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Chemo- and Regioselective Assembly of Polysubstituted Pyridines and Isoquinolines from Isocyanides, Arynes, and Terminal Alkynes

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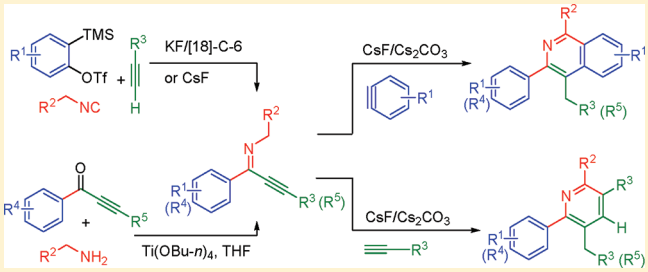
Supporting Information

ABSTRACT: We have disclosed a general and efficient synthetic strategy for polysubstituted pyridines and isoquinolines with high chemo- and regioselectivity. In this methodology, 1-alkynyl imines act as the key compound to undergo a sequential alkynyl imine−allenyl imine isomerization/aza-Diels−Alder reaction/aromatization. In the first place, 1-alkynyl imines were formed in situ by a highly selective multicomponent reaction of isocyanides, arynes, and terminal alkynes and reacted with another molecule of arynes or terminal alkynes to furnish target heterocyclic products in a highly efficient and atom-economic manner. On the other hand, we attempted to prepare 1-alkynyl imines by other approaches to undergo a similar reaction sequence to afford polysubstituted pyridines and isoquinolines with a wider range. Different from the first approach, the second approach utilized the preprepared 1-alkynyl imines to introduce the related different substitutents into the final products: arynes or terminal alkynes bearing substituents different from those of 1-alkynyl imines have been successfully applied for the synthesis a wide variety of pyridines and isoquinolines with diversity.



INTRODUCTION

Pyridines are a class of important heterocycles and appear in many naturally occurring bioactive compounds, pharmaceutical molecules, and chiral ligands in polysubstituted form.[1−3] Examples include the well-known alkaloids lycodine,[2a] the A_3 adenosine receptor antagonist,[2b] and *N*,*N*-dimethylaminopyridine (DMAP) analogue[2c] commonly applied in organic synthesis (Figure 1). In addition, isoquinoline skeleton possesses interesting bioactivities and acts as the fundamental part of numerous natural products and synthetic pharmaceuticals (Figure 1).[1a−c,2a,3] Because of their wide range of activities, the syntheses of pyridines and isoquinolines remain a topic of current interest.[4,5] However, some of the approaches have significant disadvantages, including harsh conditions and lengthy or complicated procedures.[4−6]

We have previously reported an efficient and highly chemo- and regioselective approach to polysubstituted pyridines and isoquinolines through a strategy of multicomponent/isomerization/aza-Diels−Alder/aromatization sequential reactions from the multicomponent reaction of aryne, isocyanide, and terminal alkyne: in situ generated intermediate **A** could isomerize to *N*-allenyl imine **B** after 1,5-hydride shift in the presence of CsF (eq 1, Scheme 1). Imine **B** further underwent aza-Diels−Alder reaction with another molecule of aryne or alkyne, which was followed by subsequent aromatization to afford the target heterocyclic products.[7] Therefore, we envisioned that 1-alkynyl imines **A** may be preprepared and reacted with other substituted arynes or alkynes to construct pyridine or isoquinolines (eq 2, Scheme 1). With this new approach, various substituents could be introduced into the different location of the final heterocyclic products, which may increase the diversity dramatically. Herein, we report full details of these studies.

RESULTS AND DISCUSSION

The reaction of 2-(trimethylsilyl)phenyl triflate **1a**[8a] (1.3 equiv), benzyl isocyanide **2a** (1.0 equiv), and phenylacetylene **3a** (1.0 equiv) was conducted in the presence of CsF (2.0 equiv) in MeCN at room temperature (Table 1, entry 1). As originally observed, *N*-benzyl 1-alkynyl imine **4a** was obtained in 81% yield, together with isoquinoline **5a** and pyridine **6a** in 6% and 2% yields, respectively. Thus, we then focused on optimizing the conditions to control the selectivity of the reaction to afford one single product **5a** or **6a**. When 2.5 equiv of **1a** was employed, the reaction conducted at 40 °C afforded the desired product **5a** in 49% yield (Table 1, entry 3); 26% of **4a** remained. As reported by Larock et al., the employment of toluene in the reaction system could reduce the solubility of CsF so that the generation rate of benzyne would be slowed down.[9] Thus, toluene was added to MeCN to control the generation of the benzyne to a proper rate to react with **4a**. Luckily, the yield of **5a** was greatly improved to 74% when the reaction was carried out in toluene/MeCN (1:3, Table 1, entry

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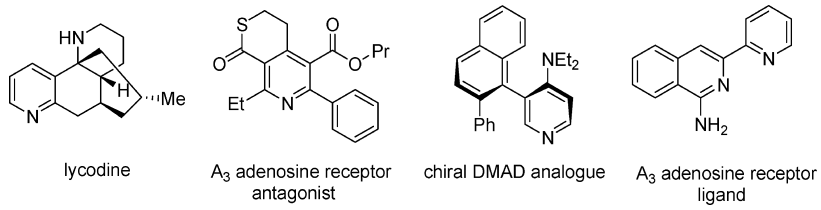


Figure 1. Application of Polysubstituted Pyridines and Isoquinolines.

Scheme 1. Strategy for the Construction of Pyridines and Isoquinolines via 1-Alkynyl Imines

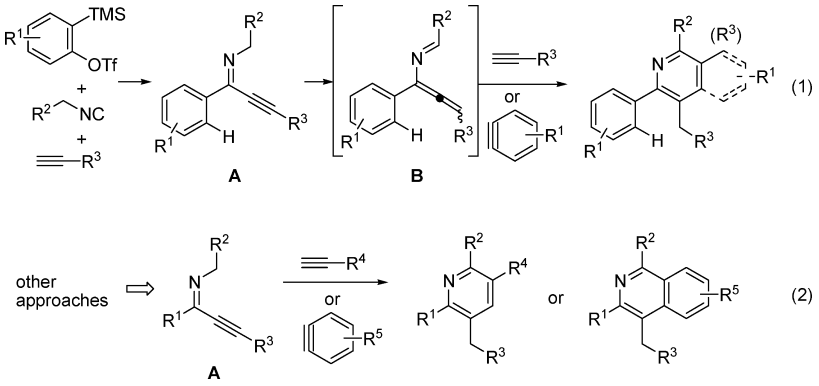
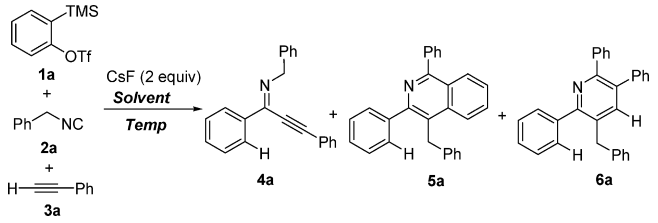


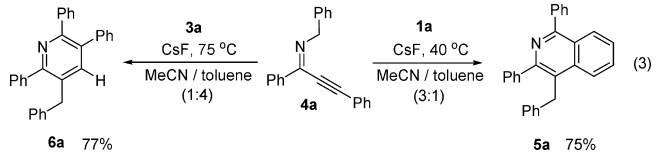
Table 1. Optimization of Conditions for the Multicomponent Reactions of Aryne, Isocyanide, and Terminal Alkyne[a]



					yield[b] (%)		
entry	**1a**/**2a**/**3a** (equiv)	solvent toluene/MeCN (v)	time (h)	*T* (°C)	**4a**	**5a**	**6a**
1	**1.3:1.0:1.0**	**0:1**	**37**	**rt**[c]	**81**	**6**	**2**
2	2.5:1.0:1.0	0:1	37	rt[c]	72	13	3
3	2.5:1.0:1.0	0:1	10	40	26	49	3
4	2.5:1.0:1.0	1:5	13	40	12	68	1
5	**2.5:1.0:1.0**	**1:3**	**18**	**40**	**2**	**74**	**0.6**
6	1.3:1.0:2.0	1:1	22	75	0	16	57
7	1.3:1.0:2.5	4:1	48	75	0	6	69
8	**1.3:1.0:3.0**	**4:1**	**48**	**75**	**0**	**0.4**	**76**
9	1.3:1.0:3.0	5:1	40	85	0	0.3	70

[a]The reactions were conducted using **1a**, **2a** (1.0 mmol), **3a**, and CsF (2.0 equiv, based on **1a**) in 5 mL of solvent. Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl. [b]Yield of isolated product based on the isocyanide **2a** used. [c]rt = room temperature.

5) and the yield of **6a** was reduced to 0.6% and only 2% of **4a** left. We reasoned that increasing the amount of alkyne could disfavor the addition of a second equivalent of benzyne, and therefore promote the formation of pyridine **6a**. Then, the reactions with a larger portion of toluene and alkyne were checked. To our pleasure, by using 3.0 equiv of **3a**, the yield of product **6a** was dramatically increased to 76% at 75 °C in toluene/MeCN (4:1, Table 1, entry 8); the yield of **5a** was 0.4%, and no **4a** was detected. Furthermore, the 1-alkynyl imine **4a** was isolated to react with benzyne precursor **1a** or alkyne **3a** under the optimized conditions (Table 1, entries 5 and 8). As predicted, these two procedures all went smoothly; isoquinoline **5a** and pyridine **6a** could be furnished in 75% and 77% yields, respectively (eq 3).



To examine the scope of the multicomponent reaction, we then employed a variety of aryne precursors **1**,[8] isocyanides **2**, and terminal alkynes **3** under the optimized conditions (Table 1, entry 5) to generate substituted isoquniolines **5**. As indicted in Table 2, the phenyl acetylene derivatives **3** with an electron-withdrawing group or an electron-donating group on the phenyl ring could be smoothly employed (Table 2, entries 1−6). Moreover, ethyl propiolate **3d** was also applicable in the

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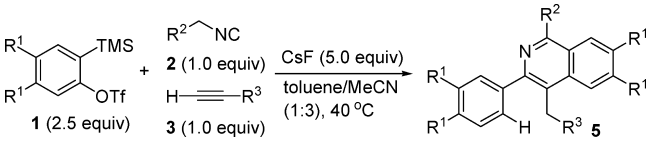
Table 2. Multicomponent Reactions for the Synthesis of Isoquinolines 5[a]



entry	1, R^1	2, R^2	3, R^3	yield of 5[c] (%)
1	H (**1a**)	Ph (**2a**)	Ph (**3a**)	74 (**5a**)
2	**1a**	**2a**	*p*-ClC_6H_4 (**3b**)	75 (**5b**)
3	**1a**	**2a**	*p*-EtC_6H_4 (**3c**)	67 (**5c**)
4	**1a**	*p*-Tol (**2b**)	**3a**	79 (**5d**)
5	**1a**	1-naphthyl (**2c**)	**3b**	72 (**5e**)
6	Me (**1b**)	*p*-FC_6H_4 (**2d**)	**3b**	76 (**5f**)
7[b]	**1a**	**2a**	CO_2Et (**3d**)	71 (**5g**)
8[b]	**1b**	**2b**	**3d**	64 (**5h**)
9[b]	**1a**	**2c**	**3d**	57 (**5i**)
10[b]	**1a**	*p*-BrC_6H_4 (**2e**)	**3d**	77 (**5j**)
11[b]	**1b**	**2d**	**3d**	79 (**5k**)

[a]Unless otherwise specified, the reactions were conducted using **1** (1.25 mmol), **2** (0.5 mmol), **3** (0.5 mmol), and CsF (2.5 mmol) in 1.88 mL of MeCN and 0.63 mL of toluene at 40 °C overnight. [b]The reactions were conducted using **1** (1.25 mmol), **2** (0.5 mmol), **3d** (0.5 mmol), [18]-crown-6 (3.0 mmol), and KF (2.5 mmol) in 2.5 mL of THF at 0 °C overnight. [c]Yield of isolated product based on the isocyanide **2** used.

reaction and afforded corresponding products **5g–k** in moderate to good yields (Table 2, entries 7–11). In addition to benzyl and *p*-methyl benzyl isocyanides, naphth-1-ylmethyl-, *p*-fluoro-, and *p*-bromo-substituted benzyl isocyanides also participated in the reaction to afford the desired products (Table 2, entries 5, 6, and 9–11). However, it should be noted that this reaction is not applicable to the alkyl-substituted terminal alkynes.

The structure of the product **5g** was further established by the X-ray diffraction studies (Figure 2).[10]

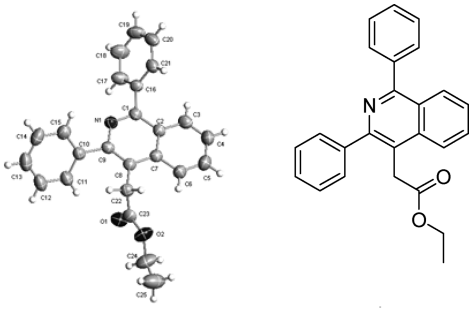
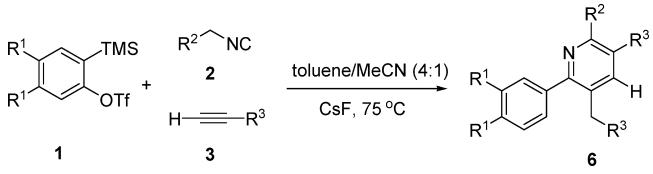


Figure 2. ORTEP representation of **5g** with thermal ellipsoids at the 30% probability level.

Further experiments were conducted to extend the multicomponent reaction to generate substituted pyridines under the optimized conditions (Table 1, entry 8). The results are presented in Table 3. When terminal aryl alkynes were employed, the reaction proceeded smoothly to give the corresponding polysubstituted pyridines **6a–f** in good yields (Table 3, entries 1–6); the reaction afforded the products **6g** and **6h** in lower yields while employing terminal alkyl alkynes (Table 3, entries 7 and 8); the reaction employing electron-

Table 3. Multicomponent Reactions for the Synthesis of Pyridines 6[a]



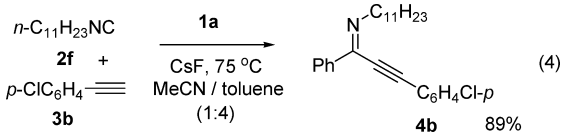
entry	1, R^1	2, R^2	3, R^3	yields of 6[b] (%)
1	H (**1a**)	Ph (**2a**)	Ph (**3a**)	76 (**6a**)
2	**1a**	**2a**	*p*-EtC_6H_4 (**3c**)	65 (**6b**)
3	**1a**	*p*-Tol (**2b**)	**3a**	73 (**6c**)
4	**1a**	**2b**	*p*-ClC_6H_4 (**3b**)	81 (**6d**)
5	Me (**1b**)	**2b**	**3b**	70 (**6e**)
6	**1b**	*p*-FC_6H_4 (**2d**)	**3b**	77 (**6f**)
7[c]	**1a**	**2a**	*n*-C_6H_{13} (**3e**)	31 (**6g**)
8[d]	**1a**	**2a**	*c*-C_3H_5 (**3f**)	43 (**6h**)
9[e]	**1a**	**2a**	*p*-FC_6H_4CO (**3g**)	53 (**6i**)

[a]Unless otherwise specified, the reactions were conducted using **1** (0.65 mmol), **2** (0.5 mmol), **3** (1.5 mmol), and CsF (1.3 mmol) in 0.5 mL of MeCN and 2 mL of toluene at 75 °C for 2 d. [b]Yield of isolated product based on the isocyanide **2** used. [c]The reaction was conducted in 0.25 mL of MeCN and 2.25 mL of toluene for 91 h. [d]The reaction was carried out in a sealed tube with a screw cap. [e]The reaction was conducted in 2.5 mL of MeCN at rt overnight.

deficient alkyne **3g** afforded corresponding product **6i** in moderate yield (Table 3, entry 9).

It should be noted that two possible regioisomers **6** and **6′** could be generated, in principle, when terminal alkynes reacted with *N*-allenyl imines (Figure 3, **TS** and **TS′**); however, the reactions showed an excellent regioselectivity referring to alkynes to give 3-substituted pyridines **6** as the single regioisomer, which was established by the NOESY study of **6c** and **6e–i**. The regioselectivity may be rationalized as the steric effect between R^3 group of the alkynes and the linear structure of the allene moiety in **TS′**, thus, **TS** is favored, generating polysubstituted pyridines **6**.

It is interesting to observe that when alkyl isocyanide **2f** was used, the reaction stopped at the stage of the 1-alkynyl imine **4b** (eq 4), indicating the aryl group (R^2) is vital for the



isomerization from **A** to **B** (Scheme 1). Similar multicomponent couplings have been reported.[11]

In addition to symmetric arynes, various nonsymmetric arynes were also applicable in these reactions. When 4-fluoro-2-(trimethylsilyl)phenyl triflate **1c** was employed, it was surprising to observe the regioisomer **6j** was produced exclusively in 82% yield (Scheme 2). This was probably due to the strong electron-withdrawing effect of the fluoro substituent which causes the *meta* position bears more negative charge than the *para* position (Scheme 2); thus, nucleophilic attack of isocyanide to aryne occurred preferentially at the *para* position to give the electronically favored product.[12b,13,14]

For contrast, 4-methyl-2-(trimethylsilyl)phenyl triflate **1d** was applied as the benzyne precursor, and a 1:1 mixture of two

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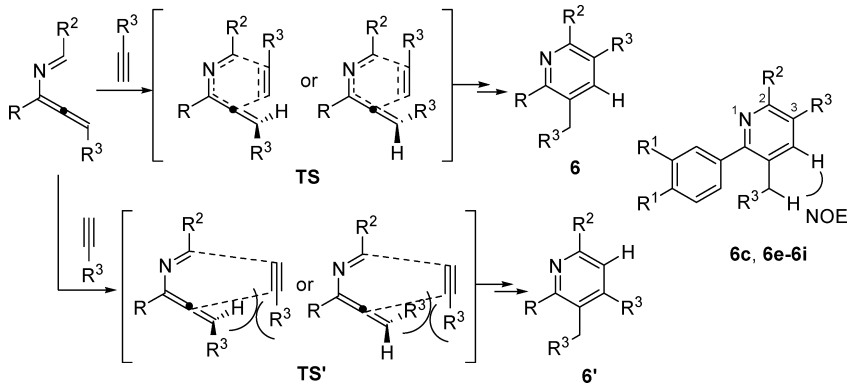
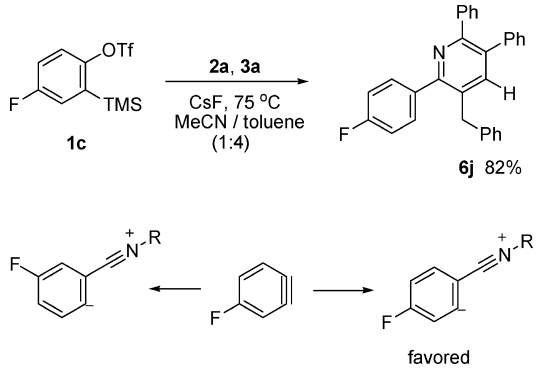
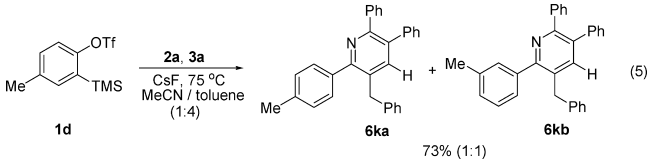


Figure 3. Rationale for the exclusive formation of pyridines **6**.

Scheme 2

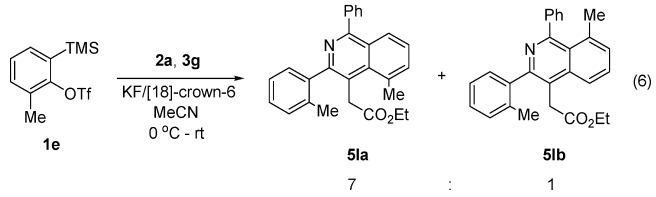


regioisomers **6ka** and **6kb** was formed as determined by ^{1}H NMR analysis (eq 5).[12,13]

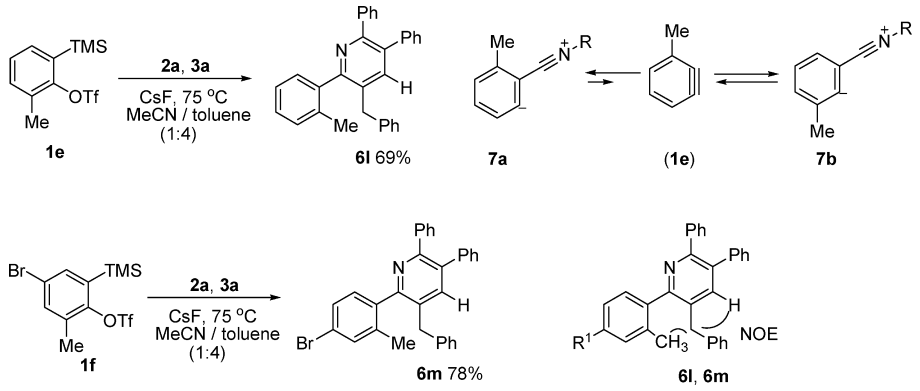


In the case of using 6-methyl-2-(trimethylsilyl)phenyl triflate **1e** as the benzyne precursor, two regioisomers may be generated in principle. Interestingly, the reaction occurred with a perfect regioselectivity to furnish **6l** as the only product in good yield (Scheme 3). The different regioselectivities would be ascribable to the reversibility of the zwitterions in the nucleophilic addition of an isocyanide to *o*-methyl aryne. Owing to the electron-donating character of the methyl group, **7a** (bearing the anionic moiety at the *meta* position of the methyl group) would be thermodynamically more stable among two possible zwitterions. In contrast, formation of the other zwitterion (**7b**) should be kinetically favored because of less steric repulsion between the methyl group and the incoming isocyanide.[8c,12] In this reaction, the thermodynamically stable zwitterion **7a** was favored, therefore leading to the final product **6l**. Similar result was observed when using **1f** as aryne precursor and the sole isomer **6m** was afforded in 78% yield. The structures of **6l** and **6m** were confirmed by their NOESY analyses (Scheme 3).

Moreover, aryne precursor **1e** was also employed in the reaction to afford isoquinolines. Similarly, the nucleophilic attack of isocyanide to aryne selectively occurred at the *ortho* position, and the Diels–Alder reaction of another molecule of nonsymmetric aryne proceeded with good selectivity to afford two regioisomers **5la** and **5 lb** in 55% combined yield (eq 6). The major isomer **5la** was isolated and confirmed by the NOESY analysis.



Scheme 3



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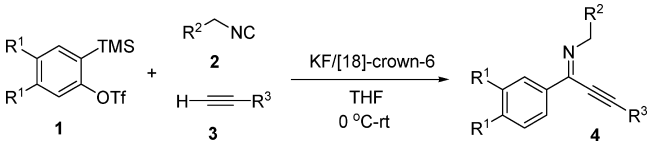
One of the most attractive features of the above multicomponent reaction is that four molecules could be directly assembled into the target heterocyclic compounds in a highly efficient, regioselective, and atom-economical manner. However, we also realized that at least two substituents in the product **5** or **6** were always identical, which seriously limited the diversity of the current transformation. This inspired us to further explore an approach for the synthesis of pyridines and isoquinolines with a much better diversity. According to the mechanistic studies (eq 3), the reaction intermediate 1-alkynyl imine **4a** could be isolated and utilized to generate pyridine **6a** or isoquinoline **5a**. Thus, polysubstituted pyridines or isoquinolines may be constructed by introducing differently substituted alkynes or arynes to react with preprepared 1-alkynyl imines by known methods.[15] Therefore, we started to develop a novel and efficient strategy to synthesize pyridine derivatives with different susbstituents with 1-alkynyl imines as the starting material.

Initially, 1-alkynyl imines **4** were synthesized via the previously explored multicomponent reaction of arynes, isocyanides, and terminal alkynes (Table 4).[7] By using CsF as

Table 4. Multi-component Reaction for the Synthesis of 1-Alkynyl Imines 4[a]



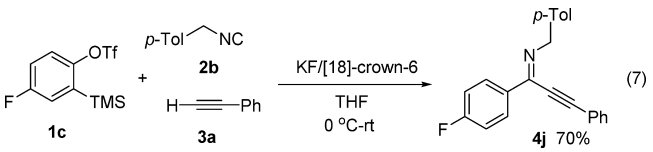
entry	1, R^1	2, R^2	3, R^3	yields of 4[d] (%)
1	H (**1a**)	*p*-Tol (**2b**)	Ph (**3a**)	72[b]; 71[c] (**4c**)
2	**1a**	**2b**	*p*-$MeOC_6H_4$ (**3h**)	62[c] (**4d**)
3	**1a**	*p*-FC_6H_4 (**2d**)	*p*-ClC_6H_4 (**3b**)	73[c] (**4e**)
4	**1a**	**2b**	*n*-C_4H_9 (**3i**)	22[b]; 40[c] (**4f**)
5	**1a**	**2b**	*c*-C_3H_5 (**3f**)	49[c] (**4g**)
6	**1a**	1-naphthyl (**2c**)	**3f**	25[b]; 41[c] (**4h**)
7	Me (**1b**)	**2b**	**3a**	68[c] (**4i**)

[a]The reactions were conducted using **1** (1.5 mmol), **2** (1.0 mmol), and **3** (1.2 mmol). [b]The reaction was conducted with CsF (3.0 mmol) in 5 mL of MeCN at rt. [c]The reaction was conducted with KF (3.0 mmol) and [18]-crown-6 (3.5 mmol) in 5 mL of THF at 0 °C to rt overnight. [d]Yield of isolated product based on the isocyanide **2** used.

the fluoride anion source, the yields were rather low when R^3 was an alkyl group (Table 4, entries 4 and 6). Notably, pyridines and isoquinolines could always be produced in the presence of CsF, thus leading to the relatively low yields of 1-alkynyl imines. When a combination of KF and [18]-crown-6 was employed as the fluoride anion source, the yields of **4** were improved (Table 4, entries 4 and 6).

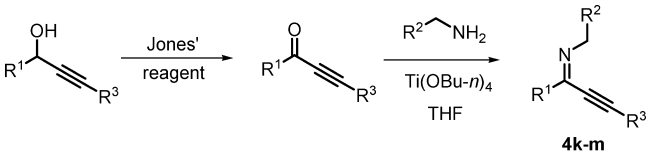
As shown in Table 4, differently substituted 1-aryl-1-alkynyl imines could be furnished in moderate to good yields via this multicomponent reaction. For the terminal alkynes substituted with either aryl or alkyl groups, the reactions afforded expected products smoothly. The reaction also showed good regioselectivity when nonsymmetric aryne precursor **1c** was employed to produce *p*-fluoro-substituted **4j** as the only product (eq 7), which was inconsistent with the regioselectivity of the previous reaction (Scheme 2).

On the other hand, the condensation reaction of 1-alkynyl ketones and substituted benzyl amines in the presence of



$Ti(OBu\text{-}n)_4$ was also used to generate 1-alkynyl imines **4k–m** (Scheme 4).[15]

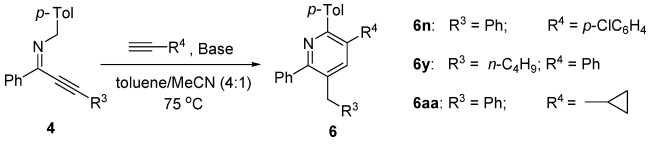
Scheme 4. Condensation Reaction for the Synthesis of 1-Alkynyl Imines 4



4k: R^1 = *p*-ClC_6H_4, R^2 = *p*-Tol, R^3 = Ph; 76%
4l: R^1 = *p*-BrC_6H_4, R^2 = Ph, R^3 = *n*-C_4H_9; 90%
4m: R^1 = *p*-$MeOC_6H_4$, R^2 = *p*-Tol, R^3 = Ph; 51%

By using this method, a variety of different substitutents could be introduced into the alkynyl imines, not limited by the reported synthetic methods of aryne precursors.[8] On the other hand, compared with the multicomponent reaction (Scheme 3), the condensation strategy would not give regioisomers. Efforts were then made to choose the proper base for the reaction to synthesize pyridines **6** (Table 5). CsF was first

Table 5. Base Effect on the Synthesis of Pyridines 6 from 1-Alkynyl Imines 4[a]



entry	base	base (equiv)	yield of 6[b] (%)
1	CsF	3.0	72 (**6n**)
2	Cs_2CO_3	3.0	79 (**6n**)
3	**Cs_2CO_3**	**2.0**	**78 (6n)**
4	CsF	2.0	22 (**6y**)
5	**Cs_2CO_3**	**2.0**	**54 (6y)**
6[c]	CsF	2.0	35 (**6aa**)
7[c]	**Cs_2CO_3**	**2.0**	**46 (6aa)**

[a]The reactions were conducted using 1-alkynyl imines **4** (0.5 mmol) and alkynes (1.5 mmol) in 2 mL of toluene and 0.5 mL of MeCN at 75 °C. [b]Yield of isolated product based on the 1-alkynyl imine **4** used. [c]The reaction was conducted using alkyne (2.5 mmol) in a sealed tube with a screw cap.

introduced as the base according to the result presented in Tables 2 and 3.[7] When R^3 or R^4 was alkyl group, the yields of **6y** and **6aa** were rather low (Table 5, entries 4 and 6). By applying Cs_2CO_3, the yields of **6** were improved (Table 5, entries 5 and 7).

With the optimized conditions (Table 5, entry 3), we next synthesized a series of polysubstituted pyridines from these preprepared 1-alknyl imines. When R^1, R^2, R^3, and R^4 were all aryl groups, the expected products **6n–v** could be obtained smoothly in moderate to good yields (Table 6, entries 1–9). Alkynes **3** and 1-alkynyl imines **4** bearing alkyl groups were also applicable in the reaction. In the case that R^3 is the cyclopropyl

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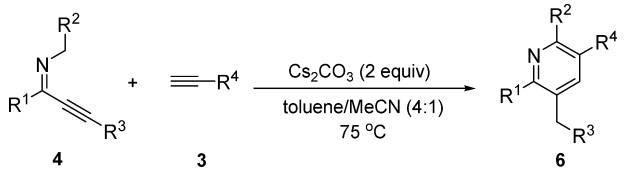
Table 6. Synthesis of Pyridines 6 from 1-Alkynyl Imines 4[a]



4 3 6

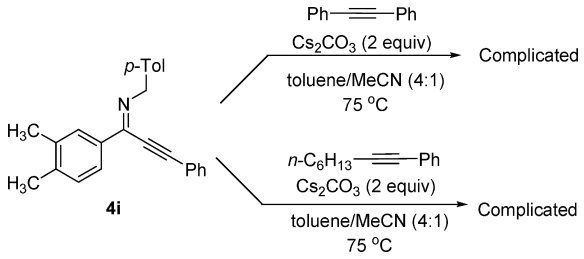
	4			3	
entry	R^1	R^2	R^3	R^4	yield of **6**[b] (%)
1	Ph	*p*-Tol	Ph (**4c**)	*p*-ClC_6H_4 (**3b**)	78 (**6n**)
2	Ph	*p*-Tol	*p*-$MeOC_6H_4$ (**4d**)	**3b**	58 (**6o**)
3	Ph	*p*-FC_6H_4	*p*-ClC_6H_4 (**4e**)	Ph (**3a**)	74 (**6p**)
4	*p*-FC_6H_4	*p*-Tol	Ph (**4j**)	*p*-EtC_6H_4 (**3c**)	80 (**6q**)
5	*p*-ClC_6H_4	*p*-Tol	Ph (**4k**)	**3c**	62 (**6r**)
6	*p*-$MeOC_6H_4$	*p*-Tol	Ph (**4m**)	**3b**	76 (**6s**)
7	3,4-MeC_6H_3	*p*-Tol	Ph (**4i**)	**3b**	73 (**6t**)
8	3,4-MeC_6H_3	*p*-Tol	Ph (**4i**)	*m*-$NO_2C_6H_4$ (**3j**)	81 (**6u**)
9	3,4-MeC_6H_3	*p*-Tol	Ph (**4i**)	2-Py (**3k**)	83 (**6v**)
10	Ph	*p*-Tol	*c*-C_3H_5 (**4g**)	**3a**	69 (**6w**)
11	Ph	1-naphthyl	*c*-C_3H_5 (**4h**)	**3a**	68 (**6x**)
12	Ph	*p*-Tol	*n*-C_4H_9 (**4f**)	**3a**	54 (**6y**)
13	*p*-BrC_6H_4	Ph	*n*-C_4H_9 (**4l**)	**3b**	38 (**6z**)
14[c]	Ph	*p*-Tol	Ph (**4c**)	*c*-C_3H_5 (**3f**)	46 (**6aa**)

[a]The reactions were conducted using 1-alkynyl imines **4** (1.0 equiv), alkynes **3** (3.0 equiv), and Cs_2CO_3 (2.0 equiv) in toluene/MeCN (4:1) at 75 °C. [b]Yield of isolated product based on the 1-alkynyl imine **4** used. [c]The reaction was conducted using 1-alkynyl imine **4c** (1.0 equiv) and alkyne **3f** (5.0 equiv) in a sealed tube with a screw cap.

group, products **6w** and **6x** were afforded in 69% and 68% yield, respectively (Table 6, entries 10 and 11). Nevertheless, by employing *n*-butyl group as R^3 (Table 6, entries 12, 13) or cyclopropyl group as R^4 (Table 6, entry 14), the reactions gave the corresponding products in relatively low yields. It should be noted that product **6v** bears two pyridine rings, indicating its potential to be developed as useful ligands.[1c,f]

Moreover, we tested the reactivity of internal alkynes 1,2-diphenylethyne and oct-1-ynylbenzene in this reaction (Scheme 5). However, the reactions did not give pyridine product.

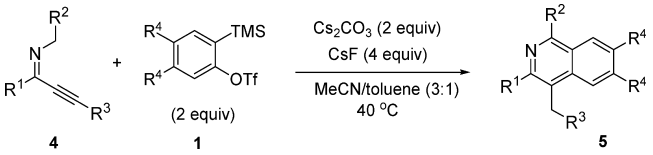
Scheme 5. Reactions with Internal Alkynes



Starting from 1-alkynyl imines, a variety of poly substituted isoquinolines **5m–q** could also be synthesized by introducing arynes in the presence of Cs_2CO_3 in moderate to good yields (Table 7). A satistafctory result was observed even when an alkyl group, i.e. cyclopropyl, was introduced (**5n**, Table 7, entry 2).

On the basis of our studies above, a plausible mechanism is illustrated in Scheme 6. First, isocyanide **2** attacks aryne nucleophilically to generate the zwitterion **8**.[10,12,16] After protonation with terminal alkyne **3**,[17] subsequent nucleophilic addition of the in situ generated alkynyl anion occurs, affording 1-alkynyl imine **4** as the pivotal intermediate. Notably, **4** could

Table 7. Synthesis of Isoquinolines 5 from 1-Alkynyl Imines 4[a]



4 1 5

	4			1	
entry	R^1	R^2	R^3	R^4	yield of **5**[b] (%)
1	Ph	Ph	Ph (**4a**)	Me (**1b**)	48 (**5m**)
2	Ph	*p*-Tol	*c*-C_3H_5 (**4g**)	H (**1a**)	51 (**5n**)
3	3,4-MeC_6H_3	*p*-Tol	Ph (**4i**)	**1a**	56 (**5o**)
4	*p*-FC_6H_4	*p*-Tol	Ph (**4j**)	**1a**	72 (**5p**)
5	*p*-ClC_6H_4	*p*-Tol	Ph (**4k**)	**1b**	57 (**5q**)

[a]The reactions were conducted using **4** (1.0 equiv), **1** (2.0 equiv), CsF (4.0 equiv), and Cs_2CO_3 (2.0 equiv) in toluene/MeCN (1:3) at 40 °C. [b]Yield of isolated product based on the 1-alkynyl imine **4** used.

be introduced into the following transformations by either in the in situ generated form (path **i**) or isolated from the multicomponent reaction or the condensation reaction of 1-alkynyl ketone and substituted benzyl amine (path **ii**). In the presence of CsF or Cs_2CO_3, **4** might isomerize to form 1-allenyl imine intermediate **9** which then undergo aza-Diels–Alder reaction with aryne or alkyne to form **10a** or **10b**.[18] Subsequent aromatization gives isoquinoline **5** or pyridine **6**.

CONCLUSION

In conclusion, we have developed a novel procedure for the efficient and diversified assembly of polysubstituted pyridines and isoquinolines from the multicomponent reaction of arynes, isocynides, and terminal alkynes, which included 1-alkynyl imines as the key intermediate, followed by alkynyl imine–

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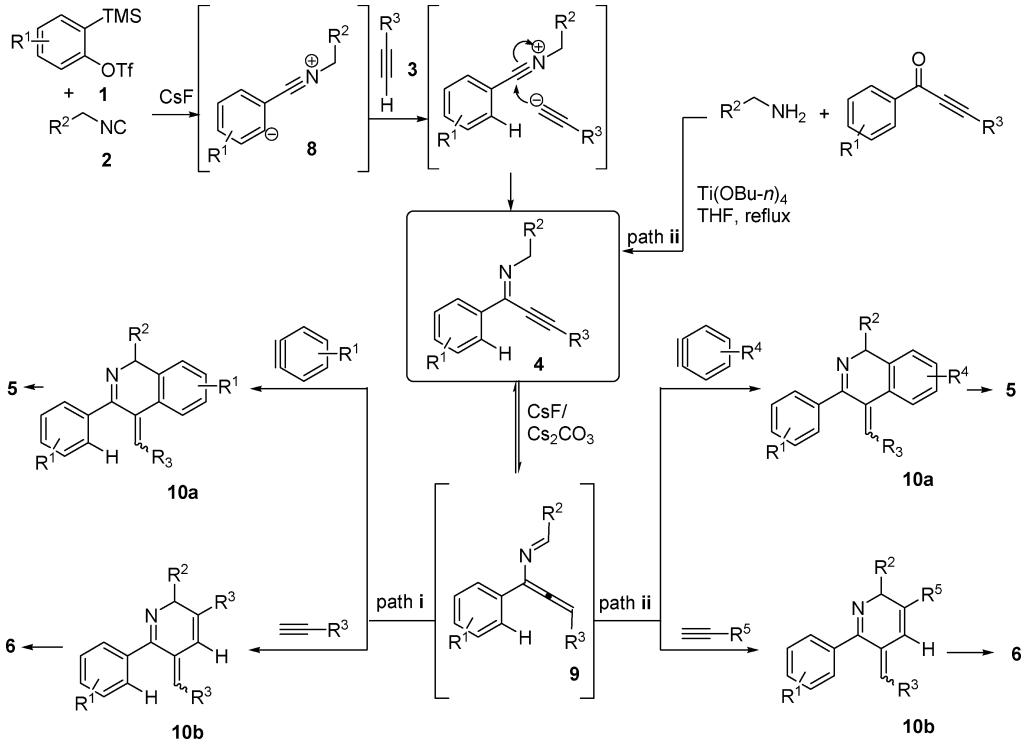
Scheme 6



allenyl imine isomerization/aza-Diels–Alder reaction/aromatization sequence. Moreover, we synthesized a series of 1-alkynyl imines through other approaches, which have been successfully employed in the similar sequential reactions. By the newly developed strategy, the diversity of pyridines and isoquinolines has been greatly enriched.

EXPERIMENTAL SECTION

General Information. All reactions were performed under a purified N_2 atmosphere. Anhydrous solvents were distilled prior to use: THF, Et_2O, and toluene were distilled from sodium benzophenone; MeCN was distilled from P_2O_5; CH_2Cl_2 was distilled from CaH_2. Petroleum ether refers to the fraction with boiling point in the range 60–90 °C. All ^1H NMR and ^{13}C NMR spectra were measured in $CDCl_3$ with TMS as the internal standard. Chemical shifts are expressed in ppm, and J values are given in Hz. Melting points are uncorrected. 2-(Trimethylsilyl)aryl triflates **1** were prepared according to the known methods.[8a,13,19] The characterization data for compounds **4a,b**, **5a–h,la,lb**, **6a–j,l,m** have been reported in the Supporting Information of our previous communication.[7]

General Procedure for the Synthesis of Isoquinolines 5i–k. Under nitrogen atmosphere, KF (145 mg, 2.5 mmol) was added to a solution of 2-(trimethylsilyl)phenyl triflate **1a** (395 mg, 1.25 mmol), isocyanide **2c** (84 mg, 0.5 mmol), propiolate **3d** (49 mg, 0.5 mmol), and [18]-crown-6 (792 mg, 3.0 mmol) in 2.5 mL of anhydrous THF. The reaction mixture was then stirred at 0 °C overnight. When the reaction was complete as monitored by TLC, the reaction mixture was filtered through a short column of silica gel eluted with Et_2O. The filtrate was concentrated under reduced pressure to afford the residue, which was separated by silica gel chromatography (petroleum ether/ethyl acetate = 15/1) to afford **5i** (119 mg, 57%).

*Ethyl 2-(1-(naphthalen-1-yl)-3-phenylisoquinolin-4-yl)acetate (**5i**):* mp 115–117 °C; ^1H NMR (400 MHz, $CDCl_3$) 8.04 (d, J = 8.4 Hz, 1H), 7.98 (d, J = 8.4 Hz, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.76 (t, J = 8.4 Hz, 1H), 7.69–7.61 (m, 5H), 7.51–7.34 (m, 7H), 4.28 (q, J = 7.2 Hz, 2H), 4.17 (s, 2H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 171.8, 159.4, 152.7, 140.7, 136.9, 136.4, 133.7, 132.5, 130.8, 129.7, 128.8, 128.6, 128.2, 128.2, 127.9, 127.9, 127.3, 126.7, 126.2, 126.1, 125.8, 125.2, 123.5, 120.9, 61.2, 35.7, 14.2; IR (KBr) 2981, 1719, 1244, 1216, 1179, 1024, 775 cm^{-1}; MS m/z 417 (M^+, 89), 416 (100), 342 (70); HRMS (EI) calcd for $C_{29}H_{23}NO_2$ 417.1729, found 417.1725.

*Ethyl 2-(1-(4-Bromophenyl)-3-phenylisoquinolin-4-yl)acetate (**5j**).* Following the procedure for the preparation of **5i**, the reaction of **1a** (395 mg, 1.25 mmol), **2e** (98 mg, 0.5 mmol), **3d** (49 mg, 0.5 mmol), KF (145 mg, 2.5 mmol), and [18]-crown-6 (792 mg, 3.0 mmol) in 2.5 mL of anhydrous THF afforded 171 mg (77%) of **5j**: mp 101–103 °C; ^1H NMR (400 MHz, $CDCl_3$) 8.09 (d, J = 8.4 Hz, 1H), 7.99 (d, J = 8.4 Hz, 1H), 7.77 (t, J = 8.4 Hz, 1H), 7.66–7.59 (m, 6H), 7.56 (t, J = 8.4 Hz, 1H), 7.48–7.40 (m, 3H), 4.22 (q, J = 7.2 Hz, 2H), 4.09 (s, 2H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 171.7, 158.5, 152.7, 140.7, 138.5, 136.8, 131.8, 131.4, 130.7, 129.6, 128.3, 128.0, 127.9, 126.8, 125.6, 123.7, 123.0, 120.7, 61.2, 35.6, 14.2; IR (KBr) 2980, 1720, 1488, 1187, 1070, 1011, 795 cm^{-1}; MS m/z 447 (M^+, 67), 445 (M^+, 67), 372 (100), 169 (90); HRMS (EI) calcd for $C_{25}H_{20}NO_2Br$(79) 445.0677, found 445.0686.

*Ethyl 2-(3-(3,4-Dimethylphenyl)-1-(4-fluorophenyl)-6,7-dimethylisoquinolin-4-yl)acetate (**5k**).* Following the procedure for the preparation of **5i**, the reaction of **1b** (408 mg, 1.25 mmol), **2d** (68 mg, 0.5 mmol), **3d** (49 mg, 0.5 mmol), KF (145 mg, 2.5 mmol), and [18]-crown-6 (792 mg, 3.0 mmol) in 2.5 mL of anhydrous THF afforded 174 mg (79%) of **5k**: mp 82–84 °C; ^1H NMR (400 MHz, $CDCl_3$) 7.80 (s, 1H), 7.70–7.67 (m, 3H), 7.40 (s, 1H), 7.34 (d, J = 8.4 Hz, 1H), 7.20–7.14 (m, 3H), 4.22 (q, J = 7.2 Hz, 2H), 4.06 (s, 2H), 2.47 (s, 3H), 2.37 (s, 3H), 2.29 (s, 6H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 171.9, 162.8 (J_{C-F} = 246.7 Hz), 157.3, 152.0, 140.7, 138.5, 136.3, 136.2, 136.0, 136.0, 135.7 (J_{C-F} = 1.8 Hz), 131.8 (J_{C-F} = 8.4 Hz), 130.8, 129.2, 127.1, 126.9, 124.5, 123.2, 119.5, 115.0 (J_{C-F} = 21.4 Hz), 60.8, 35.6, 20.7, 20.2, 19.7, 19.4, 14.1; IR (KBr) 2977, 1732, 1508, 1225, 1050, 842 cm^{-1}; MS m/z 441 (M^+, 95), 440 (73), 368 (100); HRMS (EI) calcd for $C_{29}H_{28}NO_2F$ 441.2104, found 441.2108.

*Multicomponent Reaction of **1c**, **2a**, and **3a** Leading to Pyridines **6ka** and **6kb**.* Under nitrogen atmosphere, CsF (198 mg, 1.3 mmol) was added to a solution of 4-methyl-2-(trimethylsilyl)phenyl triflate **1d** (203 mg, 0.65 mmol), benzyl isocyanide **2a** (59 mg, 0.5 mmol), and phenyl ethyne **3a** (153 mg, 1.5 mmol) in 0.5 mL of anhydrous MeCN

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and 2 mL of anhydrous toluene. The reaction mixture was then stirred at 75 °C for 2 days. When the reaction was complete as monitored by TLC, the reaction mixture was filtered through a short column of silica gel eluted with Et_2O. The filtrate was concentrated under reduced pressure to afford the residue, which was separated by silica gel chromatography (petroleum ether/ethyl acetate = 20/1) to afford **6ka** and **6kb** (1:1, 150 mg, 73%): oil; ^{1}H NMR (400 MHz, $CDCl_3$) 7.53 (d, J = 6.4 Hz, 2H), 7.49 (d, J = 8.0 Hz, 2H), [7.41−7.32 (m), 7.41−7.32 (m), 6H], [7.31−7.13 (m), 7.31−7.13 (m), 26H], [7.11−7.06 (m), 7.11−7.06 (m), 4H], 4.12 (s, 2H), 4.09 (s, 2H), 2.38 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 157.7, 157.5, 154.5, 154.5, 140.8, 140.8, 140.4, 140.4, 140.1, 140.0, 139.8, 139.8, 137.7, 137.4, 134.4, 134.3, 132.2, 132.0, 130.1, 130.1, 130.0, 129.6, 129.5, 129.2, 128.8, 128.8, 128.7, 128.6, 128.5, 128.5, 128.2, 128.2, 127.9, 127.9, 127.7, 127.7, 127.5, 127.5, 127.0, 127.0, 126.2, 126.2, 38.2, 38.2, 21.4, 21.2; IR (KBr) 3023, 1539, 1425, 769 cm^{-1}; MS m/z 411 (M^+, 55), 410 (70), 55 (100); HRMS (EI) calcd for $C_{31}H_{25}N$ 411.1987, found 411.1992.

General Procedure for the Preparation of 1-Alkynyl Imines 4c−j. Under nitrogen atmosphere, KF (174 mg, 3.0 mmol) was added to a solution of 2-(trimethylsilyl)phenyl triflate **1a** (447 mg, 1.5 mmol), 4-methylbenzyl isocyanide **2b** (131 mg, 1.0 mmol), phenyl ethyne **3a** (122 mg, 1.2 mmol), and [18]-crown-6 (924 mg, 3.5 mmol) in 5 mL of anhydrous THF. The reaction mixture was stirred at 0 °C for 2 h and then at room temperature overnight. When the reaction was complete as monitored by TLC, the reaction mixture was filtered through a short column of silica gel eluted with Et_2O. The filtrate was concentrated under reduced pressure to afford the residue, which was separated by silica gel chromatography (petroleum ether/ethyl acetate = 30/1) to afford **4c** (219 mg, 71%).

*N-(1,3-Diphenylprop-2-ynylidene)(p-tolyl)methanamine (**4c**):* oil; ^{1}H NMR (400 MHz, $CDCl_3$) 8.17−8.14 (m, 2H), 7.60−7.57 (m, 2H), 7.41−7.33 (m, 8H), 7.15 (d, J = 8.0 Hz, 2H), 5.11 (s, 2H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 151.0, 137.4, 136.8, 136.2, 132.1, 130.4, 129.6, 129.1, 128.5, 128.2, 127.9, 127.6, 121.4, 98.7, 81.7, 59.9, 21.1; IR (neat) 2924, 2202, 1593, 1565, 1445, 1316, 1059, 1027 cm^{-1}; MS m/z 309 [M^+, 100], 191 (78), 105 (79); HRMS (EI) calcd for $C_{23}H_{19}N$ 309.1517, found 309.1515.

*N-(3-(4-Methoxyphenyl)-1-phenylprop-2-ynylidene)(p-tolyl)-methanamine (**4d**).* Following the procedure for the preparation of **4c**, the reaction of **1a** (447 mg, 1.5 mmol), **2b** (131 mg, 1.0 mmol), **3h** (158 mg, 1.2 mmol), KF (174 mg, 3.0 mmol), and [18]-crown-6 (924 mg, 3.5 mmol) in 5 mL of anhydrous THF afforded 210 mg (62%) of **4d**: mp 79−81 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 8.16−8.14 (m, 2H), 7.53 (d, J = 8.4 Hz, 2H), 7.41−7.39 (m, 3H), 7.34 (d, J = 7.6 Hz, 2H), 7.15 (d, J = 7.6 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 5.09 (s, 2H), 3.77 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 160.7, 151.3, 137.6, 137.0, 136.2, 133.8, 130.3, 129.0, 128.1, 127.9, 127.6, 114.2, 113.4, 99.3, 81.0, 59.8, 55.2, 21.0; IR (neat) 2924, 2200, 1601, 1563, 1508, 1289, 1248, 1169, 1023, 833 cm^{-1}; MS m/z 339 [M^+, 100], 324 (43); HRMS (EI) calcd for $C_{24}H_{21}NO$ 339.1623, found 339.1618.

*N-(3-(4-Chlorophenyl)-1-phenylprop-2-ynylidene)(4-fluorophenyl)methanamine (**4e**).* Following the procedure for the preparation of **4c**, the reaction of **1a** (447 mg, 1.5 mmol), **2d** (135 mg, 1.0 mmol), **3b** (163 mg, 1.2 mmol), KF (174 mg, 3.0 mmol), and [18]-crown-6 (924 mg, 3.5 mmol) in 5 mL of anhydrous THF afforded 253 mg (73%) of **4e**: oil; ^{1}H NMR (400 MHz, $CDCl_3$) 8.12 (d, J = 8.0 Hz, 2H), 7.53 (d, J = 8.0 Hz, 2H), 7.44−7.36 (m, 7H), 7.03 (t, J = 8.4 Hz, 2H), 5.06 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 161.9 (J_{C-F} = 242.9 Hz), 151.2, 137.2, 136.1, 135.5 (J_{C-F} = 3.1 Hz), 133.4, 130.7, 129.4 (J_{C-F} = 8.9 Hz), 129.0, 128.3, 127.6, 119.7, 115.2 (J_{C-F} = 21.1 Hz), 97.7, 82.3, 59.3; IR (neat) 2918, 2203, 1588, 1508, 1488, 1220, 1091, 1027 cm^{-1}; MS m/z 347 (M^+, 36), 240 (67), 212 (100), 163 (76); HRMS (EI) calcd for $C_{22}H_{15}NFCl$ 347.0877, found 347.0872.

*N-(1-Phenylhept-2-ynylidene)(p-tolyl)methanamine (**4f**).* Following the procedure for the preparation of **4c**, the reaction of **1a** (447 mg, 1.5 mmol), **2b** (131 mg, 1.0 mmol), **3i** (98 mg, 1.2 mmol), KF (174 mg, 3.0 mmol), and [18]-crown-6 (924 mg, 3.5 mmol) in 5 mL of anhydrous THF afforded 116 mg (40%) of **4f**: oil; ^{1}H NMR (400 MHz, $CDCl_3$) 8.08−8.06 (m, 2H), 7.39−7.37 (m, 3H), 7.29 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H), 4.98 (s, 2H), 2.53 (t, J = 7.2 Hz, 2H), 2.33 (s, 3H), 1.67−1.62 (m, 2H), 1.54−1.49 (m, 2H), 0.96 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 151.5, 137.8, 137.1, 136.1, 130.2, 129.0, 128.1, 127.9, 127.6, 101.4, 74.1, 59.6, 30.4, 22.0, 21.1, 19.1, 13.5; IR (neat) 2930, 2209, 1568, 1448, 1280, 1026 cm^{-1}; MS m/z 288 [$(M - 1)^+$, 15], 246 (100), 105 (77); HRMS (EI) calcd for $C_{21}H_{23}N$ 289.1830, found 289.1825.

*N-(3-Cyclopropyl-1-phenylprop-2-ynylidene)(p-tolyl)-methanamine (**4g**).* Following the procedure for the preparation of **4c**, the reaction of **1a** (447 mg, 1.5 mmol), **2b** (131 mg, 1.0 mmol), **3f** (80 mg, 1.2 mmol), KF (174 mg, 3.0 mmol), and [18]-crown-6 (924 mg, 3.5 mmol) in 5 mL of anhydrous THF afforded 134 mg (49%) of **4g**: oil; ^{1}H NMR (400 MHz, $CDCl_3$) 8.04−8.02 (m, 2H), 7.39−7.35 (m, 3H), 7.28 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H), 4.94 (s, 2H), 2.33 (s, 3H), 1.56−1.53 (m, 1H), 1.00−0.96 (m, 2H), 0.93−0.89 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 151.3, 137.8, 137.1, 136.1, 130.2, 129.0, 128.1, 127.9, 127.6, 104.9, 69.5, 59.6, 21.1, 9.5, 0.2; IR (neat) 3016, 2211, 1594, 1567, 1280, 1027, 917 cm^{-1}; MS m/z 272 [$(M - 1)^+$, 45], 141 (100), 105 (90); HRMS (EI) calcd for $C_{20}H_{19}N$ 273.1517, found 273.1519.

*N-(3-Cyclopropyl-1-phenylprop-2-ynylidene)(naphthalen-1-yl)-methanamine (**4h**).* Following the procedure for the preparation of **4c**, the reaction of **1a** (447 mg, 1.5 mmol), **2c** (167 mg, 1.0 mmol), **3f** (80 mg, 1.2 mmol), KF (174 mg, 3.0 mmol), and [18]-crown-6 (924 mg, 3.5 mmol) in 5 mL of anhydrous THF afforded 127 mg (41%) of **4h**: oil; ^{1}H NMR (400 MHz, $CDCl_3$) 8.17 (d, J = 8.0 Hz, 1H), 8.07−8.04 (m, 2H), 7.87 (d, J = 8.0 Hz, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.58−7.37 (m, 7H), 5.40 (s, 2H), 1.58−1.55 (m, 1H), 1.02−0.98 (m, 2H), 0.94−0.90 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 151.7, 137.8, 136.1, 133.8, 131.9, 130.3, 128.6, 128.1, 127.6, 127.4, 125.8, 125.6, 125.6, 125.5, 124.0, 105.6, 69.5, 57.7, 9.6, 0.2; IR (neat) 3060, 2212, 1690, 1593, 1567, 1282, 920 cm^{-1}; MS m/z 308 [$(M - 1)^+$, 95], 141 (100), 280 (48); HRMS (EI) calcd for $C_{23}H_{19}N$ 309.1517, found 309.1520.

*N-(1-(3,4-Dimethylphenyl)-3-phenylprop-2-ynylidene)(p-tolyl)-methanamine (**4i**).* Following the procedure for the preparation of **4c**, the reaction of **1b** (489 mg, 1.5 mmol), **2b** (131 mg, 1.0 mmol), **3a** (122 mg, 1.2 mmol), KF (174 mg, 3.0 mmol), and [18]-crown-6 (924 mg, 3.5 mmol) in 5 mL of anhydrous THF afforded 229 mg (68%) of **4i**: mp 49−51 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.94 (s, 1H), 7.88 (d, J = 7.6 Hz, 1H), 7.57−7.55 (m, 2H), 7.34−7.30 (m, 5H), 7.16−7.12 (m, 3H), 5.10 (s, 2H), 2.30 (s, 3H), 2.27 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 151.1, 139.3, 136.9, 136.3, 136.1, 135.2, 132.0, 129.5, 129.4, 129.0, 128.4, 128.3, 127.9, 125.4, 121.5, 98.3, 81.9, 59.8, 21.0, 19.7, 19.6; IR (neat) 2958, 2928, 2211, 1725, 1270, 1122, 1071 cm^{-1}; MS m/z 337 (M^+, 100), 105 (36); HRMS (EI) calcd for $C_{25}H_{23}N$ 337.1830, found 337.1829.

*N-(1-(4-Fluorophenyl)-3-phenylprop-2-ynylidene)(p-tolyl)-methanamine (**4j**).* Following the procedure for the preparation of **4c**, the reaction of **1c** (395 mg, 1.25 mmol), **2b** (109 mg, 0.83 mmol), **3a** (102 mg, 1.0 mmol), KF (145 mg, 2.5 mmol), and [18]-crown-6 (792 mg, 3.0 mmol) in 4.2 mL of anhydrous THF afforded 190 mg (70%) of **4j**: oil; ^{1}H NMR (400 MHz, $CDCl_3$) 8.16−8.12 (m, 2H), 7.61−7.58 (m, 2H), 7.41−7.38 (m, 3H), 7.33 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 8.0 Hz, 2H), 7.08 (t, J = 8.0 Hz, 2H), 5.07 (s, 2H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 164.3 (J_{C-F} = 248.2 Hz), 149.8, 136.8, 136.4, 133.7 (J_{C-F} = 2.3 Hz), 132.2, 129.8, 129.6 (J_{C-F} = 8.3 Hz), 129.1, 128.6, 128.0, 121.3, 115.2 (J_{C-F} = 21.8 Hz), 98.9, 81.4, 59.9, 21.1; IR (neat) 2921, 2202, 1597, 1497, 1475, 1221, 1124 cm^{-1}; MS m/z 327 [M^+, 35], 196 (100), 129 (80), 224 (65); HRMS (EI) calcd for $C_{23}H_{18}NF$ 327.1423, found 327.1426.

Condensation of Alkyn-1-ones with Arylmethanamine in the Presence of Ti(OBu-*n*)$_4$ Leading to 1-Alkynyl Imines 4k−m.[15a] A solution of 4-methylbenzylamine (423 mg, 3.49 mmol) in 1.0 mL of anhydrous THF was added dropwise to a solution of 1-(4-chlorophenyl)-3-phenylprop-2-yn-1-one (420 mg, 1.75 mmol) and titanium(IV) butoxide (1.0 g, 2.94 mmol) in 9 mL of anhydrous THF under nitrogen atmosphere. The resulting yellow mixture was stirred at room temperature for 3.5 h. The mixture was poured into water (30

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mL), and the water layer was extracted by CH_2Cl_2 (20 mL × 2). The organic layer was combined and dried over $MgSO_4$. After evaporation, the residue was separated by silica gel chromatography (petroleum ether/ethyl acetate = 30/1) to afford **4k** (456 mg, 76%).

*N-(1-(4-Chlorophenyl)-3-phenylprop-2-ynylidene)(p-tolyl)-methanamine (**4k**):* oil; ^{1}H NMR (400 MHz, $CDCl_3$) 8.08 (d, J = 8.0 Hz, 2H), 7.59 (d, J = 7.2 Hz, 2H), 7.39−7.31 (m, 7H), 7.15 (d, J = 8.0 Hz, 2H), 5.07 (s, 2H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 149.8, 136.6, 136.5, 136.4, 135.9, 132.1, 129.8, 129.1, 128.9, 128.6, 128.4, 128.0, 121.2, 99.0, 81.3, 60.0, 21.1; IR (neat) 2918, 2200, 1586, 1486, 1309, 1091, 1012, 837 cm^{-1}; MS m/z 343 [M$^+$, 15], 129 (100), 212 (94), 240 (64); HRMS (EI) calcd for $C_{23}H_{18}NCl$ 343.1128, found 343.1126.

*N-(1-(4-Bromophenyl)hept-2-ynylidene)(phenyl)methanamine (**4l**).* A solution of benzylamine (373 mg, 3.49 mmol) in 1.0 mL of anhydrous THF was added dropwise to a solution of 1-(4-bromophenyl)hept-2-yn-1-one (462 mg, 1.75 mmol) and titanium(IV) butoxide (1.0 g, 2.94 mmol) in 9 mL of anhydrous THF under nitrogen atmosphere. The resulting yellow mixture was heated to reflux for 1.5 h and then cooled to room temperature. The mixture was poured into water (30 mL), and the water layer was extracted by CH_2Cl_2 (20 mL × 2). The organic layer was combined and dried over $MgSO_4$. After evaporation, the residue was separated by silica gel chromatography (petroleum ether/ethyl acetate = 30/1) to afford **4l** (556 mg, 90%): oil. ^{1}H NMR (400 MHz, $CDCl_3$) 7.94 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H), 7.40−7.32 (m, 4H), 7.27−7.24 (m, 1H), 4.98 (s, 2H), 2.54 (t, J = 7.2 Hz, 2H), 1.67−1.63 (m, 2H), 1.53−1.48 (m, 2H), 0.96 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 150.6, 139.9, 136.6, 131.2, 129.2, 128.4, 127.9, 126.7, 124.8, 102.0, 73.7, 59.9, 30.3, 22.0, 19.1, 13.5; IR (neat) 2957, 2930, 2209, 1587, 1483, 1280, 1069, 1009 cm^{-1}; MS m/z 353 [M(Br^{79})$^+$, 10], 91 (100); HRMS (EI) calcd for $C_{20}H_{20}NBr(79)$ 353.0779, found 353.0785.

*N-(1-(4-Methoxyphenyl)-3-phenylprop-2-ynylidene)(p-tolyl)-methanamine (**4m**).* Following the procedure for the preparation of **4l**, the reaction of 4-methylbenzylamine (423 mg, 3.49 mmol), 1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-one (413 mg, 1.75 mmol), and titanium(IV) butoxide (1.0 g, 2.94 mmol) in 10 mL of anhydrous THF afforded 303 mg (51%) of **4m**: mp 63−65 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 8.10 (d, J = 8.8 Hz, 2H), 7.60 (d, J = 7.6 Hz, 2H), 7.42−7.39 (m, 3H), 7.33 (d, J = 7.6 Hz, 2H), 7.15 (d, J = 7.6 Hz, 2H), 6.93 (d, J = 8.8 Hz, 2H), 5.07 (s, 2H), 3.85 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 161.6, 150.4, 137.1, 136.2, 132.2, 130.5, 129.6, 129.2, 129.1, 128.6, 128.0, 121.6, 113.5, 98.3, 81.8, 59.8, 55.4, 21.1; IR (neat) 2928, 2202, 1604, 1510, 1310, 1253, 1167, 1031 cm^{-1}; MS m/z 339 [M$^+$, 73], 208 (100), 236 (97), 193 (84); HRMS (EI) calcd for $C_{24}H_{21}NO$ 339.1623, found 339.1627.

General Procedure for the Synthesis of Isoquinolines 5m−q. Under nitrogen atmosphere, CsF (304 mg, 2.0 mmol) and Cs_2CO_3 (326 mg, 1.0 mmol) were added at room temperature to a stirred solution of **1b** (326 mg, 1.0 mmol) in 0.47 mL of anhydrous MeCN and 0.16 mL of anhydrous toluene. The reaction mixture was heated at 40 °C. A solution of **4a** (148 mg, 0.5 mmol) in 1.41 mL of anhydrous MeCN and 0.47 mL of anhydrous toluene was injected into the reaction mixture by a microinfusion pump at the rate of 0.1 mL/h. When the injection was over, the mixture was stirred at 40 °C for an additional 1 h. Then the reaction mixture was filtered through a short column of silica gel eluted with Et_2O. The filtrate was concentrated under reduced pressure to afford the residue, which was separated by silica gel chromatography (petroleum ether/ethyl acetate = 20/1) to afford 5 m (96 mg, 48%).

*4-Benzyl-6,7-dimethyl-1,3-diphenylisoquinoline (**5m**):* mp 100−102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.87 (s, 1H), 7.77−7.75 (m, 2H), 7.66 (s, 1H), 7.56−7.46 (m, 5H), 7.34−7.23 (m, 5H), 7.18 (t, J = 7.2 Hz, 1H), 7.12 (d, J = 7.2 Hz, 2H), 4.48 (s, 2H), 2.35 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 158.2, 151.6, 141.4, 141.2, 140.4, 140.1, 136.3, 135.8, 130.2, 129.5, 128.5, 128.2, 128.2, 128.0, 127.8, 127.5, 127.4, 125.9, 124.9, 124.4, 124.0, 34.9, 20.8, 20.2; IR (KBr) 2920, 1551, 1494, 1448, 1406, 1025, 909 cm^{-1}; MS m/z 398 [(M − 1)$^+$, 100], 237 (38); HRMS (EI) calcd for $C_{30}H_{25}N$ 399.1987, found 399.1992.

*4-(Cyclopropylmethyl)-3-phenyl-1-p-tolylisoquinoline (**5n**).* Following the procedure for the preparation of **5m**, the reaction of **4g** (130 mg, 0.48 mmol), **1a** (283 mg, 0.95 mmol), CsF (289 mg, 1.9 mmol), and Cs_2CO_3 (310 mg, 0.95 mmol) in 1.8 mL of anhydrous MeCN and 0.6 mL of anhydrous toluene afforded 85 mg (51%) of **5n**: oil; ^{1}H NMR (400 MHz, $CDCl_3$) 8.25 (d, J = 8.4 Hz, 1H), 8.16 (d, J = 8.4 Hz, 1H), 7.74 (t, J = 7.6 Hz, 1H), 7.63−7.56 (m, 4H), 7.51 (t, J = 7.6 Hz, 1H), 7.44−7.23 (m, 5H), 3.07 (d, J = 6.4 Hz, 2H), 2.43 (s, 3H), 1.03−0.97 (m, 1H), 1.43−1.39 (m, 2H), 0.07−0.05 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 158.3, 151.6, 141.9, 138.1, 137.0, 136.5, 130.1, 130.0, 129.7, 128.9, 128.3, 127.9, 127.4, 127.3, 126.1, 125.9, 124.4, 32.4, 21.3, 12.0, 5.5; IR (KBr) 2924, 1573, 1445, 1218, 1211 cm^{-1}; MS m/z 349 (M$^+$, 100), 320 (59), 272 (40); HRMS (EI) calcd for $C_{26}H_{23}N$ 349.1830, found 349.1833.

*4-Benzyl-3-(3,4-dimethylphenyl)-1-p-tolylisoquinoline (**5o**).* Following the procedure for the preparation of **5m**, the reaction of **4i** (169 mg, 0.5 mmol), **1a** (298 mg, 1.0 mmol), CsF (304 mg, 2.0 mmol), and Cs_2CO_3 (326 mg, 1.0 mmol) in 1.88 mL of anhydrous MeCN and 0.62 mL of anhydrous toluene afforded 116 mg (56%) of **5o**: mp 73−75 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 8.16 (d, J = 8.8 Hz, 1H), 7.89 (d, J = 8.8 Hz, 1H), 7.67 (d, J = 7.6 Hz, 2H), 7.57 (t, J = 7.6 Hz, 1H), 7.47 (t, J = 7.6 Hz, 1H), 7.37 (s, 1H), 7.33−7.24 (m, 5H), 7.20−7.08 (m, 4H), 4.52 (s, 2H), 2.45 (s, 3H), 2.26 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 159.2, 152.6, 141.3, 138.8, 138.2, 137.1, 137.0, 136.1, 136.0, 130.9, 130.2, 129.9, 129.2, 128.9, 128.5, 128.2, 128.2, 126.8, 126.1, 125.9, 125.8, 124.9, 124.3, 35.1, 21.3, 19.8, 19.5; IR (KBr) 2920, 1727, 1456, 1271, 1123 cm^{-1}; MS m/z 412 [(M − 1)$^+$, 100], 57 (87); HRMS (EI) calcd for $C_{31}H_{27}N$ 413.2144, found 413.2147.

*4-Benzyl-3-(4-fluorophenyl)-1-p-tolylisoquinoline (**5p**).* Following the procedure for the preparation of **5m**, the reaction of **4j** (164 mg, 0.5 mmol), **1a** (298 mg, 1.0 mmol), CsF (304 mg, 2.0 mmol), and Cs_2CO_3 (326 mg, 1.0 mmol) in 1.88 mL of anhydrous MeCN and 0.62 mL of anhydrous toluene afforded 145 mg (72%) of **5p**: mp 90−92 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 8.18 (d, J = 8.4 Hz, 1H), 7.89 (d, J = 8.4 Hz, 1H), 7.66 (d, J = 7.6 Hz, 2H), 7.60−7.48 (m, 4H), 7.34 (d, J = 7.6 Hz, 2H), 7.27−7.24 (m, 3H), 7.11 (d, J = 7.6 Hz, 2H), 7.05 (t, J = 8.0 Hz, 2H), 4.50 (s, 2H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 162.5 (J_{C-F} = 244.5 Hz), 159.4, 151.2, 140.8, 138.4, 137.2 (J_{C-F} = 3.6 Hz), 136.9, 136.8, 131.2 (J_{C-F} = 8.8 Hz), 130.1, 130.1, 129.0, 128.6, 128.2, 128.1, 126.4, 126.1, 125.9, 124.8, 124.4, 114.9 (J_{C-F} = 21.2 Hz), 35.0, 21.3; IR (KBr) 2921, 1604, 1509, 1385, 1224, 1182 cm^{-1}; MS m/z 402 [(M − 1)$^+$, 100], 388 (21); HRMS (EI) calcd for $C_{29}H_{22}NF$ 403.1736, found 403.1733.

*4-Benzyl-3-(4-chlorophenyl)-6,7-dimethyl-1-p-tolylisoquinoline (**5q**).* Following the procedure for the preparation of **5m**, the reaction of **4k** (172 mg, 0.5 mmol), **1b** (326 mg, 1.0 mmol), CsF (304 mg, 2.0 mmol), and Cs_2CO_3 (326 mg, 1.0 mmol) in 1.88 mL of anhydrous MeCN and 0.62 mL of anhydrous toluene afforded 127 mg (57%) of **5q**: mp 171−173 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.90 (s, 1H), 7.66−7.64 (m, 3H), 7.48 (d, J = 7.6 Hz, 2H), 7.34−7.17 (m, 7H), 7.10 (d, J = 7.6 Hz, 2H), 4.44 (s, 2H), 2.46 (s, 3H), 2.36 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 158.5, 150.3, 140.9, 140.5, 139.9, 138.2, 137.1, 136.5, 135.8, 133.5, 130.9, 130.0, 129.0, 128.6, 128.1, 128.1, 127.5, 126.0, 125.0, 124.4, 123.8, 34.8, 21.4, 20.8, 20.3; IR (KBr) 2918, 1493, 1451, 1087, 1014, 907 cm^{-1}; MS m/z 447 (M$^+$, 100), 432 (45); HRMS (EI) calcd for $C_{31}H_{26}NCl$ 447.1754, found 447.1750.

General Procedure for the Synthesis of Pyridines 6n−z and 6aa. Under nitrogen atmosphere, Cs_2CO_3 (326 mg, 1.0 mmol) was added at room temperature to a stirred solution of **3b** (205 mg, 1.5 mmol) in 0.13 mL of anhydrous MeCN and 0.5 mL of anhydrous toluene. The reaction mixture was heated at 75 °C. A solution of **4c** (155 mg, 0.5 mmol) in 0.37 mL of anhydrous MeCN and 1.5 mL of anhydrous toluene was injected into the reaction mixture by a microinfusion pump at the rate of 0.1 mL/h. When the injection was over, the mixture was stirred at 75 °C for an additional 1 h. Then the reaction mixture was filtered through a short column of silica gel eluted with Et_2O. The filtrate was concentrated under reduced pressure to afford the residue, which was separated by silica gel

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chromatography (petroleum ether/ethyl acetate = 20/1) to afford **6n** (173 mg, 78%).

*3-Benzyl-5-(4-chlorophenyl)-2-phenyl-6-p-tolylpyridine (**6n**):* mp 144−146 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.59−7.56 (m, 2H), 7.48 (s, 1H), 7.43−7.38 (m, 3H), 7.30−7.18 (m, 7H), 7.11−7.02 (m, 6H), 4.11 (s, 2H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 157.7, 154.5, 140.7, 140.3, 140.1, 138.4, 137.6, 136.8, 133.1, 132.0, 130.8, 129.9, 129.2, 128.8, 128.6, 128.6, 128.5, 128.2, 128.1, 128.0, 126.3, 38.1, 21.2; IR (KBr) 2924, 1494, 1433, 1092, 1015 cm^{-1}; MS *m*/*z* 444 [(M − 1)$^+$, 65], 430 (40), 57 (100); HRMS (EI) calcd for $C_{31}H_{24}NCl$ 445.1597, found 445.1595.

*3-(4-Chlorophenyl)-5-(4-methoxybenzyl)-6-phenyl-2-p-tolylpyridine (**6o**).* Following the procedure for the preparation of **6n**, the reaction of **4d** (140 mg, 0.41 mmol), **3b** (164 mg, 1.2 mmol), and Cs_2CO_3 (261 mg, 0.8 mmol) in 0.4 mL of anhydrous MeCN and 1.6 mL of anhydrous toluene afforded 113 mg (58%) of **6o**: mp 151−153 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.60−7.56 (m, 2H), 7.46 (s, 1H), 7.43−7.37 (m, 3H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.10 (d, *J* = 8.4 Hz, 2H), 7.04−6.97 (m, 4H), 6.80 (d, *J* = 8.4 Hz, 2H), 4.04 (s, 2H), 3.76 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 158.0, 157.6, 154.4, 140.6, 140.1, 138.5, 137.5, 136.8, 133.1, 133.1, 132.4, 132.3, 130.8, 129.9, 129.8, 129.3, 128.6, 128.5, 128.1, 128.0, 114.0, 55.2, 37.2, 21.2; IR (KBr) 2954, 1511, 1433, 1248, 1092, 1035 cm^{-1}; MS *m*/*z* 474 [(M − 1)$^+$, 15], 416 (86), 302 (100), 233 (95); HRMS (EI) calcd for $C_{32}H_{26}NOCl$ 475.1703, found 475.1706.

*3-(4-Chlorobenzyl)-6-(4-fluorophenyl)-2,5-diphenylpyridine (**6p**).* Following the procedure for the preparation of **6n**, the reaction of **4e** (101 mg, 0.29 mmol), **3a** (91 mg, 0.9 mmol), and Cs_2CO_3 (195 mg, 0.6 mmol) in 0.3 mL of anhydrous MeCN and 1.2 mL of anhydrous toluene afforded 97 mg (74%) of **6p**: mp 133−135 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.54−7.51 (m, 3H), 7.45−7.36 (m, 6H), 7.30−7.27 (m, 4H), 7.24−7.21 (m, 1H), 6.98 (d, *J* = 8.4 Hz, 2H), 6.90−6.85 (m, 3H), 4.08 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 162.5 (J_{C-F} = 245.1 Hz), 157.6, 153.7, 140.8, 140.0, 139.5, 138.6, 135.9 (J_{C-F} = 4.1 Hz), 133.8, 131.8 (J_{C-F} = 8.0 Hz), 130.4, 130.1, 129.5, 129.1, 128.7, 128.4, 128.3, 128.2, 127.5, 127.3, 114.8 (J_{C-F} = 21.3 Hz), 29.7; IR (KBr) 2918, 2849, 1491, 1217, 1157, 1015, 842 cm^{-1}; MS *m*/*z* 448 [(M − 1)$^+$, 100], 57 (39); HRMS (EI) calcd for $C_{30}H_{21}NFCl$ 449.1347, found 449.1350.

*3-Benzyl-5-(4-ethylphenyl)-2-(4-fluorophenyl)-6-p-tolylpyridine (**6q**).* Following the procedure for the preparation of **6n**, the reaction of **4j** (164 mg, 0.5 mmol), **3c** (195 mg, 1.5 mmol), and Cs_2CO_3 (326 mg, 1.0 mmol) in 0.5 mL of anhydrous MeCN and 2.0 mL of anhydrous toluene afforded 183 mg (80%) of **6q**: mp 160−162 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.56−7.53 (m, 3H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.27−7.22 (m, 2H), 7.20−7.17 (m, 1H), 7.10−7.05 (m, 8H), 7.02 (d, *J* = 8.0 Hz, 2H), 4.08 (s, 2H), 2.63 (q, *J* = 7.6 Hz, 2H), 2.29 (s, 3H), 1.22 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 162.7 (J_{C-F} = 245.4 Hz), 156.2, 154.7, 143.2, 141.1, 140.2, 137.4, 137.2, 137.1, 136.4 (J_{C-F} = 3.2 Hz), 134.5, 131.7, 131.1 (J_{C-F} = 8.8 Hz), 129.9, 129.4, 128.7, 128.6, 128.5, 127.8, 126.3, 115.0 (J_{C-F} = 21.3 Hz), 38.2, 28.5, 21.2, 15.4; IR (KBr) 3027, 1602, 1508, 1433, 1224, 1156, 1016, 909 cm^{-1}; MS *m*/*z* 456 [(M − 1)$^+$, 100], 91 (10); HRMS (EI) calcd for $C_{33}H_{28}NF$ 457.2206, found 457.2205.

*3-Benzyl-2-(4-chlorophenyl)-5-(4-ethylphenyl)-6-p-tolylpyridine (**6r**).* Following the procedure for the preparation of **6n**, the reaction of **4k** (172 mg, 0.5 mmol), **3c** (195 mg, 1.5 mmol), and Cs_2CO_3 (326 mg, 1.0 mmol) in 0.5 mL of anhydrous MeCN and 2.0 mL of anhydrous toluene afforded 147 mg (62%) of **6r**: mp 127−129 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.53−7.49 (m, 3H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.28−7.24 (m, 3H), 7.09−7.06 (m, 6H), 7.02 (d, *J* = 8.0 Hz, 2H), 4.08 (s, 2H), 2.63 (q, *J* = 7.2 Hz, 2H), 2.29 (s, 3H), 1.22 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 155.9, 154.8, 143.2, 141.2, 140.2, 138.8, 137.4, 137.1, 137.1, 134.7, 134.0, 131.7, 130.7, 129.9, 129.4, 128.8, 128.6, 128.5, 128.3, 127.8, 126.3, 38.2, 28.5, 21.2, 15.4; IR (KBr) 2965, 1490, 1433, 1091, 1014, 908, 834 cm^{-1}; MS *m*/*z* 472 [(M − 1)$^+$, 100], 57 (31); HRMS (EI) Calcd for $C_{33}H_{28}NCl$ 473.1910, found 473.1916.

*3-Benzyl-5-(4-chlorophenyl)-2-(4-methoxyphenyl)-6-p-tolylpyridine (**6s**).* Following the procedure for the preparation of **6n**, the reaction of **4m** (170 mg, 0.5 mmol), **3b** (205 mg, 1.5 mmol), and Cs_2CO_3 (326 mg, 1.0 mmol) in 0.5 mL of anhydrous MeCN and 2.0 mL of anhydrous toluene afforded 181 mg (76%) of **6s**: mp 150−152 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.53 (d, *J* = 8.4 Hz, 2H), 7.45 (s, 1H), 7.30−7.19 (m, 7H), 7.09 (d, *J* = 8.4 Hz, 4H), 7.03 (d, *J* = 8.4 Hz, 2H), 6.94 (d, *J* = 8.4 Hz, 2H), 4.12 (s, 2H), 3.82 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 159.6, 157.3, 154.4, 140.8, 140.4, 138.5, 137.5, 136.9, 133.1, 132.8, 132.6, 131.8, 130.8, 130.6, 129.9, 128.8, 128.6, 128.6, 128.4, 126.3, 113.6, 55.3, 38.2, 21.2; IR (KBr) 2918, 1508, 1432, 1248, 1175, 907 cm^{-1}; MS *m*/*z* 474 [(M − 1)$^+$, 100], 55 (10); HRMS (EI) calcd for $C_{32}H_{26}NOCl$ 475.1703, found 475.1697.

*3-Benzyl-5-(4-chlorophenyl)-2-(3,4-dimethylphenyl)-6-p-tolylpyridine (**6t**).* Following the procedure for the preparation of **6n**, the reaction of **4i** (169 mg, 0.5 mmol), **3b** (205 mg, 1.5 mmol), and Cs_2CO_3 (326 mg, 1.0 mmol) in 0.5 mL of anhydrous MeCN and 2.0 mL of anhydrous toluene afforded 173 mg (73%) of **6t**: mp 140−142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.44 (s, 1H), 7.35 (s, 1H), 7.30−7.23 (m, 5H), 7.20−7.14 (m, 4H), 7.09−7.07 (m, 4H), 7.02 (d, *J* = 8.0 Hz, 2H), 4.10 (s, 2H), 2.28 (s, 6H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 157.9, 154.4, 140.5, 140.5, 138.6, 137.7, 137.4, 136.9, 136.4, 136.3, 133.0, 132.8, 131.9, 130.8, 130.5, 130.0, 129.3, 128.8, 128.6, 128.5, 128.4, 126.6, 126.2, 38.2, 21.2, 19.8, 19.5; IR (KBr) 2971, 1496, 1434, 1090, 1018 cm^{-1}; MS *m*/*z* 472 [(M − 1)$^+$, 8], 279 (95), 167 (100), 149 (100); HRMS (EI) calcd for $C_{33}H_{28}NCl$ 473.1910, found 473.1907.

*3-Benzyl-2-(3,4-dimethylphenyl)-5-(3-nitrophenyl)-6-p-tolylpyridine (**6u**).* Following the procedure for the preparation of **6n**, the reaction of **4i** (133 mg, 0.4 mmol), **3j** (176 mg, 1.2 mmol), and Cs_2CO_3 (261 mg, 0.8 mmol) in 0.4 mL of anhydrous MeCN and 1.6 mL of anhydrous toluene afforded 157 mg (81%) of **6u**: mp 87−89 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 8.10−8.07 (m, 2H), 7.51 (s, 1H), 7.42−7.36 (m, 3H), 7.30−7.17 (m, 7H), 7.11 (d, *J* = 7.6 Hz, 2H), 7.02 (d, *J* = 7.6 Hz, 2H), 4.14 (s, 2H), 2.30 (s, 3H), 2.28 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) 158.7, 154.6, 148.2, 141.9, 140.5, 140.3, 137.8, 137.4, 136,7, 136.4, 136.3, 135.8, 132.2, 131.6, 130.5, 130.0, 129.3, 129.0, 128.8, 128.8, 128.6, 126.5, 126.3, 124.2, 121.9, 38.1, 21.2, 19.8, 19.6; IR (KBr) 2920, 1531, 1440, 1348, 1101, 1022, 909 cm^{-1}; MS *m*/*z* 484 (M$^+$, 100), 437 (36); HRMS (EI) calcd for $C_{33}H_{28}N_2O_2$ 484.2151, found 484.2150.

*5′-Benzyl-6′-(3,4-dimethylphenyl)-2′-p-tolyl-2,3′-bipyridine (**6v**).* Following the procedure for the preparation of **6n**, the reaction of **4i** (169 mg, 0.5 mmol), **3k** (155 mg, 1.5 mmol), and Cs_2CO_3 (326 mg, 1.0 mmol) in 0.5 mL of anhydrous MeCN and 2.0 mL of anhydrous toluene afforded 183 mg (83%) of **6v**: mp 124−126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 8.61 (d, *J* = 1.1 Hz, 1H), 7.84 (s, 1H), 7.35−7.29 (m, 5H), 7.22 (t, *J* = 7.2 Hz, 2H), 7.16−7.06 (m, 5H), 7.03−6.97 (m, 3H), 4.13 (s, 2H), 2.27 (s, 6H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 158.5, 158.0, 154.5, 149.5, 140.7, 140.4, 137.7, 137.4, 137.0, 136.3, 136.1, 135.4, 133.1, 131.8, 130.4, 129.8, 129.1, 128.7, 128.5, 128.3, 126.5, 126.0, 125.1, 121.6, 38.1, 21.1, 19.7, 19.4; IR (KBr) 2918, 1589, 1497, 1428, 907 cm^{-1}; MS *m*/*z* 439 [(M − 1)$^+$, 12], 84 (100); HRMS (EI) calcd for $C_{32}H_{28}N_2$ 440.2252, found 440.2255.

*3-(Cyclopropylmethyl)-2,5-diphenyl-6-p-tolylpyridine (**6w**).* Following the procedure for the preparation of **6n**, the reaction of **4g** (134 mg, 0.49 mmol), **3a** (150 mg, 1.47 mmol), and Cs_2CO_3 (319 mg, 0.98 mmol) in 0.5 mL of anhydrous MeCN and 2.0 mL of anhydrous toluene afforded 127 mg (69%) of **6w**: mp 92−94 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.88 (s, 1H), 7.66 (d, *J* = 7.6 Hz, 2H), 7.52−7.47 (m, 2H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.38−7.31 (m, 7H), 7.06 (d, *J* = 7.6 Hz, 2H), 2.72 (d, *J* = 7.2 Hz, 2H), 2.33 (s, 3H), 1.05−0.90 (m, 1H), 0.56 (q, *J* = 8.0 Hz, 2H), 0.20−0.17 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 157.1, 154.1, 140.6, 140.4, 139.5, 137.3, 137.1, 134.2, 133.2, 130.0, 129.6, 129.3, 128.4, 128.2, 128.0, 127.7, 126.9, 36.6, 21.2, 11.3, 4.9; IR (KBr) 3002, 1427, 1181, 1019, 908 cm^{-1}; MS *m*/*z* 374 [(M − 1)$^+$, 100], 298 (17); HRMS (EI) calcd for $C_{28}H_{25}N$ 375.1987, found 375.1991.

*3-(Cyclopropylmethyl)-6-(naphthalen-1-yl)-2,5-diphenylpyridine (**6x**).* Following the procedure for the preparation of **6n**, the reaction of **4h** (127 mg, 0.41 mmol), **3a** (125 mg, 1.23 mmol), and Cs_2CO_3 (267 mg, 0.82 mmol) in 0.4 mL of anhydrous MeCN and 1.6 mL of

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anhydrous toluene afforded 115 mg (68%) of **6x**: mp 168−170 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 8.01 (s, 1H), 7.86−7.73 (m, 3H), 7.60 (d, J = 7.6 Hz, 2H), 7.45−7.25 (m, 7H), 7.14−7.09 (m, 5H), 2.74 (d, J = 6.8 Hz, 2H), 1.09−0.95 (m, 1H), 0.59−0.55 (m, 2H), 0.21−0.18 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 157.1, 154.2, 140.4, 139.5, 139.0, 138.0, 136.2, 134.0, 133.7, 132.2, 129.3, 129.0, 128.4, 128.1, 128.1, 128.0, 127.9, 127.8, 126.9, 126.1, 125.8, 125.4, 124.9, 36.8, 11.2, 5.0; IR (KBr) 3056, 1428, 1380, 1021, 909 cm^{-1}; MS m/z 410 [$(M - 1)^+$, 100], 105 (20); HRMS (EI) calcd for $C_{31}H_{25}N$ 411.1987, found 411.1981.

*3-Pentyl-2,5-diphenyl-6-p-tolylpyridine (**6y**).* Following the procedure for the preparation of **6n**, the reaction of **4f** (145 mg, 0.5 mmol), **3a** (153 mg, 1.5 mmol), and Cs_2CO_3 (326 mg, 1.0 mmol) in 0.5 mL of anhydrous MeCN and 2.0 mL of anhydrous toluene afforded 105 mg (54%) of **6y**: mp 96−98 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.60−7.58 (m, 3H), 7.46−7.37 (m, 3H), 7.31−7.22 (m, 7H), 7.00 (d, J = 8.4 Hz, 2H), 2.71 (t, J = 8.0 Hz, 2H), 2.27 (s, 3H), 1.65−1.53 (m, 2H), 1.28−1.24 (m, 4H), 0.83 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 157.1, 153.9, 140.7, 140.3, 139.9, 137.3, 137.2, 134.2, 133.8, 130.0, 129.6, 129.2, 128.5, 128.2, 128.0, 127.7, 126.9, 32.0, 31.6, 30.7, 22.3, 21.2, 13.9; IR (KBr) 2956, 2927, 2863, 1428, 1021, 829 cm^{-1}; MS m/z 391 (M^+, 3], 167 (100), 57 (100); HRMS (EI) calcd for $C_{29}H_{29}N$ 391.2300, found 391.2304.

*2-(4-Bromophenyl)-5-(4-chlorophenyl)-3-pentyl-6-phenylpyridine (**6z**).* Following the procedure for the preparation of **6n**, the reaction of **4l** (177 mg, 0.5 mmol), **3b** (205 mg, 1.5 mmol), and Cs_2CO_3 (326 mg, 1.0 mmol) in 0.5 mL of anhydrous MeCN and 2.0 mL of anhydrous toluene afforded 93 mg (38%) of **6z**: mp 113−115 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.60−7.57 (m, 3H), 7.47 (d, J = 8.4 Hz, 2H), 7.37−7.35 (m, 2H), 7.27−7.22 (m, 5H), 7.15 (d, J = 8.4 Hz, 2H), 2.70 (t, J = 8.0 Hz, 2H), 1.65−1.50 (m, 2H), 1.34−1.25 (m, 4H), 0.88−0.83 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 156.3, 154.1, 139.8, 139.6, 139.3, 138.3, 134.2, 133.5, 133.3, 131.3, 130.8, 130.8, 130.0, 128.5, 128.0, 127.8, 122.2, 32.0, 31.6, 30.7, 22.3, 13.9; IR (neat) 2919, 2852, 1491, 1432, 1092, 1011, 908 cm^{-1}; MS m/z 490 [$(M - 1)^+$ or $(M + 1)^+$, 88], 352 (45), 57 (100); HRMS (EI) calcd for $C_{28}H_{25}NClBr(79)$ 489.0859, found 489.0862; $C_{28}H_{25}NClBr(81)$ 491.0838, found 491.0841.

*3-Benzyl-5-cyclopropyl-2-phenyl-6-p-tolylpyridine (**6aa**).* Following the procedure for the preparation of **6n**, the reaction of **4c** (155 mg, 0.5 mmol), **3f** (165 mg, 2.5 mmol), and Cs_2CO_3 (326 mg, 1.0 mmol) in 0.5 mL of anhydrous MeCN and 2.0 mL of anhydrous toluene afforded 86 mg (46%) of **6aa**: oil; ^{1}H NMR (400 MHz, $CDCl_3$) 7.63 (d, J = 7.2 Hz, 2H), 7.49 (d, J = 7.2 Hz, 2H), 7.37−7.32 (m, 3H), 7.28−7.19 (m, 6H), 7.06−7.02 (m, 3H), 4.03 (s, 2H), 2.39 (s, 3H), 2.10−1.90 (m, 1H), 0.91−0.87 (m, 2H), 0.64−0.62 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 156.7, 155.5, 140.6, 140.5, 137.6, 137.4, 134.9, 134.7, 131.7, 129.5, 129.3, 128.7, 128.6, 128.5, 128.0, 127.7, 126.1, 38.3, 21.3, 12.9, 9.7; IR (KBr) 2919, 2850, 1436, 906 cm^{-1}; MS m/z 374 [$(M - 1)^+$, 11], 57 (100), 71 (100); HRMS (EI) calcd for $C_{28}H_{25}N$ 375.1987, found 375.1984.

■ ASSOCIATED CONTENT

Supporting Information

Characterization data for compounds **4a**, **4b**, **5a−h**, **5la**, **5 lb**, and **6a−j,l,m** have been reported in the Supporting Information of our previous communication.[7] Copies of ^{1}H/^{13}C NMR spectra of all new compounds; 2D ^{1}H−^{1}H NOESY spectra of **6o,s,u,w,y**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

[§]Prof. Huang passed away on March 6, 2010. He was fully in charge of this project. Prof. Luling Wu is finishing Prof. Huang's projects with assistance from Prof. Shengming Ma.

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(10) Crystal data for compound **5g**: $C_{25}H_{21}NO_2$, MW 367.43, monoclinic, space group $P2(1)/n$, Mo Kα, final R indices [$I > 2\sigma(I)$], R1 = 0.0529, wR2 = 0.1244, a = 18.1979(13) Å, b = 11.8241(9) Å, c = 20.1682(14) Å, α = 90°, β = 114.8350(10)°, γ = 90°, V = 3938.3(5) Å^3, T = 293(2) K, Z = 8, reflections collected/unique 22603/8547 (R_{int} = 0.0514), parameters 508. Supplementary crystallographic data

have been deposited at the Cambridge Crystallographic Data Centre, CCDC 715782.

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