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Solvent-Free Cross-Dehydrogenative Coupling Reactions under High Speed Ball-Milling Conditions Applied to the Synthesis of Functionalized Tetrahydroisoquinolines

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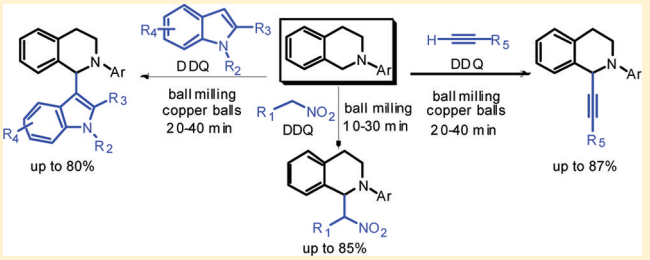
Supporting Information

ABSTRACT: Solvent-free reaction using a high-speed ball milling technique has been first applied to cross-dehydrogenative coupling (CDC) reactions between tetrahydroisoquinolines and three types of pronucleophiles such as nitroalkanes, alkynes, and indoles. All coupling products were obtained in good yields at short reaction times (no more than 40 min). When alkynes and indoles were used as pronucleophile, the reactions can be catalyzed efficiently by recoverable copper balls without any additional metal catalyst.

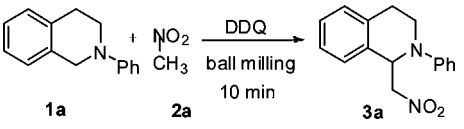


The cross-dehydrogenative coupling (CDC) reaction of two different C−H bonds of pronucleophiles and proelectrophiles will avoid the preparation of functional groups and make synthetic schemes shorter and more efficient. Three types of reactions have been reported on the basis of the direct sp^3 C−H bond activation adjacent to a nitrogen atom for the C−C bond formations:[1] (a) sp^3−sp^3 coupling, (b) sp^3−sp^2 coupling, (c) sp^3−sp coupling.

Because of the importance of the CDC reaction, many research groups are currently investigating various types of metal catalysts, oxidants, and solvents in CDC reactions. Copper-catalyzed oxidative CDC reactions were reported by Li and others, where ^{t}BuOOH,[2a−i] O_2,[2j] NBS,[2k] and diethyl azodicarboxylate (DEAD)[2l] were used as efficient oxidants. Rhodium−T-HYDRO (70% in water),[3] iron−$(^t\text{BuO})_2$/^{t}BuOOH,[4] vanadium−^{t}BuOOH,[5] and ruthenium−O_2[6] systems also showed high catalytic activity in CDC reactions. When platinum was used, coupling products could be obtained in the absence of oxidant.[7] Although good results could be achieved in all cases, these reactions still possess some limitations, such as requiring the use of unrecoverable metal catalysts, explosive oxidants, or volatile organic solvents. Only one was recently reported as adopting recyclable silica-supported iron terpyridine complex for CDC reactions of tertiary amines with various carbon nucleophiles.[8] However, a relatively long reaction time and high temperature were required. Examples of the reactions without any metal still remain rare. Until recently, Todd's[9] work had shown this interesting transformation by using 2,3-dichloro-5,6-dicyanoquinone (DDQ) as oxidant in the absence of metal catalyst, while in Shu's[10] work $PhI(OAc)_2$ was employed. In both cases, excessive nitroalkanes were required as reactant and solvent. Our previous works[11] on mechanically activated solvent-free reactions inspired us to introduce an alternative method for this important bond formation that does not require the presence of solvents and additional unrecoverable metal catalysts. High speed ball milling (HSBM) is a method that has been shown to be a viable alternative to solution-based chemistry, where high concentrations of materials in the reaction vials will be presented.[12] Furthermore, the synthesis of nitrogen-containing compounds, especially tetrahydroisoquinoline derivatives which are widely present in nature, has attracted much attention in industrial and academic research because of their biological and pharmaceutical properties.[13] Thus, we report herein the application of this nonconventional methodology for the preparation of tetrahydroisoquinoline derivatives through DDQ-promoted CDC reactions.

Recently, DDQ has been investigated as a powerful oxidation agent for oxidative carbon−carbon coupling reaction.[14] In this paper, we initially chose the reaction between tetrahydroisoquinoline **1a** (1 mmol) and nitromethane **2a** (2 mmol) as a model in the presence of DDQ (1 mmol) without any metal catalyst. Silica gel was added as grinding aid (Scheme 1).

Scheme 1. Coupling Reaction of 2-Phenyltetrahydroisoquinoline with Nitromethane



The reactions were conducted in a custom-made 10 mL screw-capped stainless steel vial and milled with two stainless

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steel balls of 8.0 mm diameter in a high-energy vibrational micromill at a frequency of 30 Hz at room temperature. The reaction progress was monitored by taking out a mixture example and dissolved in dichloromethane using TLC. At the end of the experiment, all the reaction mixture was scratched off from the vessel, then directly separated and purified by column chromatography without any aqueous workup. To our delight, 85% of **3a** was isolated in 10-min reaction time at a 30 Hz frequency. When the reaction was performed at lower frequencies such as 20 Hz, a few substrates were still present in the crude, probably due to diminished amount of energy per impact.[15]

Figure 1 showed the results of the coupling reaction of **1a** with **2a** induced by ball milling at different frequencies and

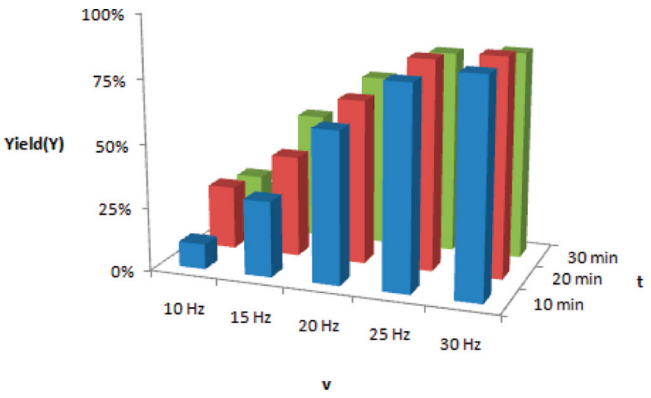


Figure 1. Influence of frequency (v) and milling time (t) on the yield of **3a** (for reaction conditions cf. Table 1).

milling time. As expected, yield (Y) rises along the increased frequencies (v), yet no significant improvement was obtained along the time-axis (t). Ball-milling with pause also resulted in lower conversion. It is worth mentioning that the best results were obtained when 1 equiv of DDQ was used. An excess of oxidant was detrimental to the yield of the product, whereas less than 1 equiv of DDQ would result in incomplete conversion of the starting materials.

To further study the effect of the grinding auxiliary, various grinding auxiliaries were examined respectively. Silica gel was found to be the most effective among those grinding auxiliaries. (Table 1, entry 1). It might act as both the grinding-aid agent

Table 1. Influence of Grinding Auxiliary on sp^3 C–H and sp^3 C–H Bond CDC Reactions[a]

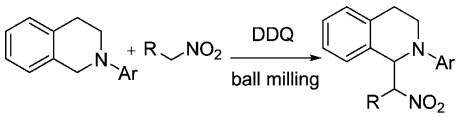
entry	grinding auxiliary	weight (g)	time (min)	yield[b] (%)
1	silica gel	0.5	10	85
2	silica gel	2	10	60
3	NaCl	2	10	78
4	γ-Al_2O_3 (neutral)	0.5	10	70
5			30	58

[a]Reaction conditions: **1a** (1 mmol), nitromethane (2 mmol), DDQ (1 mmol). [b]Isolated yields based on **1**.

and absorbent in the reaction. In the absence of grinding auxiliary, substrates could not be mixed efficiently, leading to the poor yield (Table 1, entry 5). Adding a relatively great amount of grinding auxiliary, the yield decreased rapidly because of the diluted reagent concentrations (Table 1, entry 2).

With the best reaction conditions in hand, we extended the methodology to various nitroalkanes in the presence of 2-substituted tetrahydroisoquinoline. The representative results were summarized in Table 2. Nitroalkanes reacted rapidly with

Table 2. Coupling Reaction of Tetrahydroisoquinolines with Nitroalkanes via Ball Milling[a]



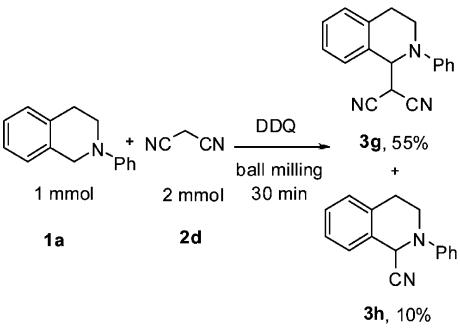
1 **2** **3**

entry	Ar	R	product	time (min)	yield[b] (%)
1	Ph	H	**3a**	10 (120[c])	85 (89[d])
2	Ph	Me	**3b**	15 (180[c])	75 (78[d])
3	Ph	Et	**3c**	15 (180[c])	76 (70[d])
4	4-MeOPh	H	**3d**	20 (120[c])	80 (75[d])
5	4-MeOPh	Me	**3e**	30 (210[c])	70 (65[d])
6	4-MeOPh	Et	**3f**	30 (210[c])	70 (60[d])

[a]Reaction conditions: amine (1 mmol), nitroalkanes (2 mmol), DDQ (1 mmol) and 0.5 g of silica gel were added in the stainless steel vial and milled with two stainless steel balls. [b]Isolated yields based on **1**. [c]Comparative experiment under stirring condition: amine (1 mmol), nitroalkanes (10 mL), DDQ (1 mmol). [d]Isolated yields of the comparative experiment.

2-phenyltetrahydroisoquinoline **1a** (Table 2, entries 1–3). A relatively long time was needed when 2-(methoxyphenyl)-tetrahydroisoquinoline **1b** was used as proelectrophiles (Table 2, entries 4–6). Moreover, malononitrile was also viable participant which reacted with 2-phenyltetrahydroisoquinoline **1a** to give comparable yield by this solvent and metal-free CDC reaction. As shown in Scheme 2, 55% of coupling product **3g** was afforded

Scheme 2. Coupling Reaction of 2-Phenyltetrahydroisoquinoline with Malononitrile



along with 10% of **3h**, due to oxidative degradation of malononitrile with the cleavage of the C–CN bond by DDQ.[2e]

On the basis of the above successful sp^3 C–H bond and sp^3 C–H bond CDC reactions under ball milling conditions, the application of this approach to other two types of CDC reaction was examined. As we began our studies on sp^3 C–H bond and sp C–H bond coupling reactions, 2-phenyl-tetrahydroisoquinoline **1a** and ethynylbenzene **4a** were taken as the model substrate. Treatment of **1a** (1 mmol) and **4a** (2 mmol) with 1 equiv of DDQ by ball milling only afforded **5a** in low yield (25%) (Scheme 3). Attempts to improve the reaction yield by changing the ratio of reactants, amount of oxidant, and milling time failed.

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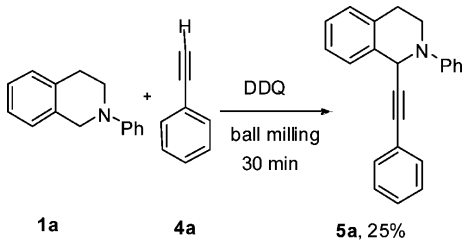
Scheme 3. Coupling Reaction of 2-Phenyltetrahydroisoquinoline with Ethynylbenzene



Traces of copper were reported to play an important role in the CDC reaction,[2,4b] with high efficiency even in the ppm range.[16] Thus, we made an approach to adding various copper catalysts to the reactions. Good results were obtained in all cases, even when trace of copper powder, the most economic and practical catalyst, was used (Table 3, entries 1−5). The work of catalyst recovery in this reaction inspired us for our investigations regarding the use of copper ball to promote this sp^3 C−H and sp C−H bond CDC reaction.[12e] To our delight, the reaction proceeded smoothly by using two copper balls (d = 8.0 mm) instead of the original stainless steel balls without additional catalysts and 78% of **5a** was afforded after 20 min milling at a frequency of 30 Hz (Table 3, entry 6). After the reaction was completed, the catalyst was recovered simply by removing the copper ball from the reaction media.

Table 3. Effects of Metal Catalysts on sp^3 C−H and sp C−H Bond-Coupling Reaction[a]

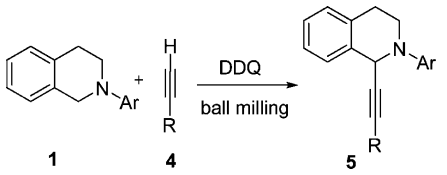
entry	catalyst (mol %)	time (min)	yield of **5a**[b] (%)
1		40	22 (25)[c]
2	CuBr (5)	20	75
3	$Cu(OAC)_2 \cdot H_2O$ (5)	20	79
4	$Cu(OTf)_2$ (5)	20	70
5	Copper powder (5)	20	73
6	*d*	20	78

[a]**1a** (1 mmol), **4a** (1.1 mmol), DDQ (1 mmol), catalyst, and 0.5 g of silica gel were added in the stainless steel vial and milled with two stainless steel balls. [b]Isolated yields based on **1a**. [c]2 mmol **4a** was used. [d]Two copper balls was used without additional catalyst.

Various α-alkynylamine derivatives were generated in good yields under the above conditions.[17] For aromatic alkynes, the electron-rich aryl group gave slightly lower yields of desired products, whereas the electron-poor substituent afforded the best yields among all results for being apt to form an alkynylcopper intermediate (Table 4, entries 1−3 and 7−9). The reaction also provided good yields of the desired products for aliphatic alkynes and propiolate (Table 4, entries 5, 6, and 10). The electronic nature of aryl substituent of tetrahydroisoquinolines affected the reactivity as well. A slightly lower yield was afforded when 2-(methoxyphenyl)tetrahydroisoquinoline was used as proelectrophile, probably due to the unstability of methoxyphenyl under oxidative conditions (Table 4, entries 7−10).

Subsequently, sp^3 C−H bond and *aryl*-sp^2 C−H bond CDC reactions were also investigated under the above reaction conditions. The reaction did not proceed without copper balls. As shown in Table 5, various indoles reacted smoothly with tetrahydroisoquinolines in the presence of DDQ and two copper balls (d = 8.0 mm) under ball-milling conditions.[18]

Table 4. Coupling Reaction of Tetrahydroisoquinolines with Alkynes via Ball Milling[a]



entry	Ar	R	product	time (min)	yield[b] (%)
1	Ph	Ph	**5a**	20	78
2	Ph	4-Me C_6H_4	**5b**	20	74
3	Ph	4-F C_6H_4	**5c**	20	87
4	Ph	2-Py	**5d**	40	69
5	Ph	Pr	**5e**	30	67
6	Ph	CH_3OCO	**5f**	30	73
7	4-$MeOC_6H_4$	Ph	**5g**	30	75
8	4-$MeOC_6H_4$	4-MeC_6H_4	**5h**	30	70
9	4-$MeOC_6H_4$	4-F C_6H_4	**5i**	20	84
10	4-$MeOC_6H_4$	CH_3OCO	**5j**	30	72

[a]Reaction conditions: amine (1 mmol), alkynes (1.1 mmol), DDQ (1 mmol), 0.5 g of silica gel, two copper balls were used without additional catalyst. [b]Isolated yields based on **1**.

A slight excess of tetrahydroisoquinolines was conducive to the conversion. The reactions of tetrahydroisoquinolines with free indoles (NH) or *N*-methylindoles containing electron-donating or electron-withdrawing groups gave reasonable yields of the desired products **7**. The presence of electron-donating groups (**6c**) or electron-withdrawing groups (**6d**) at the C-5 position of indole did not show any significant influence on the product yield under the present reaction conditions (Table 5, entries 3 and 4). Thus, the herein-reported reaction conditions are advantageous because of their short reaction time and recoverable catalyst compared to traditional solvent-free reactions under heating conditions.[2b−d]

This method is also amenable to larger scale preparation, as 10.0 mmol of *N*-phenyltetrahydroisoquinoline **1a** was converted into the corresponding 1-(nitromethyl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline **3a** (80%) and 1-(phenylethynyl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline **5a** (75%) within 20 and 30 min, respectively.[19] The reaction between indole (8.0 mmol) and *N*-phenyltetrahydroisoquinoline **1a** (10.0 mmol) in the presence of DDQ (8.0 mmol) after 40 min also showed an appreciable yield of 1-(1*H*-indol-3-yl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline **7a** (70%).[19]

In conclusion, we have reported an efficient DDQ-mediated solvent-free CDC reaction to afford tetrahydroisoquinoline derivatives. Three types of reactions based on functionalization of sp^3 C−H bonds adjacent to a nitrogen atom proceeded rapidly under ball milling condition. For nitroalkanes and malononitrile, R−C−H-functionalized products were obtained without any metal catalyst. For alkynes and indoles, copper balls were used both as the reacting catalyst and milling balls; the recovery of the catalyst would be as simple as removing the copper ball from the reaction media. Additionally, a scale-up procedure for these mechanically activated cross-dehydrogenative coupling reactions is realizable. The scope and limitations of the reaction are under further study.

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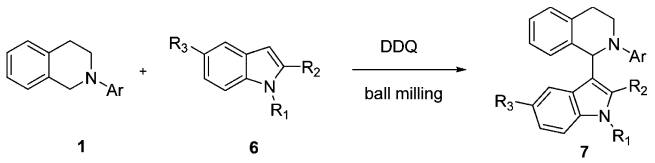
Table 5. Coupling Reaction of Tetrahydroisoquinolines with Indoles via Ball Milling[a]



entry	Ar	R^1	R^2	R^3	product	time (min)	yield[b] (%)
1	Ph	H	H	H	**7a**	30 (overnight[c])	77 (79[c])
2	Ph	CH_3	H	H	**7b**	40 (overnight[c])	80 (44[c])
3	Ph	H	H	OCH_3	**7c**	20 (overnight[c])	70 (57[c])
4	Ph	H	H	Br	**7d**	30	70
5	Ph	H	CH_3	H	**7e**	40 (overnight[c])	75 (61[c])
6	4-$MeOC_6H_4$	H	H	H	**7f**	30	67
7	4-$MeOC_6H_4$	CH_3	H	H	**7g**	40 (overnight[c])	80 (71[c])
8	4-$MeOC_6H_4$	H	H	OCH_3	**7h**	40 (overnight[c])	72 (65[c])
9	4-$MeOC_6H_4$	H	CH_3	H	**7i**	40	70

[a]Reaction conditions: amine (1 mmol), indoles (0.8 mmol), DDQ (0.8 mmol), 0.5 g of silica gel, two copper balls were used without additional catalyst. [b]Isolated yields based on indoles. [c]The reaction time and isolated yields from ref 2d.

EXPERIMENTAL SECTION

General Methods. All reagents were purchased from commercial sources and used without treatment, unless otherwise indicated. The reactions were conducted in a high-energy vibrational micromill (volume of stainless steel vial: 10 mL; 50 mL; diameter of stainless steel balls: 8.0 mm; diameter of copper balls: 8.0 mm, 12.0 mm). Melting points (mp) were obtained on a digital melting point apparatus and uncorrected. ^{1}H and ^{13}C NMR were recorded at 400 and 100 MHz, respectively, and TMS was used as internal standard. IR spectra (KBr) were recorded on an FT-IR spectrophotometer. Mass spectra were measured with a HRMS-APCI instrument or a low-resolution MS instrument using ESI or EI ionization. *N*-Aryltetrahydroisoquinoline **1** was prepared according to the published procedures.[20]

sp^3 C–H and sp^3 C–H Coupling Reaction: 1-(Nitromethyl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (3a). Typical Procedure. The following components were added to the screw-capped stainless steel vial: *N*-phenyltetrahydroisoquinoline **1a** (0.209 g, 1 mmol), nitromethane **2a** (0.122 g, 2 mmol), DDQ (0.227 g, 1 mmol), and silica gel (0.5 g), along with two stainless steel balls (d = 8.0 mm). Then, the vial was placed in a vibrational micromill, and the contents were ball milled at 30 Hz. At the end of the experiment, all of the reaction mixture was scratched off the vessel and then directly separated and purified by column chromatography. Elution of the column with PE/EtOAc (15: 1) afforded the product **3a**[2c] as a white crystal: mp 88.2–89.3 °C (lit.[2c] mp 89.0–90.0 °C); ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.30–7.08 (m, 6H), 7.11 (d, J = 6.8 Hz, 2H), 6.96 (d, J = 7.6 Hz, 1H), 6.83 (m, 1H), 5.53 (dd, $J_1 = J_2$ = 7.2 Hz, 1H), 4.86 (dd, J = 11.6, 7.4 Hz, 1H), 4.55 (dd, J = 11.6, 6.8 Hz, 1H), 3.71–3.54 (m, 2H), 3.04 (ddd, J = 14.4, 8.4, 6.0 Hz, 1H), 2.74 (ddd, J = 16.4, 4.8, 4.8 Hz, 1H) ;^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 148.3, 135.1, 132.8, 129.4, 129.1, 128.0, 126.9, 126.6, 119.3, 115.0, 78.8, 58.2, 42.1, 26.6. Anal. Calcd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.44. Found: C, 71.78; H, 6.04; N, 10.37.

1-(1-Nitroethyl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (3b[2c]): yellow viscous liquid; ratio of isolated diastereoisomers 1.8. The major isomer: ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 5.20 (d, J = 8.4 Hz, 1H), 5.02 (dq, J = 8.4, 6.8 Hz, 1H), 3.62–3.49 (m, 2H), 1.52 (d, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 148.7, 135.5, 131.9, 129.3, 129.2, 128.2, 128.1, 126.0, 119.2, 115.4, 85.4, 62.8, 42.8, 26.5, 16.5. The minor isomer: ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 5.24 (d, J = 9.2 Hz, 1H), 4.87 (dq, J = 8.8, 6.8 Hz, 1H), 3.82 (ddd, J = 13.6, 8.0, 5.6 Hz, 2H), 1.69 (d, J = 6.8 Hz, 3H);^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 149.0, 134.7, 133.7, 129.3, 129.0, 128.6, 127.1, 126.5, 118.7, 114.4, 88.9, 61.2, 43.6, 26.9, 17.6. Other overlapped peaks: ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.28–7.16 (m), 7.16–7.04 (m), 7.01–6.93 (m), 6.82–6.78 (m), 3.09–2.99 (m), 2.93–2.81 (m).

1-(1-Nitropropyl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (3c[2j]): yellow viscous liquid; ratio of isolated diastereoisomers 1.7. The major isomer: ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 5.12 (d, J = 9.6 Hz, 1H), 4.86 (td, J = 10.2, 2.8 Hz, 1H), 3.70–3.47 (m, 2H), 2.26–2.02 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 149.2, 135.7, 132.7, 129.7, 129.6, 129.3, 128.3, 126.0, 119.5, 116.0, 93.3, 62.5, 42.7, 26.1, 25.0, 11.1. The minor isomer: ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 5.23 (d, J = 9.2 Hz, 1H), 4.67 (td, J = 10.2, 2.8 Hz, 1H), 3.88–3.80 (m, 2H), 1.88–1.76 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 149.1, 134.8, 134.0, 129.7, 129.5, 128.8, 127.4, 126.8, 118.7, 114.3, 96.4, 61.0, 43.9, 27.2, 25.4, 11.1. Other overlapped peaks: ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.29–7.13 (m), 6.99–6.90 (m), 6.83–6.74 (m), 3.11–3.01 (m), 2.93–2.81 (m), 0.96–0.91 (m).

1-(Nitromethyl)-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (3d[2c]): yellow viscous liquid; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.26–7.10 (m, 4H), 6.89 (d, J = 9.2 Hz, 2H), 6.79 (d, J = 8.8 Hz, 2H), 5.37 (dd, J = 8.4, 6.0 Hz, 1H), 4.81 (dd, J = 12.0, 8.8 Hz, 1H), 4.55 (dd, J = 12.0, 6.0 Hz, 1H), 3.74 (s, 3H), 3.59–3.51 (m, 2H), 3.00 (ddd, J = 16.4, 9.4, 6.8 Hz, 1H), 2.68 (ddd, J = 16.4, 4.0, 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 154.1, 143.2, 135.6, 133.0, 129.6, 128.0, 127.1, 126.8, 119.0, 114.9, 79.2, 59.2, 55.9, 43.5, 26.2.

1-(1-Nitroethyl)-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (3e[2c]): yellow viscous liquid; ratio of isolated diastereoisomers 1.7. The major isomer: ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 3.72 (s, 3H), 3.56–3.44 (m, 2H); 1.53 (d, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 153.6, 143.3, 135.7, 131.9, 129.1, 128.2, 127.9, 125.9, 118.8, 114.5, 85.7, 63.5, 55.6, 44.1, 26.1, 16.7. The minor isomer: ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 4.85 (dq, J = 13.6, 6.8 Hz, 1H), 3.81–3.73 (m, 2H), 3.74 (s, 3H), 1.67 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 153.4, 143.7, 134.9, 133.5, 128.8, 127.9, 127.1, 126.4, 118.1, 114.6, 88.8, 62.2, 55.6, 45.1, 26.4, 17.2. Other overlapped peaks: ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.25–7.08 (m), 7.02–6.98 (m), 6.93–6.87 (m), 6.83–6.75 (m), 5.06–4.94 (m), 3.02–2.92 (m), 2.84–2.73 (m).

1-(1-Nitropropyl)-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (3f[2j]): yellow viscous liquid; ratio of isolated diastereoisomers 2.0. The major isomer: ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 4.90 (d, J = 10.0 Hz, 1H), 4.66 (td, J = 9.6, 3.2 Hz, 1H), 3.70 (s, 3H), 2.19–2.02 (m); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 153.5, 135.5, 132.3, 128.6, 127.8, 125.7, 118.9, 114.3, 93.2, 62.9, 55.5, 43.6, 25.4, 24.7, 10.8. The minor isomer :^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 5.01 (d, J = 9.2 Hz, 1H), 4.66 (td, J = 9.2, 5.2 Hz, 1H), 3.74 (s, 3H), 1.88–1.75 (m); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 153.0, 134.7, 133.6, 128.7, 127.0, 126.3, 117.3, 114.6, 95.9, 61.6, 55.6, 44.7, 26.3, 25.0, 10.7. Other overlapped peaks: ^{1}H NMR ($CDCl_3$, 400 MHz,

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ppm) δ 7.25−7.11 (m), 7.00−6.95 (m), 6.92−6.78 (m), 6.77−6.69 (m), 3.84−3.75 (m), 3.62−3.42 (m), 3.05−2.92 (m), 2.83−2.71 (m); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 143.5, 129.3.

2-(2-Phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-malononitrile (3g[2e]): brown viscous liquid; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.44 (d, *J* = 7.6 Hz, 1H), 7.38−7.21 (m, 5H), 6.98 (d, *J* = 8.0 Hz, 3H), 5.34 (d, *J* = 4.4 Hz, 1H), 4.19 (d, *J* = 4.4 Hz, 1H), 3.80 (ddd, *J* = 12.0, 6.8, 4.8 Hz, 1H), 3.50 (ddd, *J* = 12.0, 6.0, 6.0 Hz, 1H), 3.16 (ddd, *J* = 16.4, 5.8, 5.8 Hz, 1H), 3.03 (ddd, *J* = 16.4, 6.4, 6.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 147.5, 135.4, 130.5, 129.7, 129.1, 129.0, 127.2, 126.8, 120.9, 116.3, 112.1, 111.7, 61.4, 43.4, 29.6, 27.6.

2-Phenyl-1,2,3,4-tetrahydroisoquinoline-1-carbonitrile (3h[10]): colorless crystal; mp 96.2−97.1 °C (lit.[10] mp 99−101 °C); ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.40−7.18 (m, 6H), 7.07 (d, *J* = 8.0 Hz, 2H), 7.00 (dd, J_1 = J_2 = 7.4 Hz, 1H), 5.50 (s, 1H), 3.77 (dddd, *J* = 12.0, 4.8, 2.8, 1.2 Hz, 1H), 3.48 (ddd, *J* = 12.0, 10.8, 4.0 Hz, 1H), 3.16 (ddd, *J* = 16.4, 10.4, 6.0 Hz, 1H), 2.97 (ddd, *J* = 16.4, 3.2, 3.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 148.2, 134.5, 129.4, 129.2, 128.6, 126.9, 126.7, 121.8, 117.6, 117.5, 53.3, 44.3, 28.7.

sp^3 C−H and sp C−H Coupling Reaction: 1-(Phenylethynyl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (5a[2a]): Typical Procedure. The following components were added to the screw-capped stainless steel vial: *N*-phenyltetrahydroisoquinoline **1a** (0.209 g, 1 mmol), ethynylbenzene **4a** (0.123 g, 1.1 mmol), DDQ (0.227 g, 1 mmol), and silica gel (0.5 g), along with two copper balls (*d* = 8.0 mm). Then, the vial was placed in a vibrational micromill, and the contents were ball milled at 30 Hz. At the end of the experiment, all of the reaction mixture was scratched off the vessel then directly separated and purified by column chromatography. Elution of the column with PE/CH_2Cl_2/EtOEt (50:10:0.1) afforded the product **5a**[2a] as a white viscous liquid: ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.38−7.15 (m, 11H), 7.11 (d, *J* = 8.4 Hz, 2H), 6.88 (dd, J_1 = J_2 = 7.2 Hz, 1H), 5.63 (s, 1H), 3.79−3.61 (m, 2H), 3.15 (ddd, *J* = 16.0, 10.0, 6.0 Hz, 1H), 2.98 (ddd, *J* = 16.0, 4.0, 4.0 Hz, 1H);^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 149.4, 135.3, 134.3, 131.6 (2C), 129.0 (2C), 128.8, 128.0 (2C), 127.9, 127.3, 127.1, 126.2, 122.9, 119.6, 116.6 (2C), 88.6, 84.8, 52.4, 43.6, 29.1.

1-(*p*-Tolylethynyl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (5b): colorless crystal; mp 56.9−61.1 °C; IR (KBr) 3048, 3024, 2950, 2916, 2849, 2202, 1901, 1598, 1508, 1453, 1375, 1263, 1216, 1020, 934 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.39−7.25 (m, 3H), 7.24−7.13 (m, 5H), 7.10 (d, *J* = 8.4 Hz, 2H), 7.00 (d, *J* = 8.0 Hz, 2H), 6.87 (dd, J_1 = J_2 = 7.2 Hz, 1H), 5.62 (s, 1H), 3.78−3.62 (m, 2H), 3.13 (ddd, *J* = 16.0, 10.0, 6.0 Hz, 1H), 2.97 (ddd, *J* = 16.0, 3.6, 3.6 Hz, 1H), 2.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 149.3, 137.8, 135.3, 134.2, 131.4 (2C), 128.9 (2C), 128.7, 128.6 (2C), 127.2, 127.0, 126.1, 122.9, 119.8, 119.4, 116.5 (2C), 87.8, 84.8, 52.3, 43.5, 29.0, 21.5; MS (ESI) 324 ([M + H]$^+$); HRMS(ESI) $C_{24}H_{22}N$ ([M + H]$^+$) calcd 324.1752, found 324.1753.

1-((4-Fluorophenyl)ethynyl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (5c): colorless crystal; mp 115.5−116.1 °C; IR (KBr) 3064, 3028, 2992, 2924, 2843, 1597, 1504, 1450, 1370, 1279, 1204, 1154, 1138, 1032, 1016, 935 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.41−7.16 (m, 8H), 7.11 (d, *J* = 8.0 Hz, 2H), 6.94−6.84 (m, 3H), 5.62 (s, 1H), 3.80−3.70 (m, 1H), 3.69−3.60 (m, 1H), 3.14 (ddd, *J* = 16.0, 10.4, 6.0 Hz, 1H), 2.98 (ddd, *J* = 16.0, 3.8, 3.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 163.6 (d, $^1J_{C-F}$ = 246.9 Hz), 149.3, 135.1, 134.2, 133.4 (d, $^3J_{C-F}$ = 8.2 Hz) (2C), 129.0 (2C), 128.8, 127.2, 127.1, 126.1, 119.5, 118.9 (d, $^4J_{C-F}$ = 3.2 Hz), 116.5 (2C), 115.2 (d, $^2J_{C-F}$ = 21.9 Hz) (2C), 88.3, 83.6, 52.3, 43.5, 29.0; MS (ESI) 328 ([M + H]$^+$); HRMS(ESI) $C_{23}H_{19}FN$ ([M + H]$^+$) calcd 328.1502, found 328.1500.

1-(Pyridin-2-ylethynyl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (5d): brown crystal; mp 81.1−83.4 °C; IR (KBr) 3049, 3002, 2923, 2842, 2210, 1932, 1596, 1580, 1494, 1463, 1425, 1372, 1277, 1261, 1204, 1149, 1031, 1018, 994 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 8.46 (d, *J* = 4.4 Hz, 1H), 7.51 (td, *J* = 8.0, 1.8 Hz, 1H), 7.41−7.03 (m, 10H), 6.85 (dd, J_1 = J_2 = 7.2 Hz, 1H), 5.65 (s, 1H), 3.81−3.64 (m, 2H), 3.13 (ddd, *J* = 19.0, 10.0, 6.4 Hz, 1H), 2.98 (ddd, *J* = 16.0, 4.0, 4.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 149.6, 149.1, 143.0, 135.7, 134.5, 134.3, 129.0 (2C), 128.8, 127.4, 127.2, 126.2, 122.5, 119.5, 116.3 (2C), 88.7, 84.1, 52.1, 43.6, 29.0; MS (ESI) 311 ([M + H]$^+$); HRMS(ESI) $C_{22}H_{19}N_2$ ([M + H]$^+$) calcd 311.1548, found 311.1547.

1-(Pent-1-yn-1-yl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (5e): colorless crystal; mp 50.4−51.8 °C; IR (KBr) 3062, 3022, 2959, 2921, 2867, 2838, 2251, 1934, 1597, 1497, 1450, 1427, 1383, 1337, 1274, 1220, 1204, 1140, 1026 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.31−7.24 (m, 3H), 7.22−7.12 (m, 3H), 7.04 (d, *J* = 7.6 Hz, 2H), 6.84 (dd, J_1 = J_2 = 7.2 Hz, 1H), 5.40 (s, 1H), 3.73−3.66 (m, 1H), 3.62−3.54 (m, 1H), 3.09 (ddd, *J* = 16.0, 10.0, 6.0 Hz, 1H), 2.92 (ddd, *J* = 16.0, 4.0, 4.0 Hz, 1H), 2.07 (td, *J* = 7.0, 2.4 Hz, 2H), 1.40 (q, *J* = 7.2 Hz, 2H), 0.84 (t, *J* = 8.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 149.4, 136.0, 134.0, 128.9 (2C), 128.7, 127.1, 126.8, 126.0, 119.2, 116.4 (2C), 85.0, 79.2, 77.3, 77.0, 76.9, 51.8, 43.2, 29.0, 22.3, 20.9, 13.5; MS (ESI) 276 ([M + H]$^+$); HRMS(ESI) $C_{20}H_{22}N$ ([M + H]$^+$) calcd 276.1752, found 276.1762.

Methyl 3-(2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-propiolate (5f): colorless crystal; mp 60.0−61.0 °C; IR (KBr) 3062, 3000, 2936, 2848, 2223, 1704, 1596, 1501, 1434, 1374, 1251, 1199, 1150, 1052, 1016, 940 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.38−7.11 (m, 6H), 7.04 (dd, *J* = 8.2, 2.8 Hz, 2H), 6.91 (dd, J_1 = J_2 = 7.2 Hz, 1H), 5.53 (s, 1H), 3.79−3.70 (m, 1H), 3.68 (s, 3H), 3.63−3.54 (m, 1H), 3.13 (ddd, *J* = 15.6, 10.4, 5.2 Hz, 1H), 2.95 (ddd, *J* = 16.0, 3.2, 3.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 153.6, 148.6, 134.4, 132.7, 129.2 (2C), 128.9, 127.7, 127.2, 126.4, 120.2, 116.5 (2C), 86.6, 76.4, 52.7, 51.8, 43.6, 28.8; MS (ESI) 292 ([M + H]$^+$); HRMS(ESI) $C_{19}H_{18}NO_2$ ([M + H]$^+$) calcd 292.1338, found 292.1329.

1-(Phenylethynyl)-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (5g[2a]): colorless crystal; mp 101.6−102.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.33 (s, 1H), 7.26−7.03 (m, 10H), 6.87 (d, *J* = 7.6 Hz, 2H), 5.49 (s, 1H), 3.78 (s, 3H), 3.70−3.46 (m, 2H), 3.14 (ddd, *J* = 16.0, 10.8, 6.8 Hz, 1H), 2.93 (d, *J* = 16.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 154.4, 144.3, 135.7, 134.2, 131.8 (2C), 129.2, 128.2 (2C), 128.1, 127.6, 127.3, 126.3, 123.3, 120.3 (2C), 114.7 (2C), 88.9, 85.8, 55.9, 54.7, 44.7, 29.5. Anal. Calcd for $C_{24}H_{21}NO$: C, 84.92; H, 6.24; N, 4.31. Found: C, 84.86; H, 6.27; N, 4.20.

1-(*p*-Tolylethynyl)-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (5h): colorless crystal; mp 84.9−86.3 °C; IR (KBr) 3019, 3004, 2956, 2908, 2826, 2051, 1511, 1463, 1451, 1364, 1250, 1208, 1121, 1105, 1032, 938, 927 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.35−7.29 (m, 1H), 7.25−7.05 (m, 7H), 6.99 (d, *J* = 8.0 Hz, 2H), 6.92−6.82 (m, 2H), 5.48 (s, 1H), 3.77 (s, 3H), 3.69−3.48 (m, 2H), 3.12 (ddd, *J* = 16.4, 10.8, 6.4 Hz, 1H), 2.92 (ddd, *J* = 16.4, 3.6, 3.6 Hz, 1H), 2.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 154.0, 144.0, 137.8, 135.4, 133.8, 131.4 (2C), 128.8, 128.6 (2C), 126.9, 125.9, 120.0 (2C), 114.2 (2C), 87.6, 85.5, 55.5, 54.4, 44.2, 29.1, 21.5; MS (ESI) 354 ([M + H]$^+$); HRMS(ESI) $C_{25}H_{24}NO$ ([M + H]$^+$) calcd 354.1858, found 354.1866.

1-((4-Fluorophenyl)ethynyl)-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (5i): colorless crystal; mp 70.2−72.1 °C; IR (KBr) 3003, 2935, 2897, 2831, 2049, 1894, 1599, 1506, 1465, 1371, 1246, 1154, 1032, 968, 938 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.35−7.28 (m, 1H), 7.26−7.04 (m, 7H), 6.93−6.81 (m, 4H), 5.48 (s, 1H), 3.78 (s, 3H), 3.64−3.50 (m, 2H), 3.13 (ddd, *J* = 16.8, 10.8, 6.4 Hz, 1H), 2.92 (ddd, *J* = 16.0, 3.2, 3.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 162.1 (d, $^1J_{C-F}$ = 246.8 Hz), 154.1, 143.9, 135.2, 133.9, 133.4 (d, $^3J_{C-F}$ = 8.1 Hz) (2C), 128.9, 127.3, 127.0, 126.0, 120.0 (2C), 119.0 (d, $^4J_{C-F}$ = 1.8 Hz), 115.2 (d, $^2J_{C-F}$ = 21.9 Hz) (2C), 114.3 (2C), 88.2, 84.4, 55.6, 54.4, 44.3, 29.1; MS (ESI) 358 ([M + H]$^+$); HRMS(ESI) $C_{24}H_{21}FNO$ ([M + H]$^+$) calcd 358.1607, found 358.1614.

Methyl 3-(2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)propiolate (5j): yellow crystal; mp 72.6−75.0 °C IR (KBr) 3066, 3008, 2955, 2910, 2837, 2217, 1717, 1513, 1432, 1378, 1244, 1137, 1032, 938, 820 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, ppm) δ 7.27−7.13 (m, 4H), 7.02 (d, *J* = 9.0 Hz, 2H), 6.86 (d, *J* = 9.0 Hz, 2H), 5.38 (s, 1H), 3.78 (s, 3H), 3.67 (s, 3H), 3.56−3.50 (m, 2H), 3.12 (ddd, *J* = 16.4, 8.4, 8.4 Hz, 1H), 2.89 (ddd, *J* = 16.4, 3.2, 3.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 154.2, 153.4, 142.9, 133.9,

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132.6, 128.9, 127.4, 127.0, 126.0, 119.7 (2C), 114.2 (2C), 86.4, 76.5, 55.3, 53.7, 52.4, 44.0, 28.7; MS (ESI) 322 ([M + H]$^+$); HRMS(ESI) $C_{20}H_{20}NO_3$ ([M + H]$^+$) calcd 322.1443, found 322.1435

sp^3 C−H and Aryl-sp^2 C−H Coupling Reaction: 1-(1*H*-Indol-3-yl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (7a[2d]). Typical Procedure. The following components were added to the screw-capped stainless steel vial: *N*-phenyltetrahydroisoquinoline **1a** (0.209 g, 1 mmol), indole **6a** (0.09 g, 0.8 mmol), DDQ (0.182 g, 0.8 mmol), and silica gel (0.5 g), along with two copper balls (d = 8.0 mm). Then, the vial was placed in a vibrational micromill and the contents were ball milled at 30 Hz. At the end of the experiment, all the reaction mixture was scratched off the vessel then directly separated and purified by column chromatography. Elution of the column with PE/EtOAc (20:1) afforded the product **7a**[2d] as a white crystal: mp 180.0−181.0 °C (lit.[2d] mp 179.0−180.0 °C); ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.90 (s, 1H), 7.53 (d, J = 7.6 Hz, 1H), 7.31−7.10 (m, 8H), 7.04−6.96 (m, 3H), 6.76 (m, 1H), 6.61 (s, 1H), 6.16 (s, 1H), 3.62 (dd, J = 6.8, 4.8 Hz, 2H), 3.06 (ddd, J = 16.0, 7.6, 7.6 Hz, 1H), 2.80 (d, J = 16.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 149.6, 137.3, 136.4, 135.4, 129.0 (2C), 128.7, 127.9, 126.5, 126.3, 125.6, 124.0, 122.0, 120.0, 119.5, 119.2, 118.0, 115.7 (2C), 110.9, 56.7, 42.4, 26.8. Anal. Calcd for $C_{23}H_{20}N_2$: C, 85.15; H, 6.21; N, 8.63. Found: C, 84.82; H, 6.25; N, 8.59.

1-(1-Methyl-1*H*-indol-3-yl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (7b[2d]): white crystal; mp 118.6−120.1 °C (lit.[2d] mp 113.0−114.0 °C); ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.53 (d, J = 8.0 Hz, 1H), 7.30−7.10 (m, 8H), 7.04−6.95 (m, 3H), 6.75 (dd, J_1 = J_2 = 7.2 Hz, 1H), 6.48 (s, 1H), 6.16 (s, 1H), 3.68−3.57 (m, 2H), 3.63 (s, 3H), 3.05 (ddd, J = 16.0, 8.8, 6.4 Hz, 1H), 2.80 (ddd, J = 16.0, 4.2, 4.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 149.5, 137.4, 137.1, 135.3, 129.0 (2C), 128.6 (2C), 127.8, 126.7, 126.4, 125.5, 121.5, 120.0, 118.9, 117.8, 117.5, 115.5 (2C), 109.0, 56.6, 42.2, 32.7, 26.7.

1-(5-Methoxy-1*H*-indol-3-yl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (7c[2d]): colorless crystal; mp 179.3−180.3 °C (lit.[2d] mp 172.0−174.0 °C); ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.80 (s, 1H), 7.33−7.08 (m, 7H), 7.01 (d, J = 8.0 Hz, 2H), 6.87 (d, J = 2.0 Hz, 1H), 6.82−6.73 (m, 2H), 6.56 (d, J = 2.0 Hz, 1H), 6.13 (s, 1H), 3.65 (s, 3H), 3.62−3.56 (m, 2H), 3.07 (ddd, J = 16.0, 7.6, 7.6 Hz, 1H), 2.81 (ddd, J = 16.0, 4.4, 4.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 153.7, 149.8, 137.3, 135.4, 131.4, 129.0 (2C), 128.6, 127.8, 126.8, 126.5, 125.5, 124.8, 118.6, 118.1, 116.1 (2C), 112.2, 111.5, 101.8, 56.9, 55.7, 42.2, 27.1.

1-(5-Bromo-1*H*-indol-3-yl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (7d): colorless crystal; mp 189.4−191.3 °C; IR (KBr) 3396, 3015, 2997, 2900, 1593, 1492, 1334, 1312, 1284, 1213, 1132, 1090, 1031, 937, 752, 646 cm^{-1};^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.93 (s, 1H), 7.59 (s, 1H), 7.33−7.07 (m, 8H), 7.00 (d, J = 8.0 Hz, 2H), 6.81 (m, 1H), 6.59 (s, 1H), 6.06 (s, 1H), 3.65−3.50 (m, 2H), 3.05 (ddd, J = 16.0, 8.4, 8.4 Hz, 1H), 2.80 (d, J = 16.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 149.7, 136.9, 135.3, 135.0, 129.1 (2C), 128.8, 128.0, 127.8, 126.7, 125.7, 125.2, 124.9, 122.6, 119.0, 118.7, 116.4 (2C), 112.9, 112.3, 56.8, 42.7, 26.8; MS (EI) m/z 404 (95), 403 (56), 402 (100), 401 (37), 311(79), 310 (93), 309 (85), 308 (73), 299 (52), 298 (58), 297 (57), 296 (45), 218 (33), 217 (50), 208 (23), 206 (32); HRMS calcd for $C_{23}H_{19}BrN_2$ 402.0736, found 402.0732.

1-(2-Methyl-1*H*-indol-3-yl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (7e[2d]): colorless crystal; mp 90.7−93.6 °C (lit.[2d] mp 80−85 °C); ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.65 (s, 1H), 7.14 (d, J = 8.0 Hz, 5H), 7.08−6.93 (m, 6H), 6.87 (m, 1H), 6.80 (m, 1H), 5.94 (s, 1H), 3.72−3.52 (m, 2H), 3.12−2.95 (m, 2H), 1.99 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 150.8, 137.8, 135.1, 134.7, 133.1, 128.6 (2C), 128.5, 128.1, 126.1, 125.9, 120.6, 120.1, 119.3 (2C), 119.0, 113.3, 109.9, 57.2, 45.9, 28.0, 12.4.

1-(1*H*-Indol-3-yl)-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (7f[2d]): colorless crystal; mp 164.7−165.8 °C (lit.[2d] mp 162.0−163.0 °C); ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.88 (s, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.27 (d, J = 8.0 Hz, 1H), 7.20−7.07 (m, 5H), 7.01−6.89 (m, 3H), 6.77 (d, J = 9.2 Hz, 2H), 6.53 (d, J = 1.6 Hz 1H), 5.94 (s, 1H), 3.73 (s, 3H), 3.58−3.41 (m, 2H), 3.02 (ddd, J = 16.0, 10.0, 6.0 Hz, 1H), 2.79 (ddd, J = 16.0, 3.2, 3.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 153.1, 144.5, 137.4, 136.3, 135.2, 128.7, 128.0, 126.7, 126.3, 125.5, 124.2, 121.8, 120.1, 119.5 (2C), 119.4, 119.0, 114.3 (2C), 110.8, 58.0, 55.6, 43.8, 26.9.

1-(1-Methyl-1*H*-indol-3-yl)-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (7g): colorless crystal; mp 145.1−146.4 °C; IR (KBr) 3446, 3060, 3031, 2927, 2904, 2828, 1510, 1460, 1330, 1270, 1241, 1188, 1135, 1038, 925, 830, 756, 746 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.40 (d, J = 8.0 Hz, 1H), 7.25−7.08 (m, 6H), 7.01−6.89 (m, 3H), 6.77 (d, J = 9.2 Hz, 2H), 6.39 (s, 1H), 5.96 (s, 1H), 3.74 (s, 3H), 3.63 (3, 3H), 3.62−3.42 (m, 2H), 3.02 (ddd, J = 16.0, 10.0, 6.0 Hz, 1H), 2.79 (d, J = 16.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 153.0, 144.5, 137.5, 137.0, 135.2, 128.8, 128.7, 128.1, 127.1, 126.3, 125.5, 121.4, 120.1, 119.2 (2C), 118.9, 117.5, 114.3 (2C), 108.9, 57.7, 55.6, 43.6, 32.7, 26.8; MS (ESI) 369 ([M + H]$^+$); HRMS(ESI) $C_{25}H_{25}N_2O$ ([M + H]$^+$) calcd 369.1967, found 369.1966.

1-(5-Methoxy-1*H*-indol-3-yl)-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (7h[2d]): yellow crystal; mp 56.3−58.5 °C (lit.[2d] mp 55.0−60.0 °C); ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.80 (s, 1H), 7.21−7.08 (m, 5H), 6.93 (d, J = 8.8 Hz, 2H), 6.80−6.74 (m, 3H), 6.70 (d, J = 2.0 Hz, 1H), 6.47 (d, J = 2.8 Hz, 1H), 5.92 (s, 1H), 3.74 (s, 3H), 3.64 (s, 3H), 3.56−3.37 (m, 2H), 3.05 (ddd, J = 16.0, 10.0, 6.0 Hz, 1H), 2.80 (ddd, J = 16.4, 3.6, 3.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 153.6, 153.3, 144.7, 137.5, 135.1, 131.3, 128.6, 128.0, 127.2, 126.3, 125.5, 125.1, 120.1 (2C), 118.2, 114.2, 112.1, 111.4 (2C), 101.8, 58.4, 55.7, 55.6, 43.5, 27.3.

1-(2-Methyl-1*H*-indol-3-yl)-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (7i): colorless crystal; mp 183.4−184.5 °C; IR (KBr) 3349, 3065, 3016, 2950, 2921, 2898, 2782, 2699, 1509, 1460, 1365, 1234, 1124, 1014, 934 833, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.61 (s, 1H), 7.20−7.08 (m, 3H), 7.05 (d, J = 7.8 Hz, 1H), 7.01−6.95 (m, 2H), 6.92 (d, J = 7.8, 1H), 6.88−6.82 (m, 3H), 6.65 (d, J = 8.8 Hz, 2H), 5.60 (s, 1H), 3.69 (s, 3H), 3.55 (ddd, J = 11.6, 5.6, 5.6 Hz, 1H), 3.47−3.35 (m, 1H), 3.16 (ddd, J = 16.4, 5.6, 5.6 Hz, 1H), 3.02 (ddd, J = 16.4, 5.6, 5.6 Hz, 1H), 1.96 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 154.7, 145.4, 138.4, 134.9, 133.4, 128.3, 127.9, 125.8, 125.8, 123.3 (2C), 120.5, 119.4, 119.1, 113.7 (2C), 113.1, 109.8, 59.3, 55.4, 48.7, 29.3, 12.1; MS (ESI) 369 ([M + H]$^+$); HRMS(ESI) $C_{25}H_{25}N_2O$ ([M + H]$^+$) calcd 369.1967, found 369.1965.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) For the influence of grinding auxiliary on sp^3 C−H and *aryl*-sp^2 C−H bond CDC reactions, see the Supporting Information.
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