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Graphical Abstract

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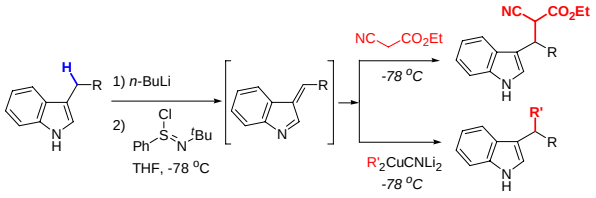
Jun-ichi Matsuo,* Yumi Tanaki and Hiroyuki Ishibashi*
Division of Pharmaceutical Sciences, Graduate School of Natural Science and Technology, Kanazawa University, Kakuma-machi, Kanazawa 920-1192, Japan.



one-pot oxidative C-C bond formation

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One-pot oxidative carbon-carbon bond formation of 3-benzylic and 3-allylic indoles with carbon nucleophiles

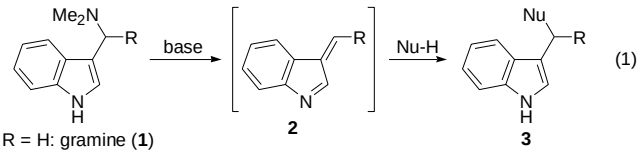
Jun-ichi Matsuo,* Yumi Tanaki and Hiroyuki Ishibashi*

Division of Pharmaceutical Sciences, Graduate School of Natural Science and Technology, Kanazawa University, Kakuma-machi, Kanazawa 920-1192, Japan.

Abstract— Indolenines were generated at –78 °C from 3-benzylic or 3-allylic indoles by dehydrogenation with *N-tert*-butylbenzenesulfinimidoyl chloride, and a carbon-carbon bond was formed at –78 °C in a one-pot manner by treating these indolenines with various carbon nucleophiles such as active methylene compounds or organocuprates.

1. Introduction

3-Alkylindoles are frequently found as a part of biologically important natural products and pharmaceutical agents, and they have been synthesized by various methods.[1,2] Since the first report by Snyder in 1944,[3a] the reaction of carbon nucleophiles with 3-(*N*,*N*-dimethylaminomethyl)indole (gramine, **1**) or its derivatives has been an important and conventional method for the synthesis of various 3-substituted indoles (eq. 1).[4] The C-C bond formation proceeds via reactive indolenines **2**[3b] which are usually generated from **1** in the presence of nucleophile (e.g. ethyl acetamidomalonate) under several conditions; employment of base at high temperature,[3a,c] employment of base and *N*-alkylating agent (e.g. iodomethane and methylsulfate) at room temperature,[3d] and employment of tri-*n*-butylphosphine in refluxing acetonitrile.[3e] The similar fragmentation reaction to **2** is considered to proceed from isolable intemediates such as 3-(1-arylsulfonylalkyl)indole,[5] 3-(alkoxymethyl)indole,[3b] 3-(hydroxymethyl)indole,[6] 3-(ethylthiomethy)indole,[7] and 3-(1-phenyl-*N*-methylaminomethyl)indole.[8] Indolenines **2** are believed to be included in a variety of reactions such as synthesis of bisindolylalkanes from indoles and aldehydes.[9] Also, it is considered that indolenine moiety may be an intermediate in the mechanism of the action of the dehydrogenase enzymes.[10] Thus, indolenine intermediate works important role in chemical syntheses and in biochemical transformations. It was reported that free indolenines **2** were unstable, but sulfuric acid or hydrogen chloride salts of these indolenines were prepared as stable compounds by reaction of indoles with aromatic aldehydes in the presence of the corresponding acid.[11]



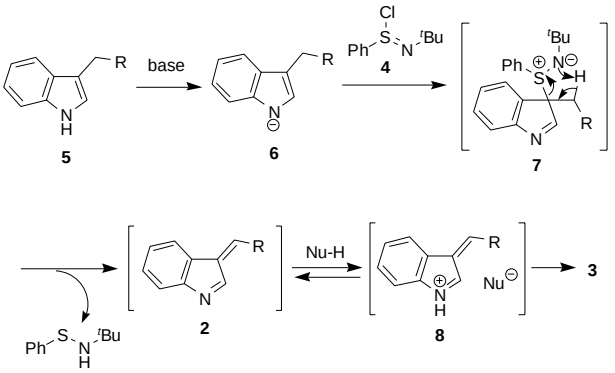
(1)

We have been studying mild oxidative C-H activation[12] of organic molecules with *N-tert*-butylbenzenesulfinimidoyl chloride (**4**)[13] to generate a reactive intermediate followed by trapping it with carbon nucleophiles. This method provides a unique C-C bond formation at a position where it is difficult to form a new C-C bond by other methods. For example, one-pot oxidative Mannich reactions of *N*-Cbz amines[14a] and lactams[14b] and oxidative Michael addition of 1,3-dicarbonyl compounds[14c] have been carried out efficiently.[15] In the course of our study, we considered the possibility for generating free indolenine intermediate **2** by oxidative activation of 3-alkylindole **5** with **4** (Scheme 1). Thus, metallated indole **6** reacts with **4** at the 3-position of indole to afford an intermediate **7** in which elimination should proceed via a five-membered transition state to form free indolenine **2** at low temperature. Thus-formed reactive intermediate **2** would react with carbon nucleophile to give indole derivative **3** in a one-pot manner. One-pot introduction of a carbon-carbon bond onto the alkyl substituents of 3-alkylindoles (**5** to **3**) is a challenging route

* Corresponding author. Tel.: +81-76-234-4439; fax: +81-76-234-4439; e-mail: jimatsuo@p.kanazawa-u.ac.jp.

for derivatizing them, and, to the best of our knowledge, such one-pot bond formation has not been reported to date.

We would like to report here a new method for generating free indolenine **2** by dehydrogenation of 3-alkylindoles **5** with **4** at –78 °C, and unexpectedly high reactivity of indolenine **2** toward carbon nucleophiles such as ethyl cyanoacetate. The reaction profile of organometallic agents toward **2** is also described.



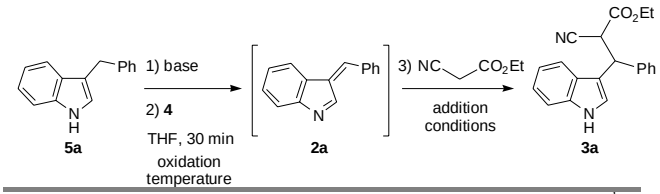
Scheme 1. Generation of indolenine **2** by oxidation of **5** with **4** and one-pot carbon-carbon bond formation.

2. Results and discussion

2.1. One-pot C-C bond formation of 3-benzylic and 3-allylic indoles with active methylene compounds

First, suitable reaction conditions for oxidation of 3-benzylindole (**5a**) with **4** were investigated (Table 1). Lithiation of **5a** with *n*-BuLi followed by reaction with **4** at –78 °C proceeded immediately. In order to trap the indolenine intermediate **2a**, ethyl cyanoacetate was added. Although gramine derivatives were reported to react with active methylene compounds above at room temperature,[3,4] the present C-C bond formation proceeded at surprisingly low temperature (at –78 °C) to afford adduct **3a** in 81% yield (entry 1). Moreover, the intermediate **2a** reacted even at –100 °C (entry 2). Elevation of reaction temperature from –78 °C to room temperature did not improve the yield of **3a**. The use of lithium hexamethyldisilazide (LHMDS) instead of *n*-BuLi also gave **3a** in 81% yield (entry 3). It was noted that lithium ion was superior to sodium or potassium ion as a counter cation of metallated indole **6**, since sodium hexamethyldisilazide (NHMDS) and potassium hexamethyldisilazide (KHMDS) gave **3a** in 61 and 33% yields, respectively (entries 4 and 5). The effect of metal ion might be explained by regioselectivity (C-3 vs. N) in the reaction of **6** and **4**. The use of diisopropylethylamine as a base gave only a trace amount of the desired product **3a** (entry 6).

Table 1. Generation of free indolenine **2a** by oxidation of **5a** with **4** and successive addition of ethyl cyanoacetate.[a]

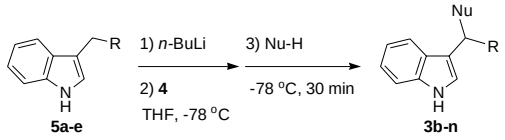


entry	base	oxidation temperature	addition conditions	yield (%)[b]
1	*n*-BuLi	-78 °C	-78 °C, 30 min	81
2	*n*-BuLi	-100 °C	-100 °C, 30 min	63
3	LHMDS	-78 °C	-78 °C, 30 min	81
4	NHMDS	-78 °C	-78 °C, 30 min	61
5	KHMDS	-78 °C	-78 °C, 30 min	33
6	*i*-Pr_2NEt	-78 °C to rt	-78 °C to rt	trace

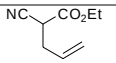
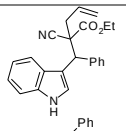
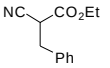
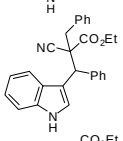
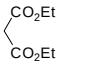
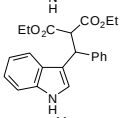
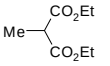
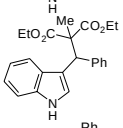
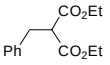
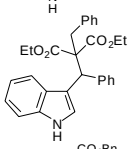
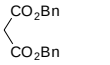
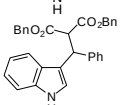
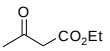
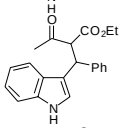
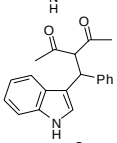
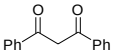
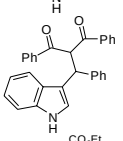
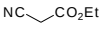
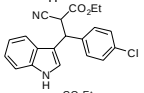
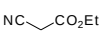
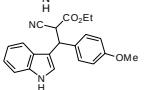
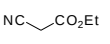
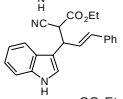
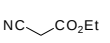
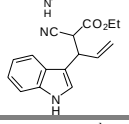
[a] **5a** (1.0 equiv), base (1.3 equiv), **4** (1.5 equiv) and ethyl cyanoacetate (1.5 equiv) were employed.
[b] Isolated yield. A mixture of diastereomers (D.r.(diastereomer ratio) = 50:50) was obtained in each case.

We then investigated the substrate generality of **4**-mediated oxidative alkylation of 3-alkylindoles (Table 2). In addition to ethyl cyanoacetate, ethyl allylcyanoacetate and ethyl benzylcyanoacetate reacted to afford the corresponding alkylated products in 83% and 78% yields, respectively (entries 1 and 2). Malonic acid esters (entries 3-6), ketoesters (entry 7), and 1,3-diketones (entries 8 and 9) also reacted to give the products in moderate to good yields, whereas the reaction with nitromethane proceeded very sluggishly (12% yield). Next, several 3-benzylic and 3-allylic indoles were subjected to this oxidative alkylation. 3-(4-Chlorobenzyl)indole (**5b**) and 3-(4-methoxybenzyl)indole (**5c**) reacted smoothly to afford the corresponding adducts **3k** (78%) and **3l** (72%), respectively. 3-Cinnamylindole (**5d**) also reacted with ethyl cyanoacetate regioselectively to afford **3m** in 84% yield, while 3-allylindole (**5e**) gave **3n** in 36% yield along with its regioisomer **3n'** (11%). On the other hand, the present oxidative C-C bond formation of 3-methylindole and 3-ethylindole with ethy cyanoacetate gave only a trace amount of products. The unprecedented high reactivity of **2** toward active methylene compounds may be ascribed to facilitated attack of carbanion to protonated indolenine **8** under neutral conditions (see Scheme 1).

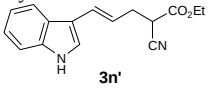
Table 2. Oxidative carbon-carbon bond formation of 3-benzylic and 3-allylic indoles with various carbon nucleophiles bearing active methylene or methine protons.



5a: R = Ph; **5b**: R = 4-ClC_6H_4; **5c**: R = 4-MeOC_6H_4; **5d**: R = CH=CHPh; **5e**: R = CH=CH_2

entry	indol	NuH	product		yield (%)[a]
1	**5a**			**3b**	83[b]
2	**5a**			**3c**	78[c]
3	**5a**			**3d**	66 (78)[d]
4	**5a**			**3e**	75
5	**5a**			**3f**	55
6	**5a**			**3g**	71
7	**5a**			**3h**	54[d,e]
8	**5a**			**3i**	56
9	**5a**			**3j**	63
10	**5b**			**3k**	78[f]
11	**5c**			**3l**	72[f]
12	**5d**			**3m**	84[g]
13	**5e**			**3n**	36[h]

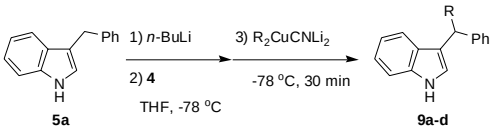
[a] Isolated yield. [b] D.r. = 64:36. [c] D.r. = 67:33. [d] Determined by ^{1}H NMR analysis using an internal standard. [e] D.r. = 56:44. [f] D.r. = 50:50. [g] D.r. = 60:40. [h] D.r. = 60:40. Regioisomer **3n'** was also obtained in 11% yield



2.2. One-pot C-C bond formation of 3-benzylindole (5a) with organometallic agents

Organometallic agents were next examined as a nucleophile in the present one-pot C-C bond formation of **5a**. After screening some organometallic reagents, alkyllithium (MeLi, 25% yield) and Grignard reagents (MeMgBr, 32% yield; PhMgBr, 35% yield) were found to be not suitable for the present carbon-carbon bond formation, while alkylzinc (Me_2Zn, 50% yield; Et_2Zn, 70% yield) gave the alkylated products in moderate yields. It was found that higher-order cyanocuprates gave the desired alkylated and arylated products in good yields (Table 3). Methyl, *n*-butyl, *t*-butyl, and phenyl groups were introduced smoothly at the benzylic position of **5a**.

Table 3. Oxidative carbon-carbon bond formation of **5a** with various higher-order cyanocuprates.[a]



entry	R	product	yield (%)[b]
1	Me	**9a**	54
2	*n*-Bu	**9b**	77
3	*t*-Bu	**9c**	54
4	Ph	**9d**	82

[a] About reaction conditions, see Table 1.
[b] Determined by ^{1}H NMR analysis.

3. Conclusion

3-Benzylic and 3-allylic indoles were activated by oxidation with **4** to form free indolenines **2** at –78 °C, and various carbon nucleophiles such as active methylene compounds and organocuprates reacted with them at –78 °C in a one-pot manner. The present oxidative activation of indoles with **4** will be applicable to various types of nucleophiles and to stereoselective bond formation because of high reactivity observed on **2**. The present method can be regarded as a new method for generating free indolenine. Recently, Ir[16]- or Pd[17]-catalyzed direct alkylation of indoles with benzylic or allylic alcohols to the corresponding 3-alkylindoles has been reported.[18] Various 3-alkylindoles are now readily prepared, and the present method will be useful for rapid and further derivatization of 3-alkylindoles. Therefore, a diverse chemical library of 3-substituted indoles can be constructed and it would provide an opportunity to discover a more potent drug candidate.

4. Experimental

4.1. General

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Shimadzu FTIR-8100. ^{1}H

NMR spectra were recorded on a JEOL JNM EX270 (270 MHz) or a JEOL JNM GSX500 (500 MHz) spectrometer; chemical shifts (δ) are reported in parts per million relative to tetramethylsilane. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. ^{13}C NMR spectra were recorded on a JEOL JNM GSX500 (500 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in parts per million relative to tetramethylsilane with the solvent resonance as the internal standard $CDCl_3$ and DMSO-d_6. High resolution mass spectra (HRMS) were recorded on a JEOL JMS-SX-102A mass spectrometer. Elemental analyses were carried out on a Yanaco CHN Corder MT-5. Analytical TLC was performed on Merck precoated TLC plates (silica gel 60 GF254, 0.25 mm). Silica-gel column chromatography was carried out on silica gel 60N (Kanto Kagaku Co., Ltd., spherical, neutral, 63–210 μm). Preparative thin-layer chromatography (PTLC) was carried out on silica gel Wakogel B-5F. THF was distilled under argon from sodium/benzophenone ketyl. All oxidative carbon-carbon bond formations were carried out under argon in dried glassware with magnetic stirring.

N-*tert*-Butylbenzenesufinimidoyl chloride (**4**) was prepared according to the modified literature procedure[19] of employing 1.3 equivalents of *N*,*N*-dichloro-*tert*-butylamine, and **1** was stored in a refrigerator. 3-Alkylindoles (**5a**,[20] **5b**,[20] **5d**,[17] and **5e**[17]) were prepared by the reported methods. Ethyl allylcyanoacetate and ethyl benzylcyanoacetate were prepared by alkylation of ethyl cyanoacetate (*t*-BuOK and alkylating agent). Other active methylene compounds and methine compounds were purchased and used after distillation.

4.2. Typical procedure for the oxidative C-C bond formation of 3-alkylindole with active methylene compounds (Table 1, entry 1)

To a stirred solution of **5a** (50 mg, 0.241 mmol) in THF (3 mL) was added dropwise a solution of *n*-BuLi (1.65 *N* in hexane, 0.19 mL, 0.31 mmol) at –78 °C. After the mixure was stirred for 15 min at the same temperature, a solution of **4** (77 mg, 0.36 mmol) in THF (1 mL) was added at –78 °C. After the mixture was stirred for 30 min at the same temperature, ethyl cyanoacetate (0.04 mL, 0.38 mmol) was added at –78 °C, and the reaction mixture was stirred for 30 min at the same temperature. The reaction mixture was then treated with saturated aqueous $NaHCO_3$, and the resulting mixture was extracted with ethyl acetate (three times). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by thin layer chromatography on silica gel (hexane/ethyl acetate = 5/1) to afford **3a** (62 mg, 0.195 mmol, 81%) as a white solid.

4.2.1. 2-Cyano-3-(1*H*-indol-3-yl)-3-phenylpropionic Acid Ethyl Ester (3a)[8b]

A mixture of diastereomers (63:27); white solid: mp 79.5-80.5 °C (hexane-ethyl acetate) [lit.[8b] 91-93 °C (from aqueous AcOH)]; ^{1}H NMR (500 MHz, $CDCl_3$, major diastereomer) δ 1.10 (t, *J* = 7.5 Hz, 3H), 4.07-4.20 (m, 2H), 4.32 (d, *J* = 6.7 Hz, 1H), 5.04 (d, *J* = 6.7 Hz, 1H), 7.01-7.08 (m, 1H), 7.23-7.39 (m, 6H), 7.46 (d, *J* = 7.3 Hz, 2H), 8.15 (s, 1H); ^{1}H NMR (500 MHz, $CDCl_3$, minor diastereomer) δ 1.08 (t, *J* = 7.5 Hz, 3H), 4.07-4.20 (m, 2H), 4.19 (d, *J* = 6.7 Hz, 1H), 5.10 (d, *J* = 6.7 Hz, 1H), 7.01-7.08 (m, 1H), 7.15-7.20 (m, 1H), 7.23-7.39 (m, 6H), 7.50 (d, *J* = 2.4 Hz, 1H), 8.19 (s, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$, major diastereomer) δ 13.6, 43.1, 44.2, 62.9, 111.3, 113.1, 116.1, 118.6, 119.6, 122.1, 122.5, 126.5, 127.6, 127.9, 128.6, 136.0, 139.6, 165.2; ^{13}C NMR (67.8 MHz, $CDCl_3$, minor diastereomer) δ 13.7, 43.1, 45.0, 62.8, 111.3, 114.5, 116.3, 118.8, 119.7, 122.2, 122.4, 126.0, 127.8, 128.3, 128.6, 136.2, 138.6, 165.3.

4.2.2. 2-Allyl-2-Cyano-3-(1*H*-indol-3-yl)-3-phenylpropionic Acid Ethyl Ester (3b)

Diastereomers were separated by preparative TLC (hexane/benzene/ethyl acetate = 8/8/1). The less polar diastereomer; white powder: mp 107.5-108.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.99 (t, *J* = 7.0 Hz, 3H), 2.67 (dd, *J* = 6.7 Hz, 14 Hz, 1H), 2.79 (dd, *J* = 7.9 Hz, 14 Hz, 1H), 4.01 (q, *J* = 7.0 Hz, 2H), 4.78 (s, 1H), 5.11-5.15 (m, 2H), 5.72-5.80 (m, 1H), 7.13 (t, *J* = 7.6 Hz, 1H), 7.20 (t, *J* = 7.3 Hz, 2H), 7.24-7.28 (m, 2H), 7.36 (d, *J* = 7.9 Hz, 1H), 7.58 (d, *J* = 7.3 Hz, 2H), 7.64 (d, *J* = 7.9 Hz, 1H), 7.71 (d, *J* = 2.4 Hz, 1H), 8.34 (s, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 13.7, 41.7, 48.4, 56.7, 62.5, 111.3, 113.1, 118.1, 119.5, 120.0, 120.1, 122.5, 122.5, 127.5, 127.8, 128.5, 128.6, 130.8, 135.3, 139.5, 168.1; IR ($CHCl_3$, cm^{-1}) 3021, 2359, 1736, 1211; Anal. Calcd for $C_{23}H_{22}N_2O_2$: C, 77.07; H, 6.19; N, 7.82. Found: C, 76.74; H, 6.16; N, 7.68.

The more polar diastereomer; white powder: mp 150.5-151 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.99 (t, *J* = 7.0 Hz, 3H), 2.40 (dd, *J* = 6.7 Hz, 13.7 Hz, 1H), 2.72 (dd, *J* = 7.9 Hz, 13.7 Hz, 1H), 4.01 (q, *J* = 7.0 Hz, 2H), 4.78 (s, 1H), 5.16 (d, *J* = 4.9 Hz, 1H), 5.18 (s, 1H), 5.76-5.82 (m, 1H), 7.00 (t, *J* = 7.6 Hz, 1H), 7.12 (t, *J* = 7.0 Hz, 1H), 7.25-7.36 (m, 5H), 7.55 (d, *J* = 6.7 Hz, 2H), 7.80 (d, *J* = 2.4 Hz, 1H), 8.24 (s, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 13.7, 42.1, 48.6, 55.3, 62.6, 111.0, 114.2, 118.6, 119.0, 119.6, 120.7, 121.9, 122.4, 126.8, 127.9, 128.6, 129.6, 130.6, 135.5, 138.1, 168.2; IR ($CHCl_3$, cm^{-1}) 3478, 2359, 1740, 1227; Anal. Calcd for $C_{23}H_{22}N_2O_2$: C, 77.07; H, 6.19; N, 7.82. Found: C, 76.83; H, 6.18; N, 7.76.

4.2.3. 2-Benzyl-2-Cyano-3-(1*H*-indol-3-yl)-3-phenylpropionic Acid Ethyl Ester (3c)

Diastereomers were separated by preparative TLC (benzene/ethyl acetate = 100/1). The less polar diastereomer; white amorphous: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.81 (t, *J* = 7.2 Hz, 3H), 3.19 (d, *J* = 13.6 Hz, 1H), 3.36 (d, *J* = 13.6 Hz, 1H), 3.79-3.89 (m, 2H), 4.94 (s, 1H), 7.14-7.26 (m, 10H), 7.38 (d, *J* = 8.1 Hz, 1H), 7.61 (d, *J* = 8.1 Hz, 2H), 7.72 (d, *J* = 8.1 Hz, 1H), 7.82 (d, *J* = 2.4 Hz, 1H), 8.38 (s, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 13.5, 43.2, 49.0, 58.6, 62.4, 111.4, 113.2, 118.2, 119.5, 120.0, 122.6, 122.7, 127.5, 127.6, 127.9, 128.4, 128.5, 128.7,

129.9, 134.5, 135.4, 139.5, 168.0; IR ($CHCl_3$, cm^{-1}) 3476, 1736; HRMS (EI) Calculated for $C_{27}H_{24}N_2O_2$: 408.18378. Found: 408.18390.

The more polar diastereomer; white amorphous: ^1H NMR (500 MHz, $CDCl_3$) δ 0.80 (t, J = 7.1 Hz, 3H), 2.88 (d, J = 13.4 Hz, 1H), 3.28 (d, J = 13.4 Hz, 1H), 3.80-3.89 (m, 2H), 4.94 (s, 1H), 7.02 (t, J = 7.4 Hz, 1H), 7.13 (t, J = 7.6 Hz, 1H), 7.20-7.40 (m, 10H), 7.65 (d, J = 7.3 Hz, 2H), 7.77 (d, J = 2.4 Hz, 1H), 8.14 (s, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 13.5, 43.7, 49.3, 56.9, 62.5, 111.0, 114.3, 118.7, 119.2, 119.7, 121.9, 122.4, 126.9, 127.7, 127.9, 128.4, 128.7, 129.8, 129.8, 134.2, 135.5, 138.2, 168.1; IR ($CHCl_3$, cm^{-1}) 3478, 2245, 1736, 1242; HRMS (EI) Calculated for $C_{27}H_{24}N_2O_2$: 408.18378. Found: 408.18410.

4.2.4. Ethyl 2-[1*H*-indol-3-yl(phenyl)methyl]malonate (3d)[8d]

White silky filber: mp 183.5-184.0 °C (hexane-ethyl acetate) [ref.[8d] 165-167 °C (from EtOH)]; ^1H NMR (500 MHz, $CDCl_3$) δ 0.97 (t, J = 7.1 Hz, 3H), 1.00 (t, J = 7.1 Hz, 3H), 3.95-4.30 (m, 4H), 4.29 (d, J = 11.8 Hz, 1H), 5.08 (d, J = 11.8 Hz, 1H), 7.02 (t, J = 7.7 Hz, 1H), 7.10-7.14 (m, 3H), 7.20-7.26 (m, 3H), 7.36 (d, J = 7.6 Hz, 2H), 7.54 (d, J = 8.1 Hz, 1H), 8.09 (s, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 13.7, 13.7, 42.6, 58.4, 61.4, 61.4, 111.0, 116.9, 119.3, 119.4, 120.9, 122.2, 126.7, 126.7, 128.2, 128.3, 136.2, 141.4, 167.8, 168.0.

4.2.5. Ethyl 2-[1*H*-indol-3-yl(phenyl)methyl]-2-methylmalonate (3e)

Pale yellow oil: ^1H NMR (500 MHz, $CDCl_3$) δ 0.93 (t, J = 7.0 Hz, 3H), 1.10 (t, J = 7.0 Hz, 3H), 1.66 (s, 3H), 3.91-3.99 (m, 2H), 4.08 (q, J = 7.0 Hz, 2H), 5.36 (s, 1H), 6.99 (t, J = 7.6 Hz, 1H), 7.09-7.15 (m, 2H), 7.18-7.21 (m, 2H), 7.27 (d, J = 7.9 Hz, 1H), 7.40 (d, J = 2.4 Hz, 1H), 7.44 (dd, J = 7.0 Hz, 1.5 Hz, 3H), 8.11 (s, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 13.5, 13.7, 19.1, 46.7, 59.2, 61.3, 61.3, 110.8, 115.2, 119.1, 119.2, 121.9, 122.4, 126.5, 127.7, 127.9, 130.3, 135.3, 140.2, 171.2, 171.5; IR ($CHCl_3$, cm^{-1}) 3480, 2350, 1728; HRMS (EI) Calculated for $C_{23}H_{25}NO_4$: 379.17836. Found 379.17920.

4.2.6. Ethyl 2-benzyl-2-[1*H*-indol-3-yl(phenyl)methyl]malonate (3f)

Colorless needles: mp 135.5-136.0 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 0.85 (t, J = 7.3 Hz, 3H), 1.01 (t, J = 7.3 Hz, 3H), 3.43 (d, J = 14.0 Hz, 1H), 3.60 (d, J = 14.0 Hz, 1H), 3.84-4.03 (m, 4H), 5.16 (s, 1H), 6.98-7.01 (m, 3H), 7.10-7.19 (m, 7H), 7.31 (d, J = 8.5 Hz, 1H), 7.40 (d, J = 7.9 Hz, 3H), 7.72 (d, J = 2.4 Hz, 1H), 8.11 (s, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 13.4, 13.6, 42.0, 48.3, 60.8, 60.9, 64.4, 110.8, 115.3, 118.8, 119.3, 121.8, 122.9, 126.5, 126.6 127.5, 127.8, 127.9, 130.2, 130.3, 135.4, 136.8, 140.4, 170.1, 171.1; IR ($CHCl_3$, cm^{-1}) 3480, 1717; Anal. Calcd for $C_{27}H_{29}NO_4$: C, 76.46; H, 6.42; N, 3.07. Found: C, 76.63; H, 6.51; N, 3.09.

4.2.7. Benzyl 2-[1*H*-indol-3-yl(phenyl)methyl]malonate (3g)

White powder: mp 135.8-136.2 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 4.42 (d, J = 12.0 Hz, 1H), 4.90-4.97 (m, 4H), 5.12 (d, J = 12.0 Hz, 1H), 6.94 (d, J = 7.3 Hz, 2H), 7.02-7.05 (m, 4H), 7.16-7.28 (m, 11H), 7.32 (d, J = 7.3 Hz, 2H), 7.51 (d, J = 7.9 Hz, 1H), 7.87 (s, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 42.9, 58.3, 67.1, 67.1, 111.0, 116.4, 119.2, 119.5, 121.1, 122.2, 126.5, 126.7, 127.9, 128.0, 128.0, 128.1, 128.1, 128.3, 128.4, 135.0, 135.1, 136.2, 141.1, 167.6, 167.7; IR ($CHCl_3$, cm^{-1}) 3478, 2386, 1755, 1732; Anal. Calcd for $C_{32}H_{27}NO_4$: C, 78.51; H, 5.56; N, 2.86. Found: C, 78.45; H, 5.60; N, 2.92.

4.2.8. Ethyl 2-[1*H*-indol-3-yl(phenyl)methyl]-3-oxobutanoate (3h)[8c]

A mixture of diastereomers (83:17); white powder: mp 162-162.5 °C (from hexane/benzene = 1:1) [ref.[8c] 162-163 °C (EtOH)]; ^1H NMR (500 MHz, $CDCl_3$, major diastereomer) δ 0.97 (t, J = 7.3 Hz, 3H), 2.04 (s, 3H), 3.94-4.00 (m, 2H), 4.50 (d, J = 11.6 Hz, 1H), 5.09 (d, J = 11.6 Hz, 1H), 7.01-7.35 (m, 9H), 7.54 (d, J = 7.9 Hz, 1H), 8.03 (s, 1H); ^1H NMR (500 MHz, $CDCl_3$, minor diastereomer) δ 0.99 (t, J = 7.3 Hz, minor diastereomer 3H), 2.14 (s, 3H), 3.94-4.00 (m, 2H), 4.38 (d, J = 12.3 Hz, 1H), 5.06 (d, J = 12.2 Hz, 1H), 7.01-7.35 (m, 9H), 7.54 (d, J = 7.9 Hz, 1H), 8.06 (s, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$, major diastereomer) δ 13.8, 30.3, 42.6, 61.4, 65.9, 111.0, 117.3, 119.4, 119.5, 120.7, 122.3, 126.8, 128.1, 128.1, 128.4, 128.6, 136.2, 141.3, 168.0.

4.2.9. 3-[1*H*-Indol-3-yl(phenyl)methyl]pentane-2,4-dione (3i)[8d]

Colorless plates: mp 153.5-154.0 °C (from hexane-ethyl acetate = 5:2) [lit.[8d] mp 150-152 °C (from EtOH)]; ^1H NMR (500 MHz, $CDCl_3$) δ 1.93 (s, 3H), 2.05 (s, 3H), 4.64 (d, J = 12.2 Hz, 1H), 5.09 (d, J = 12.2 Hz, 1H), 7.04 (t, J = 7.0 Hz, 1H), 7.11-7.16 (m, 3H), 7.23 (t, J = 7.6 Hz, 2H), 7.30 (t, J = 7.9 Hz, 3H), 7.53 (d, J = 7.9 Hz, 1H), 8.09 (brs, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 27.6, 31.3, 43.2, 75.3, 111.1, 116.6, 119.0, 119.8, 121.2, 122.6, 126.3, 126.8, 128.1, 128.6, 136.2, 141.3, 203.5, 204.1; IR ($CHCl_3$, cm^{-1}) 3478, 1721, 1696, 1356.

4.2.10. 2-[1*H*-Indol-3-yl(phenyl)methyl]-1,3-diphenylpropane-1,3-dione (3j)

White powder: mp 171-172 °C; ^1H NMR (500 MHz, DMSO) δ 5.34 (d, J = 11.5 Hz, 1H), 6.89-7.02 (m, 4H), 7.07 (t, J = 7.6 Hz, 2H), 7.20 (d, J = 7.8 Hz, 1H), 7.37-7.41 (m, 4H), 7.50-7.57 (m, 5H), 7.61 (s, 1H), 8.03 (d, J = 7.0 Hz, 2H), 8.08 (d, J = 7.0 Hz, 2H), 10.8 (brs, 1H); ^{13}C NMR (125.7 MHz, DMSO) δ 43.7, 60.0, 111.1, 116.7, 118.3, 118.5, 121.0, 122.1, 125.9, 126.5, 127.7, 128.5, 128.5, 128.6, 128.6, 128.7, 133.4, 135.8, 136.3, 136.4, 142.6, 193.4, 194.4; IR ($CHCl_3$, cm^{-1}) 3480, 1728; HRMS (EI) Calculated for $C_{30}H_{23}O_2N$: 429.17288. Found: 429.17405.

4.2.11. 2-Cyano-3-(1*H*-indol-3-yl)-3-(4-chlorophenyl)propionic Acid Ethyl Ester (3k)

A mixture of diastereomers (50:50); colorless oil: ^1H NMR (500 MHz, $CDCl_3$) δ 1.09 (t, J = 7.3 Hz, 3H), 1.13 (t, J = 7.3 Hz, 3H), 4.07-4.16 (m, 5H), 4.31 (d, J = 6.1 Hz, 1H), 5.02 (d, J = 6.7 Hz, 1H), 5.08 (d, J = 6.1 Hz, 1H), 7.01-7.10 (m, 2H), 7.17-7.38 (m, 15H), 7.46 (d, J = 2.4 Hz, 1H), 8.23 (s, 1H), 8.28 (s, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 13.7,

13.8, 42.4, 42.5, 44.0, 44.8, 63.0, 111.3, 111.4, 112.8, 114.3, 115.9, 116.0, 118.6, 118.8, 119.9, 120.0, 122.0, 122.1, 122.7, 122.8, 125.9, 126.4, 128.9, 129.0, 129.4, 129.8, 133.6, 133.8, 136.1, 136.2, 137.1, 138.2, 165.0, 165.0; IR ($CHCl_3$, cm^{-1}) 3476, 1745, 1223; HRMS (EI) Calculated for $C_{20}H_{17}N_2O_2Cl$: 352.09786. Found 352.09807.

4.2.12. 2-Cyano-3-(1*H*-indol-3-yl)-3-(4-methoxyphenyl)propionic Acid Ethyl Ester (3l)

A mixture of diastereomers (50:50); white powder: mp 128-128.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.08 (t, J = 7.0 Hz, 3H), 1.12 (t, J = 7.0 Hz, 3H), 3.74 (s, 3H), 3.75 (s, 3H), 4.07-4.16 (m, 5H), 4.30 (d, J = 6.1 Hz, 1H), 4.99 (d, J = 6.1 Hz, 1H), 5.05 (d, J = 6.7 Hz, 1H), 6.80-6.84 (m, 4H), 7.00 (t, J = 7.3 Hz, 1H), 7.04 (t, J = 7.3 Hz, 1H), 7.15-7.36 (m, 11H), 7.45 (d, J = 2.4 Hz, 1H), 8.21 (brs, 1H), 8.25 (brs, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 13.7, 13.8, 42.4, 42.5, 44.5, 45.2, 55.2, 55.2, 62.8, 62.8, 111.2, 111.3, 113.6, 114.0, 114.1, 115.1, 116.2, 116.4, 118.8, 119.0, 119.8, 121.9, 122.0, 122.4, 122.5, 126.1, 126.6, 128.5, 128.6, 128.9, 129.0, 129.1, 129.5, 130.7, 131.8, 136.1, 136.3, 159.0, 159.1, 165.3, 165.3; IR ($CHCl_3$, cm^{-1}) 3478, 2253, 1744, 1512, 1252; HRMS (EI) Calculated for $C_{21}H_{20}O_3N_2$: 348.14740. Found: 348.14812.

4.2.13. 2-Cyano-3-(1*H*-indol-3-yl)-5-phenylpenta-4-enoic Acid Ethyl Ester (3m)

A mixture of diastereomers (60:40); colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$, major diastereomer) δ 1.20 (t, J = 7.0 Hz, 3H), 4.05-4.08 (m, 1H), 4.21 (q, J = 7.0 Hz, 2H), 4.60-4.63 (m, 1H), 6.51-6.70 (m, 2H), 7.11-7.39 (m, 9H), 7.64 (d, J = 7.9 Hz, 1H), 8.23 (brs, 1H); ^{1}H NMR (500 MHz, $CDCl_3$, minor diastereomer) δ 1.06 (t, J = 7.0 Hz, 3H), 4.05-4.08 (m, 3H), 4.60-4.63 (m, 1H), 6.51-6.70 (m, 2H), 7.11-7.39 (m, 9H), 7.64 (d, J = 7.9 Hz, 1H), 8.26 (s, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$, mixture of diastereomers) δ 13.7, 14.0, 41.2, 41.3, 44.6, 44.7, 62.8, 62.8, 111.4, 111.6, 112.6, 113.7, 115.8, 116.1, 118.3, 118.8, 119.9, 120.0, 122.2, 122.4, 122.5, 122.7, 125.5, 125.6, 126.2, 126.5, 126.6, 127.5, 127.9, 127.9, 128.6, 132.6, 133.8, 136.1, 136.2, 136.3, 136.4, 165.2; IR ($CHCl_3$, cm^{-1}) 3478,2359, 1745; HRMS (EI) Calculated for $C_{22}H_{20}N_2O_2$: 344.15248. Found 344.15233.

4.2.14. 2-Cyano-3-(1*H*-indol-3-yl) penta-4-enoic Acid Ethyl Ester (3n)

A mixture of diastereomers (60:40); colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$, major diastereomer) δ 1.24 (t, J = 7.0 Hz, 3H), 3.99 (d, J = 6.1 Hz, 1H), 4.22 (q, J = 7.0 Hz, 2H), 4.44-4.47 (m, 1H), 5.25-5.37 (m, 2H), 6.13-6.28 (m, 1H), 7.11-7.24 (m, 3H), 7.38 (d, J = 7.9 Hz, 1H), 7.59 (t, J = 8.2 Hz, 1H), 8.20 (brs, 1H); ^{1}H NMR (500 MHz, $CDCl_3$, minor diastereomer) δ 1.08 (t, J = 7.0 Hz, 3H), 3.99 (d, J = 6.1 Hz, 1H), 4.07 (q, J = 7.0 Hz, 2H), 4.44-4.47 (m, 1H), 5.25-5.37 (m, 2H), 6.13-6.28 (m, 1H), 7.11-7.24 (m, 2H), 7.31 (d, J = 2.4 Hz, 1H), 7.36 (d, J = 7.9 Hz, 1H), 7.59 (t, J = 8.2 Hz, 1H), 8.23 (brs, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$, mixture of diastereomers) δ 13.7, 13.9, 41.6, 44.2, 44.3, 111.4, 111.5, 112.2, 113.4, 115.6, 116.0, 117.5, 118.2, 118.7, 118.8, 119.7, 119.9, 122.2, 122.4, 122.5, 122.6, 125.6, 126.2, 134.3, 136.0, 136.2, 136.3, 165.2, 165.3; IR ($CHCl_3$, cm^{-1}) 3478, 2361, 1743; HRMS (EI) Calculated for $C_{16}H_{16}N_2O_2$: 268.12118. Found 268.12117.

4.3. Typical experimental procedure for oxidative C-C bond formation of 3-benzylindole 5a with higher-order cyanocuprates (Table 3, entry 4)

A solution of $Ph_2Cu(CN)Li_2$ was prepared as follows; to a stirred solution of copper(I) cyanide (61.2 mg, 0.68 mmol) in Et_2O (4 mL) was added dropwise a solution of phenyllithium (1.14 *N* in cyclohexane-ether, 1.06 ml, 1.21 mmol) at –20 °C for 1 h.

To a stirred solution of **5a** (50 mg, 0.24 mmol) in THF (3 mL) was added dropwise a solution of *n*-BuLi (1.61 *N* in hexane, 0.20 mL, 0.32 mmol) at –78 °C. After the mixure was stirred at the same temperature for 15 min, a solution of **4** (83 mg, 0.38 mmol) in THF (1 mL) was added at –78 °C. After the mixture was stirred at the same temperature for 30 min, a solution of $Ph_2Cu(CN)Li_2$ was added at –78 °C with a cannula, and the reaction mixture was stirred at the same temperature for 30 min. the product **9d** was obtained as usual manner.

4.3.1 3-(1-Phenylethyl)indole (9a)[5a]

White solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.70 (t, J = 7.3 Hz, 3H), 4.37 (q, J = 7.3 Hz, 1H), 6.98-7.37 (m, 10H), 7.96 (s, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 22.4, 36.9, 111.0, 119.2, 119.7, 121.0, 121.9, 122.3, 125.9, 127.4, 128.3, 128.7, 136.6, 146.8.

4.3.2. 3-(1-Phenylpentyl)indole (9b)

Colorless plates: mp 74.5-75.5 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.86 (t, J = 7.0 Hz, 3H), 1.27-1.35 (m, 4H), 1.96-2.03 (m, 1H), 2.14-2.21 (m, 1H), 4.14 (t, J = 7.6 Hz, 1H), 6.97-7.02 (m, 2H), 7.11 (d, J = 8.1 Hz, 1H), 7.15 (d, J = 7.8 Hz, 1H), 7.23-7.30 (m, 5H), 7.44 (d, J = 8.1 Hz, 1H), 7.83 (s, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 14.0, 22.8, 30.3, 35.9, 42.9, 111.0, 119.2, 119.5, 120.7, 120.9, 121.9, 125.8, 127.1, 127.9, 128.2, 136.5, 145.6; IR ($CHCl_3$, cm^{-1}) 3481, 1456; HRMS (EI) Calculated for $C_{21}H_{19}N$: 263.16740. Found 263.16743.

4.3.3. 3-(2,2-Dimethyl-1-phenylpropyl)indole (9c)

White powder: mp 87.5-88.5 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.04 (s, 9H), 4.15 (s, 1H), 7.02-7.40 (m, 9H), 7.58 (d, J = 7.7 Hz, 1H), 7.98 (s, 1H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 29.0, 35.2, 53.6, 110.7, 117.8, 119.0 119.1, 121.0, 121.8, 125.7, 127.5, 128.8, 130.0, 135.1, 143.3; IR ($CHCl_3$, cm^{-1}) 3481, 1456; HRMS (EI) Calculated for $C_{21}H_{19}N$: 263.16740. Found 263.16682.

4.3.4. 3-Diphenylmethylindole (9d)[21]

White needles: mp 124.5-124.8 °C (lit.[21] 121 °C); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.66 (s, 1H), 6.54 (d, J = 2.2 Hz, 1H), 6.96-6.99 (m, 1H), 7.14-7.28 (m, 12H), 7.33 (d, J = 8.1 Hz, 1H), 7.88 (s, 1H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 48.8, 111.0, 119.4, 119.9, 122.1, 124.0, 126.2, 127.0, 128.3, 129.0, 136.7, 143.9.

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