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ENVIRONMENTALLY FRIENDLY SYNTHESIS OF *N*-METHYLATED NITROGEN HETEROCYCLES FROM AN AQUEOUS SOLUTION OF METHYLAMINE AND DIOLS

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Abstract – *N*-Methylated nitrogen heterocycles are important compounds which are very common in organic, pharmaceutical, and material chemistry. Development of new environmentally friendly catalytic methods for the synthesis of *N*-methylated heterocycles using cost-effective and readily-available starting materials is strongly demanded. Herein, we report the efficient synthesis of *N*-methylated heterocycles using readily-available aqueous solution of methylamine and various diols catalyzed by iridium complexes. This catalytic system is attractive because of its high atom economy exhausting water as a sole by-product.

The *N*-methylated nitrogen heterocycle is one of the most attractive organic cyclic compounds because of its high biological and pharmaceutical activities.[1] Conventionally, *N*-methylated nitrogen heterocycles are synthesized via methylation of the corresponding secondary nitrogen heterocycles, that have the N-H moiety, with hazardous methylating reagents such as methyl iodide and dimethyl sulfate.[2] Also, *N*-methylated nitrogen heterocycles are produced via the reductive amination using toxic formaldehyde.[2,3] Although the above-mentioned reactions are well documented, they require the employment of toxic starting materials. Additionally, they may generate stoichiometric amounts of wasteful salts as byproducts. Therefore, environmentally friendly reactions to produce *N*-methylated nitrogen heterocycles are in strong demand.

The synthesis of *N*-heterocycles through the formation of two C-N bonds starting from primary amines and diols[4,5] is an attractive method because of the ease of handling, cost effectiveness, and lower toxicity of the starting materials. The advantage of this reaction is further reinforced by its atom efficiency because water is the only byproduct. This type of reaction has also been applied to the synthesis of *N*-methylated nitrogen heterocycles from methylamine and easily available diols.[6] The synthetic utility of

this reaction in terms of its environmental friendliness will be improved by the development of a catalytic system in aqueous conditions because of the ease of handling of aqueous methylamine.

We previously reported a series of *N*-alkylation reactions of amines using alcohols catalyzed by iridium complexes bearing pentamethylcyclopentadienyl (Cp*) ligands $[Cp^*IrCl_2]_2$ (Figure 1).[7,8] This catalytic system is also effective for *N*-heterocyclization of primary amines with diols[7b,7c] and oxidative cyclization of amino alcohols.[7a,7c] The water-soluble triammine iridium catalyst **A** efficiently promotes multialkylation of aqueous ammonia with alcohols.[7a] Recently, we disclosed that *N*-heterocyclic carbene (NHC)-ligated iridium catalysts **B**-**F** exhibit prominent activity for selective mono-alkylation of aqueous ammonia and selective mono- or di-methylation of amines with methanol.[8b,8c] The NHC ligand should allow fine-tuning of the iridium catalyst in the *N*-alkylation reaction. Herein, we report a new efficient system for the synthesis of *N*-methylated nitrogen heterocycles in water from diols and easily-available methylamine using iridium catalysts bearing NHC ligands.

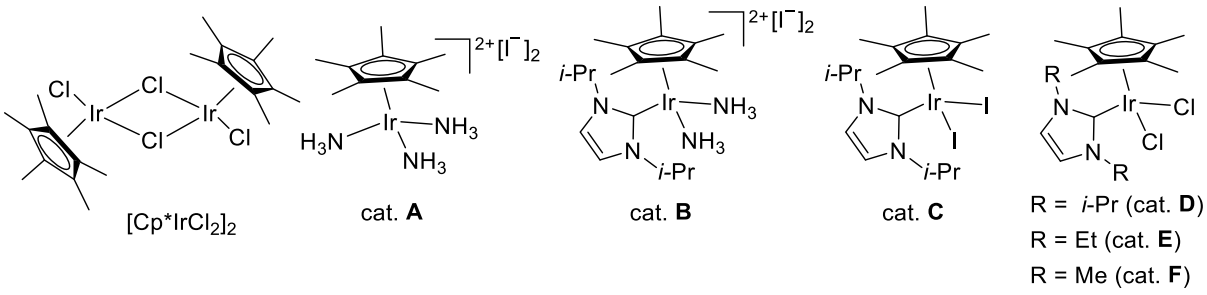
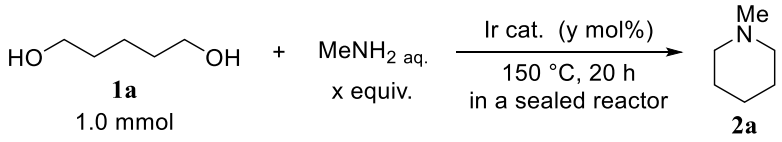


Figure 1. A series of iridium catalysts for *N*-alkylation reactions

First, the synthesis of *N*-methylpiperidine from aqueous methylamine and 1,5-pentanediol was examined to optimize the reaction conditions by screening the iridium catalysts and the amount of aqueous methylamine in a sealed reactor at 150 °C (Table 1). When the reaction of 1,5-pentanediol (1.0 mmol) with 40% aqueous methylamine (10 mmol) was performed in a sealed reactor at 150 °C for 20 hours in the presence of the $[Cp^*IrCl_2]_2$ (0.050 mmol, 1.0 mol% Ir), *N*-methylpiperidine was obtained in only 25% yield (entry 1). The water-soluble triammine complex **A** also exhibited low catalytic activity (entry 2). Conversely, substitution of one of the ammine ligands with NHC ligand bearing isopropyl groups on its nitrogen atoms (cat. **B**) considerably improved the yield of **2a** (entry 3). The yield of **2a** slightly increased using the diiodo complex **C**, which corresponds to the removal of the ammine ligand from catalyst **B** (entry 4). Dichloro complexes **D** showed similar catalytic activity (entry 5). Altering the substituents of NHC ligands on its nitrogen atoms to ethyl (cat. **E**) or methyl (cat. **F**) groups significantly decreased the yield of **2a** (entries 6 and 7). Considering the availability of the iridium complexes, complex **D** was

determined to be the best catalyst. The loading amount of methylamine could be lowered to 5 mmol which resulted in a slight decrease in the product yield (entry 8).

Table 1. Optimization of reaction conditions on the synthesis of *N*-methylpiperidine

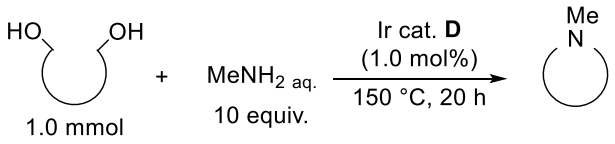


entry	cat.	x	y	conv. (%)[a]	yield (%)[a]
1	$[Cp^*IrCl_2]_2$	10	0.50	53	25
2	**A**	10	1.0	53	26
3	**B**	10	1.0	100	87
4	**C**	10	1.0	100	91
5	**D**	10	1.0	100	91
6	**E**	10	1.0	98	74
7	**F**	10	1.0	79	40
8	**D**	5.0	1.0	100	78

[a]Determined by GC.

Employing the optimized reaction conditions, the scope of the reactions of various aliphatic diols with aqueous methylamine was explored (Table 2). First, 1,4-butanediol (**1b**) was converted to *N*-methylpyrrolidine (**2b**) as a five-membered *N*-heterocycle in high yield (entry 1). Sterically hindered 1,2-dimethylpyrrolidine (**2c**) and 1,2-dimethylpiperidine (**2d**) were also formed in good yields (entries 2 and 3). 1,4-Dimethylpiperidine (**2e**) and *N*-methylmorpholine (**2f**) were synthesized from the corresponding diols in high yields (entries 4 and 5).

Table 2. Reactions of various aliphatic diols with aqueous methylamine catalyzed by cat. **D**

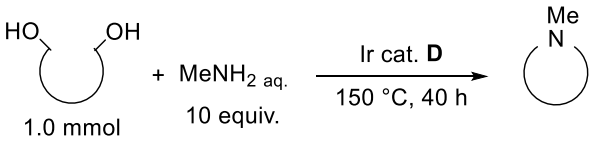


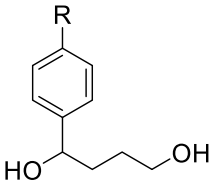
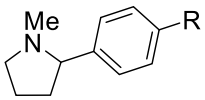
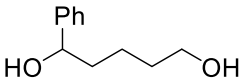
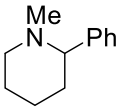
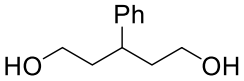
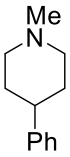
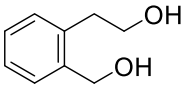
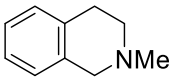
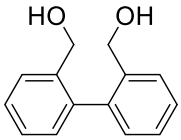
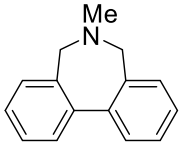
entry	diol	product	yield (%)[a]
1	1,4-butanediol (**1b**)	(**2b**)	87
2	1,4-pentanediol (**1c**)	(**2c**)	61[b]
3[c]	1,5-hexanediol (**1d**)	(**2d**)	61
4[c]	3-methyl-1,5-pentanediol (**1e**)	(**2e**)	75
5[c]	diethylene glycol (**1f**)	(**2f**)	89

[a]Determined by GC. [b]Determined by ^{1}H NMR. [c]Reaction time is 40 h.

Aliphatic diols and aromatic diols were applicable to this catalytic system, producing the corresponding *N*-methylated heterocycles (Table 3). Various 2-aryl-*N*-methylpyrrolidines (**2g-2j**) that had both electron-withdrawing and electron-donating groups were isolated in moderate to good yields (entries 1-4). The reactions of diols with an electron-withdrawing substituent required extended reaction times and higher catalyst loading (entries 2 and 3). The 2-phenyl-*N*-methylpiperidine (**2k**) was also obtained in 76% yield (entry 5). 4-Phenyl-*N*-methylpiperidine (**2l**) was produced in 61% yield (entry 6). The *ortho*-phenylene-bridged diol **2m** was converted to 1,2,3,4-tetrahydro-*N*-methylisoquinoline (**2m**) (entry 7). The reaction of 2,2'-biphenyldimethanol (**1n**) proceeded smoothly to produce a seven-membered *N*-heterocycle **2n** in 99% yield (entry 8).

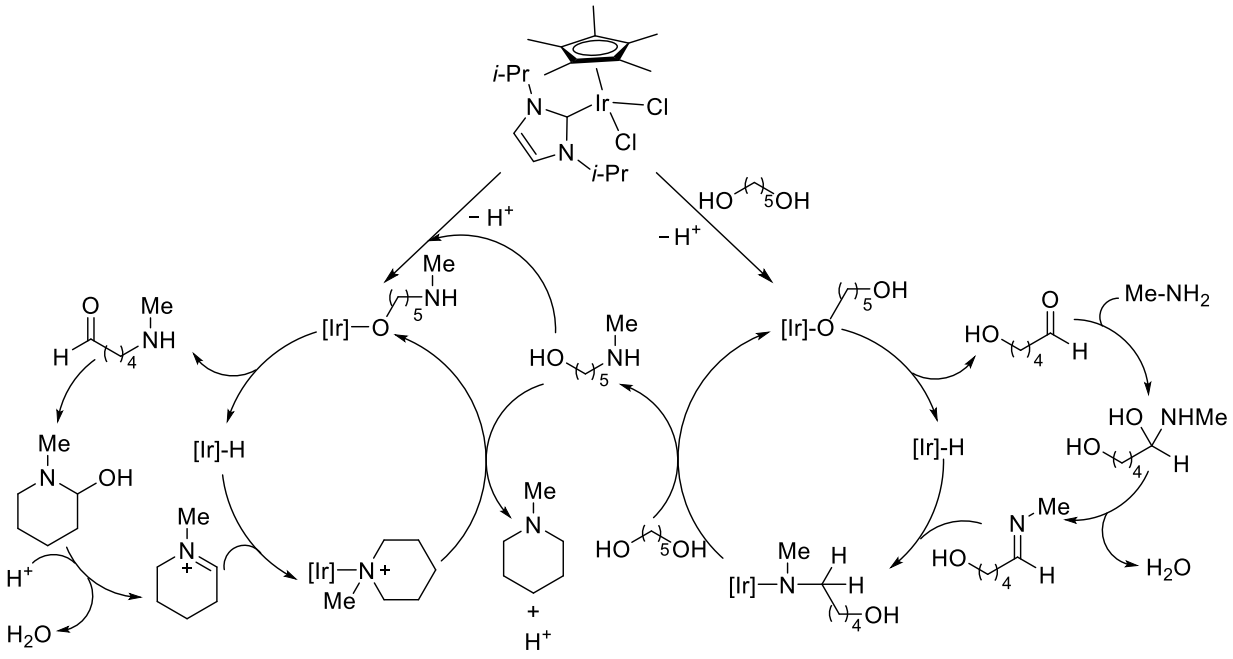
Table 3. Reactions of various aromatic diols with aqueous methylamine catalyzed by cat. **D**



entry	diol	catalyst (mol%)	product	yield (%)[a]
				
1	R = H (**1g**)	1.0	**2g**	72
2[b]	R = F (**1h**)	3.0	**2h**	69
3[b]	R = Cl (**1i**)	3.0	**2i**	67
4	R = OMe (**1j**)	1.0	**2j**	64
5	 (**1k**)	1.0	 (**2k**)	76
6[b]	 (**1l**)	5.0	 (**2l**)	60
7[b]	 (**1m**)	3.0	 (**2m**)	82
8	 (**1n**)	1.0	 (**2n**)	99

[a]Yield of isolated product. [b]Reaction time is 72 h.

The proposed mechanism is shown in Scheme 1. Similar to our previous reports on *N*-alkylation reactions,[8c] the diol and iridium complex first forms an iridium alkoxide intermediate in the presence of excess amount of methylamine as a base. The following *β*-H elimination produces an iridium-hydride and a carbonyl compound, which undergoes dehydrative condensation with methylamine to produce an imine intermediate. The resulting imine is hydrogenated by iridium hydride to afford an amino alcohol. The cascade of second dehydrogenation of the remaining alcohol moiety, intramolecular dehydrative condensation, and hydrogenation steps furnish the *N*-methylated heterocycle products to complete the catalytic cycle.



Scheme 1. Plausible reaction mechanism

In conclusion, we investigated the efficient synthesis of *N*-methylated nitrogen heterocycles in water using a readily available aqueous solution of methylamine and various diols catalyzed by NHC iridium complexes. Reactions of both aliphatic and aromatic diols with aqueous methylamine proceeded smoothly to afford the desired *N*-methylated heterocycles in moderate to excellent yields. These reactions are attractive because they have a high atom economy for exhausting water as the sole byproduct and no need of using any organic solvents or toxic reagents.

EXPERIMENTAL

All experiments and manipulations were performed under argon atmosphere using standard Schlenk techniques. The ^{1}H nuclear magnetic resonance (NMR) spectra were measured in $CDCl_3$ at 25 °C using tetramethylsilane (TMS) as an internal reference (0.0 ppm) with a JEOL ECX-500 spectrometer operating at 500 MHz and ECS-400 spectrometer operating at 400 MHz. The ^{13}C NMR spectra were measured in $CDCl_3$ (77.16 ppm) at 25 °C with a JEOL ECX-500 spectrometer operating at 125 MHz and ECS-400 spectrometer operating at 100 MHz. Gas chromatography analyses were performed on a GL-Sciences GC-4000 Plus gas chromatograph with a capillary column (InertCap for Amines). Gas chromatography-Mass spectrometry analysis was conducted on a Shimadzu GCMS-QP5050A. Column chromatography was carried out by using Wako-gel C-200. The complexes, $[Cp^*IrCl_2]_2$[9] (Cp*: pentamethylcyclopentadienyl), **A**,[8a] **B**,[8b] **C**,[8b] **D**,[8c] **E**,[10] and **F**[8b] were prepared according to the literature methods.

Starting Materials. 1-Phenyl-1,4-butanediol (**1g**) was prepared by the reduction of methyl 3-benzoylpropionate.[11] 1-(4-Fluorophenyl)-1,4-butanediol (**1h**) was prepared by the reduction of 3-(4-fluorobenzoyl)propionic acid.[12] 1-(4-Chlorophenyl)-1,4-butanediol (**1i**) was prepared by the reduction of 3-(4-chlorophenyl)propionic acid.[12] 1-(4-Methoxyphenyl)-1,4-butanediol (**1j**) was prepared by the reduction of 3-(4-methoxybenzoyl)propionic acid.[12] 1-Phenyl-1,5-pentanediol (**1k**) was prepared by the reduction of 4-benzoylbutyric acid.[13] 3-Phenyl-1,5-pentanediol (**1l**) was prepared by the reduction of 3-phenylglutaric acid.[14] 2-Hydroxymethylbenzeneethanol (**1m**) was prepared by the reduction of 3-isochromanone.[15] 2,2'-Biphenyldimethanol (**1n**) was prepared by the reduction of 2,2'-diphenic anhydride.[16]

1,2-Dimethylpyrrolidine,[17] 1,2-dimethylpiperidine,[18] and 1,4-dimethylpiperidine[18] for GC standard sample were prepared by the reaction of formaldehyde and formic acid with 2-methylpyrrolidine, 2-methylpiperidine, and 4-methylpiperidine, respectively.[19] All other reagents were commercially available and were used as received.

General Procedure for the Reaction of 1,5-Pentanediol with Aqueous Methylamine Giving *N*-Methylpiperidine in Aqueous Media under Various Conditions Shown in Table 1. In a stainless reactor bomb, catalyst (1.0 mol%), 1,5-pentanediol (1.0 mmol), and 40% aqueous methylamine (5 or 10 mmol) were placed. Then, the reactor was sealed with a stainless stopper, and the mixture was stirred at 150 °C for 20 h. The mixture was diluted with dry THF (30 mL). The conversion of 1,5-pentanediol and the yield of *N*-methylpiperidine were determined by GC analysis using biphenyl as an internal standard.

General Procedure for the Reactions of Various Aliphatic Diols with Aqueous Methylamine Catalyzed by D Giving *N*-Methylated Nitrogen Heterocycles Shown in Table 2 (entries 1 and 3-5). In a stainless reactor bomb, catalyst (1.0 mol%), diol (1.0 mmol), and 40% aqueous methylamine (10 mmol) were placed. Then, the reactor was sealed with a stainless stopper, and the mixture was stirred at 150 °C for 20 or 40 h. The mixture was diluted with dry THF (30 mL). For entries 1 and 3-5, the conversion of diols and the yield of *N*-methylated nitrogen heterocycles were determined by GC analysis using biphenyl as an internal standard.

Procedure for the Reaction of 1,4-Pentanediol with Aqueous Methylamine Catalyzed by D Giving 1,2-Dimethylpyrrolidine Shown in Table 2 (entry 2). In a stainless reactor bomb, catalyst (1.0 mol%), 1,4-pentanediol (1.0 mmol), and 40% aqueous methylamine (10 mmol) were placed. Then, the reactor was sealed with a stainless stopper, and the mixture was stirred at 150 °C for 20 h. The mixture was diluted with dry THF (30 mL). The conversion of diol was determined by GC analysis using biphenyl as an internal standard. The yield of 1,2-dimethylpyrrolidine was determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard.

General Procedure for the Reactions of Various Aromatic Diols with Aqueous Methylamine Catalyzed by D Giving *N*-Methylated Nitrogen Heterocycles Shown in Table 3 (entries 1-7). In a stainless reactor bomb, catalyst (1.0 or 3.0 or 5.0 mol%), diol (1.0 mmol), and 40% aqueous methylamine (10 mmol) were placed. Then, the reactor was sealed with a stainless stopper, and the mixture was stirred at 150 °C for 40 or 72 h. The mixture was diluted with dry THF (30 mL). After evaporation of the solvent, the products were isolated by silica gel column chromatography.

Procedure for the Reactions of 2,2'-Biphenyldimethanol with Aqueous Methylamine Catalyzed by D Giving *N*-Methyl-6,7-dihydro-5*H*-dibenzo[*c*,*e*]azepine Shown in Table 3 (entry 8). In a stainless reactor bomb, catalyst (1.0 mol%), diol (1.0 mmol), and 40% aqueous methylamine (10 mmol) were placed. Then, the reactor was sealed with a stainless stopper, and the mixture was stirred at 150 °C for 40 h. The mixture was diluted with dry THF (30 mL). After evaporation of the solvent, hexane was poured into the CH_2Cl_2 solution of the product, followed by removal of the solid by filtration. The pure product was obtained by evaporation of the filtrate.

***N*-Methyl-2-phenylpyrrolidine (2g):**[20,21] yellow oil; eluent: $CHCl_3$/MeOH (70:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ; 7.36-7.30 (m, 4H), 7.27-7.22 (m, 1H), 3.28-3.23 (m, 1H), 3.04 (t, *J* = 8.7 Hz, 1H), 2.34-2.25 (m, 1H), 2.23-2.14 (m, 1H), 2.18 (s, 3H), 2.03-1.90 (m, 1H), 1.85-1.73 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ; 143.0, 128.5, 127.7, 127.2, 71.8, 57.2, 40.6, 35.1, 22.5.

2-(4-Fluorophenyl)-*N*-methylpyrrolidine (2h):[20] yellow oil; eluent: $CHCl_3$/MeOH (50:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ; 7.31-7.29 (m, 2H), 7.03-6.99 (m, 2H), 3.25-3.21 (m, 1H), 3.01 (t, *J* = 8.3 Hz, 1H), 2.30-2.25 (m, 1H), 2.19-2.13 (m, 1H), 2.15 (s, 3H), 2.01-1.91 (m, 1H), 1.84-1.68 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ; 162.1 (d, *J* = 245 Hz), 139.0, 129.0 (d, *J* = 8.4 Hz), 115.3 (d, *J* = 21.6 Hz), 71.1, 57.1, 40.6, 35.3, 22.5.

2-(4-Chlorophenyl)-*N*-methylpyrrolidine (2i):[21] yellow oil; eluent: $CHCl_3$/MeOH (60:1, 50:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ; 7.30-7.27 (m, 4H), 3.25-3.21 (m, 1H), 3.01 (t, *J* = 8.6 Hz, 1H), 2.31-2.25 (m, 1H), 2.20-2.12 (m, 1H), 2.15 (s, 3H), 2.02-1.90 (m, 1H), 1.83-1.66 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ; 142.0, 132.7, 129.0, 128.6, 71.1, 57.1, 40.6, 35.4, 22.6.

2-(4-Methoxyphenyl)-*N*-methylpyrrolidine (2j):[21] orange oil; eluent: $CHCl_3$/MeOH (50:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ; 7.27-7.25 (m, 2H), 6.88-6.86 (m, 2H), 3.81 (s, 3H), 3.25-3.21 (m, 1H), 2.96 (t, *J* = 8.6 Hz, 1H), 2.28-2.23 (m, 1H), 2.18-2.11 (m, 1H), 2.15 (s, 3H), 2.01-1.90 (m, 1H), 1.83-1.71 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ; 158.8, 135.1, 128.7, 113.9, 71.3, 57.1, 55.4, 40.5, 35.1, 22.4.

***N*-Methyl-2-phenylpiperidine (2k):**[22] yellow oil; eluent: CH_2Cl_2/MeOH (50:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ; 7.31-7.28 (m, 4H), 7.25-7.21 (m, 1H), 3.04-3.02 (m, 1H), 2.74 (dd, *J* = 11.2 Hz, 2.6 Hz, 1H),

2.13-2.05 (m, 1H), 1.99 (s, 3H), 1.82-1.80 (m, 1H), 1.74-1.69 (m, 3H), 1.63-1.55 (m, 1H), 1.42-1.31 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ; 145.1, 128.5, 127.6, 127.1, 71.3, 57.7, 44.7, 36.1, 26.3, 25.1.

***N*-Methyl-4-phenylpiperidine (2l):**[23] yellow oil; eluent: $CHCl_3$/MeOH (15:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ; 7.32-7.29 (m, 2H), 7.24-7.18 (m, 3H), 2.98 (d, *J* = 11.7 Hz, 2H), 2.52-2.44 (m, 1H), 2.32 (s, 3H), 2.08-2.02 (m, 2H), 1.84-1.77 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ; 146.5, 128.6, 127.0, 126.3, 56.5, 46.7, 42.2, 33.7.

1,2,3,4-Tetrahydro-*N*-methylisoquinoline (2m):[20] yellow oil; eluent: $CHCl_3$/MeOH (50:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ; 7.14-7.09 (m, 3H), 7.02-7.01 (m, 1H), 3.58 (s, 2H), 2.92 (t, *J* = 6.0 Hz, 2H), 2.68 (t, *J* = 6.0 Hz, 2H), 2.46 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ; 134.9, 134.0, 128.8, 126.5, 126.2, 125.7, 58.2, 53.1, 46.3, 29.4.

***N*-Methyl-6,7-dihydro-5*H*-dibenzo[*c*,*e*]azepine (2n):**[24] yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ; 7.52-7.50 (m, 2H), 7.48-7.42 (m, 2H), 7.39-7.35 (m, 4H), 3.37 (s, 4H), 2.46 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ; 141.2, 134.6, 129.9, 128.2, 127.80, 127.79, 57.4, 43.2.

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