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Iridium-Catalyzed Direct Cyclization of Aromatic Amines with Diols

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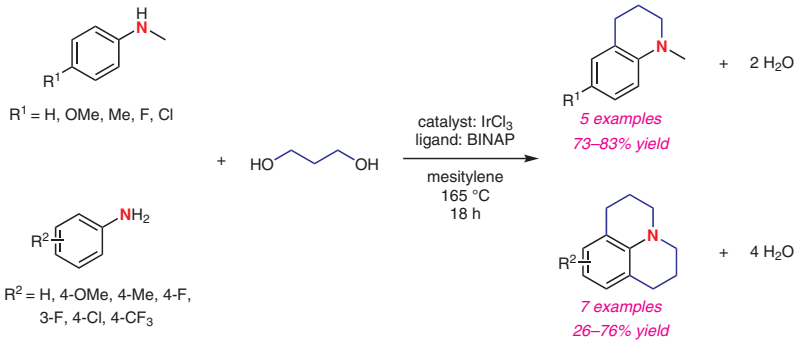

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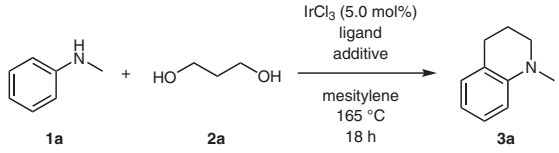
Abstract We developed an environmentally friendly iridium-catalyzed direct cyclization of aromatic amines with diols that generates the corresponding N-heterocyclic compounds with water as the sole by-product. Thus, under conditions of 165 °C for 18 hours, the direct cyclization of *N*-methylanilines with 1,3-propanediol by using an $IrCl_3$ catalyst with *rac*-BINAP as a ligand in mesitylene afforded the corresponding tetrahydroquinoline derivatives with yields ranging from 73 to 83%. Under similar reaction conditions, direct cyclization of anilines with 1,3-propanediol produced the corresponding tetrahydrobenzoquinolizine derivatives with yields ranging from 26 to 76%.

Key words iridium catalyst, aromatic amines, diols, cyclization, N-heterocycles

Nitrogen heterocyclic structures are important building blocks for the synthesis of biologically active compounds and organic electronic materials.[1] Although the synthesis of heterocyclic compounds has attracted a great deal of attention in recent years, the conventional synthesis method usually requires multiple steps. These steps include the preparation of the following reagents before the cyclization reaction is performed: (1) a toxic halogenation reagent, (2) and an alkyne reagent and/or (3) an alkene reagent.[2] As a result, a large amount of waste (excessive halogen reagent, inorganic salt, and numerous unit process steps are required) is discharged from the synthesis process. Direct catalytic cyclization reactions are promising synthetic tools to generate N-heterocyclic compounds.[3,4] Previous studies have proposed environmentally friendly direct N-alkylation reactions such as Fe-catalyzed N-alkylation of amines with alcohols[5] and Ru-catalyzed N-alkylation of amines with carboxylic acid.[6] Here, we report an iridium-catalyzed direct cyclization of aromatic amines with diols to generate the corresponding N-heterocyclic compounds through dehydrative N-alkylation with alcohol moieties and intramolecular C–H activation.[4]

First, we tested and optimized the reaction conditions for the Ir-catalyzed direct cyclization of *N*-methylaniline with 1,3-propanediol (Table 1). At 165 °C for 18 hours, the

Table 1 Ir-catalyzed Direct Cyclization of *N*-Methylaniline with 1,3-Propanediol[a]



Entry	Ligand (mol%)[b]	Additive (mol%)[b]	Yield (%)[c]
1	*rac*-BINAP (7.5)	Na_2CO_3 (8.0)	39
2	*rac*-BINAP (7.5)	n.a.	75 (73)
3	*rac*-BINAP (7.5)	*p*-TsOH (10)	71
4	*rac*-BINAP (7.5)	*p*-TsOH (20)	62
5	PPh_3 (7.5)	n.a.	14
6	dppp (7.5)	n.a.	7
7	dppe (7.5)	n.a.	12
8[d]	*rac*-BINAP (7.5)	n.a.	38
9	*rac*-BINAP (2.5)	n.a.	15
10[e]	*rac*-BINAP (7.5)	n.a.	38
11	n.a.	n.a.	3

[a] *Reaction conditions*: *N*-methylaniline (**1**: 2.5 mmol), 1,3-propanediol (**2**: 1.0 mmol), $IrCl_3$ (5.0 mol% based on **2**), ligand (7.5 mol% based on **2**), mesitylene (1.0 mL).
[b] n.a. = not applicable.
[c] NMR yield and isolated yield in parentheses
[d] 130 °C
[e] 1.0 mmol of **1a** was used.

direct cyclization of *N*-methylaniline (**1a**: 2.5 mmol) with 1,3-propanediol (**2a**: 1.0 mmol) by using $IrCl_3$ as a catalyst (5.0 mol% based on **2**), and *rac*-BINAP (7.5 mol% based on **2**) as a ligand as well as Na_2CO_3 (8.0 mmol) as a base in mesitylene (1.0 mL) generated the cyclization product **3a** in 39% yield (entry 1).

The cyclization reaction without a base generated **3a** in 73% isolated yield (entry 2). The identical reaction using 10 or 20 mol% *p*-TsOH produced **3a** in 71% and 62% yield, respectively (entries 3 and 4).[7] Under similar conditions, when triphenylphosphine (PPh_3: 7.5 mmol) was used as a ligand without additive, a yield of 14% of **3a** was observed (entry 5). The reactions in the presence of $IrCl_3$ and other ligands resulted in lower yields of the desired product **3a** (entries 6 and 7). The reaction with use of the *rac*-BINAP ligand (7.5 mol% based on **2**) at 130 °C for 18 hours produced **3a** in 38% yield (entry 8). Reducing the amount of *rac*-BINAP ligand to 2.5 mol% generated **3a** in 15% yield (entry 9), and reducing the amount of **1a** to 1.0 mmol resulted in 38% yield of **3a** (entry 10). When the reaction was carried out in the absence of any ligand, **3a** was obtained in only 3% yield (entry 11).[8] The reaction with an excess of diol afforded a trace amount of **3a** under similar reaction conditions. Therefore, an excess amount of amine was required for the effective direct cyclization to obtain tetrahydroquinolines. The most effective direct cyclization was achieved by treatment of *N*-methylaniline (**1a**: 2.5 mmol) with 1,3-propanediol (**2a**: 1.0 mmol) in the presence of an Ir catalyst (5.0 mol%) and a BINAP ligand (7.5 mol%) at 165 °C.[9]

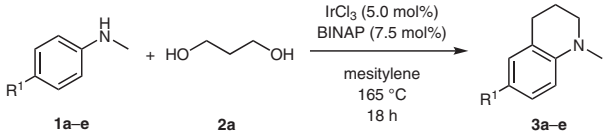
Having the optimized conditions in hand, we proceeded to investigate the reaction of various *N*-methylanilines with 1,3-propanediol (Table 2).[10] 1,2,3,4-Tetrahydro-6-methoxy-1-methylquinoline (**3b**) was formed in 77% yield from 4-methoxy-*N*-methyl-aniline (**1b**) (bearing an electron-donating group at the *para* position of *N*-methylaniline) and **2a** (entry 2).

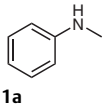
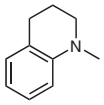
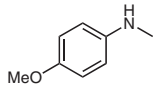
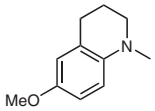
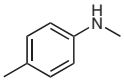
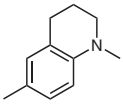
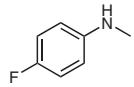
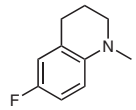
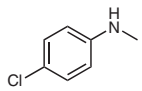
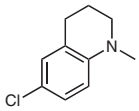
The reaction of 4-methyl-*N*-methylaniline (**1c**) with **2a** generated 1,2,3,4-tetrahydro-1,6-dimethylquinoline (**3c**) in 80% yield (entry 3). The cyclization of *N*-methylaniline (containing a F group at the *para* position) with **2a** also produced the corresponding tetrahydroquinoline compound **3d** in 83% yield (entry 4). The reaction of **1e** (containing an electron-withdrawing group at the *para* position of *N*-methylaniline) with **2a** led to the corresponding tetrahydroquinoline **3e** in 82% yield (entry 5).

The direct cyclization was successfully applied for the synthesis of indole. Thus, the reaction between *N*-methylaniline (**1a**) and ethylene glycol (**2b**) generated 1-methylindole (**6**) in 45% yield (Scheme 1).[4a,c,11]

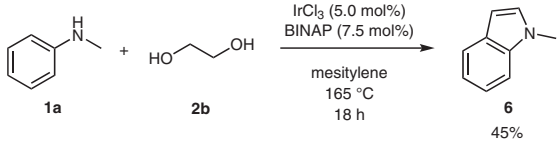
On the other hand, the reaction of *N*-methylaniline (**1a**) with 1,4-butanediol (**2c**) resulted in diamine product **7** in 61% yield (Scheme 2).

Table 2 Ir-catalyzed Direct Cyclization of *N*-Methylanilines with 1,3-Propanediol[a]



Entry	Amines **1**	Product **3**	Yield (%)[b]
1	 **1a**	 **3a**	73
2	 **1b**	 **3b**	77
3	 **1c**	 **3c**	80
4	 **1d**	 **3d**	83
5	 **1e**	 **3e**	82

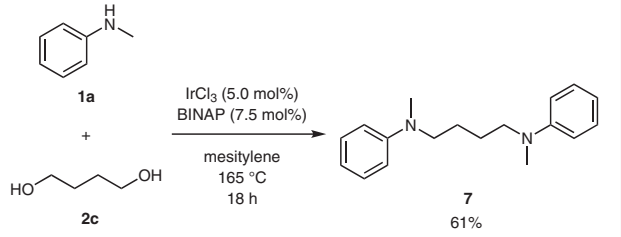
[a] *Reaction conditions*: *N*-methylaniline (**1**: 2.5 mmol), 1,3-propanediol (**2**: 1.0 mmol), $IrCl_3$ (5.0 mol% based on **2**), BINAP (7.5 mol% based on **2**), mesitylene (1.0 mL), 165 °C, 18 h.
[b] Isolated yield.



Scheme 1 Reaction of *N*-methylaniline with ethylene glycol

The cyclization reaction of *N*-methylanilines with diols took place in the presence of an Ir catalyst with BINAP to give a series of 1,2,3,4-tetrahydroquinolines **3a–e** and indole **6** through intramolecular C–H activation.[4d]

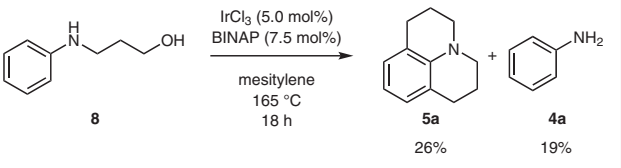
In addition, direct cyclization of anilines with 1,3-propanediol was performed by using similar reaction conditions (Table 3).[12,13,14] Thus, under conditions of 165 °C for 18 hours, direct cyclization of aniline (**4a**: 1.0 mmol) with **2a**



Scheme 2 Reaction of *N*-methylaniline with 1,4-butanediol

(1.3 mmol) in the presence of an $IrCl_3$ catalyst (5.0 mmol based on the diol) and *rac*-BINAP ligand (7.5 mmol) in mesitylene (0.5 mL) generated tetrahydrobenzoquinolizine **5a** in 73% yield (entry 1). The reaction of *p*-anisidine (**4b**) (bearing an electron-donating group at the *para* position of aniline) with **2a** afforded the corresponding tetrahydrobenzoquinolizine **5b** in 67% yield (entry 2). The reaction of 4-methylaniline (**4c**) with **2a** also generated **5c** in 76% yield (entry 3). The reaction of 4-fluoroaniline (**4d**; that contains an electron-withdrawing group at the *para* position of aniline) with **2a** led to the corresponding tetrahydroquinolizine **5d** in 75% yield (entry 4). Tetrahydroquinolizine derivative **5e** was obtained in 59% yield from the reaction of 3-fluoroaniline (**4e**) with **2a** (entry 5). The reaction of 4-chloroaniline (**4f**) with **2a** led to the production of the corresponding tetrahydroquinolizine **5f** in 75% yield (entry 6). The reaction of 4-trifluoromethylaniline (**4g**) with **2a** also generated **5g** in 26% yield (entry 7).[15]

Under our direct cyclization conditions, 3-(phenylamino)-propan-1-ol (**8**) afforded **5a** in 26% yield and **4a** in 19% yield, without use of 1,3-propanediol (Scheme 3).

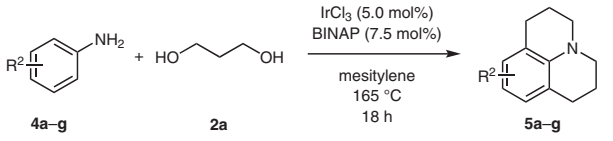


Scheme 3 Direct cyclization of 3-(phenylamino)propan-1-ol (**8**)

Furthermore, the treatment of 3-(phenylamino)propan-1-ol (**8**) with 4-methylaniline (**4b**) under similar reaction conditions gave **5a** in 9% yield and **5b** in 26% yield (Scheme 4, equation 1). Additionally, the reaction of 3-(phenylamino)propan-1-ol (**8**) with *N*-methylaniline (**3a**) afforded **5a** in 12%, **3a** in 52%, and aniline (**4a**) in 21% isolated yield (Scheme 4, equation 2).[4c] These results indicate that the direct cyclization took place after the reaction of 3-(phenylamino)propan-1-ol (**8**) with anilines **4b** and **3a** (see Supporting Information).

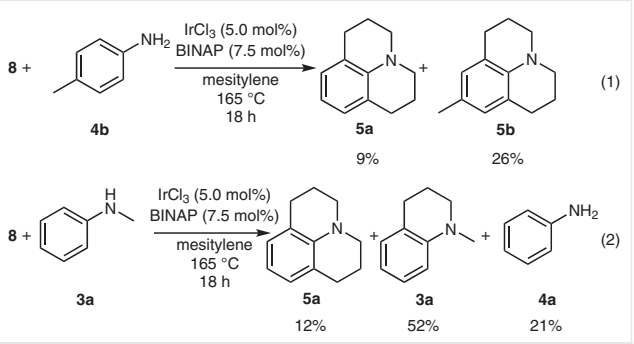
Moreover, the cyclization reaction of aniline (**4a**) with 1,3-propoanediol (**2a**) did not occur under our reaction conditions with 4 Å molecular sieves.[16] These results suggest that water might contribute to the N-alkylation of the alcohol and that the direct cyclization by effective formation of Ir–hydride complexes occurs via Ir–H_2O species.[7]

Table 3 Ir-catalyzed Direct Cyclization of Anilines with 1,3-Propandiol[a]



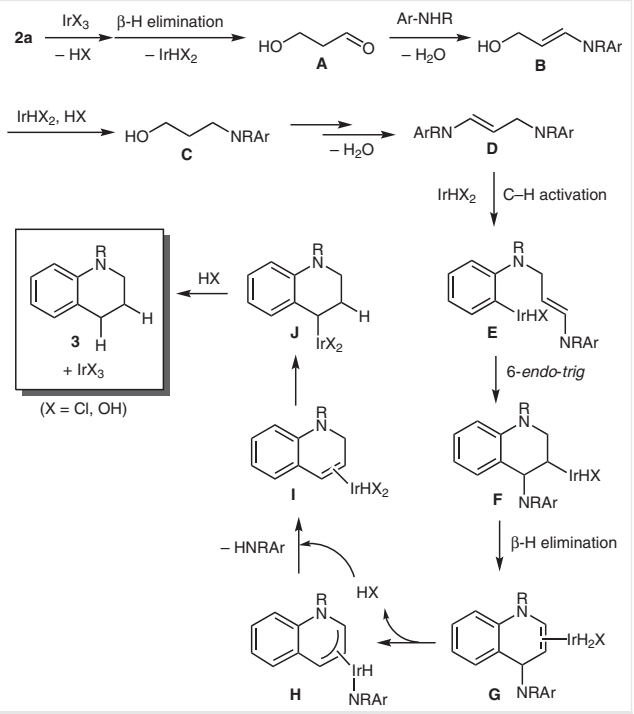
Entry	Amines **4**	Product **5**	Yield (%)[b]
1	**4a**	**5a**	73
2	**4b**	**5b**	67
3	**4c**	**5c**	76
4	**4d**	**5d**	75
5	**4e**	**5e**	59
6	**4f**	**5f**	75
7[c]	**4g**	**5g**	26

[a] *Reaction conditions*: aniline (**4**: 1.0 mmol), 1,3-propanediol (**2**: 1.3 mmol), $IrCl_3$ (5.0 mol% based on **2**), BINAP (7.5 mol% based on **2**), mesitylene (0.5 mL) 165 °C, 18 h.
[b] Isolated yield.
[c] 2.0 mL of mesitylene was used.



Scheme 4

Although the exact reaction mechanism is still not clear at present, a possible reaction pathway is proposed on the basis of the above information and literature precedent[4,17] as shown in Scheme 5. The coordination of the Ir catalyst to **2a** affords aldehyde **A** through β-H elimination. The produced aldehyde **A** reacts with aniline to form intermediate **B** via imine. The obtained **B** undergoes hydrogenation by the Ir–H complex to generate amine **C** which is subjected to similar Ir-catalyzed reactions to produce **D**. The intermediate **D** would be converted into **F** through intramolecular C–H activation and 6-*endo-trig* cyclization. Subsequently, the β-H elimination from **F** would lead to π-allyl-Ir intermediate **H** via **G**. The release of aniline from **H** should lead to product **3** and regenerate the Ir catalyst via intermediates **I** and **J**.



Scheme 5 A proposed reaction pathway

In conclusion, we have developed an Ir-catalyzed direct cyclization of aromatic amines with diols through dehydrative N-alkylation with alcohol moieties and intramolecular C–H activation. The inactive N–H and C–H bonds of aromatic amines have been transformed into N–C and C–C bonds. Thus, the direct cyclization of *N*-methylanilines and diols with an $IrCl_3$ catalyst and BINAP as a ligand, afforded a series of tetrahydroquinoline derivatives and an indole with water as the sole by-product. Under similar reaction conditions, the direct cyclization of anilines with 1,3-propanediol led to the corresponding tetrahydrobenzoquinolizine derivatives with water as the sole by-product.

The reaction tolerated various functional groups and gave unreported julolidine derivatives (**5e** and **5g**). We believe that our reaction systems offer an alternative to the synthesis of julolidine derivatives.[2a,4e,18] Further investigations on the reaction mechanism as well as synthetic application of this protocol are currently underway and the results will be reported in due course.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610995.

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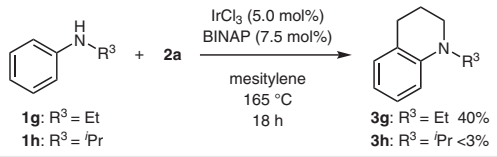
(8) In entry 11, **2a** was not detected in ^{1}H NMR analysis (conversion: 100%). The main product seems to be *N,N'*-diphenyl-1,3-propanediamine (45% NMR yield).

(9) In entry 2, *N*-methyl-*N*-propylaniline was also detected.[4e] The ratio of **3a** to *N*-methyl-*N*-propylaniline was 18:1 (^{1}H NMR analysis). A similar ratio of **3a** to *N*-methyl-*N*-propylaniline was observed in entries 3 and 4.

(10) (a) The reaction of *N*-ethylaniline (**1g**) with 1,3-propanediol (**2a**) gave 1-ethyl-1,2,3,4-tetrahydroquinoline (**3g**) in 40% yield. The reaction of *N*-propylamine (**1h**) with 1,3 -propanediol (**2a**) gave 1-isopropyl-1,2,3,4-tetrahydroquinoline (**3h**) in <3% yield. Both reactions included the corresponding diamine compound (like **7**) (**3g**/**7g** = 1:1 and **3h**/**7h** = 1:39).

Compound 3g:[10a] ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.13 (t, *J* = 7.0 Hz, 3 H), 1.92–1.98 (m, 2 H), 2.74 (t, *J* = 6.2 Hz, 2 H), 3.26 (t, *J* = 5.8 Hz, 2 H), 3.34 (q, *J* = 7.1 Hz, 2 H), 6.54 (tt, *J* = 0.93 Hz, 7.3 Hz, 1 H), 6.59 (d, *J* = 8.4 Hz, 1 H), 6.93 (dd, *J* = 1.2 Hz, 7.2 Hz, 1 H), 7.02–7.06 (m, 1 H) ppm. HRMS: *m*/*z* calcd for $C_{11}H_{15}N$ [M]$^+$: 161.1204; found: 161.1197.

Compound 3h:[10a] ^{1}H NMR ($CDCl_3$, 600 MHz): δ = 1.17 (d, *J* = 6.6 Hz, 6 H), 1.88–1.92 (m, 2 H), 2.73 (t, *J* = 6.6 Hz, 2 H), 3.14 (t, *J* = 6.0 Hz, 2 H), 4.10 (sept, *J* = 6.7 Hz, 1 H), 6.52–6.56 (m, 1 H), 6.68 (d, *J* = 7.8 Hz, 1 H), 6.94 (d, *J* = 6.6 Hz, 1 H), 7.03–7.06 (m, 1 H) ppm. HRMS: *m*/*z* calcd for $C_{12}H_{17}N$ [M]$^+$: 175.1361; found: 175.1359. (b) Abarca, B.; Adam, R.; Ballesteros, R. *Org. Biomol. Chem.* **2012**, *10*, 1826.



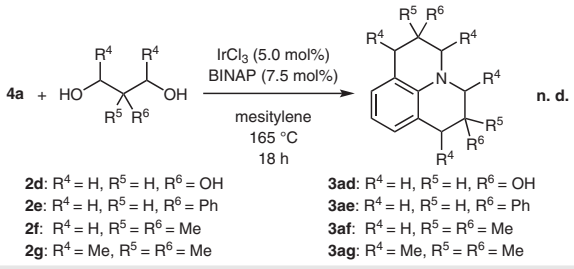
Scheme 6

(11) (a) Zhang, M.; Xie, F.; Wang, X.-T.; Yan, F.; Wang, T.; Chen, M.; Ding, Y. *RSC Adv.* **2013**, *3*, 6022. (b) Kasuga, T.; Takamura, K.; Hara, R.; Takagi, U. *Jpn. Kokai Tokkyo Koho* **1996**, 08319273. (c) Joule, J. A. *Sci. Synth.* **2001**, *10*, 361. (d) Nisida, T.; Tokuda, Y.; Tsuchiya, M. *J. Chem. Soc., Perkin Trans. 2* **1995**, *4*, 823.

(12) **General Procedure and Characterization Data**:

Ir-catalyzed direct cyclization of 3-fluoro-aniline (**4e**) with 1,3-propanediol (**2a**) (Table 3, entry 5): To a vial was added 3-fluoro-aniline (111.1 mg, 1.0 mmol), $IrCl_3{\cdot}3H_3O$ (11.5 mg, 5.0 mol%), and *rac*-BINAP (30.4 mg, 7.5 mol%) under air. Furthermore, mesitylene (0.5 mL) and then 1,3-propanediol (98.9 mg, 1.3 mmol) were added and the reaction mixture was stirred at 165 °C for 18 h. After the reaction, the resulting mixture was diluted with hexane. Then, the reaction mixture was filtrated with a filter paper and concentrated in vacuo. The resulting residue was purified by flash column chromatography on SiO_2 (^{t}BuOMe/hexane 1:15) to yield 2,3,6,7-tetrahydro-8-fluoro-*1H,5H*-benzo[*ij*]quinolizine (**5e**) in 59% yield (73.2 mg) as a pale yellow solution.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.92–1.98 (m, 4 H), 2.68–2.72 (m, 4 H), 3.09–3.12 (m, 4 H), 6.24 (t, J_{HF} = 8.8 Hz, 1 H), 6.70 (t, J_{HF} = 7.5 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.3 (d, $^3J_{CF}$ = 5.9 Hz), 21.3, 22.2, 27.3, 49.6, 50.0, 102.0 (d, $^2J_{CF}$ = 22.9 Hz), 108.5 (d, $^2J_{CF}$ = 21.7 Hz), 116.8 (d, $^4J_{CF}$ = 2.4 Hz), 126.8 (d, $^3J_{CF}$ = 10.8 Hz), 144.1, (d, $^3J_{CF}$ = 8.4 Hz), 159.7 (d, $^1J_{CF}$ = 241.3 Hz) ppm. ^{19}F-NMR (470 MHz, $CDCl_3$): δ = −124.2 ppm. HRMS: *m*/*z* calcd for $C_{12}H_{14}FN$ [M]$^+$: 191.1110; found: 191.1110.



Scheme 7

(13) the reaction **4a** with **2d**–**g**, the desired products **3ad**–**ag** were not detected (Scheme 7) by ^{1}H NMR analysis

(14) The reaction of **4a** with 1,4-butanediol (**2c**) resulted in a double N-alkylation to afford 1-phenylpyrrolidine in 76% yield (see Supporting Information).

(15) Compound **5g** was unstable and gradually decomposed under chromatographic conditions.

(16) Under similar reaction conditions with 4 Å molecular sieves, the reaction of aniline (**4a**) with 1,3-propanediol (**2a**) gave quinoline in 7% yield and no tetrahydrobenzoquinolizine **5a**.

(17) (a) García-González, M. C.; Hernández-Vázquez, E.; Vengochea-Gómez, F. A.; Miranda, L. D. *Tetrahedron Lett.* **2018**, *59*, 848. (b) Ouyang, K.; Hao, W.; Zhang, W.-X.; Xi, Z. *Chem. Rev.* **2015**, *115*, 12045. (c) Ikeda, Y.; Takano, K.; Kodama, S.; Ishii, Y. *Organometallics* **2014**, *33*, 3998, and references therein.

(18) For example: LD 490 (Coumarin 6H) [CAS: 58336-35-9].