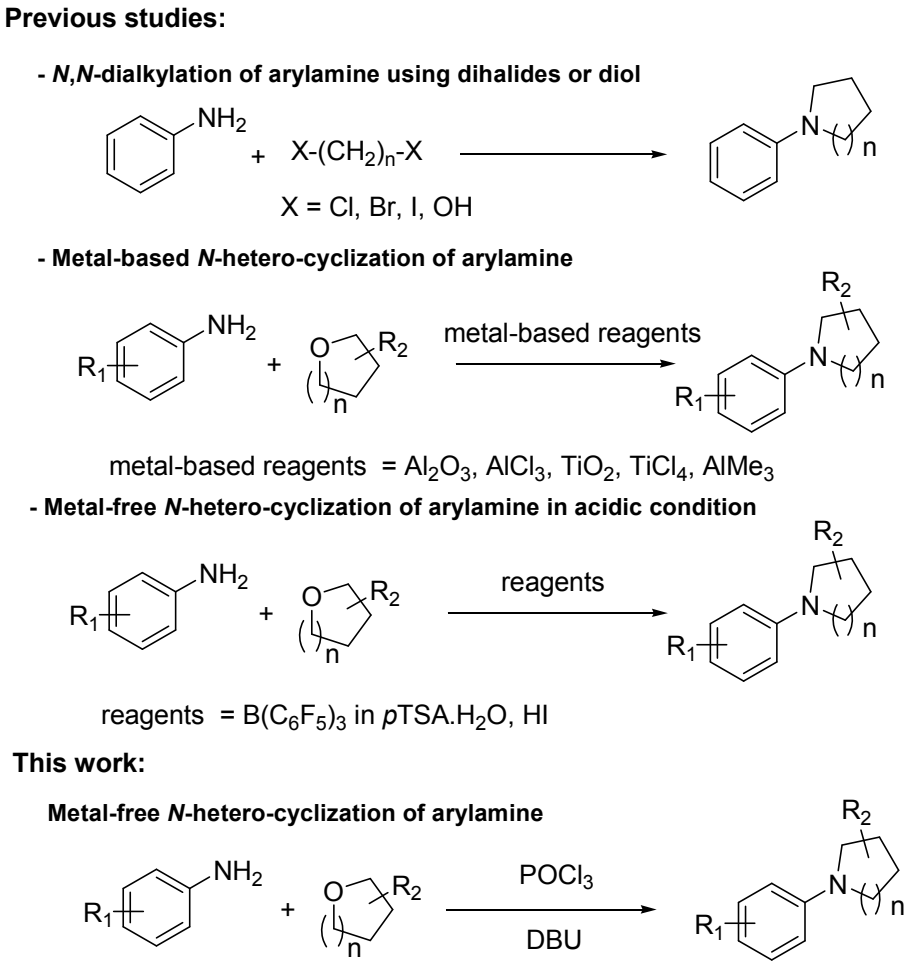


Gilteritinib (approved in 2018) Ivosidenib (approved in 2018)

Figure 1. FDA approved drugs containing azacycles

Due to a variety of applications involving azacycle structures, several synthetic methods were reported to prepare *N*-substituted azacycle compounds: the reaction of primary arylamines with dihalides or diols,[3] reduction of tertiary lactams or azacyclodienes formed by cyclocondensation between dicarbonyl compounds and an amine,[4] and a cross-coupling reaction of *N*-unsubstituted azacycles and aryl halides.[5] An intramolecular C(sp^3)-N coupling reaction was also reported to prepare *N*-substituted azacycles.[6] The reaction of a primary amine with cyclic ethers to prepare azacycles is an attractive method, as water is the co-product formed during condensation. Several protocols using arylamines and cyclic ethers have been described; the first method to synthesize *N*-phenylpyrollidine was the reaction of tetrahydrofuran and aniline, using activated alumina at 400 °C.[7] Other metal-based approaches have been utilized for the synthesis of *N*-substituted

azacycles, including Al_2O_3, $AlCl_3$, $TiCl_4$ or $AlMe_3$.[8] Recently, several methods were developed using non-metal catalysts. Zhang and co-workers employed $B(C_6F_5)_3$ and *p*TSA.H_2O to synthesize *N*-substituted azacycles via a frustrated Lewis pairs pathway.[9] Other metal-free protocols using HI or $BF_3.Et_2O$ were also developed.[10] However, these methods employ acid or Lewis acid catalysts that may be incompatible with acid-sensitive functional groups. To overcome the issues of previously reported azacycle syntheses, herein we report a metal-free and efficient base-mediated synthesis of five- or six-membered ring azacycle compounds (Scheme 1).



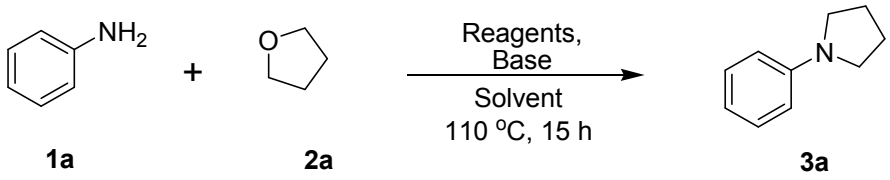
Scheme 1. Synthesis of *N*-substituted azacycles**.**

RESULTS AND DISCUSSION

Synthetic chemistry of target products utilizing metal-free methods is a highly desirable green methodology. For the development of a novel metal-free reaction, phosphoramidates can be attractive intermediates for the preparation of target products since they are known precursors that have been practically used to synthesize amines, imines, and heterocycles such as aziridines.[11] Thus, we envisioned that a synthesis of azacycles utilizing phosphoramidic dichloride intermediates starting from amines would be realizable, and we hypothesized that reactions of amines with $POCl_3$ could be employed for *in situ* generation of phosphoramidic dichloride, which are active intermediates leading to azacycles. Such utilization of this base reaction system could be a novel approach to prepare *N*-unsubstituted azacycles. To test our hypothesis, aniline was selected as a model substrate in the initial study. Reaction with tetrahydrofuran (THF) was performed in xylene at 110 °C for 15 h, and the yield of the corresponding azacycle was investigated. First, reactions with a series of Lewis acids including $CuCl_2$, $FeCl_3$, $ZnCl_2$, $ZrCl_4$, and $BiCl_2$ were surveyed. However, the product was not obtained in most of the experiments (Table 1). When $SnCl_2$ was employed, the product was obtained in low yield. In addition, treatment with CaI_2, or $CaBr_2$ did not produce the azacycle. In this study, $POCl_3$ were employed for the synthesis of *N*-aryl substituted azacycle, and it was found that the reaction with $POCl_3$ provided the target azacycle with an improved yield (35%). Next, we investigated the base effect on the synthesis of *N*-substituted azacycles. Employment of K_2CO_3, $NaHCO_3$, triethylamine, 4-dimethylaminopyridine (DMAP), KOH, and NaOH resulted in low yields of azacycles. When Cs_2CO_3 was used as a base, the yield of azacycle increased to 70%, but was still unsatisfactory. However, when DBU was used in the reaction, the desired azacycle was prepared in significantly increased yield (95%). Screening of solvents was also performed to

further optimize the reaction conditions. Reactions in MeCN, DMF, and DCE resulted in no reaction. When toluene and $PhCF_3$ were used as the reaction solvent, the yield of the azacycle was enhanced to 44% and 45%, respectively. When xylene was employed in the reaction, the yield of the corresponding azacycle increased significantly (95%).

Table 1. Screening of reaction conditions for the preparation of azacycles[a].



1a **2a** **3a**

Entry	Reagents	Base	Solvent	Yield[b] (%)
1	$CuCl_2$	-	xylene	NR[c]
2	$FeCl_3$	-	xylene	NR[c]
3	$ZnCl_2$	-	xylene	NR[c]
4	$ZrCl_4$	-	xylene	NR[c]
5	$BiCl_2$	-	xylene	NR[c]
6	$MnCl_2$	-	xylene	NR[c]
7	$SnCl_2$	-	xylene	24
8	CaI_2	-	xylene	NR[c]
9	$CaBr_2$	-	xylene	NR[c]
10	$POCl_3$	-	xylene	35
11	$POCl_3$	K_2CO_3	xylene	44
12	$POCl_3$	$CsCO_3$	xylene	70
13	$POCl_3$	$NaHCO_3$	xylene	41
14	$POCl_3$	Et_3N	xylene	42

15	$POCl_3$	DMAP	xylene	NR[c]
16	$POCl_3$	KOH	xylene	23
17	$POCl_3$	NaOH	xylene	22
18	$POCl_3$	DBU	xylene	95
19	$POCl_3$	DBU	toluene	44
20	$POCl_3$	DBU	$PhCF_3$	45
21	$POCl_3$	DBU	MeCN	NR[c]
22	$POCl_3$	DBU	DMF	NR[c]
23	$POCl_3$	DBU	DCE	NR[c]
24[d]	$POCl_3$	DBU	xylene	91
25[e]	$POCl_3$	DBU	xylene	88

[a] Reaction conditions: compound **1a** (1 mmol), THF **2a** (20 mmol), reagents (1.5 mmol), Base (2 mmol), solvent (3 mL), 110 ^oC, 15 h; [b] Isolated yield after purification of flash column chromatography; [c] No reaction; [d] compound **1a** (1 mmol), THF **2a** (10 mmol), $POCl_3$ (1.5 mmol), DBU (2 mmol), xylene (3 mL), 110 ^oC, 15 h; [e] compound **1a** (1 mmol), THF **2a** (5 mmol), $POCl_3$ (1.5 mmol), DBU (2 mmol), xylene (3 mL), 110 ^oC, 15 h

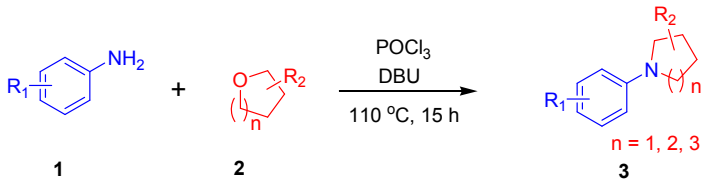
To better understand the effect of reagents and base on the reaction, reactions of aniline with a series of equivalents of $POCl_3$ and DBU were performed to produce the desired azacycle (see Table S1 in supporting information). The reaction results indicated that the highest yield of azacycle was observed in the presence of 1.5 equiv. of $POCl_3$ and 2.0 equiv. of DBU (95%), but

further addition of $POCl_3$ and DBU did not enhance the yield. In addition, we further investigated the use of different amounts of THF in the synthesis of azacycle. The yield of azacycle product increased in proportion to the amount of reagent (88% for 5 equiv. of THF and 91% for 10 equiv. of THF). In particular, employment of 20 equiv. of THF produced the target azacycle in high yield, although there was no significant difference in yield between employment of 20 equiv., 30 equiv., and 40 equiv. of THF.

With optimized reaction conditions in hand, the scope of this protocol for the synthesis of azacycles from arylamines and cyclic ethers was explored (Scheme 2). Most of the target azacycles were prepared in high yields via treatment of various arylamines with cyclic ethers. The synthesis of azacycles from arylamines and cyclic ethers was not significantly influenced by the electronic properties of substituents on the aromatic ring. Arylamines bearing electron-donating groups (methyl-, methoxyl-) and electron-withdrawing groups (nitro-, chloro-, fluoro-) reacted well with cyclic ethers under the optimal reaction conditions, yielding the desired *N*-aryl-substituted azacycles in high yields (Scheme 2, **3b-j**). Naphthylamine, 3,4-(methylenedioxy)amine, and 1,4-benzodioxan-6-amine were also employed with tetrahydrofuran, affording the corresponding azacycles in 92%, 82%, and 80% yield, respectively (Scheme 2, **3k-m**). Besides, *N*,*N*-dimethyl-*p*-phenylenediamine bearing a nitrogen and 2-aminopyridine, a hetrocyclic amine, were used with tetrahydrofuran, yielding the corresponding azacycles in 76%, and 55% yield, respectively (Scheme 2, **3n-o**). It was noteworthy that mono-substitution of the aniline such as *p*-*t*-Bu-substituted arylamine did not result in a big difference from that of aniline in the reaction. However, the reaction of 3,5- and 2,6-disubstituted anilines provided the desired products in lower yields (Scheme 2, **3e-f**). The tolerance of different cyclic ethers was also explored. Even though 2-methyltetrahydrofuran is

more sterically hindered than THF, it successfully reacted with various aryl amines (such as aniline, amines containing electron-donating and electron-withdrawing groups, and naphthylamine) to yield the corresponding products in high yields (Scheme 2, **3p-s**). In addition, tetrahydropyran, a six-membered cyclic ether, and oxepane, a seven-membered cyclic ether, were employed for the synthesis of azacycles, and the yields were somewhat lower (Scheme 2, **3t-u**). 1,4-Dioxane, a heterocyclic compounds, was also used to react with tetrahydrofuran, giving the corresponding azacycles in 57% yield (Scheme 2, **3v**).

Scheme 2. Scope of synthesis of azacycloalkanes[a]



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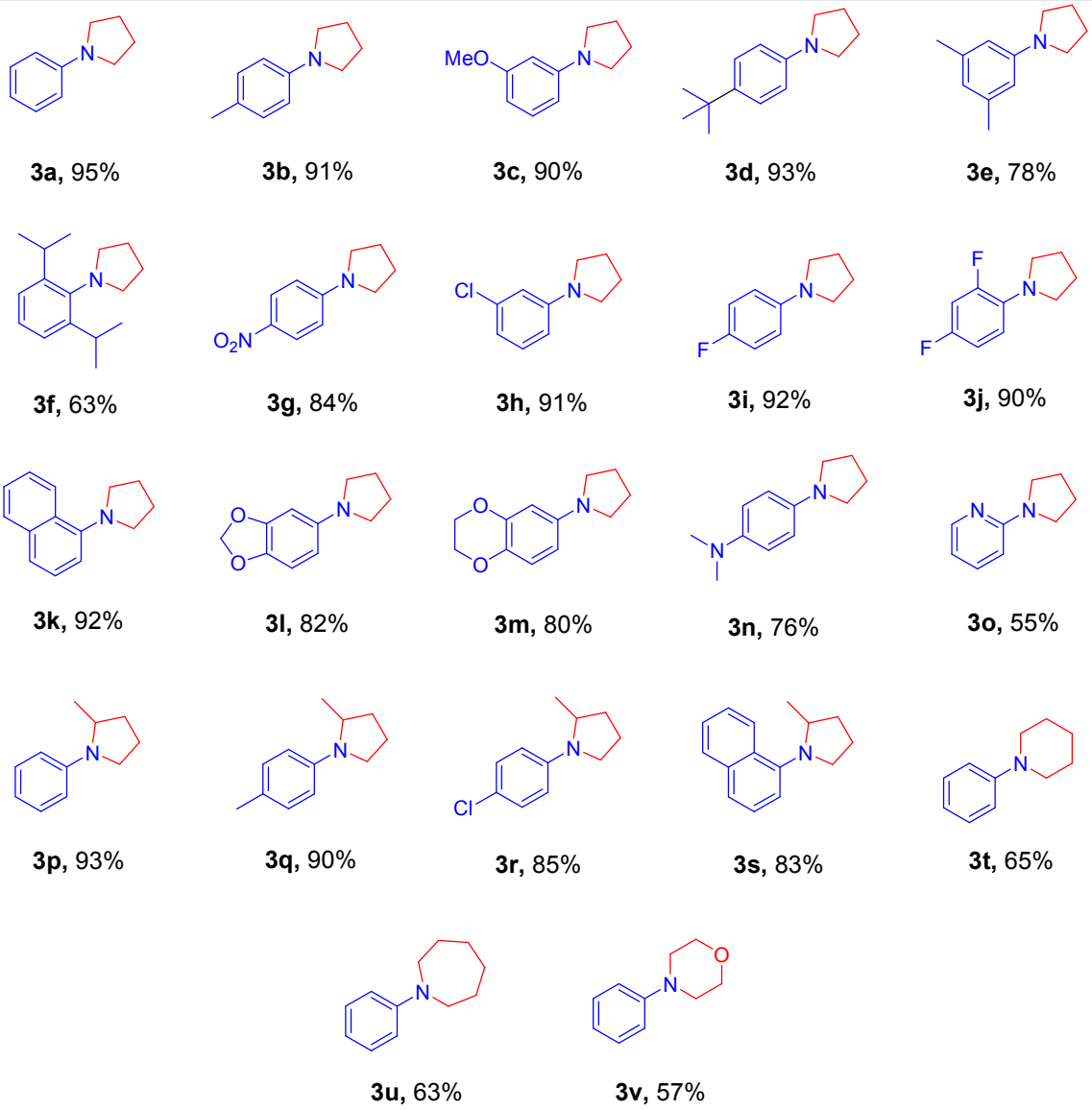
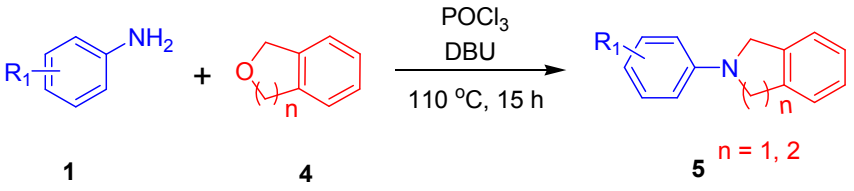


[a] Reaction conditions: compound **1** (1 mmol), cyclic ethers **2** (20 mmol), $POCl_3$ (1.5 mmol), DBU (2 mmol), xylene (3 mL), 110 °C, 15 h

From these positive synthesis results, the scope of utilizing $POCl_3$ was extended to the synthesis of nitrogen-containing fused heterocyclic ring materials from arylamines. In particular, tetrahydroisoquinolines and isoindolines are important azacycle motifs in many biological active pharmaceuticals and natural products.[12] The treatment of aniline with phthalan readily resulted in successful synthesis of the corresponding azacycle in 93% yield (Scheme 3, **5a**). Furthermore, the electronic effect of substituents on the aryl amine was not significantly different from those shown in Scheme 3. The reaction of various arylamines bearing electron-donating groups or electron-withdrawing groups with phthalan also produced the corresponding isoindolines in satisfactory yields (Scheme 3, **5b-e**). In addition, the reaction of arylamines with isochroman under the same reaction conditions produced tetrahydroisoquinolines in high yields (Scheme 3, **5f-i**). These results suggest that $POCl_3$ and DBU could serve as an important reagent combination for the efficient conversion of arylamines to *N*-aryl substituted five- and six-membered azacycles.

Scheme 3. Scope of synthesis of isoindolines and tetrahydroisoquinolines[a]



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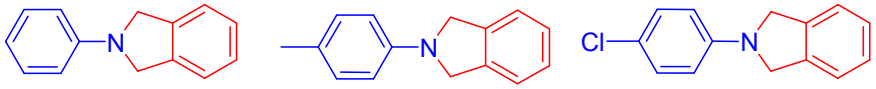
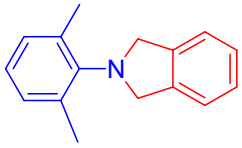


5a, 93%

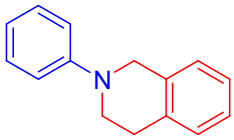
5b, 94%

5c, 93%

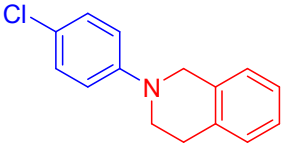
5d, 92%



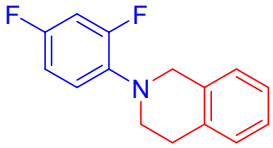
5e, 83%



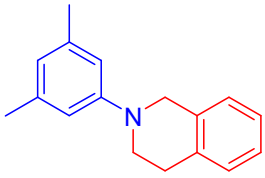
5f, 65%



5g, 88%



5h, 85%

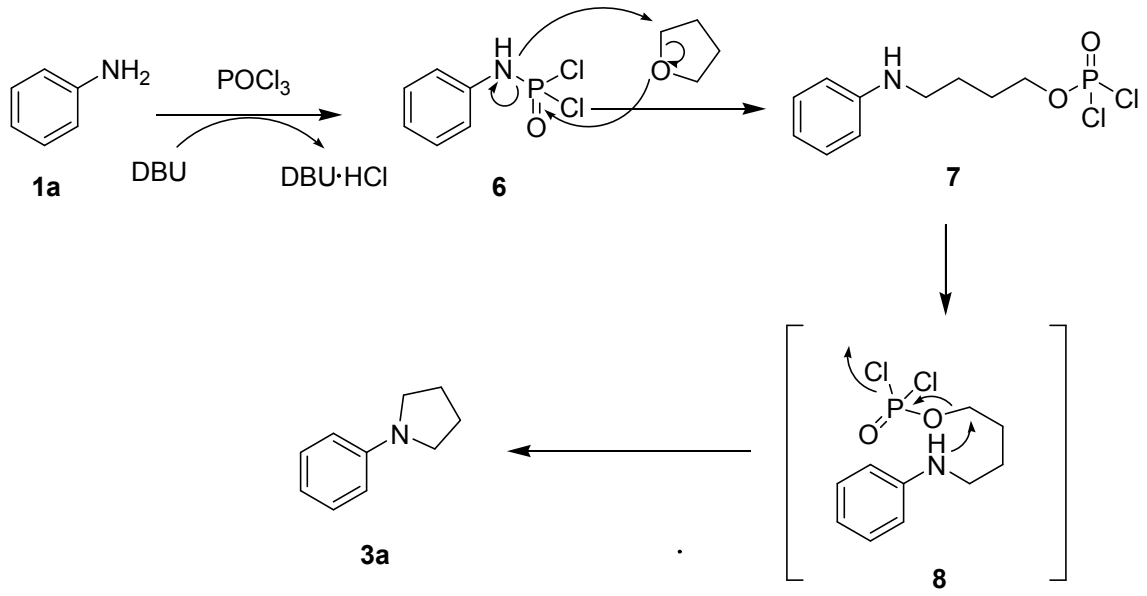


5i, 83%

[a] Reaction conditions: compound 1 (1 mmol), cyclic ethers 4 (1.5 mmol), $POCl_3$ (1.5 mmol), DBU (2 mmol), xylene (3 mL), 110 °C, 15 h

To gain a mechanistic insight into this method, control experiments were performed. When $POCl_3$ and DBU were employed, the reaction successfully produced phosphoramidic dichloride **6**, while employment of $POCl_3$ alone or employment of DBU alone did not yield the phosphoramidic dichloride. Besides, the controlled experiment using the prepared phosphoramidic dichloride was performed. It was found that the reaction of the prepared phosphoramidic dichloride **6** with THF under the same condition produced the corresponding

product successfully. Thus, a plausible reaction pathway based on our results can be proposed, as shown in Scheme 4. The initial addition of $POCl_3$ and DBU to arylamine **1** probably affords phosphoramidic dichloride **6**. Then, THF reacts with phosphoramidic dichloride **6** to provide **7**. Intramolecular attack of the nitrogen on the carbon near phosphorus atom gives the desired product, 1-phenyl-pyrrolidine **3a**.



Scheme 4. Proposed reaction mechanism for N-heterocyclization from arylamine.

CONCLUSION

In summary, a novel metal-free method for the synthesis of *N*-aryl-substituted azacycles from arylamines and cyclic ethers has been developed. In the present study, the combination of $POCl_3$ and DBU is crucial to produce the desired products. Using this method, *N*-aryl substituted five- and six-membered azacycles were prepared in high yields. Moreover, the reaction protocol is

simple and efficient. We expect that this novel method will be useful for the synthesis of a variety of five- and six-membered azacycles from cyclic ethers.

Experimental section

General Information

All reactions were performed in 20-mL vials with Teflon caps. Commercial chemicals and solvents were used without any purification. Reaction progress was analyzed by thin-layer chromatography (TLC) using silica gel 60 F254 pre-coated aluminum plate from Merck and TLC spots were observed under UV light (254nm) exposure. Flash chromatography was carried out using 230–400 mesh silica gel and analytical grade solvents. Stuart SMP10 Melting Point Apparatus was used to record melting points of products. Structure elucidation by NMR (^{1}H and ^{13}C NMR) was performed on Bruker Avance 400 MHz spectrometer. The chemical shifts were reported in δ units (ppm) relative to the residual protonated solvent resonance, the coupling constants (J) quoted in Hz, and multiplicity of signals was abbreviated as follows: singlet (s); doublet (d); doublet of doublet (dd); triplet (t); multiplet (m). The high resolution mass spectra (HRMS) were analyzed on 6200 series TOF/6500 series Q-TOF B.08.00.

General procedure of the synthesis of azacyles 3a-3r

To a 20 mL vial containing a stirring mixture of aniline (**1a**) (0.093 g, 1.00 mmol) and DBU (0.304 g, 2.00 mmol) in xylene (3 mL) was added dropwise $POCl_3$ (0.230 g, 1.50 mmol) at room temperature. The mixture was then heated at 90 °C for 15 min. Tetrahydrofuran (1.6 mL, 20 mmol) were added to the reaction mixture and the vial was closed tightly with Teflon cap. The reaction mixture was allowed to heat at 110 °C for 15 h. The reaction was cooled down to the ambient temperature, then saturated aqueous $NaHCO_3$ (10 mL) and brine (10mL) were added to

the mixture. The aqueous mixture was extracted with Et_2O and the organic layer was dried over anhydrous sodium sulfate and subsequently concentrated under reduced pressure. The crude product was then purified by flash column chromatography on silica gel with 2% diethyl ether in *n*-hexane as eluent to afford the desired product **3a** (0.140 g, 95% yield).

*1-phenylpyrrolidine (**3a**)*.[8e] Light yellow oil (0.140 g, 95% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (t, J = 7.2 Hz, 2H), 6.72 (t, J = 7.2 Hz, 1H), 6.63 (d, J = 8.0 Hz, 2H), 3.39-3.29 (m, 4H), 2.11-2.00 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.0, 129.1 (2C), 115.4, 111.7 (2C), 47.6 (2C), 25.5 (2C); HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{10}H_{14}N$ = 148.1126; found 148.1129..

*1-p-tolylpyrrolidine (**3b**)*.[8e] White solid (0.147 g, 91% yield); m.p. 41-43 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (d, J = 8.0 Hz, 2H), 6.56 (d, J = 8.0 Hz, 2H), 3.35-3.25 (m, 4H), 2.31 (s, 3H), 2.10-2.00 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.1, 129.6 (2C), 124.5, 111.8 (2C), 47.9 (2C), 25.4 (2C), 20.3; HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{11}H_{16}N$ = 162.1283; found 162.1285.

*1-(3-methoxyphenyl)pyrrolidine (**3c**)*.[8e] Colorless oil (0.160 g, 90% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (t, J = 8.0 Hz, 1H), 6.27 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 6.24 (dd, J = 8.0 Hz, 2.0 Hz, 1H), 6.16 (t, J = 2.0 Hz, 1H), 3.84 (s, 3H), 3.35-3.26 (m, 4H), 2.07-2.00 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 149.3, 129.8, 104.9, 100.5, 97.9, 55.1, 47.7 (2C), 25.5 (2C); HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{11}H_{16}NO$ = 178.1232; found 178.1237.

*1-(4-tert-butylphenyl)pyrrolidine (**3d**)*.[9] White solid (0.189 g, 93% yield); m.p. 40-42 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, J = 8.8 Hz, 2H), 6.58 (d, J = 8.8 Hz, 2H), 3.35-3.27 (m, 4H), 2.05-2.00 (m, 4H), 1.34 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.9, 137.9, 125.9 (2C), 111.3 (2C), 47.7 (2C), 33.7, 31.6 (3C), 25.5 (2C); HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{14}H_{22}N$ = 204.1752; found 204.1751..

*1-(3,5-dimethylphenyl)pyrrolidine (**3e**).*[13] Colorless oil (0.137 g, 78% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.38 (s, 1H), 6.26 (s, 2H), 3.35-3.29 (m, 4H), 2.32 (s, 6H), 2.05-1.97 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 138.7 (2C), 117.5, 109.7 (2C), 47.6 (2C), 25.5 (2C), 21.7 (2C); HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{12}H_{18}N$ = 176.1439; found 176.1441..

*1-(2,6-diisopropylphenyl)pyrrolidine (**3f**).*[9] Colorless oil (0.146 g, 63% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (t, J = 7.2 Hz, 1H), 7.15 (d, J = 7.2 Hz, 2H), 3.36-3.20 (m, 6H), 2.11-2.00 (m, 4H), 1.25 (d, J = 6.0 Hz, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.1, 142.9, 126.3 (2C), 123.9 (2C), 52.8 (2C), 28.0 (2C), 26.6 (2C), 24.5 (4C); HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{16}H_{26}N$ = 232.2065; found 232.2067.

*1-(4-nitrophenyl)pyrrolidine (**3g**).*[9] Yellow solid (0.162 g, 84% yield); m.p. 167-169 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 9.2 Hz, 2H), 6.49 (d, J = 9.2 Hz, 2H), 3.37-3.29 (m, 4H), 2.15-2.05 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9, 136.6, 126.3 (2C), 110.4 (2C), 47.9 (2C), 25.4 (2C); HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{10}H_{13}N_2O_2$ = 193.0977; found 193.0978..

*1-(3-chlorophenyl)pyrrolidine (**3h**).*[9] Colorless oil (0.165 g, 91% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (t, J = 8.0 Hz, 1H), 6.64 (dd, J = 7.6 Hz, 1.2 Hz, 1H), 6.55 (t, J = 2.0 Hz, 1H), 6.45 (dd, J = 8.4 Hz, 2.0 Hz, 1H), 3.32-3.25 (m, 4H), 2.07-2.00 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.8, 134.9, 130.0, 115.1, 111.4, 109.8, 47.6 (2C), 25.4 (2C); HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{10}H_{13}ClN$ = 182.0737; found 182.0736.

*1-(4-fluorophenyl)pyrrolidine (**3i**).*[8e] Colorless oil (0.153 g, 92% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03-6.93 (m, 2H), 6.55-6.47 (m, 2H), 3.33-3.20 (m, 4H), 2.10-2.00 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0&153.6 (d, $^1J_{C\text{-}F}$ = 231.8 Hz, 1C), 144.8, 115.5&115.3 (d, $^2J_{C\text{-}F}$ = 21.9 Hz, 2C), 112.1&112.0 (d, $^3J_{C\text{-}F}$ = 4.6 Hz, 2C), 48.1 (2C), 25.5 (2C); HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{10}H_{13}FN$ = 166.1032; found 166.1037.

*1-(2,4-difluorophenyl)pyrrolidine (**3j**)*.[8e] Colorless oil (0.166 g, 90% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85-6.72 (m, 2H), 6.70-6.59 (m, 1H), 3.30-3.20 (m, 4H), 2.07-1.90 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0-153.5 (dd, $^1J_{C\text{-}F}$ = 238.3 Hz, $^3J_{C\text{-}F}$ = 12.4 Hz, 1C), 153.1-150.5 (dd, $^1J_{C\text{-}F}$ = 243.4 Hz, $^3J_{C\text{-}F}$ = 10.9 Hz, 1C), 134.3, 115.2, 110.5&110.3 (d, $^2J_{C\text{-}F}$ = 18.2 Hz, 1C), 104.7-104.2 (t, $^2J_{C\text{-}F}$ = 25.5 Hz, 1C), 50.0 (2C), 25.0 (2C); HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{10}H_{12}F_2N$ = 184.0938; found 184.0940.

*1-(naphthalen-1-yl)pyrrolidine (**3k**)*.[8e] Light yellow oil (0.182 g, 92% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29-8.22 (m, 1H), 7.88-7.82 (m, 1H), 7.52-7.45 (m, 3H), 7.40 (t, J = 7.6 Hz, 1H), 7.01 (d, J = 7.6 Hz, 1H), 3.48-3.38 (m, 4H), 2.12-2.02 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.7, 135.0, 128.3, 128.2, 125.9, 125.5, 124.8, 124.3, 121.3, 111.4, 52.7 (2C), 24.8 (2C); HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{14}H_{16}N$ = 198.1283; found 198.1284.

*1-(benzo[d][1,3]dioxol-5-yl)pyrrolidine (**3l**)*.[14] Light yellow solid (0.157 g, 82% yield); m.p. 68-70 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 (d, J = 8.4 Hz, 1H), 6.25 (d, J = 1.6 Hz, 1H), 5.99 (d, J = 7.2 Hz, 1H), 5.87 (s, 2H), 3.30-3.20 (m, 4H), 2.07-1.97 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.3, 144.5, 138.1, 108.7, 103.0, 100.4, 94.5, 48.4 (2C), 25.4 (2C); HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{11}H_{14}NO_2$ = 192.1025; found 192.1028.

*1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)pyrrolidine (**3m**)*.[15] Yellowish oil (0.165 g, 80% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 (dd, J = 9.2 Hz, J = 3.2 Hz, 1H), 6.14 (d, J = 6.8 Hz, 2H), 4.28 – 4.20 (m, 4H), 3.22(t, J = 6.8 Hz, 4H), 2.01 -1.96 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.94, 143.73, 117.51, 105.42, 105.23, 100.36, 64.86, 64.24, 48.14 (2C), 25.38 (2C); HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{12}H_{16}NO_2$ = 206.1181; found 206.1182.

*N,N-dimethyl-4-(pyrrolidin-1-yl)aniline (**3n**)*.[16] White solid (0.145 g, 76% yield); m.p. 68-70 °C ^{1}H NMR (400 MHz, $(CD_3)_2CO$) δ 6.73 (d, J = 8.8 Hz, 2H), 6.49 (d, J = 8.5 Hz, 2H), 3.30-3.00

(m, 4H), 2.75 (s, 6H), 1.97-1.91 (m, 4H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 142.84, 141.74, 115.69 (2C), 112.71 (2C), 47.85 (2C), 41.50 (2C), 24.95 (2C); HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{12}H_{19}N_2$ = 191.1548; found 191.1547.

*2-(pyrrolidin-1-yl)pyridine (**3o**)*.[17] Yellow oil (0.082 g, 55% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 4.8 Hz, 1H), 7.48-7.41 (m, 1H), 6.52 (t, J = 6.0 Hz, 1H), 6.36 (d, J = 8.4 Hz, 1H), 3.50-3.40 (m, 4H), 2.09-2.00 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 148.1, 136.9, 111.0, 106.5, 46.6 (2C), 25.5 (2C); HRMS (ESI) m/z $(M+H)^+$ calcd for $C_9H_{13}N_2$ = 149.1079; found 149.1080.

*2-methyl-1-phenylpyrrolidine (**3p**)*.[8e] Light yellow oil (0.151 g, 93% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.23 (m, 2H), 6.84 (t, J = 8.8 Hz, 1H), 6.63 (d, J = 8.0 Hz, 2H), 3.96-3.87 (m, 1H), 3.51-3.43 (m, 1H), 3.25-3.16 (m, 1H), 2.19-1.97 (m, 3H), 1.79-1.70 (m, 1H), 1.22 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.2, 129.2 (2C), 115.1, 111.8 (2C), 53.6, 48.2, 33.1, 23.3, 19.4; HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{11}H_{16}N$ = 162.1283; found 162.1285.

*2-methyl-1-p-tolylpyrrolidine (**3q**)*.[8e] Colorless oil (0.159 g, 90% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.06 (d, J = 6.4 Hz, 2H), 6.55 (d, J = 6.0 Hz, 2H), 3.90-3.80 (m, 1H), 3.47-3.38 (m, 1H), 3.23-3.10 (m, 1H), 2.28 (s, 3H), 2.15-1.95 (m, 3H), 1.75-1.65 (m, 1H), 1.20 (d, J = 5.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.3, 129.7 (2C), 124.2, 111.9 (2C), 53.7, 48.5, 33.2, 23.4, 20.3, 19.5; HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{12}H_{18}N$ = 176.1439; found 176.1438.

*1-(4-chlorophenyl)-2-methylpyrrolidine (**3r**)*.[9] White solid (0.167 g, 85% yield); m.p. 41-43 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, J = 8.8 Hz, 2H), 6.51 (t, J = 6.0 Hz, 2H), 3.90-3.80 (m, 1H), 3.47-3.38 (m, 1H), 3.23-3.10 (m, 1H), 2.28 (s, 3H), 2.15-1.95 (m, 3H), 1.75-1.65 (m, 1H), 1.20 (d, J = 5.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.7, 128.9 (2C), 119.9, 112.8 (2C),

53.8, 48.3, 33.1, 23.3, 19.1; HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{11}H_{15}ClN$ = 196.0893; found 196.0894.

*2-methyl-1-(naphthalen-1-yl)pyrrolidine (**3s**)*.[18] Light yellow oil (0.176 g, 83% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30-8.25 (m, 1H), 7.88-7.82 (m, 1H), 7.55-7.40 (m, 4H), 7.07 (t, J = 7.6 Hz, 1H), 3.92-3.75 (m, 2H), 3.00-2.90 (m, 1H), 2.32-2.13 (m, 1H), 2.10-2.00 (m, 1H), 1.95-1.82 (m, 1H), 1.80-1.70 (m, 1H), 1.11 (d, J = 5.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.9, 134.8, 130.1, 128.1, 125.8, 125.6, 124.7, 124.5, 122.0, 114.1, 55.7, 55.4, 33.6, 23.5, 18.7; HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{15}H_{18}N$ = 212.1439; found 212.1437.

*1-phenylpiperidine (**3t**)*.[9] Colorless oil (0.105 g, 65% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.24 (m, 2H), 6.98 (d, J = 7.6 Hz, 2H), 6.86 (t, J = 7.2 Hz, 1H), 3.30-3.15 (m, 4H), 1.85-1.72 (m, 4H), 1.68-1.55 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3, 129.0 (2C), 119.2, 116.6 (2C), 50.7 (2C), 25.9 (2C), 24.3; HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{11}H_{16}N$ = 162.1283; found 162.1283.

*1-phenylazepane (**3u**)*.[19] Light yellow oil (0.111 g, 63% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.20 (m, 2H), 6.72 (d, J = 8.0 Hz, 2H), 6.64 (t, J = 7.2 Hz, 1H), 3.47 (t, J = 9.2 Hz, 4H), 1.85- 1.75 (m, 4H), 1.59 -1.55 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.86, 129.24 (2C), 115.08, 111.17 (2C), 49.04 (2C), 27.79 (2C), 27.17 (2C); HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{12}H_{18}N$ = 176.1439; found 176.1440.

*4-phenylmorpholine (**3v**)*.[20] Light brown solid (0.093 g, 57% yield); m.p. 52-54 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.28 (m, 2H), 7.03-6.90 (m, 3H), 3.90 (t, J = 4.4 Hz, 4H), 3.19 (t, J = 4.8 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.2, 129.2 (2C), 120.1, 115.7 (2C), 67.0 (2C), 49.4 (2C); HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{10}H_{14}NO$ = 164.1075; found 164.1078.

General procedure of the synthesis of azacyles 5a-5e

To a 20 mL vial containing a stirring mixture of aniline (**1a**) (0.093 g, 1.00 mmol) and DBU (0.304 g, 2.00 mmol) in xylene (3 mL) was added dropwise $POCl_3$ (0.230 g, 1.50 mmol) at room temperature. The mixture was then heated at 90 °C for 15 min. Phthalan (0.180 g, 1.50 mmol) was added to the reaction mixture and the vial was closed tightly with Teflon cap. The reaction mixture was allowed to heat at 110 °C for 15 h. The reaction was cooled down to the ambient temperature, then saturated aqueous $NaHCO_3$ (10 mL) and brine (10mL) were added to the mixture. The aqueous mixture was extracted with Et_2O and the organic layer was dried over anhydrous sodium sulfate and subsequently concentrated under reduced pressure. The crude product was then purified by flash column chromatography on silica gel with 2% diethyl ether in *n*-hexane as eluent to afford the desired product **5a** (0.181 g, 93% yield).

*2-phenylisoindoline (**5a**)*.[8e] White solid (0.181 g, 93% yield); m.p. 171-173 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.32 (m, 6H), 6.80 (t, J = 7.2 Hz, 1H), 6.73 (d, J = 8.0 Hz, 2H), 4.70 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.1, 137.9 (2C), 129.4 (2C), 127.2 (2C), 122.6 (2C), 116.2, 111.4 (2C), 53.8 (2C); HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{14}H_{14}N$ = 196.1126; found 196.1129.

*2-p-tolylisoindoline (**5b**)*.[21] White solid (0.197 g, 94% yield); m.p. 196-198 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.30 (m, 4H), 7.16 (d, J = 8.4 Hz, 2H), 6.66 (d, J = 8.4 Hz, 2H), 4.67 (s, 4H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.2, 138.1 (2C), 129.9 (2C), 127.1 (2C), 125.3, 122.6 (2C), 111.7 (2C), 54.0 (2C), 20.3; HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{15}H_{16}N$ = 210.1283; found 210.1285.

*2-(4-chlorophenyl)isoindoline (**5c**)*.[8e] White solid (0.214 g, 93% yield); m.p. 170-172 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.30 (m, 4H), 7.26 (d, J = 9.2 Hz, 2H), 6.61 (d, J = 8.8 Hz, 2H), 4.65 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.7, 137.6 (2C), 129.2 (2C), 127.3 (2C), 122.6

(2C), 121.1, 112.6 (2C), 53.9 (2C); HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{14}H_{13}ClN$ = 230.0737; found 230.0738.

*2-(4-nitrophenyl)isoindoline (**5d**).*[22] Yellow solid (0.222 g, 92% yield); m.p. 266-268 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, J = 9.2 Hz, 2H), 7.43-7.35 (m, 4H), 6.64 (d, J = 9.2 Hz, 2H), 4.80 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.3, 137.5, 136.3 (2C), 127.8 (2C), 126.4 (2C), 122.7 (2C), 110.5 (2C), 54.0 (2C); HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{14}H_{13}N_2O_2$ = 241.0977; found 241.0975.

*2-(2,6-dimethylphenyl)isoindoline (**5e**).*[23] White solid (0.186 g, 83% yield); m.p. 60-62 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.30 (m, 4H), 7.15-7.05 (m, 3H), 4.69 (s, 4H), 2.32 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.1, 140.1 (2C), 138.9 (2C), 128.7 (2C), 126.7 (2C), 126.9, 122.5 (2C), 57.2 (2C), 18.7 (2C); HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{16}H_{18}N$ = 224.1439; found 224.1438.

General procedure of the synthesis of azacyles 5f-5i

To a 20 mL vial containing a stirring mixture of aniline (**1a**) (0.093 g, 1.00 mmol) and DBU (0.304 g, 2.00 mmol) in xylene (3 mL) was added dropwise $POCl_3$ (0.230 g, 1.50 mmol) at room temperature. The mixture was then heated at 90 °C for 15 min. Isochroman (0.201 g, 1.50 mmol) was added to the reaction mixture and the vial was closed tightly with Teflon cap. The reaction mixture was allowed to heat at 110 °C for 15 h. The reaction was cooled down to the ambient temperature, then saturated aqueous $NaHCO_3$ (10 mL) and brine (10mL) were added to the mixture. The aqueous mixture was extracted with Et_2O and the organic layer was dried over anhydrous sodium sulfate and subsequently concentrated under reduced pressure. The crude product was then purified by flash column chromatography on silica gel with 2% diethyl ether in *n*-hexane as eluent to afford the desired product **5f**(0.136 g, 65% yield).

*2-phenyl-1,2,3,4-tetrahydroisoquinoline (**5f**)*.[8e] White solid (0.136 g, 65% yield); m.p. 45-47 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.31 (m, 2H), 7.26-7.18 (m, 4H), 7.03 (d, J = 8.0 Hz, 2H), 6.89 (t, J = 7.6 Hz, 1H), 4.46 (s, 2H), 3.61 (t, J = 6.0 Hz, 2H), 3.03 (t, J = 5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5, 134.9, 134.4, 129.2 (2C), 128.5, 126.5, 126.3, 126.0, 118.7, 115.2 (2C), 50.8, 46.6, 29.1; HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{15}H_{16}N$ = 210.1283; found 210.1284.

*2-(4-chlorophenyl)-1,2,3,4-tetrahydroisoquinoline (**5g**)*.[8e] White solid (0.215 g, 88% yield); m.p. 69-71 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.25 (m, 6H), 6.91 (d, J = 9.2 Hz, 2H), 4.41 (s, 2H), 3.56 (t, J = 6.0 Hz, 2H), 3.01 (t, J = 6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 134.7, 134.0, 129.0 (2C), 128.5, 126.5 (2C), 126.1, 123.4, 116.2 (2C), 50.7, 46.5, 28.9; HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{15}H_{15}ClN$ = 244.0893; found 244.0895..

*2-(2,4-difluorophenyl)-1,2,3,4-tetrahydroisoquinoline (**5h**)*.[8e] White solid (0.209 g, 85% yield); m.p. 85-87 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.15 (m, 3H), 7.15-7.10 (m, 1H), 7.05-6.96 (m, 1H), 6.92-6.78 (m, 2H), 4.29 (s, 2H), 3.42 (t, J = 5.6 Hz, 2H), 3.02 (t, J = 6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1-156.9 (dd, $^1J_{C\text{-}F}$ = 211.4 Hz, $^3J_{C\text{-}F}$ = 11.6 Hz, 1C), 156.8-154.4 (dd, $^1J_{C\text{-}F}$ = 217.3 Hz, $^3J_{C\text{-}F}$ = 11.7 Hz, 1C), 136.4&136.3 (d, $^3J_{C\text{-}F}$ = 8.8 Hz, 1C), 134.2 (2C), 128.9, 126.4, 126.3, 125.9, 120.1&120.0 (d, $^3J_{C\text{-}F}$ = 5.1 Hz, 1C), 110.8-110.5 (dd, $^2J_{C\text{-}F}$ = 21.1 Hz, $^4J_{C\text{-}F}$ = 3.6 Hz, 1C), 105.0-104.5 (t, $^2J_{C\text{-}F}$ = 25.5 Hz, 1C), 53.1, 49.3 (d, $^4J_{C\text{-}F}$ = 3.7 Hz, 1C), 28.8; HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{15}H_{14}F_2N$ = 246.1094; found 246.1097.

*2-(3,5-dimethylphenyl)-1,2,3,4-tetrahydroisoquinoline (**5i**)*.[24] White solid (0.197 g, 83% yield); m.p. 49-51 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.15 (m, 4H), 6.67 (s, 2H), 6.55 (s, 1H), 4.43 (s, 2H), 3.57 (t, J = 5.6 Hz, 2H), 3.02 (t, J = 6.0 Hz, 2H), 2.35 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.8, 138.7 (2C), 134.9, 134.6, 128.5, 126.5, 126.3, 126.0, 120.8, 113.2 (2C), 51.0, 46.7, 29.3, 21.8 (2C); HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{17}H_{20}N$ = 238.1596; found 238.1597.

*Phenylphosphoramidic dichloride (**6**)*.[25] To a 20 mL vial containing a stirring mixture of aniline (**1a**) (0.093 g, 1.00 mmol) and DBU (0.304 g, 2.00 mmol) in xylene (3 mL) was added dropwise $POCl_3$ (0.230 g, 1.50 mmol) at room temperature. The mixture was then stirred at 90 °C for 30 min, quenched with saturated ammonium chloride, and extracted with CH_2Cl_2 (2 × 10 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The resulting residue was then purified by flash column chromatography on silica gel with hexane-EtOAc as eluent to afford the desired product **6** (0.178 g, 85%). White solid (0.178 g, 85% yield); m.p. 80-82 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (t, J = 8.4 Hz, 2H), 7.27-7.20 (m, 3H), 7.11-7.00 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.3, 129.7 (2C), 125.2, 121.1 (2C); ^{31}P NMR ($CDCl_3$) δ 8.43; HRMS (ESI) m/z $(M+H)^+$ calcd for $C_6H_7Cl_2NOP$ = 209.9642; found 209.9645.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: ^{1}H and ^{13}C NMR spectra of compounds **3a-3v**, **5a-5i**, and **6**. Screening of reaction conditions for the preparation of azacycles the products (PDF)

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Notes

The authors declare no competing financial interest.

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