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碘介导下通过氧化性 C—C 键形成合成 β-硝基胺与 α-胺基腈类化合物

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摘要 以分子碘为单一氧化剂, 开发了一种无过渡金属催化的 C—C 键形成反应. 该反应可通过易得的叔胺分别与硝基烷、三甲基氰硅烷和亚磷酸酯合成 β-硝基胺、α-胺基腈和 α-胺基膦酸酯类化合物. 该合成方法具有操作简单, 底物适用范围广, 而且可以成功实现克级规模的合成.

关键词 碘; C—C 键形成; 叔胺; β-硝基胺; α-胺基腈

Synthesis of β-Nitroamines and α-Aminonitriles by I_2-Mediated Oxidative C—C Bond Formation

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Abstract A transition-metal-free C—C bond formation reaction is developed employing molecular iodine as the sole oxidant to access β-nitroamines, α-aminonitriles and α-aminophosphonates from readily accessible tertiary amines with nitroalkanes, trimethylsilyl cyanide and phosphite, respectively. The present synthetic approach is operationally simple, has a broad substrate scope, and can be successfully conducted on a gram scale.

Keywords iodine; C—C bond formation; tertiary amine; β-nitroamine; α-aminonitrile

1 Introduction

β-Nitroamine[1] and α-aminonitrile[2] are privileged structural motifs widely distributed in natural products and biologically active molecules. For example, nitrotyrasanguinarine is a nitrated benzophenanthridine alkaloid isolated from *Hypecoum* species.[3] Dihydrosanguinarine bearing a nitromethane moiety (**I**) exhibited potent anticancer activity against PC-3, HCT-15, and MCF-7 cell lines.[4] 8-Cyano berberine derivative **II** possesses anti-human cytomegalovirus (HCMV) activity.[5] 1-Cyano-2-aryl-1,2,3,4-tetrahydroisoquinoline (CATHIQ, **III**) was demonstrated to have significant cytotoxicity on NB4 and MKN-45 cells and apoptosis induction.[6] Moreover, β-nitroamine and α-aminonitrile derivatives are also valuable synthetic intermediates in organic chemistry.[7]

Consequently, the preparation of β-nitroamines and α-aminonitriles has received considerable attention from synthetic chemists. The most straightforward synthetic

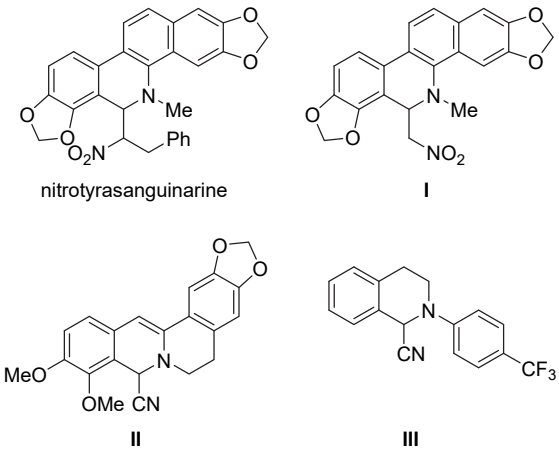

Figure 1 Representative natural products and bioactive molecules containing a β-nitroamine or α-aminonitrile motif.

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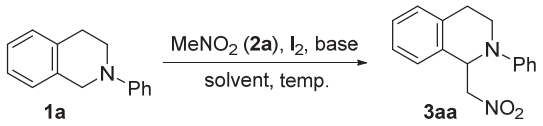
strategy is oxidative C—C bond formation reaction of corresponding amines with nitroalkanes or cyanides,[8] which have been previously realized using peroxides[9] or under photoredox conditions.[10] In addition, such transformations were also achieved via aerobic oxidation in the presence of transition metals,[11] SO_2Cl_2[12] or iodine[13] as the catalyst. In spite of these elegant achievements, facile and practical protocols to synthesize *β*-nitroamines and *α*-aminonitriles are still highly desirable and may benefit the drug discovery field. To the best of our knowledge, the synthesis of these compounds employing molecular iodine as the sole oxidant have not been investigated to date. With our interest in iodine-promoted C—C bond construction,[14] we herein describe an I_2-mediated oxidative C—C bond formation reaction of tertiary amines with nitroalkanes and trimethylsilyl cyanide to access *β*-nitroamines and *α*-aminonitriles, respectively, under transition-metal-free conditions.

2 Results and discussion

Initially, *N*-phenyl tetrahydroisoquinoline (**1a**) and nitromethane (**2a**) were selected as the model substrates for the investigation of the I_2-mediated C—C bond formation reaction (Table 1). Solvent screening (Entries 1～7) demonstrated that 1,4-dioxane is the optimum medium (Entry 7) for the present transformation. In the presence of sodium acetate (NaOAc) as a base, the reaction was complete within 1 h at the reflux temperature, affording the expected *β*-nitroamine product (**3aa**) in 84% yield (Entry 7). Lowering the reaction temperature significantly affects the formation of **3aa** (Entry 8). Further optimization suggested that 2.5 equiv. of nitromethane is the optimal for this synthetic protocol (Entry 10 *vs* Entries 7, 9 and 11). Screening of inorganic and organic bases indicated that NaOAc is the most effective one (Entry 10 *vs* Entries 12～19). The reaction was only slightly affected when it was performed in the absence of light (Entry 20). The yields of the product were decreased upon the inclusion of a free radical scavenger, 2,2,6,6-tetramethylpiperidinooxy (TEMPO) (Entry 21) or 2,6-di-*t*-butyl-*p*-cresol (BHT) (Entry 22), in the reaction system. These results revealed that the I_2-mediated C—C bond formation reaction may undergo both radical and non-radical mechanism pathways.

Having established the optimized reaction conditions, the scope and generality of this synthetic method were then investigated. As shown in Table 2, all the *N*-aryl tetrahydroisoquinolines (**1a**～**1l**, **1o**～**1p**) were smoothly converted to the corresponding *β*-nitroamine products (**3aa**～**3la**, **3oa**～**3pa**) by the reaction with nitromethane (**2a**). Using the synthesis of **3ja** as an example, the reaction was conveniently conducted on a gram scale. The structure of product **3ka** was further confirmed by X-ray crystallography (CCDC: 2259823). This synthetic process is compatible with both electron-donating groups (EDGs) (**3ba**～**3da**, **3oa**) and electron-withdrawing groups (EWGs) (**3ea**～**3ka**, **3pa**) on the *N*-aryl and tetrahydroisoquinoline moieties of the substrate. The presence of EWGs favored the formation of the products (**3fa**～**3ga**, **3ia**～**3ka**, **3pa**), which could be attributed to increased electrophilicity of the corresponding iminium intermediates (cf. compound **B** in Scheme 1). The relatively lower yield of product **3ha** could be due to the steric hindrance of the *ortho*-chlorine group. Replacement of the *N*-aryl group in the substrate

Table 1 Optimization of the reaction conditions for the synthesis of **3aa**[a]



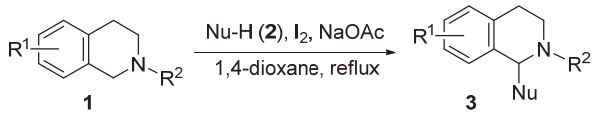
Entry	**2a**/equiv.	Base	Solvent	Temp.	*t*/h	Yield[b]/%
1	2	NaOAc	DCE	Reflux	1	Trace
2	2	NaOAc	Toluene	Reflux	1	Trace
3	2	NaOAc	DMSO	100 °C	1	34
4	2	NaOAc	^{i}PrOH	Reflux	2	59
5	2	NaOAc	MeCN	Reflux	5.5	61
6	2	NaOAc	THF	Reflux	11	58
7	2	NaOAc	1,4-Dioxane	Reflux	1	84
8	2	NaOAc	1,4-Dioxane	80 °C	1.5	32
9	1.5	NaOAc	1,4-Dioxane	Reflux	1	72
10	**2.5**	**NaOAc**	**1,4-Dioxane**	**Reflux**	**1**	**92**
11	3	NaOAc	1,4-Dioxane	Reflux	1	87
12	2.5	$NaHCO_3$	1,4-Dioxane	Reflux	4	19
13	2.5	Na_2CO_3	1,4-Dioxane	Reflux	4.5	74
14	2.5	K_2CO_3	1,4-Dioxane	Reflux	1	32
15	2.5	K_3PO_4	1,4-Dioxane	Reflux	0.5	49
16	2.5	NaOH	1,4-Dioxane	Reflux	1.5	77
17	2.5	KO^{t}Bu	1,4-Dioxane	Reflux	0.5	59
18	2.5	DBU	1,4-Dioxane	Reflux	5	Trace
19	2.5	NEt_3	1,4-Dioxane	Reflux	5	Trace
20[c]	2.5	NaOAc	1,4-Dioxane	Reflux	1.5	89
21[d]	2.5	NaOAc	1,4-Dioxane	Reflux	0.5	49
22[e]	2.5	NaOAc	1,4-Dioxane	Reflux	0.5	74

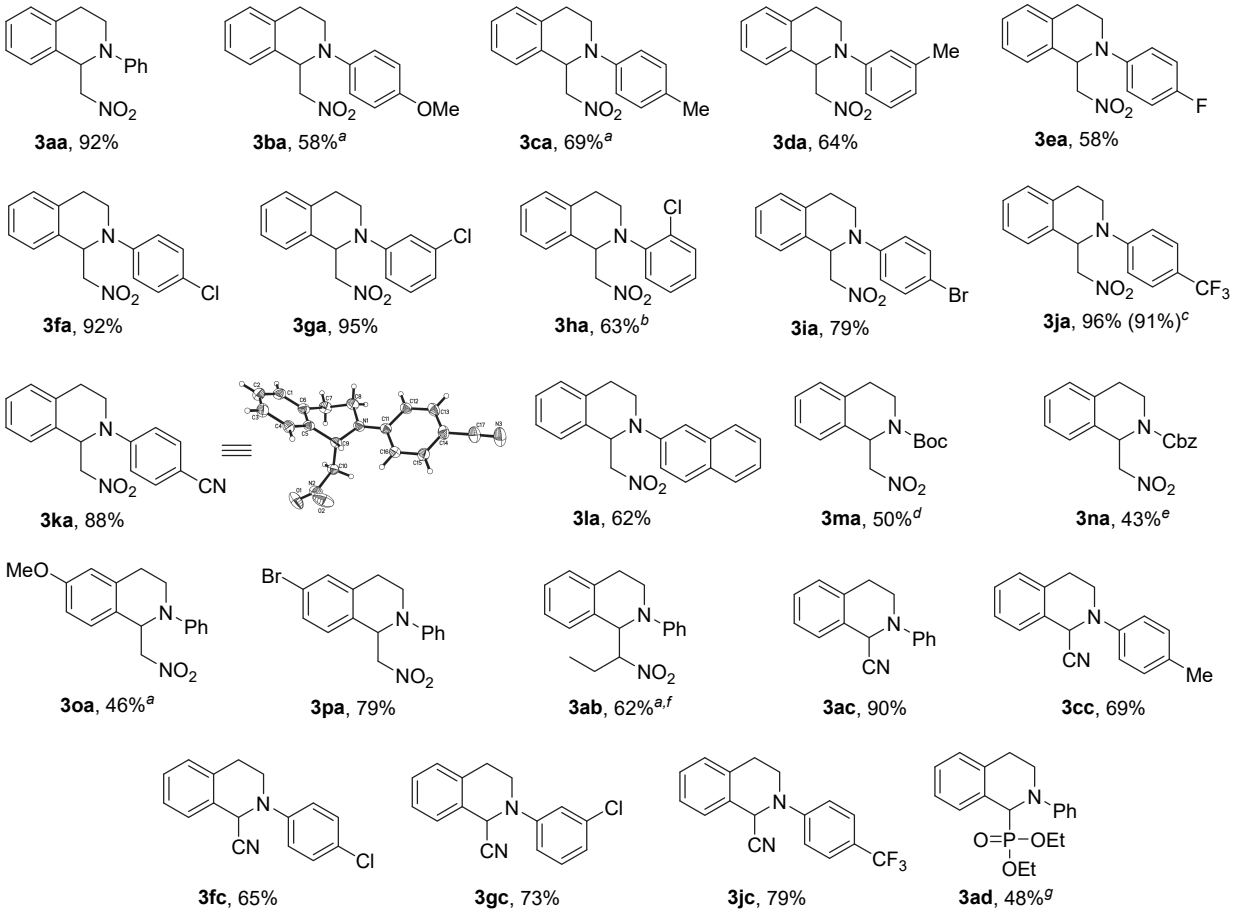
[a] Optimal reaction conditions (Entry 10): **1a** (0.5 mmol), **2a** (1.25 mmol), I_2 (1 mmol), NaOAc (2 mmol), 1,4-dioxane, reflux; DCE: 1,2-dichloroethane, DMSO: dimethyl sulfoxide, THF: tetrahydrofuran. [b] Isolated yields. [c] No light (dark). [d] With TEMPO (2.1 equiv). [e] With BHT (2.1 equiv).

Boc or Cbz also led to the formation the expected product (**3ma**～**3na**) in a moderate yield. The reaction also works with other nucleophiles such as 1-nitropropane (**3ab**), trimethylsilyl cyanide (**3ac**, **3cc**, **3fc**, **3gc**, **3jc**) and diethyl phosphite (**3ad**) instead of nitromethane, affording the corresponding *β*-nitroamine, *α*-aminonitrile and *α*-aminophosphonate products. Among them, compound **3jc** (cf. **III** in Figure 1) was identified as an anticancer lead compound.[6]

In light of the encouraging results with tetrahydroisoquinoline substrates, the scope of the I_2-mediated C—C bond formation reaction with other tertiary amines was further explored. However, the reaction of *N*,*N*,4-trimethylaniline (**1q**) with trimethylsilyl cyanide (**2c**) under the above conditions resulted in only a moderate yield of the

Table 2 Substrate scope of tetrahydroisoquinoline derivatives





[a] Reaction conditions: **1** (0.5 mmol), **2** (1.25 mmol), I_2 (1 mmol), NaOAc (2 mmol), 1,4-dioxane (6 mL), reflux. [a] At 80 °C. [b] 6% of **1h** was recovered. [c] Yield of a gram-scale reaction (5 mmol). [d] 35% of **1m** was recovered. [e] 31% of **1n** was recovered. [f] *dr* 1:1.4. [g] 21% of **1a** was recovered, with 1.5 mmol of I_2.

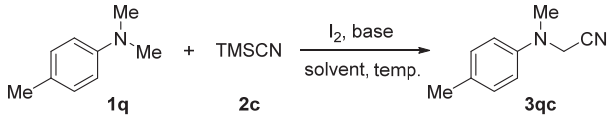
desired product (**3qc**) (Table 3, Entry 1). Further investigation (Table 3) suggested that a mixture of DCE and MeCN (V∶V=2∶1) as the solvent and 4 equiv. of iodine are the optimum reaction conditions for the formation of **3qc** (Entry 13). Then, a series of acyclic or cyclic tertiary amines were subjected to these conditions (Table 4). Both EDG- and EWG-substituted *N*,*N*-dimethylanilines were transformed into the *α*-aminonitrile products (**3qc**～**3vc**) by reacting with trimethylsilyl cyanide. An *N*-naphthyl *α*-aminonitrile (**3wc**) was also produced in a high yield by the present synthetic process. Replacing the *N*,*N*-dimethylamino group in the substrate with an *N*,*N*-diethylamino or pyrrolidine one also led to the formation of the corresponding product (**3xc**～**3yc**), but in a decreased yield. These could be due to the steric hindrance caused by such amino moieties.

On the basis of these experimental results and our previous work on I_2-promoted C—H functionalization,[15] tentative mechanisms are proposed for this C—C bond formation reaction (Scheme 1). Taking the reaction of *N*-phenyl tetrahydroisoquinoline (**1a**) as an example, iodination of **1a** by molecular iodine under basic conditions give an *N*-iodo intermediate (**A**) (*path a*). Subsequently, the cleavage of the N—I bond in the intermediate **A** and followed by deprotonation under the presence of base results in an iminium intermediate (**B**). Then, nucleophiles are added to the iminium double form products (**3**). Meanwhile, a radical pathway might also be involved in this transformation (*path b*). Iodine radical generated from homolytic cleavage of molecular iodine[16] reacts with the *α*-C—H group in the substrate (**1a**) to generate a radical intermediate (**C**). The radical recombination of **C** with an iodine radical obtains an iodide (**D**), which results in the iminium intermediate **B** after elimination. Addition of the nucleophiles to intermediate **B** subsequently produces the product (**3**).

3 Conclusions

In summary, an iodine-mediated oxidative C—C bond formation reaction of tertiary amines with nucleophiles was developed, such as nitroalkanes, trimethylsilyl cyanide

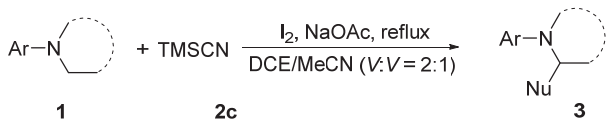
Table 3 Optimization of the reaction conditions for the synthesis of **3qc**[a]

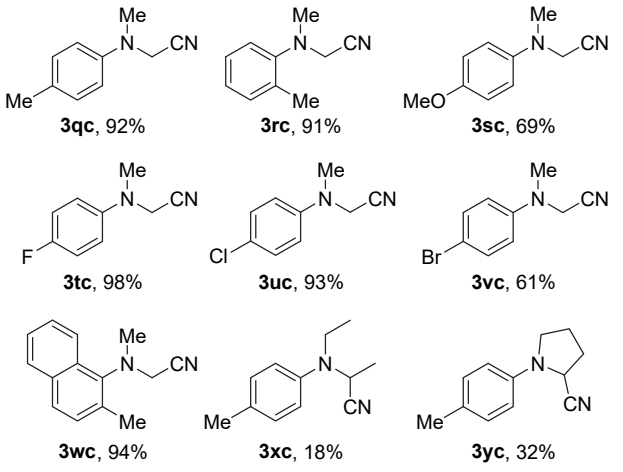


Entry	I_2/equiv.	Base	Solvent	Temp.	*t*/h	Yield[b]/%
1	2	NaOAc	1,4-Dioxane	Reflux	2.5	44
2	2	NaOAc	DMSO	100 °C	4	41
3	2	NaOAc	MeCN	Reflux	4	58
4	2	NaOAc	Toluene	Reflux	0.5	68
5	2	NaOAc	DCE	Reflux	1	72
6	3	NaOAc	DCE/MeCN (V∶V=1∶1)	Reflux	4	88
7	3	NaOAc	DCE/MeCN (V∶V=2∶1)	Reflux	2	90
8	3	NaOAc	DCE/MeCN (V∶V=3∶1)	Reflux	1.5	77
9	3	$NaHCO_3$	DCE/MeCN (V∶V=2∶1)	Reflux	2.5	82
10	3	Na_2CO_3	DCE/MeCN (V∶V=2∶1)	Reflux	3.5	46
11	3	NaOH	DCE/MeCN (V∶V=2∶1)	Reflux	4	65
12	3	NaOAc	DCE/MeCN (V∶V=2∶1)	60 °C	14	78
13	**4**	**NaOAc**	**DCE/MeCN (V∶V=2∶1)**	**Reflux**	**0.5**	**92**

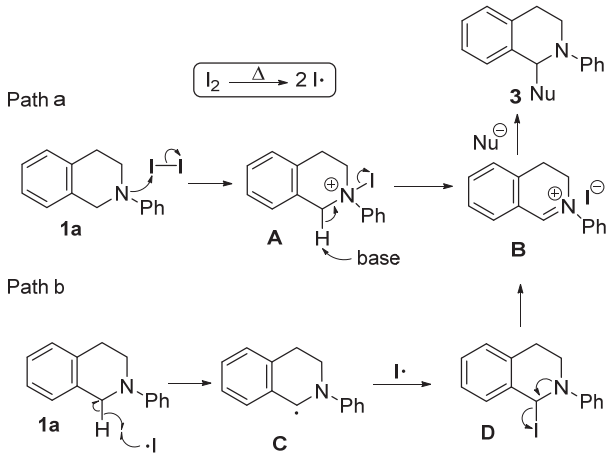
[a] Optimal reaction conditions (Entry 13): **1q** (0.5 mmol), **2c** (1.25 mmol), I_2 (2 mmol), NaOAc (4 mmol), DCE/MeCN (V∶V=2∶1), reflux; [b] Isolated yields.

Table 4 Scope of substrates[a]





[a] Reaction conditions: **1** (0.5 mmol), **2c** (1.25 mmol), I_2 (2 mmol), NaOAc (4 mmol), DCE/MeCN (V∶V=2∶1), reflux.



Scheme 1 Proposed mechanism

and phosphite, providing a facile access to various *β*-nitroamine, *α*-aminonitrile and *α*-aminophosphonate derivatives. The present synthetic process features no use of transition metals, simple operation, gram-scale synthesis, and broad substrate scope.

4 Experimental section

4.1 General information

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AV 400 MHz (100 MHz for ^{13}C NMR) spectrometer. Chemical shift values are reported with tetramethylsilane (TMS) as an internal standard. Melting points were determined on an XT4A micromelting point apparatus and were uncorrected. High-resolution mass spectra (HRMS) were obtained on a Q-TOF Mass Spectrometer equipped with an electrospray ion source (ESI), and operated in the positive mode. Flash column chromatography was performed over silica gel 200～300 mesh. 1,4-Dioxane, 1,2-dichloroethane (DCE) and MeCN used in the synthesis of products **3** were analytical reagent grade and without pretreatment.

4.2 Preparation of substrates **1**

4.2.1 Preparation of substrates **1a**～**1b**, **1i**～**1j** and **1p**

To a mixture of CuI (95 mg, 0.5 mmol) and K_3PO_4 (2.12 g, 10 mmol) in 2-propanol (5 mL) were added ethylene glycol (0.56 mL, 10 mmol), substituted 1,2,3,4-tetrahydroisoquinoline (7.5 mmol) and the corresponding iodobenzene (5 mmol) in sequence. Then, the reaction mixture was stirred at 90 °C under an atmosphere of nitrogen for 48 h. After cooling to room temperature, it was quenched with H_2O (20 mL) and extracted with EtOAc (20 mL×3). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated, and purified through silica gel column chromatography to afford the substrates **1a**～**1b**, **1i**～**1j** and **1p**.[10i]

2-Phenyl-1,2,3,4-tetrahydroisoquinoline (**1a**):[11h] Eluent: EtOAc/petroleum ether (PE), V∶V=5∶95; 848 mg, 81% yield. Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ:

7.29～7.23 (m, 2H, overlapped with the peak of chloroform), 7.16～7.09 (m, 4H), 6.97～6.93 (m, 2H), 6.83～6.77 (m, 1H), 4.37 (s, 2H), 3.53～3.49 (m, 2H), 2.96～2.92 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 150.6, 135.0, 134.6, 129.3, 128.6, 126.7, 126.4, 126.1, 118.8, 115.3, 50.8, 46.6, 29.2; HRMS (ESI-TOF) calcd for $C_{15}H_{16}N$ $[M+H]^+$ 210.1277, found 210.1276.

2-(4-Methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (**1b**):[11h] Eluent: EtOAc/PE, V∶V=5∶95; 780 mg, 65% yield. Yellow solid, m.p. 82～84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.18～7.10 (m, 4H), 6.97 (d, J=9.2 Hz, 2H), 6.86 (d, J=8.4 Hz, 2H), 4.29 (s, 2H), 3.76 (s, 3H), 3.43 (t, J=6.4 Hz, 2H), 2.97 (t, J=6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.5, 145.4, 134.65, 134.58, 128.7, 126.6, 126.3, 126.0, 118.1, 114.6, 55.7, 52.7, 48.5, 29.2; HRMS (ESI-TOF) calcd for $C_{16}H_{18}NO$ $[M+H]^+$ 240.1383, found 240.1383.

2-(4-Bromophenyl)-1,2,3,4-tetrahydroisoquinoline (**1i**): Eluent: Eluent: EtOAc/PE, V∶V=2∶98; 1.1 g, 76% yield. White solid, m.p. 64～66 °C (lit.[24] 65～67 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35～7.31 (m, 2H), 7.21～7.12 (m, 4H), 6.82～6.78 (m, 2H), 4.35 (s, 2H), 3.50 (t, J=6.0 Hz, 2H), 2.95 (t, J=6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.4, 134.7, 134.1, 131.9, 128.6, 126.58, 126.56, 126.2, 116.5, 110.5, 50.5, 46.3, 29.0; HRMS (ESI-TOF) calcd for $C_{15}H_{15}BrN$ $[M+H]^+$ 288.0383, found 288.0384.

2-(4-(Trifluoromethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline (**1j**):[11h] Eluent: EtOAc/PE, V∶V=1∶99; 1.11 g, 80% yield. White solid, m.p. 75～76 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.49 (d, J=8.4 Hz, 2H), 7.23～7.16 (m, 4H, overlapped with the peak of chloroform), 6.92 (d, J=8.4 Hz, 2H), 4.47 (s, 2H), 3.61 (t, J=6.0 Hz, 2H), 2.98 (t, J=6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.2, 134.9, 133.8, 128.4, 126.7, 126.5 (q, $J_{C\text{-}F}$=3.7 Hz), 126.4, 125.0 (q, $J_{C\text{-}F}$=268.5 Hz), 119.0 (q, $J_{C\text{-}F}$=32.4 Hz), 112.9, 49.4, 45.2, 29.0; HRMS (ESI-TOF) calcd for $C_{16}H_{15}F_3N$ $[M+H]^+$ 278.1151, found 278.1155.

6-Bromo-2-phenyl-1,2,3,4-tetrahydroisoquinoline (**1p**):[10i] Eluent: EtOAc/PE, V∶V=2∶98; 605 mg, 42% yield. White solid, m.p. 67～68 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.30～7.25 (m, 4H, overlapped with the peak of chloroform), 7.01～6.94 (m, 3H), 6.83 (t, J=7.2 Hz, 1H), 4.31 (s, 2H), 3.51 (t, J=6.0 Hz, 2H), 2.92 (t, J=6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 150.3, 137.2, 133.5, 131.4, 129.3, 129.2, 128.3, 119.9, 119.1, 115.4, 50.5, 46.4, 28.9; HRMS (ESI-TOF) calcd for $C_{15}H_{15}BrN$ $[M+H]^+$ 288.0383, found 288.0382.

4.2.2 Preparation of substrates **1c**～**1h** and **1y**

A mixture of the corresponding aniline (5 mmol) and DBU (1.14 g, 7.5 mmol) was treated dropwise with $POCl_3$ (997 mg, 6.5 mmol) at room temperature. The resulting mixture was stirred at 90 °C for 15 min, and then treated with isochromane (1.68 g, 12.5 mmol) (for the preparation of **1y**, 12.5 mmol of tetrahydrofuran was used). After stirred at 110 °C for another 10 h, the reaction was allowed to cool to the room temperature, quenched with sat. $NaHCO_3$ (15 mL) and brine (15 mL), and extracted with EtOAc (30 mL×3). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated, and purified through silica gel column chromatography to afford the substrates **1c**～**1h** and **1y**.[17]

2-(*p*-Tolyl)-1,2,3,4-tetrahydroisoquinoline (**1c**):[11h] Eluent: EtOAc/PE, V∶V=1∶99; 849 mg, 76% yield. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.19～7.08 (m, 6H), 6.91 (d, J=8.4 Hz, 2H), 4.34 (s, 2H), 3.49 (t, J=5.6 Hz, 2H), 2.96 (t, J=5.6 Hz, 2H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.7, 134.8, 134.6, 129.8, 128.7, 128.5, 126.6, 126.3, 126.0, 115.9, 51.5, 47.4, 29.2, 20.5; HRMS (ESI-TOF) calcd for $C_{16}H_{18}N$ $[M+H]^+$ 224.1434, found 224.1433.

2-(*m*-Tolyl)-1,2,3,4-tetrahydroisoquinoline (**1d**):[11h] Eluent: EtOAc/PE, V∶V=1∶99; 897 mg, 80% yield. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.19～7.12 (m, 5H, overlapped with the peak of chloroform), 6.80～6.77 (m, 2H), 6.65 (d, J=7.2 Hz, 1H), 4.38 (s, 2H), 3.53 (t, J=6.0 Hz, 2H), 2.96 (t, J=5.6 Hz, 2H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 150.7, 138.9, 135.0, 134.6, 129.1, 128.6, 126.6, 126.4, 126.1, 119.7, 116.0, 112.4, 50.9, 46.6, 29.3, 22.0; HRMS (ESI-TOF) calcd for $C_{16}H_{18}N$ $[M+H]^+$ 224.1434, found 224.1434.

2-(4-Fluorophenyl)-1,2,3,4-tetrahydroisoquinoline (**1e**):[17] Eluent: EtOAc/PE, V∶V=1∶99; 969 mg, 85% yield. Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.19～7.12 (m, 4H), 7.00～6.91 (m, 4H), 4.32 (s, 2H), 3.48 (t, J=6.0 Hz, 2H), 2.98 (t, J=6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.7 (d, $J_{C\text{-}F}$=236.5 Hz), 147.4 (d, $J_{C\text{-}F}$=2.2 Hz), 134.5, 134.3, 128.6, 126.5, 126.4, 126.0, 117.2 (d, $J_{C\text{-}F}$=7.5 Hz), 115.6 (d, $J_{C\text{-}F}$=21.8 Hz), 51.9, 47.8, 29.0; HRMS (ESI-TOF) calcd for $C_{15}H_{15}FN$ $[M+H]^+$ 228.1183, found 228.1184.

2-(4-Chlorophenyl)-1,2,3,4-tetrahydroisoquinoline (**1f**): Eluent: EtOAc/PE, V∶V=5∶99; 1.09 g, 89% yield. Yellow solid, m.p. 59～61 °C (lit.[23] 60～62 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.23～7.13 (m, 6H, overlapped with the peak of chloroform), 6.87 (d, J=8.8 Hz, 2H), 4.36 (s, 2H), 3.51 (t, J=5.6 Hz, 2H), 2.96 (t, J=5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.1, 134.7, 134.1, 129.0, 128.5, 126.55, 126.52, 126.2, 123.3, 116.2, 50.6, 46.5, 29.0; HRMS (ESI-TOF) calcd for $C_{15}H_{15}ClN$ $[M+H]^+$ 244.0888, found 244.0890.

2-(3-Chlorophenyl)-1,2,3,4-tetrahydroisoquinoline (**1g**):[10i] Eluent: EtOAc/PE, V∶V=5∶99; 968 mg, 79% yield. Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.20～7.12 (m, 5H, overlapped with the peak of chloroform), 6.89 (t, J=2.4 Hz, 1H), 6.80～6.74 (m, 2H), 4.37 (s, 2H), 3.51 (t, J=6.0 Hz, 2H), 2.95 (t, J=5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.4, 135.1, 134.9, 134.0, 130.2, 128.5, 126.6, 126.3, 118.0, 114.4, 112.6, 50.1, 45.9, 29.1; HRMS (ESI-TOF) calcd for $C_{15}H_{15}ClN$ $[M+H]^+$ 244.0888, found 244.0706.

2-(2-Chlorophenyl)-1,2,3,4-tetrahydroisoquinoline (**1h**):[10i] Eluent: EtOAc/PE, V∶V=5∶99; 1.02 g, 84%

yield. Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.39 (dd, J=7.6, 1.2 Hz, 1H), 7.24～7.08 (m, 6H, overlapped with the peak of chloroform), 6.97 (td, J=7.6, 2.0 Hz, 1H), 4.26 (s, 2H), 3.39 (t, J=5.6 Hz, 2H), 3.02 (t, J=6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.2, 134.7, 134.6, 130.8, 129.1, 128.9, 127.6, 126.5, 126.4, 125.9, 123.7, 120.7, 53.3, 50.0, 29.1; HRMS (ESI-TOF) calcd for $C_{15}H_{15}ClN$ $[M+H]^+$ 244.0888, found 244.0888.

1-(*p*-Tolyl)pyrrolidine (**1y**):[23] Eluent: EtOAc/PE, V∶V=2∶98; 508 mg, 63% yield. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.03 (d, J=8.0 Hz, 2H), 6.48 (d, J=8.4 Hz, 2H), 3.25～3.22 (m, 4H), 2.24 (s, 3H), 1.98～1.95 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 146.2, 129.7, 124.5, 111.8, 47.9, 25.5, 20.4; HRMS (ESI-TOF) calcd for $C_{11}H_{16}N$ $[M+H]^+$ 162.1277, found 162.1278.

4.2.3 Preparation of substrates **1m**～**1n**

A solution of 1,2,3,4-tetrahydroisoquinoline (666 mg, 5 mmol) in CH_2Cl_2 (10 mL) was treated with triethylamine (607 mg, 6 mmol), cooled to 0 ºC, and then treated dropwise with di-*tert*-butyl decarbonate or benzyl carbonochloridate (6 mmol). After stirred at 0 ºC for 10 min, it was allowed to warm up to room temperature and stirred for another 1 h. The reaction mixture was washed with water (10 mL×3), dried over anhydrous Na_2SO_4, concentrated, and purified through silica gel column chromatography to afford the substrate (**1m**～**1n**).[18]

tert-Butyl 3,4-dihydroisoquinoline-2(1*H*)-carboxylate (**1m**):[26] Eluent: EtOAc/PE, V∶V=11∶89; 1.14 g, 98% yield. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.18～7.08 (m, 4H), 4.57 (s, 2H), 3.64 (s, 2H), 2.83 (t, J=6.0 Hz, 2H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of tautomers, *peaks of the minor one) δ: 154.9, 134.8, 133.7, 128.7, 126.4, 126.2, 79.8, 46.0, 45.3*, 41.9*, 40.7, 29.0, 28.5; HRMS (ESI-TOF) calcd for $C_{14}H_{19}NNaO_2$ $[M+Na]^+$ 256.1308, found 256.1310.

Benzyl 3,4-dihydroisoquinoline-2(1*H*)-carboxylate (**1n**):[27] Eluent: EtOAc/PE, V∶V=16∶84; 924 mg, 69% yield. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.39～7.28 (m, 5H), 7.17～7.05 (m, 4H), 5.17 (s, 2H), 4.64 (s, 2H), 3.74～3.68 (m, 2H), 2.86～2.80 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of tautomers, *peaks of the minor one) δ: 155.6, 155.5*, 136.8, 134.7, 134.5*, 133.5*, 133.1, 128.9, 128.6, 128.1, 128.0, 126.6, 126.42, 126.39*, 126.3, 67.3, 45.83*, 45.77, 41.7*, 41.4, 29.1*, 28.8; HRMS (ESI-TOF) calcd for $C_{17}H_{18}NO_2$ $[M+H]^+$ 268.1332, found 268.1335.

4.2.4 Preparation of substrates **1w**～**1x**

To a mixture of a substituted arylamine (5 mmol) and KOH (561 mg, 10 mmol) in DMSO (20 mL) was added the corresponding alkyl halide (20 mmol of iodomethane for **1w**; 10 mmol of bromoethane for **1x**). After stirred at 50 °C for 6 h, the reaction was quenched with water (20 mL) and extracted with EtOAc (20 mL×3). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated, and purified through silica gel column chromatography to afford the substrate (**1w**～**1x**).[19]

N,*N*,2-Trimethylnaphthalen-1-amine (**1w**):[28] Eluent: EtOAc/PE, V∶V=1∶99; 760 mg, 82% yield. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.20 (d, J=8.4 Hz, 1H), 7.77 (d, J=8.0 Hz, 1H), 7.54 (d, J=8.4 Hz, 1H), 7.47～7.43 (m, 1H), 7.40～7.36 (m, 1H), 7.24 (d, J=8.4 Hz, 1H), 2.99 (s, 6H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 146.5, 133.6, 133.1, 132.9, 130.2, 128.1, 125.6, 125.1, 124.9, 124.5, 43.4, 19.4; HRMS (ESI-TOF) calcd for $C_{13}H_{16}N$ $[M+H]^+$ 186.1277, found 186.1278.

N,*N*-Diethyl-4-methylaniline (**1x**):[19] Eluent: EtOAc/PE, V∶V=1∶99; 465 mg, 57% yield. Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.02 (d, J=8.4 Hz, 2H), 6.63～6.59 (m, 2H), 3.30 (q, J=7.2 Hz, 4H), 2.23 (s, 3H), 1.12 (t, J=7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 145.8, 129.8, 124.8, 112.5, 44.5, 20.2, 12.6; HRMS (ESI-TOF) calcd for $C_{11}H_{18}N$ $[M+H]^+$ 164.1434, found 164.1436.

4.2.5 Preparation of substrate **1k**

To a mixture of 4-fluorobenzonitrile (242 mg, 2 mmol) and K_2CO_3 (415 mg, 3 mmol) in DMF (2 mL) was added 1,2,3,4-tetrahydroisoquinoline (400 mg, 3 mmol). After stirred at 140 °C for 12 h, the reaction mixture was then allowed to cool to room temperature, quenched with water (10 mL), and extracted with EtOAc (10 mL×3). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated, and purified through silica gel column chromatography to afford 4-(3,4-dihydroisoquinolin-2(1*H*)-yl)-benzonitrile (**1k**).[20] Eluent: EtOAc/PE, V∶V=9∶91; 375 mg, 80% yield. White solid, m.p. 91～92 °C (lit.[25] 90～91 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.52～7.48 (m, 2H), 7.25～7.16 (m, 4H, overlapped with the peak of chloroform), 6.87～6.83 (m, 2H), 4.49 (s, 2H), 3.62 (t, J=5.6 Hz, 2H), 2.98 (t, J=6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.2, 135.0, 133.6, 133.4, 128.2, 127.0, 126.6, 126.5, 120.5, 112.7, 98.6, 48.8, 44.6, 29.0; HRMS (ESI-TOF) calcd for $C_{16}H_{15}N_2$ $[M+H]^+$ 235.1230, found 235.1233.

4.2.6 Preparation of substrate **1l**

A mixture of $Pd_2(dba)_3$ (55 mg, 0.06 mmol) and (*R*)-(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) (75 mg, 0.12 mmol) in toluene (4 mL) was stirred at 110 °C under an atmosphere of nitrogen for 30 min. After cooling to room temperature, it was treated with KO^{t}Bu (202 mg, 1.8 mmol), 2-bromonaphthalene (249 mg, 1.2 mmol) and 1,2,3,4-tetrahydroisoquinoline (320 mg, 2.4 mmol) in sequence, and then stirred at the reflux temperature for 10 h. The reaction mixture was allowed to cool to room temperature, filtered, and washed with CH_2Cl_2 (10 mL×3). The combined filtrate was dried over anhydrous Na_2SO_4, concentrated, and purified through silica gel column chromatography to afford 2-(naphthalen-2-yl)-1,2,3,4-tetrahydroisoquinoline (**1l**).[21] Eluent: EtOAc/PE, V∶V=1∶99; 224 mg, 72% yield. White solid, m.p. 89～90 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.75～7.68 (m, 3H), 7.39 (t, J=7.2 Hz, 1H), 7.34 (dd, J=9.2, 2.8 Hz, 1H), 7.26 (t, J=7.6 Hz, 1H, overlapped with the peak of chloroform), 7.22～7.16 (m, 5H), 4.50 (s, 2H), 3.65 (t, J=6.0 Hz, 2H),

3.02 (t, J=6.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.5, 134.8, 134.4, 128.9, 128.7, 128.1, 127.5, 126.64, 126.61, 126.4, 126.3, 126.1, 123.0, 118.8, 109.3, 51.1, 47.2, 29.2; HRMS (ESI-TOF) calcd for $C_{19}H_{18}N$ $[M+H]^+$ 260.1434, found 260.1435.

4.2.7 Preparation of substrate **1o**

A mixture of bromobenzene (267 mg, 1.7 mmol) and 6-methoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (509 mg, 2.55 mmol) in DMSO (5 mL) was treated with KO^{t}Bu (477 mg, 4.25 mmol), stirred at room temperature under an atmosphere of nitrogen for 5 min, and then stirred at 100 °C for another 3.5 h. After cooling to room temperature, the reaction was quenched with brine (10 mL) and extracted with EtOAc (10 mL×3). The combined organic layer was washed with water (30 mL×3), dried over anhydrous Na_2SO_4, concentrated, and purified trhough silica gel column chromatography to afford 6-methoxy-2-phenyl-1,2,3,4-tetrahydroisoquinoline (**1o**).[22] Eluent: EtOAc/PE, V∶V=1∶99; 224 mg, 55% yield. Yellow solid, m.p. 62～63 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.30～7.25 (m, 2H, overlapped with the peak of chloroform), 7.07 (d, J=8.4 Hz, 1H), 6.97 (d, J=8.0 Hz, 2H), 6.82 (t, J=7.2 Hz, 1H), 6.76 (dd, J=8.8, 2.8 Hz, 1H), 6.70 (s, 1H), 4.35 (s, 2H), 3.79 (s, 3H), 3.54 (t, J=6.0 Hz, 2H), 2.96 (t, J=5.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 158.1, 150.6, 136.1, 129.2, 127.5, 126.7, 118.6, 115.1, 113.2, 112.4, 55.3, 50.2, 46.5, 29.4; HRMS (ESI-TOF) calcd for $C_{16}H_{18}NO$ $[M+H]^+$ 240.1383, found 240.1384.

4.3 General procedure for the synthesis of products **3aa**～**3ad**

A solution of substrate **1** (0.5 mmol) and the corresponding nucleophile (**2**, 1.25 mmol) in 1,4-dioxane (6 mL) was treated sequentially with iodine (254 mg, 1 mmol) and NaOAc (164 mg, 2 mmol), and then stirred at the reflux temperature until the complete consumption of substrate **1** (monitored by TLC). After cooling to room temperature, it was quenched with 5% $Na_2S_2O_3$ (15 mL) and extracted with EtOAc (15 mL×3). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated, and purified through silica gel column chromatography to afford the product (**3aa**～**3ad**).

1-(Nitromethyl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (**3aa**): 1 h; eluent: EtOAc/PE, V∶V=1∶99; 123 mg, 92% yield. Yellow solid, m.p. 79～81 °C (lit.[29] 84～86 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.28～7.16 (m, 5H, overlapped with the peak of chloroform), 7.12～7.10 (m, 1H), 6.96 (d, J=7.6 Hz, 2H), 6.83 (t, J=7.2 Hz, 1H), 5.53 (t, J=7.2 Hz, 1H), 4.84 (dd, J=12.0, 8.0 Hz, 1H), 4.53 (dd, J=12.0, 6.8 Hz, 1H), 3.67～3.55 (m, 2H), 3.10～3.02 (m, 1H), 2.76 (dt, J=16.4, 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.5, 135.3, 132.9, 129.5, 129.2, 128.2, 127.0, 126.7, 119.5, 115.1, 78.8, 58.2, 42.1, 26.5; HRMS (ESI-TOF) calcd for $C_{16}H_{17}N_2O_2$ $[M+H]^+$ 269.1285, found 269.1287.

2-(4-Methoxyphenyl)-1-(nitromethyl)-1,2,3,4-tetrahydroisoquinoline (**3ba**):[11h] 1 h; eluent: EtOAc/PE/NEt_3, V∶V∶V=2∶97∶1; 87 mg, 58% yield. Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.26～7.12 (m, 4H, overlapped with the peak of chloroform), 6.93～6.89 (m, 2H), 6.83～6.78 (m, 2H), 5.38 (dd, J=8.8, 6.0 Hz, 1H), 4.81 (dd, J=11.6, 8.4 Hz, 1H), 4.55 (dd, J=12.0, 5.6 Hz, 1H), 3.74 (s, 3H), 3.57～3.53 (m, 2H), 3.04～2.96 (m, 1H), 2.68 (dt, J=16.4, 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.0, 143.1, 135.5, 132.9, 129.5, 127.9, 126.9, 126.6, 118.9, 114.7, 79.0, 58.9, 55.6, 43.1, 25.8; HRMS (ESI-TOF) calcd for $C_{17}H_{19}N_2O_3$ $[M+H]^+$ 299.1390, found 299.1393.

1-(Nitromethyl)-2-(*p*-tolyl)-1,2,3,4-tetrahydoisoquinoline (**3ca**):[11h] 1 h; eluent: EtOAc/PE/NEt_3, V∶V∶V=2∶97∶1; 97 mg, 69% yield. Yellow solid, m.p. 85～86 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.23～7.05 (m, 6H, overlapped with the peak of chloroform), 6.88 (d, J=8.4 Hz, 2H), 5.50～5.45 (m, 1H), 4.83 (dd, J=12.0, 8.0 Hz, 1H), 4.54 (dd, J=12.0, 6.4 Hz, 1H), 3.66～3.53 (m, 2H), 3.09～3.01 (m, 1H), 2.73 (dt, J=16.4, 4.8 Hz, 1H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 146.4, 135.4, 132.9, 130.0, 129.3, 129.1, 128.0, 127.0, 126.7, 115.9, 78.9, 58.4, 42.3, 26.2, 20.4; HRMS (ESI-TOF) calcd for $C_{17}H_{19}N_2O_2$ $[M+H]^+$ 283.1441, found 283.1443.

1-(Nitromethyl)-2-(*m*-tolyl)-1,2,3,4-tetrahydroisoquinoline (**3da**):[11h] 1.5 h; eluent: EtOAc/PE, V∶V=1∶99; 90 mg, 64% yield. Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.26～7.10 (m, 5H, overlapped with the peak of chloroform), 6.79～6.76 (m, 2H), 6.67 (d, J=7.2 Hz, 1H), 5.53 (t, J=7.2 Hz, 1H), 4.85 (dd, J=12.0, 8.0 Hz, 1H), 4.54 (dd, J=11.6, 6.4 Hz, 1H), 3.68～3.55 (m, 2H), 3.11～3.03 (m, 1H), 2.77 (dt, J=16.4, 4.8 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.5, 139.3, 135.3, 133.0, 129.4, 129.2, 128.1, 127.0, 126.7, 120.4, 115.9, 112.2, 78.8, 58.2, 42.1, 26.5, 21.9; HRMS (ESI-TOF) calcd for $C_{17}H_{19}N_2O_2$ $[M+H]^+$ 283.1441, found 283.1445.

2-(4-Fluorophenyl)-1-(nitromethyl)-1,2,3,4-tetrahydroisoquinoline (**3ea**):[11g] 1 h; eluent: EtOAc/PE, V∶V=2∶98; 83 mg, 58% yield. Yellow solid, m.p. 55～56 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.26～7.12 (m, 4H, overlapped with the peak of chloroform), 6.95～6.87 (m, 4H), 5.42 (dd, J=8.8, 5.6 Hz, 1H), 4.82 (dd, J=12.0, 8.8 Hz, 1H), 4.55 (dd, J=12.0, 6.0 Hz, 1H), 3.62～3.53 (m, 2H), 3.05～2.97 (m, 1H), 2.70 (dt, J=16.4, 4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.2 (d, $J_{C\text{-}F}$=237.7 Hz), 145.3 (d, $J_{C\text{-}F}$=2.4 Hz), 135.3, 132.5, 129.5, 128.1, 127.0, 126.8, 118.0 (d, $J_{C\text{-}F}$=7.6 Hz), 115.9 (d, $J_{C\text{-}F}$=22.2 Hz), 78.9, 58.7, 42.8, 25.8; HRMS (ESI-TOF) calcd for $C_{16}H_{16}FN_2O_2$ $[M+H]^+$ 287.1191, found 287.1193.

2-(4-Chlorophenyl)-1-(nitromethyl)-1,2,3,4-tetrahydroisoquinoline (**3fa**):[11h] 1.5 h; eluent: EtOAc/PE, V∶V=2∶98; 139 mg, 92% yield. Yellow solid, m.p. 82～83 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.27～7.17 (m, 5H, overlapped with the peak of chloroform), 7.13～7.11 (m, 1H), 6.90～6.86 (m, 2H), 5.47 (dd, J=8.4, 6.4 Hz, 1H), 4.83 (dd, J=11.6, 8.0 Hz, 1H), 4.55 (dd, J=12.0, 6.4 Hz, 1H), 3.65～3.54 (m, 2H), 3.09～3.01 (m, 1H), 2.76 (dt, J=

16.4, 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.2, 135.1, 132.5, 129.37, 129.35, 128.3, 127.0, 126.9, 124.3, 116.5, 78.7, 58.2, 42.2, 26.2; HRMS (ESI-TOF) calcd for $C_{16}H_{16}ClN_2O_2$ $[M+H]^+$ 303.0895, found 303.0898.

2-(3-Chlorophenyl)-1-(nitromethyl)-1,2,3,4-tetrahydroisoquinoline (**3ga**):[10i] 3 h; eluent: EtOAc/PE, V∶V=2∶98; 144 mg, 95% yield. Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.27～7.10 (m, 5H, overlapped with the peak of chloroform), 6.92 (t, J=2.0 Hz, 1H), 6.84 (dd, J=8.4, 2.8 Hz, 1H), 6.78 (dd, J=8.0, 1.2 Hz, 1H), 5.50 (t, J=7.6 Hz, 1H), 4.82 (dd, J=12.0, 8.0 Hz, 1H), 4.55 (dd, J=12.0, 6.4 Hz, 1H), 3.65～3.54 (m, 2H), 3.10～3.02 (m, 1H), 2.78 (dt, J=16.4, 5.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.5, 135.3, 135.1, 132.4, 130.5, 129.3, 128.4, 127.1, 126.9, 119.2, 114.7, 112.9, 78.6, 58.0, 42.0, 26.4; HRMS (ESI-TOF) calcd for $C_{16}H_{16}ClN_2O_2$ $[M+H]^+$ 303.0895, found 303.0899.

2-(2-Chlorophenyl)-1-(nitromethyl)-1,2,3,4-tetrahydroisoquinoline (**3ha**):[10i] 3 h; eluent: EtOAc/PE, V∶V=2∶98; 96 mg, 63% yield. Yellow solid, m.p. 87～89 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36 (dd, J=8.0, 1.6 Hz, 1H), 7.29～7.24 (m, 2H, overlapped with the peak of chloroform), 7.21～7.16 (m, 2H), 7.07 (td, J=7.2, 1.6 Hz, 1H), 7.00 (td, J=7.6, 1.6 Hz, 1H), 6.84 (dd, J=7.6, 1.6 Hz, 1H), 5.28 (dd, J=10.0, 4.4 Hz, 1H), 4.83 (dd, J=12.4, 10.0 Hz, 1H), 4.58 (dd, J=12.4, 4.8 Hz, 1H), 3.57～3.48 (m, 2H), 2.86～2.78 (m, 1H), 2.60 (dt, J=16.8, 3.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.1, 136.0, 132.6, 130.8, 130.4, 129.9, 127.9, 127.4, 126.8, 126.7, 125.2, 124.3, 79.2, 59.1, 43.2, 25.2; HRMS (ESI-TOF) calcd for $C_{16}H_{16}ClN_2O_2$ $[M+H]^+$ 303.0895, found 303.0898.

2-(4-Bromophenyl)-1-(nitromethyl)-1,2,3,4-tetrahydroisoquinoline (**3ia**):[11g] 1.5 h; eluent: EtOAc/PE, V∶V=1∶99; 137 mg, 79% yield. Yellow solid, m.p. 85～86 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36～7.32 (m, 2H), 7.28～7.18 (m, 3H, overlapped with the peak of chloroform), 7.14～7.12 (m, 1H), 6.86～6.82 (m, 2H), 5.48 (t, J=7.2 Hz, 1H), 4.83 (dd, J=12.0, 8.4 Hz, 1H), 4.56 (dd, J=12.0, 6.4 Hz, 1H), 3.66～3.56 (m, 2H), 3.10～3.02 (m, 1H), 2.78 (dt, J=16.8, 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.5, 135.1, 132.5, 132.3, 129.3, 128.3, 127.0, 126.9, 116.8, 111.6, 78.6, 58.1, 42.1, 26.2; HRMS (ESI-TOF) calcd for $C_{16}H_{16}BrN_2O_2$ $[M+H]^+$ 347.0390, found 347.0396.

1-(Nitromethyl)-2-(4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline (**3ja**): Eluent: EtOAc/PE, V∶V=3∶97; 162 mg, 96% (0.5 mmol, 4 h), 1.53 g, 91% (5 mmol, 7 h); Light yellow solid, m.p. 78～79 °C (lit.[30] 81.2～82.3 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.49 (d, J=8.8 Hz, 2H), 7.28～7.19 (m, 3H, overlapped with the peak of chloroform), 7.12 (d, J=8.0 Hz, 1H), 6.99 (d, J=8.8 Hz, 2H), 5.60 (t, J=7.2 Hz, 1H), 4.84 (dd, J=11.6, 7.6 Hz, 1H), 4.57 (dd, J=12.0, 6.8 Hz, 1H), 3.71～3.61 (m, 2H), 3.13～3.05 (m, 1H), 2.84 (dt, J=16.4, 5.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 150.5, 134.9, 132.4, 129.2, 128.5, 127.1, 127.0, 126.9 (q, $J_{C\text{-}F}$=3.7 Hz), 124.7 (q, $J_{C\text{-}F}$=269.0 Hz), 120.4 (q, $J_{C\text{-}F}$=32.5 Hz), 113.3, 78.5, 57.8, 41.8, 26.6; HRMS (ESI-TOF) calcd for $C_{17}H_{16}F_3N_2O_2$ $[M+H]^+$ 337.1159, found 337.1164.

4-(1-(Nitromethyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)benzonitrile (**3ka**): 4 h; eluent: EtOAc/PE, V∶V=15∶85; 129 mg, 88% yield. White solid, m.p. 131～132 °C (lit.[11f] 125～127 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.50 (d, J=8.8 Hz, 2H), 7.31～7.21 (m, 3H, overlapped with the peak of chloroform), 7.15～7.13 (m, 1H), 6.97 (d, J=9.2 Hz, 2H), 5.63 (t, J=7.2 Hz, 1H), 4.85 (dd, J=12.0, 7.6 Hz, 1H), 4.60 (dd, J=12.4, 7.2 Hz, 1H), 3.68 (t, J=6.0 Hz, 2H), 3.15～3.08 (m, 1H), 2.90 (dt, J=16.0, 6.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 150.9, 134.7, 133.9, 132.1, 129.2, 128.8, 127.13, 127.08, 119.9, 113.2, 100.5, 78.2, 57.5, 41.8, 26.8; HRMS (ESI-TOF) calcd for $C_{17}H_{16}N_3O_2$ $[M+H]^+$ 294.1237, found 294.1241.

2-(Naphthalen-2-yl)-1(nitromethyl)-1,2,3,4-tetrahydroisoquinoline (**3la**):[26] 2.5 h; eluent: EtOAc/PE, V∶V=2∶98; 98 mg, 62% yield. Yellow solid, m.p. 130～132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.75～7.64 (m, 3H), 7.40～7.16 (m, 8H, overlapped with the peak of chloroform), 5.68 (t, J=7.2 Hz, 1H), 4.90 (dd, J=11.6, 8.0 Hz, 1H), 4.60 (dd, J=11.6, 6.0 Hz, 1H), 3.84～3.78 (m, 1H), 3.71～3.64 (m, 1H), 3.15～3.07 (m, 1H), 2.79 (dt, J=16.4, 4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 146.3, 135.3, 134.6, 132.7, 129.4, 128.3, 128.2, 127.5, 127.1, 126.8, 126.7, 126.5, 123.5, 118.2, 110.2, 78.9, 58.2, 42.3, 26.3; HRMS (ESI-TOF) calcd for $C_{20}H_{19}N_2O_2$ $[M+H]^+$ 319.1441, found 319.1446.

tert-Butyl 1-(nitromethyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (**3ma**):[31] 3 h; eluent: EtOAc/PE, V∶V=9∶91; 73 mg, 50% yield. White solid, m.p. 102～103 °C; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of tautomers, *peaks of the minor one) δ: 7.26～7.19 (m, 4H, overlapped with the peak of chloroform), 5.95～5.91* (m, 0.31H), 5.87～5.84 (m, 0.63H), 4.74～4.56 (m, 2H), 4.32～4.27 (m, 0.63H), 3.96～3.90* (m, 0.32H), 3.47～3.40* (m, 0.32H), 3.26～3.19 (m, 0.63H), 3.02～2.87 (m, 1H), 2.79～2.75 (m, 1H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of tautomers, *peaks of the minor one) δ: 154.7*, 153.9, 135.3, 135.0*, 131.9*, 131.6, 129.7, 129.2*, 128.1, 127.2*, 127.0, 126.9*, 126.8, 81.4, 80.9*, 79.2, 78.6*, 53.9, 53.1*, 39.2*, 36.8, 28.4*, 28.3*, 28.2, 28.0; HRMS (ESI-TOF) calcd for $C_{15}H_{20}N_2NaO_4$ $[M+Na]^+$ 315.1315, found 315.1318.

Benzyl 1-(nitromethyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (**3na**): 5.5 h; eluent: EtOAc/PE, V∶V=9∶91; 70 mg, 43% yield. Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, mixture of tautomers, *peaks of the minor one)) δ: 7.39～7.29 (m, 5H), 7.26～7.11 (m, 4H, overlapped with the peak of chloroform), 5.97* (dd, J=8.4, 5.6 Hz, 0.45H), 5.90 (dd, J=9.2, 4.8 Hz, 0.47H), 5.20～5.07 (m, 2H), 4.79～4.55 (m, 2H), 4.31～4.25 (m, 0.49H), 4.05～3.99* (m, 0.47H), 3.53～3.45 (m, 0.53H), 3.36～3.29* (m, 0.49H), 3.03～2.86 (m, 1H), 2.77 (dt, J=16.4, 4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of tautomers, *peaks of the minor one) δ: 157.9, 155.6, 147.42, 147.39*, 134.6, 134.3*, 128.7, 126.5*, 126.4, 126.1, 117.23,

117.16*, 115.7, 115.5*, 51.9, 47.8, 29.0; HRMS (ESI-TOF) calcd for $C_{18}H_{19}N_2O_4$ $[M+H]^+$ 327.1340, found 327.1343.

6-Methoxy-1-(nitromethyl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (**3oa**):[10i] 1.5 h; eluent: EtOAc/PE/NEt_3, V∶V∶V=9∶90∶1; 69 mg, 46% yield. Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.29～7.23 (m, 2H, overlapped with the peak of chloroform), 7.02 (d, J=8.4 Hz, 1H), 6.96 (d, J=7.6 Hz, 2H), 6.83 (t, J=7.2 Hz, 1H), 6.75～6.70 (m, 2H), 5.47 (t, J=7.6 Hz, 1H), 4.81 (dd, J=11.6, 7.6 Hz, 1H), 4.49 (dd, J=11.6, 6.8 Hz, 1H), 3.77 (s, 3H), 3.64～3.53 (m, 2H), 3.06～2.99 (m, 1H), 2.74 (dt, J=16.4, 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.2, 148.5, 136.7, 129.6, 128.2, 125.0, 119.4, 115.0, 114.1, 112.6, 78.9, 57.8, 55.3, 42.0, 26.9; HRMS (ESI-TOF) calcd for $C_{17}H_{19}N_2O_3$ $[M+H]^+$ 299.1390, found 299.1393.

6-Bromo-1-(nitromethyl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (**3pa**): 1 h; eluent: EtOAc/PE, V∶V=2∶98; 137 mg, 79% yield. Yellow solid, m.p. 97～98 °C (lit.[10i] 103～105 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33～7.24 (m, 4H, overlapped with the peak of chloroform), 7.00～6.94 (m, 3H), 6.86 (t, J=7.6 Hz, 1H), 5.48 (t, J=7.2 Hz, 1H), 4.82 (dd, J=12.0, 8.0 Hz, 1H), 4.50 (dd, J=12.0, 6.8 Hz, 1H), 3.67～3.52 (m, 2H), 3.07～2.99 (m, 1H), 2.74 (dt, J=16.8, 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.2, 137.6, 132.2, 131.9, 129.9, 129.6, 128.6, 122.0, 119.9, 115.4, 78.5, 57.8, 41.8, 26.3; HRMS (ESI-TOF) calcd for $C_{16}H_{16}BrN_2O_2$ $[M+H]^+$ 347.0390, found 347.0395.

1-(1-Nitropropyl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (**3ab**):[11g] 1 h; eluent: EtOAc/PE/NEt_3, V∶V∶V=1∶98∶1; 92 mg, 62% [as a mixture of diastereoisomers (1:1.4 by ^{1}H NMR)]; Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 1:1.4 mixture of diastereoisomers, *peaks of the minor one) δ: 7.30～7.11 (m, 6H), 6.99～6.92 (m, 2H), 6.83～6.76 (m, 1H), 5.23* (d, J=9.2 Hz, 0.42H), 5.12 (d, J=9.6 Hz, 0.58H), 4.89～4.83 (m, 0.58H), 4.70～4.64* (m, 0.42H), 3.87～3.80 (m, 0.58H), 3.69～3.47 (m, 1.48H), 3.10～3.01 (m, 1H), 2.93～2.81 (m, 1H), 2.26～2.04 (m, 1.44H), 1.87～1.77 (m, 0.58H), 0.93 (td, J=11.6, 3.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 1:1.4 mixture of diastereoisomers, *peaks of the minor one) δ: 149.1, 149.0*, 135.6, 134.8*, 134.0*, 132.6, 129.5, 129.4*, 129.3, 128.8, 128.7*, 128.31*, 128.25, 127.3, 126.7*, 126.0, 119.4, 118.6*, 115.9, 114.1*, 96.2*, 93.1, 62.2, 60.8*, 43.6*, 42.3, 26.9*, 25.7, 25.1*, 24.7, 10.78, 10.77*; HRMS (ESI-TOF) calcd for $C_{18}H_{21}N_2O_2$ $[M+H]^+$ 297.1598, found 297.1601.

2-Phenyl-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (**3ac**):[11f] 2 h; eluent: EtOAc/PE, V∶V=5∶95; 105 mg, 90% yield. White solid, m.p. 82～84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36～7.32 (m, 2H), 7.30～7.19 (m, 4H, overlapped with the peak of chloroform), 7.06 (d, J=8.0 Hz, 2H), 6.99 (t, J=7.6 Hz, 1H), 5.49 (s, 1H), 3.76～3.71 (m, 1H), 3.47～3.40 (m, 1H), 3.15～3.07 (m, 1H), 2.92 (dt, J=16.4, 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.4, 134.7, 129.7, 129.6, 129.5, 128.9, 127.2, 126.9, 121.9, 117.9, 117.6, 53.2, 44.2, 28.6; HRMS (ESI-TOF) calcd for $C_{16}H_{15}N_2$ $[M+H]^+$ 235.1230, found 235.1232.

2-(*p*-Tolyl)-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (**3cc**): 1 h; eluent: EtOAc/PE, V∶V=3∶97; 86 mg, 69% yield. White solid, m.p. 102～103 °C (lit.[29] 98～100 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32～7.21 (m, 4H, overlapped with the peak of chloroform), 7.17～7.15 (m, 2H), 7.02～6.98 (m, 2H), 5.45 (s, 1H), 3.72～3.67 (m, 1H), 3.46～3.39 (m, 1H), 3.19～3.10 (m, 1H), 2.93 (dt, J=16.0, 3.6 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 146.3, 134.6, 131.9, 130.2, 129.7, 129.5, 128.7, 127.1, 126.8, 118.4, 117.8, 54.2, 44.4, 28.6, 20.7; HRMS (ESI-TOF) calcd for $C_{17}H_{17}N_2$ $[M+H]^+$ 249.1386, found 249.1388.

2-(4-Chlorophenyl)-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (**3fc**):[11f] 2.5 h; eluent: EtOAc/PE, V∶V=3∶97; 87 mg, 65% yield. White solid, m.p. 139～140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35～7.23 (m, 6H, overlapped with the peak of chloroform), 7.03～6.99 (m, 2H), 5.46 (s, 1H), 3.74～3.68 (m, 1H), 3.50～3.43 (m, 1H), 3.19～3.11 (m, 1H), 2.97 (dt, J=16.0, 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 147.0, 134.4, 129.6, 129.4, 129.2, 129.0, 127.1, 127.02, 127.00, 118.9, 117.6, 53.1, 44.3, 28.5; HRMS (ESI-TOF) calcd for $C_{16}H_{14}ClN_2$ $[M+H]^+$ 269.0840, found 269.0843.

2-(3-Chlorophenyl)-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (**3gc**):[32] 3 h; eluent: EtOAc/PE, V∶V=5∶95; 98 mg, 73% yield. Yellow solid, m.p. 67～68 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32～7.21 (m, 5H, overlapped with the peak of chloroform), 7.02 (t, J=2.0 Hz, 1H), 6.95～6.90 (m, 2H), 5.47 (s, 1H), 3.75～3.69 (m, 1H), 3.48～3.41 (m, 1H), 3.14～3.06 (m, 1H), 2.95 (dt, J=16.4, 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.3, 135.4, 134.5, 130.6, 129.4, 129.2, 129.0, 127.1, 121.5, 117.6, 117.1, 114.9, 52.3, 44.1, 28.4; HRMS (ESI-TOF) calcd for $C_{16}H_{14}ClN_2$ $[M+H]^+$ 269.0840, found 269.0842.

2-(4-(Trifluoromethyl)phenyl)-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (**3jc**):[10g] 5 h; eluent: EtOAc/PE, V∶V=2∶98; 119 mg, 79% yield. White solid, m.p. 91～92 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.59 (d, J=8.4 Hz, 2H), 7.36～7.24 (m, 4H, overlapped with the peak of chloroform), 7.07 (d, J=8.4 Hz, 2H), 5.57 (s, 1H), 3.86～3.81 (m, 1H), 3.58～3.51 (m, 1H), 3.18～3.10 (m, 1H), 3.03 (dt, J=16.4, 4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 150.4, 134.7, 129.3, 129.2, 129.0, 127.2, 127.1, 126.9 (q, $J_{C\text{-}F}$=3.7 Hz), 124.5 (q, $J_{C\text{-}F}$=269.3 Hz), 122.5 (q, $J_{C\text{-}F}$=32.7 Hz), 117.6, 115.4, 51.2, 43.9, 28.3; HRMS (ESI-TOF) calcd for $C_{17}H_{14}F_3N_2$ $[M+H]^+$ 303.1104, found 303.1108.

Diethyl (2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-phosphonate (**3ad**): 1 h; eluent: EtOAc/PE, V∶V=25∶75; 83 mg, 48% yield. White solid, m.p. 58～59 °C (lit.[33] 61.4～63.8 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38～7.34 (m, 1H), 7.27～7.13 (m, 5H, overlapped with the peak of chloroform), 6.98 (d, J=8.0 Hz, 2H), 6.79 (t,

J=7.2 Hz, 1H), 5.19 (d, J=20.0 Hz, 1H), 4.14～3.84 (m, 5H), 3.65～3.59 (m, 1H), 3.12～2.94 (m, 2H), 1.24 (t, J=7.2 Hz, 3H), 1.13 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 149.4 (d, $J_{C\text{-}P}$=5.8 Hz), 136.5 (d, $J_{C\text{-}P}$=5.5 Hz), 130.7, 129.2, 128.8 (d, $J_{C\text{-}P}$=2.6 Hz), 128.2 (d, $J_{C\text{-}P}$=4.6 Hz), 127.5 (d, $J_{C\text{-}P}$=3.4 Hz), 125.9 (d, $J_{C\text{-}P}$=2.8 Hz), 118.5, 114.8, 63.4 (d, $J_{C\text{-}P}$=7.2 Hz), 62.4 (d, $J_{C\text{-}P}$=7.7 Hz), 59.6, 58.0, 43.5, 26.8, 16.5 (q, $J_{C\text{-}P}$=8.8, 5.5 Hz); HRMS (ESI-TOF) calcd for $C_{19}H_{24}NNaO_3P$ $[M+Na]^+$ 368.1386, found 368.1388.

4.4 General procedure for the synthesis of products 3qc～3yc

A solution of substrate **1** (0.5 mmol) and trimethylsilyl cyanide (**2c**, 1.25 mmol) in DCE/MeCN (2:1, 6 mL) was treated sequentially with iodine (508 mg, 2 mmol) and NaOAc (328 mg, 4 mmol), and then stirred at the reflux temperature until the complete consumption of substrate **1** (monitored by TLC). After cooling to room tem.p.erature, it was quenched with 5% $Na_2S_2O_3$ (15 mL) and extracted with CH_2Cl_2 (15 mL×3). The combined organic layer was dried over anhydrous Na_2SO_4, concentrated, and purified through silica gel column chromatography to afford the product (**3qc**～**3yc**).

2-(Methyl(*p*-tolyl)amino)acetonitrile (**3qc**):[8c] 0.5 h; eluent: EtOAc/PE, V∶V=9∶91; 74 mg, 92% yield. Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.10 (d, J=8.4 Hz, 2H), 6.78 (d, J=8.8 Hz, 2H), 4.09 (s, 2H), 2.93 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 145.7, 130.0, 129.9, 115.6, 115.4, 42.8, 39.5, 20.5; HRMS (ESI-TOF) calcd for $C_{10}H_{13}N_2$ $[M+H]^+$ 161.1073, found 161.1075.

2-(Methyl(*o*-tolyl)amino)acetonitrile (**3rc**):[8c] 1 h; eluent: EtOAc/PE, V∶V=9∶91; 73 mg, 91% yield. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.22～7.17 (m, 3H), 7.08～7.04 (m, 1H), 3.82 (s, 2H), 2.84 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 148.6, 132.9, 131.4, 126.9, 125.0, 120.7, 115.8, 45.1, 41.0, 17.8; HRMS (ESI-TOF) calcd for $C_{10}H_{13}N_2$ $[M+H]^+$ 161.1073, found 161.1074.

2-((4-Methoxyphenyl)(methyl)amino)acetonitrile (**3sc**):[11b] 0.5 h; eluent: V∶V=9∶91; 61 mg, 69% yield. Brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.87 (s, 4H), 4.06 (s, 2H), 3.76 (s, 3H), 2.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.4, 142.2, 117.8, 115.5, 114.8, 55.6, 44.0, 40.0; HRMS (ESI-TOF) calcd for $C_{10}H_{13}N_2O$ $[M+H]^+$ 177.1023, found 177.1023.

2-((4-Fluorophenyl)(methyl)amino)acetonitrile (**3tc**):[34] 3.5 h; eluent: EtOAc/PE, V∶V=9∶91; 80 mg, 98% yield. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.04～6.98 (m, 2H), 6.86～6.81 (m, 2H), 4.11 (s, 2H), 2.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.5 (d, $J_{C\text{-}F}$=240 Hz), 144.4 (d, $J_{C\text{-}F}$=2.3 Hz), 117.0 (d, $J_{C\text{-}F}$=7.8 Hz), 116.0 (d, $J_{C\text{-}F}$ = 22.2 Hz), 115.3, 43.3, 39.8; HRMS (ESI-TOF) calcd for $C_9H_{10}FN_2$ $[M+H]^+$ 165.0823, found 165.0824.

2-((4-Chlorophenyl)(methyl)amino)acetonitrile (**3uc**):[8c] 17.5 h; eluent: EtOAc/PE, V∶V=9∶91; 84 mg, 93% yield. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.27～7.23 (m, 2H, overlapped with the peak of chloroform), 6.79～6.75 (m, 2H), 4.13 (s, 2H), 2.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 146.4, 129.4, 125.2, 116.1, 115.3, 42.3, 39.4; HRMS (ESI-TOF) calcd for $C_9H_{10}ClN_2$ $[M+H]^+$ 181.0527, found 181.0527.

2-((4-Bromophenyl)(methyl)amino)acetonitrile (**3vc**):[8c] 8 h; eluent: EtOAc/PE, V∶V=9∶91; 69 mg, 61% yield. Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.41～7.37 (m, 2H), 6.74～6.70 (m, 2H), 4.13 (s, 2H), 2.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 146.8, 132.3, 116.4, 115.3, 112.5, 42.2, 39.4; HRMS (ESI-TOF) calcd for $C_9H_{10}BrN$ $[M+H]^+$ 225.0022, found 225.0024.

2-(Methyl(2-methylnaphthalen-1-yl)amino)acetonitrile (**3wc**): 0.5 h; eluent: EtOAc/PE, V∶V=2∶98; 99 mg, 94% yield. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.97 (d, J=8.4 Hz, 1H), 7.78 (d, J=8.0 Hz, 1H), 7.59 (d, J=8.4 Hz, 1H), 7.51～7.47 (m, 1H), 7.42～7.38 (m, 1H), 7.25 (d, J=8.4 Hz, 1H, overlapped with the peak of chloroform), 4.10～4.00 (m, 2H), 3.10 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 143.2, 134.1, 133.7, 132.2, 129.8, 128.5, 126.7, 126.6, 125.4, 123.5, 117.7, 44.5, 41.1, 19.3; HRMS (ESI-TOF) calcd for $C_{14}H_{14}N_2Na$ $[M+Na]^+$ 233.1049, found 233.1051.

2-(Ethyl(*p*-tolyl)amino)propanenitrile (**3xc**):[35] 0.5 h; eluent: EtOAc/PE, V∶V=5∶99; 17 mg, 18% yield. Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.13～7.10 (m, 2H), 6.97～6.93 (m, 2H), 4.33 (q, J=7.2 Hz, 1H), 3.34～3.18 (m, 2H), 2.30 (s, 3H), 1.50 (d, J=7.2 Hz, 3H), 1.12 (t, J=7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.3, 132.3, 129.9, 120.9, 119.5, 49.3, 44.3, 20.7, 18.6, 13.8; HRMS (ESI-TOF) calcd for $C_{12}H_{17}N_2$ $[M+H]^+$ 189.1386, found 189.1388.

1-(*p*-Tolyl)pyrrolidine-2-carbonitrile (**3yc**):[36] 0.5 h; eluent: EtOAc/PE, V∶V=2∶98; 30 mg, 32% yield. Brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.11 (d, J=8.4 Hz, 2H), 6.63～6.60 (m, 2H), 4.43～4.41 (m, 1H), 3.45～3.40 (m, 1H), 3.38～3.32 (m, 1H), 2.43～2.37 (m, 1H), 2.34～2.12 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 143.2, 130.0, 127.5, 119.4, 112.8, 49.4, 47.6, 31.5, 23.9, 20.4; HRMS (ESI-TOF) calcd for $C_{12}H_{15}N_2$ $[M+H]^+$ 187.1230, found 187.1231.

Supporting Information NMR Spectra of isolated Compounds. The Supporting Information is available free of charge via the Internet at http://sioc-journal.cn/.

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