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Very Important Publication

Synthesis of 2*H*-Indazoles *via* Tandem Palladium-Catalyzed Deacylative Cross-Coupling and Denitrogenative Cyclization of 2-Iodoazoarenes and 2-Iodoaryltriazenes with Acyldiazoacetates in One-Pot

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This paper is dedicated to Professor Kyo Han Ahn (POSTECH) on the occasion of his 60th birthday.

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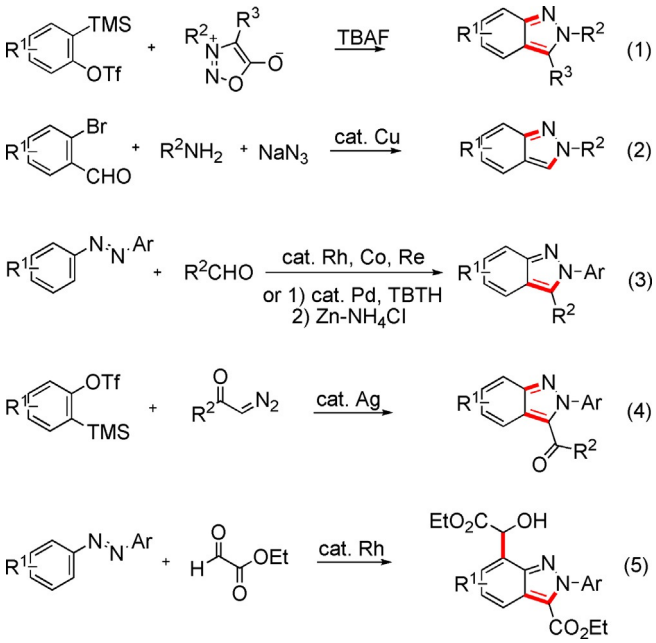
Abstract: A synthetic method to prepare a wide range of 2*H*-indazoles was developed *via* a tandem palladium-catalyzed deacylative cross-coupling reaction of 2-iodoazoarenes and 2-iodoaryltriazenes with acyldiazoacetates and denitrogenative cyclization reaction of *in situ* generated diazoacetates having azoaryl and triazenylaryl moieties in one-pot. Additionally, azoaryl-substituted diazoacetates underwent palladium-catalyzed denitrogenative cyclization to produce 2*H*-indazoles. The present reaction is a good example in which a Pd(0)-catalyst is involved in two catalytic cycles in one-pot.

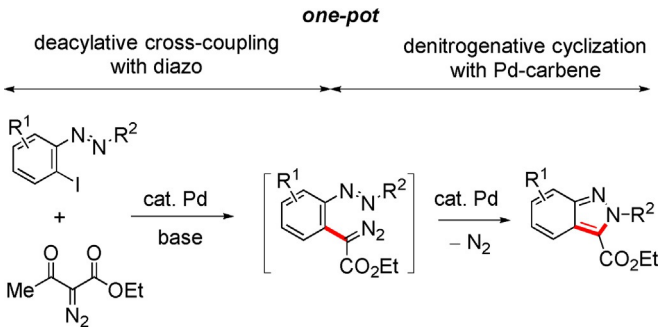
Keywords: diazoacetates; 2*H*-indazoles; 2-iodoazoarenes; palladium catalysis; tandem reactions

Introduction

Azaheterocycles have been recognized as a highly important class of compounds in drug discovery due to their biological activities and pharmaceutical, agricultural, and industrial applications.[1] 2*H*-Indazoles are useful privileged pharmacophores found in medicinally important molecules.[2] Although a large number of synthetic methods for the thermodynamically favored 1*H*-indazole has been reported,[3] there is only a limited number of methods for the regioselective synthesis of 2*H*-indazoles.[4] Thus, the development of efficient synthetic methods for providing 2*H*-indazoles from readily accessible starting material is required. To date, [3+2] dipolar cycloaddition of arynes and sydnones [Eq (1), Scheme 1],[5a] Cu-catalyzed three-component reactions of 2-bromobenzaldehydes, primary amines, and sodium azides in one-pot [Eq (2)],[5b] and Rh-, Co-, Re-, or Pd-catalyzed C–H bond addition of azobenzenes to aldehydes [Eq (3)][5c–f] have been developed. The preparation of 3-acyl-2*H*-indazoles has been much less investigated due to the number of synthetic steps, dialkylations, reaction yields, and conditions. Therefore, a synthetic approach *via* a catalytic



Scheme 1. Approaches for the synthesis of 2*H*-indazoles.



Scheme 2. Synthesis of 2*H*-indazoles *via* tandem Pd-catalyzed deacylative coupling and denitrogenative cyclization.

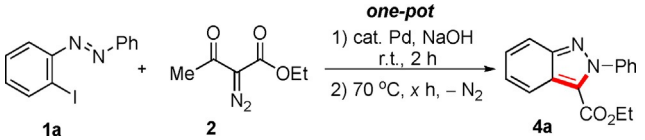
process represents a formidable challenge: Ag-catalyzed [3+2] cycloaddition of benzynes with diazocarbonyl reagents [Eq (4)][5g] and Rh-catalyzed C–H addition and cyclization of azobenzenes with α- keto aldehydes [Eq (5)].[5h]

Recently, Wang and co-workers reported Pd-catalyzed deacylative cross-coupling of aryl iodides with acyldiazoacetates for the synthesis of aryl diazoacetates.[6] On the basis of these results, we envisioned that with the same Pd catalyst, a tandem deacylative cross-coupling and denitrogenative cyclization reaction starting from 2-iodoazoarenes and 2-iodoaryltriazenes may be achievable in one-pot, thus producing 3-acyl-2*H*-indazole scaffolds through the formation of intermolecular C–C bonds and sequential intramolecular C–N bonds on the carbon that possesses a diazo group of the acyldiazoacetates. In continuation of our recent studies on the synthesis of azaheterocycles,[7] we report an efficient synthetic method for a wide range of 3-acyl-2*H*-indazoles *via* tandem Pd-catalyzed deacylative cross-coupling from 2-iodoazoarenes and 2-iodoaryltriazenes with acyldiazoacetates and denitrogenative cyclization reaction in one-pot (Scheme 2).

Results and Discussion

We initiated our investigations with the reaction of 2-iodoazobenzene (**1a**) with ethyl 2-diazo-3-oxobutanoate (**2**) in the presence of a variety of Pd catalysts (Table 1). 2-Iodoazobenzenes were prepared from the Pd-catalyzed iodination of aromatic azo compounds[8] and dehydration of 2-iodoanilines with nitrosobenzenes.[9] When $Pd(dba)_2$ and $Pd_2(dba)_3$ (5.0 mol% each) were used as catalysts in the presence of NaOH (3.0 equiv.) in ethanol at room temperature, the reactions were ineffective (entries 1 and 2). Next, a wide range of ligands, such as PCy_3, Xantphos, and dppf, was examined in the presence of $Pd_2(dba)_3CHCl_3$ (5.0 mol%). Although PCy_3 (20.0 mol%) was not effective (entry 3), Xantphos and dppf (10.0 mol%)

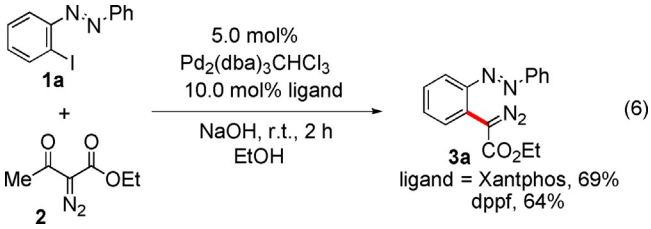
Table 1. Reaction optimization.[a]



Entry	Cat. Pd	Solvent	*t* [h]	Yield [%][b]
1	$Pd(dba)_2$	EtOH	12	0
2	$Pd_2(dba)_3$	EtOH	12	0
3[c]	$Pd_2(dba)_3CHCl_3$	EtOH	12	0
4[d]	$Pd_2(dba)_3CHCl_3$	EtOH	4	53
5[e]	$Pd_2(dba)_3CHCl_3$	EtOH	4	52
6	$Pd(PPh_3)_4$	EtOH	2	85 (83)[f]
7	$Pd(PPh_3)_4$	*t*-amyl alcohol	12	56
8	$Pd(PPh_3)_4$	*n*-propanol	6	79
9	$Pd(PPh_3)_4$	MeCN	12	79
10	$Pd(PPh_3)_4$	EtOH	2	50[g]
11	$Pd(OAc)_2/Ph_3P$	EtOH	2	43[h]

[a] *Reaction conditions:* **1a** (0.2 mmol, 1.0 equiv.), **2** (0.4 mmol, 2.0 equiv.), Pd catalyst (5.0 mol%), and NaOH (3.0 equiv.) in solvent (0.25 M) at room temperature for 2 h and then 70 °C for *x* h under N_2.
[b] NMR yield using CH_2Br_2 as an internal standard.
[c] PCy_3 (20.0 mol%) was used.
[d] Xantphos (10.0 mol%) was used.
[e] dppf (10.0 mol%) was used.
[f] Isolated yield.
[g] Under air.
[h] Ph_3P (20.0 mol%) was used.

gave the deacylative cross-coupling product (*E*)-ethyl 2-diazo-2-[2-(phenyldiazenyl)phenyl]acetate (**3a**) in 69% and 64% yields, respectively, in ethanol at room temperature for 2 h [Eq (6)].



(6)

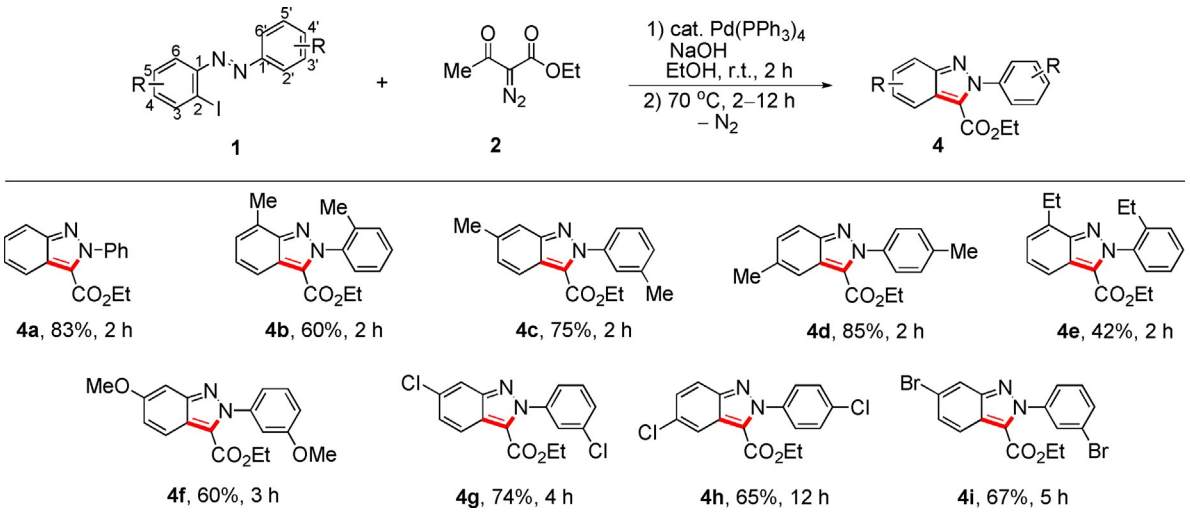
Thus, we conceived that if the diazoacetate **3a** having an azophenyl group was treated with a transition metal or heated, the denitrogenative cyclization reaction would occur, producing 2*H*-indazole **4a**. Moreover, a direct synthesis of 2*H*-indazole **4a** starting from 2-iodoazobenzene (**1a**) and ethyl 2-diazo-3-oxobutanoate (**2**) was envisaged to be possible *via* the tandem Pd-catalyzed deacylative cross-coupling reaction and the denitrogenative cyclization reaction in one-pot. The tandem reaction from **1a** and **2** occurred in one-pot, affording ethyl 2-phenyl-2*H*-indazole-3-carboxylate (**4a**) in 53% and 52% yields, respectively

(entries 4 and 5). These results indicate that the Pd-catalyzed deacylative cross-coupling reaction of 2-iodoazobenzene (**1a**) with ethyl 2-diazo-3-oxobutanoate (**2**) and a sequential denitrogenative cyclization reaction in one-pot worked moderately well. The optimum conditions were obtained from the reaction of **1a** (0.2 mmol, 1.0 equiv.) with **2** (2.0 equiv.) using $Pd(PPh_3)_4$ (5.0 mol%) and NaOH (3.0 equiv.) in EtOH at room temperature for 2 h followed by treatment at 70 °C for 2 h under N_2, providing **4a** in 83% isolated yield (entry 6). Ethanol gave the best results among the solvents, including *t*-amyl alcohol, *n*-propanol, and acetonitrile (entries 6–9). 2*H*-Indazole **4a** was obtained in 50% yield under air (enry 10). Use of $Pd(OAc)_2$ (5.0 mol%) and Ph_3P (20.0 mol%) produced **4a** in 43% yield (entry 11).

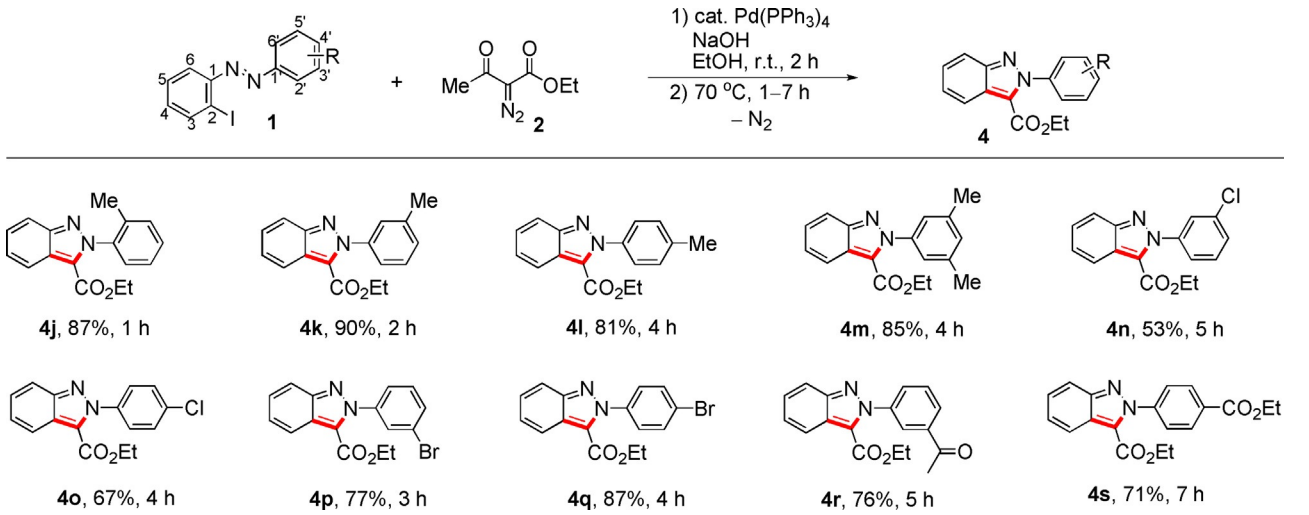
To show the efficiency and substrate scope of the present method, several 2-iodoazobenzenes with the same substituents on two aryl rings were subjected to the optimum reaction conditions (Scheme 3). Variation of the electron demand of the substituents on the aryl rings did not largely affect the efficiency of the tandem Pd-catalyzed deacylative cross-coupling and denitrogenative cyclization in one-pot. 2-Iodoazobenzenes bearing electron-donating methyl groups were smoothly converted to 2*H*-indazoles (**4b**, **4c**, and **4d**) in good yields ranging from 60% to 85%. Additionally, 2-iodo-5-methoxyazobenzene (**1f**) underwent Pd-catalyzed cross-coupling followed by cyclization to produce 2*H*-indazole **4f** in a 60% yield. However, 6-ethyl-substituted 2-iodoazobenzene (**1e**) lowered the product yield (42%) due to steric congestion. 2-Iodoazobenzenes with electron-withdrawing chloride and bromide groups afforded the desired 2*H*-indazoles **4g**–**4i** in good yield without loss of halogen functionality.

Next, we examined the substrate scope and the functional group tolerance in the reaction with a series of 2-iodoazobenzenes having substituents on one aryl ring (Scheme 4). Electronic modification of substituents on the phenyl ring of 2-iodoazobenzenes (**1**) had little effect on the reaction efficiency. Several 2*H*-indazoles (**4j**–**4m**) were obtained in good to excellent yields from 2-iodoazobenzenes with electron-donating methyl substituents. Although 3′-chloro-2-iodoazobenzene (**1n**) was transformed to **4n** in 53% yield, 4′-chloro, 3′-bromo-, and 4′-bromo-substituted 2-iodoazobenzenes were converted to the desired 2*H*-indazoles (**4o**–**4q**) in good yields ranging from 67% to 87%. Electron-withdrawing groups, such as acetyl and ethoxycarbonyl, are tolerable in the tandem Pd-catalyzed deacylative cross-coupling and denitrogenative cyclization reaction in one-pot, which makes the present method useful.

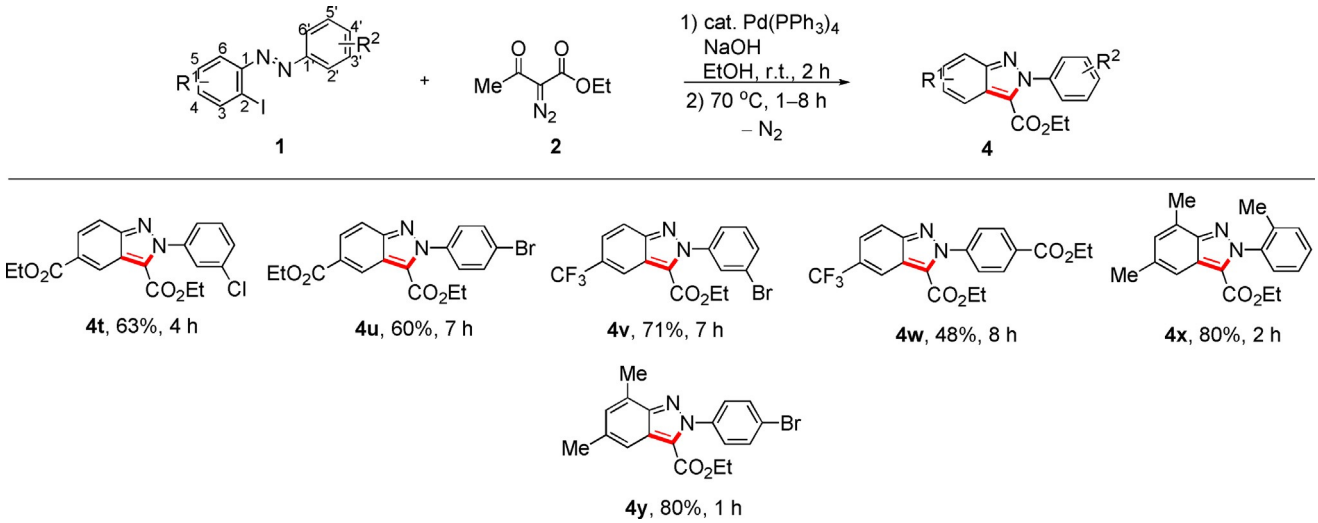
With the success of the tandem Pd-catalyzed deacylative cross-coupling and denitrogenative cyclization, we attempted the synthesis of 2*H*-indazoles from 2-iodoazobenzenes with different substituents on two aryl rings (Scheme 5). When 2-iodoazobenzenes (**1t** and **1u**) with electron-withdrawing ethoxycarbonyl, chloride, and bromide groups on each aryl ring were treated with a Pd-catalyst, the tandem reaction occurred smoothly, affording 2*H*-indazoles **4t** (63%) and **4u** (60%). In the case of the azo compound (**1v**) with trifluoromethyl and bromide groups on each aryl ring, the desired 2*H*-indazole **4v** was obtained in a 71% yield. However, the presence of strong electron-withdrawing trifluoromethyl and ethoxycarbonyl groups on each aryl ring decreased the reaction efficiency. The combination of dimethyl and methyl or bromide groups on each aryl ring gave good results, providing 2*H*-indazoles **4x** and **4y** in 80% yields, respectively.



Scheme 3. Synthesis of 2*H*-indazoles from 2-iodoazoarenes with the same substituents on two aryl rings in one-pot. *Reaction conditions:* **1** (0.2 mmol, 1.0 equiv.), **2** (2.0 equiv.), $Pd(PPh_3)_4$ (5.0 mol%), and NaOH (3.0 equiv.) in EtOH (0.8 mL) at room temperature for 2 h and then 70 °C for 2–12 h under N_2.



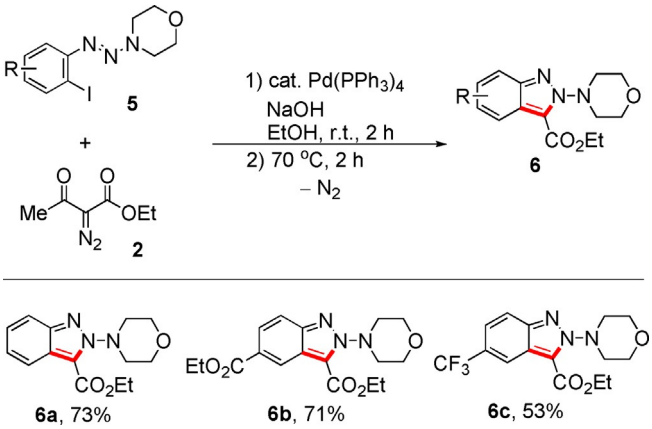
Scheme 4. Synthesis of 2*H*-indazoles from 2-iodoazoarenes with substituents on one aryl ring in one-pot. *Reaction conditions:* **1** (0.2 mmol, 1.0 equiv.), **2** (2.0 equiv.), $Pd(PPh_3)_4$ (5.0 mol%), and NaOH (3.0 equiv.) in EtOH (0.8 mL) at room temperature for 2 h and then 70 °C for 1–7 h under N_2.



Scheme 5. Synthesis of 2*H*-indazoles from 2-iodoazoarenes with different substituents on two aryl rings in one-pot. *Reaction conditions:* **1** (0.2 mmol, 1.0 equiv.), **2** (2.0 equiv.), $Pd(PPh_3)_4$ (5.0 mol%), and NaOH (3.0 equiv.) in EtOH (0.8 mL) at room temperature for 2 h and then 70 °C for 1–8 h under N_2.

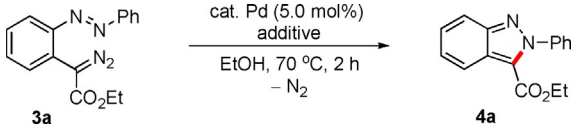
As an extension of this work, the synthesis of 2*H*-indazoles from 2-iodoaryltriazenes was investigated (Scheme 6). When (*E*)-4-[(2-iodophenyl)diazenyl]-morpholine (**5a**) was subjected to a Pd catalyst, the tandem reaction occurred smoothly, resulting in the formation of (*E*)-4-{[2-iodo-4-(trifluoromethyl)-phenyl]diazenyl}morpholine (**6a**) in 73% yield. Ethoxycarbonyl- and trifluoromethyl-substituted 2-iodoaryltriazenes are applicable to the present transformation, affording the corresponding 2*H*-indazoles (**6b** and **6c**).

Several control experiments were performed to examine what kind of factor leads to cyclization of diazoacetate **3a** *in situ* generated from 2-iodoazobenzene and ethyl 2-diazo-3-oxobutanoate (Table 2). Heating of diazoacetate **3a** in EtOH to 70 °C without a Pd catalyst and NaOH gave 2*H*-indazole **4a** in a 23% yield (entry 1).[10] Treatment of **3a** with the optimum reaction conditions gave **4a** in a 5% yield (entry 2). However, when **3a** was subjected to 5.0 mol% $Pd(PPh_3)_4$ without NaOH in EtOH, the cyclization occurred to afford **4a** in an 80% yield (entry 3), indicating that the Pd-catalyst was essential for the cyclization of diazoacetate. Exposure of **3a** to 5.0 mol% $Pd(PPh_3)_4$ and NaOH (1.0 equiv.) in EtOH resulted in the formation of **4a** in 82% yield (entry 4). These results indicate that the NaOH (2.0 equiv.) was used in the cross-coupling reaction and the NaOH (1.0 equiv.) that remained in the reaction mixture



Scheme 6. Synthesis of 2*H*-indazoles from 2-iodoaryltriazenes in one-pot. *Reaction conditions:* **5** (0.2 mmol, 1.0 equiv.), **2** (2.0 equiv.), $Pd(PPh_3)_4$ (5.0 mol%), and NaOH (3.0 equiv.) in EtOH (0.8 mL) at room temperature for 2 h and then 70 °C for 2 h under N_2.

Table 2. Cyclization of azophenyl-substituted diazoacetates.[a]



Entry	Cat. Pd	Additive (equiv.)	Yield [%][b]
1		–	23
2	$Pd(PPh_3)_4$	NaOH (3.0)	5
3	$Pd(PPh_3)_4$	–	80
4	$Pd(PPh_3)_4$	NaOH (1.0)	82
5	–	NaOH (3.0)	4
6	–	NaOH (1.0)	9

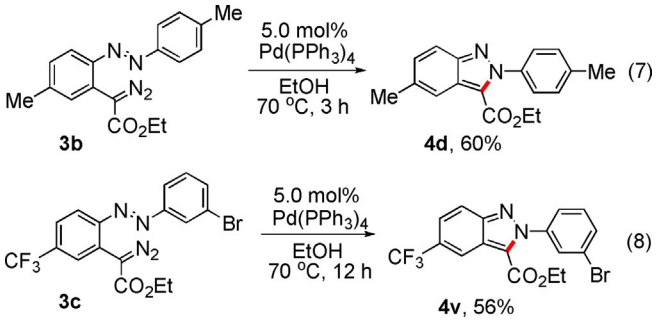
[a] *Reaction conditions:* **3a** (0.2 mmol, 1.0 equiv.), $Pd(PPh_3)_4$ (5.0 mol%), and NaOH in EtOH (0.25 M) at 70 °C for 2 h under N_2.

[b] NMR yield using CH_2Br_2 as an internal standard.

after cross-coupling reaction did not affect the efficiency of the denitrogenative cyclization. In addition, NaOH (1.0 and 3.0 equiv.) was totally ineffective, indicating that Pd catalyst is essential to the denitrogenative cyclization (entries 5 and 6).

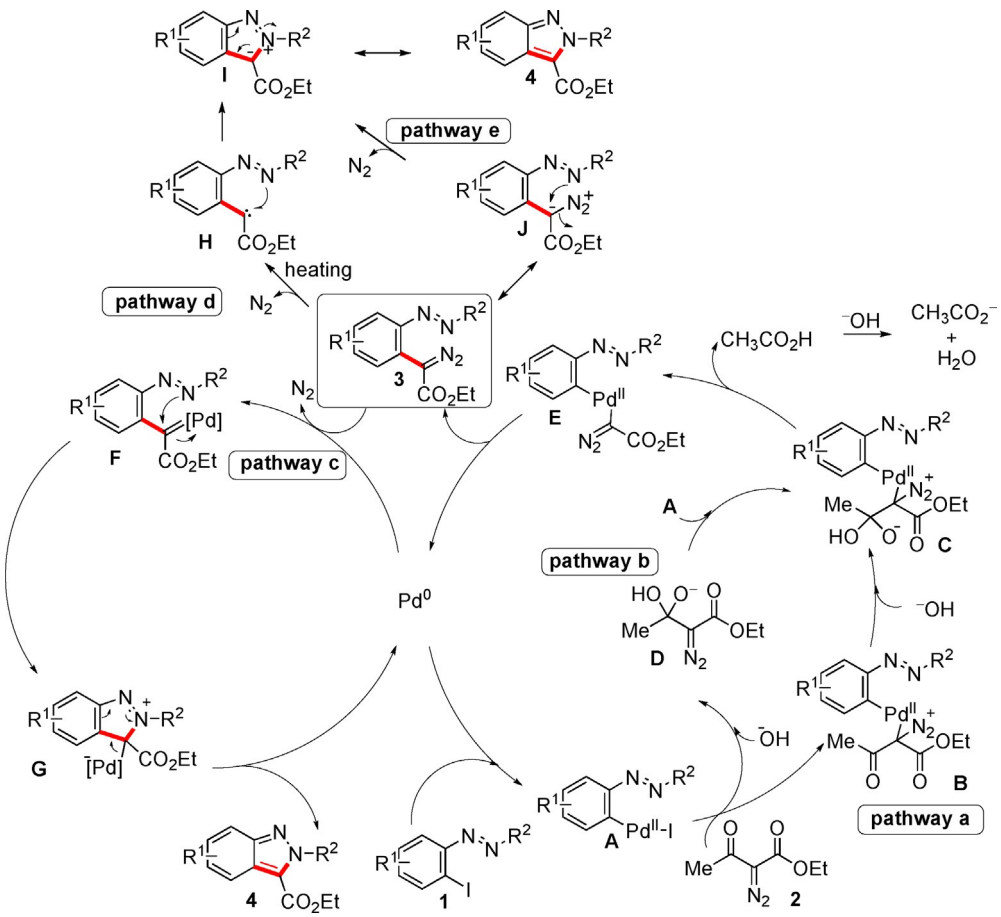
Encouraged by these results, the cyclization of diazoacetates was attempted. Diazoacetate **3b** with methyl substituents on two aryl rings was cyclized to produce 2*H*-indazole **4d** in a 60% yield [Eq. (7)]. Diazoacetate (**3c**) possessing trifluoromethyl and bromide groups on each aryl ring is applicable to the present transformation, affording the corresponding 2*H*-indazole **4v** in a 56% yield [Eq (8)].

A plausible reaction mechanism for the synthesis of 2*H*-indazoles **4** from the tandem Pd-catalyzed deacylative cross-coupling reaction of 2-iodoazoarenes and 2-iodoaryltriazenes (**1**) with ethyl 2-diazo-3-oxobutanoate (**2**) in one-pot is shown in Scheme 7. At the outset, oxidative addition of 2-iodoazoarenes and 2-iodoaryltriazenes (**1**) to Pd catalyst provides the intermediate **A**, which makes a complex with diazoacetate **2** to afford the intermediate **B** (**pathway a**).[6] Next, nucleophilic attack by hydroxide anion gives rise to intermediate **C**. When **2** initially reacts with hydroxide anion, intermediate **D** might be produced, and then coordination of **D** to **A** generates **C** (**pathway b**). Then, deacylation from **C** followed by reductive elimination from **E** produces the deacylative cross-coupling product **3** and regenerates the Pd catalyst. In **pathway c**, liberation of molecular nitrogen from **3** would provide Pd-carbene complex **F**. Next, intramolecular nucleophilic attack by the azoarene and triazene moieties produces **G**, and subsequent depalladation affords the 2*H*-indazoles **4** and regenerates the Pd catalyst. The present reaction is a good example in which the Pd(0) catalyst is involved in two catalytic cycles in one-pot. Heating of diazoacetates **3** to 70 °C partially produces carbene intermediate **H** through the evolution of nitrogen gas (entry 1, Table 2).[10] Nucleophilic attack of the diazo moiety affords nitrogen ylide **I** and subsequent resonance delivered the 2*H*-indazoles **4** (**pathway d**). In addition to the free carbene **pathway d** under 70 °C conditions, **pathway e** cannot be ruled out.



Conclusions

In conclusion, we have developed a synthetic method to prepare a wide range of 2*H*-indazoles *via* the tandem Pd-catalyzed deacylative cross-coupling reaction of 2-iodoazoarenes and 2-iodoaryltriazenes with acyldiazoacetate and denitrogenative cyclization reaction of *in situ* generated diazoacetates having the azoaryl and triazenylaryl moieties in one-pot. A Pd-catalyzed intramolecular cyclization occurred efficiently with diazoacetates having azoaryl moieties to produce 2*H*-indazoles. The two catalytic cycles are promoteded by one Pd catalyst.



Scheme 7. A plausible mechanism.

Experimental Section

General

All commercially available reagents were used as received without purification. All reaction mixtures were stirred magnetically and were monitored by thin-layer chromatography using silica gel pre-coated glass plates, which were visualized with UV light and then developed using either iodine or a solution of anisaldehyde. Flash column chromatography was carried out using silica gel (230–400 mesh). ^{1}H NMR (400 MHz) and ^{13}C{^{1}H} NMR (100 MHz) spectra were recorded on NMR spectrometers. Deuterated chloroform was used as the solvent and chemical shift values (δ) are reported in parts per million relative to the residual signals of this solvent [$\delta = 7.26$ for ^{1}H (chloroform-*d*) and $\delta = 77.16$ for ^{13}C (chloroform-*d*)]. Infrared spectra were recorded on an FT-IR spectrometer as either a thin film pressed between two sodium chloride plates or as a solid suspended in a potassium bromide disk. High resolution mass spectra (HR-MS) were obtained by fast atom bombardment (FAB) using a double focusing magnetic sector mass spectrometer and electron impact (EI) ionization technique (magnetic sector – electric sector double focusing mass analyzer) from the KBSI (Korea Basic Science Institute). Melting points were determined in open capillary tubes.

Synthetic Procedure for 2*H*-Indazoles

To a long test tube were added 2-iodoazoarene (**1**) (0.2 mmol), $Pd(PPh_3)_4$ (11.5 mg, 5.0 mol%) and NaOH (24.0 mg, 0.6 mmol) in EtOH (0.4 mL) at room temperature under N_2. Subsequently, ethyl diazoacetoacetate (**2**) (62.5 mg, 0.4 mmol) in EtOH (0.4 mL) was added dropwise into the long test tube and the resulting mixture was stirred at room temperature for 2 h under N_2. After 2 h, the resulting mixture was heated at 70 °C for 1 h. After evaporation of the solvents under vacuum, the reaction mixture was purified by column chromatography on silica gel to give the corresponding 2*H*-indazole derivatives.

Ethyl 2-phenyl-2*H*-indazole-3-carboxylate (4a): yield: 44.2 mg (83%); $R_f = 0.30$ (Et_2O:CH_2Cl_2:hexane = 1:1:20); white solid; m.p. 81–83 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 8.13 (dt, $J = 8.5$ Hz, 1.1 Hz, 1H), 7.85 (dt, $J = 8.6$ Hz, 1.0 Hz, 1H), 7.53 (s, 5H), 7.43 (ddd, $J = 8.6$ Hz, 6.7 Hz, 1.2 Hz, 1H), 7.36 (ddd, $J = 8.4$ Hz, 6.7 Hz, 1.0 Hz, 1H), 4.36 (q, $J = 7.1$ Hz, 2H), 1.35 (t, $J = 7.1$ Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): $\delta = 159.6$, 148.5, 141.1, 129.5, 128.8, 127.2, 126.5, 125.6, 125.2, 124.1, 121.7, 118.7, 61.2, 14.3; IR (film): $\nu =$ 3065, 2978, 1719, 1597, 1501, 1287 cm^{-1}; HR-MS (FAB): $m/z = 267.1135$, calcd. for $C_{16}H_{14}N_2O_2$: 267.1134.

Ethyl 7-methyl-2-(*o*-tolyl)-2*H*-indazole-3-carboxylate (4b): yield: 35.5 mg (60%); $R_f = 0.20$ (Et_2O:CH_2Cl_2:hexane =

1:1:20); red oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, J = 8.4 Hz, 1H), 7.45–7.41 (m, 1H), 7.36–7.25 (m, 4H), 7.18 (dt, J = 6.8 Hz, 1.0 Hz, 1H), 4.30 (q, J = 7.1 Hz, 2H), 2.69 (s, 3H), 2.01 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 159.5, 148.9, 140.9, 135.0, 130.6, 129.7, 129.0, 127.1, 126.4, 126.2, 126.1, 125.8, 123.3, 119.1, 61.0, 17.2, 17.1, 14.2; IR (film): ν = 3032, 2978, 1714, 1650, 1501, 1228 cm^{-1}; HR-MS (EI): m/z = 294.1369, calcd. for $C_{18}H_{18}N_2O_2$: 2 9 4.1368.

Ethyl 6-methyl-2-(*m*-tolyl)-2*H*-indazole-3-carboxylate (4c): yield: 44.0 mg (75%); R_f = 0.20 (Et_2O:CH_2Cl_2:hexane = 1:1:20); white solid; m.p. 99–101 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (d, J = 9.0 Hz, 1H), 7.58 (d, J = 9.0 Hz, 1H), 7.39 (t, J = 7.7 Hz, 1H), 7.34–7.28 (m, 3H), 7.18 (dd, J = 8.7 Hz, 1.2 Hz, 1H), 4.35 (q, J = 7.1 Hz, 2H), 2.50 (s, 3H), 2.44 (s, 3H), 1.34 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 159.6, 149.1, 141.1, 138.8, 137.1, 130.1, 128.5, 128.4, 127.0, 125.0, 123.6, 122.5, 121.1, 117.0, 61.1, 22.2, 21.4, 14.3; IR (film): ν = 2988, 2925, 1714, 1637, 1501, 1116 cm^{-1}; HR-MS (EI): m/z = 294.1368, calcd. for $C_{18}H_{18}N_2O_2$: 294.1368.

Ethyl 5-methyl-2-(*o*-tolyl)-2*H*-indazole-3-carboxylate (4d): yield: 44.2 mg (85%); R_f = 0.30 (Et_2O:CH_2 Cl_2:hexane = 1:1:20); white solid; m.p. 119–121 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (dd, J = 2.4 Hz, 1.0 Hz, 1H), 7.74 (d, J = 8.8 Hz, 1H), 7.39 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 7.25 (dd, J = 8.9 Hz, 1.5 Hz, 1H), 4.37 (q, J = 7.1 Hz, 2H), 2.51 (d, J = 0.8 Hz, 3H), 2.45 (s, 3H), 1.36 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 159.8, 147.4, 139.4, 138.8, 135.4, 129.9, 129.3, 126.2, 124.5, 124.3, 119.8, 118.3, 61.0, 22.3, 21.4, 14.4; IR (film): ν = 2975, 2918, 1715, 1514, 1287, 1120 cm^{-1}; HR-MS (EI): m/z = 294.1369, calcd. for $C_{18}H_{18}N_2O_2$: 294.1368.

Ethyl 7-ethyl-2-(2-ethylphenyl)-2*H*-indazole-3-carboxylate (4e): yield: 27.1 mg (42%); R_f = 0.40 (Et_2O:CH_2Cl_2:hexane = 1:1:20); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, J = 8.4 Hz, 1H), 7.47 (td, J = 11.2 Hz, 1.4 Hz, 1H), 7.41 (dd, J = 7.7 Hz, 1.0 Hz, 1H), 7.36–7.27 (m, 3H), 7.21 (dd, J = 6.8 Hz, 1.0 Hz, 1H), 4.29 (q, J = 7.1 Hz, 2H), 3.13 (t, J = 7.4 Hz, 2H), 2.29 (t, J = 7.7 Hz, 2H), 1.40 (t, J = 7.5 Hz, 3H), 1.26 (t, J = 7.1 Hz, 3H), 1.07 (t, J = 7.6 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 159.5, 148.0, 140.7, 140.3, 135.1, 129.9, 129.0, 127.2, 126.3, 126.2, 125.9, 124.2, 123.5, 119.0, 60.9, 24.4, 23.9, 14.5, 14.4, 14.2; IR (film): ν = 3024, 2972, 1718, 1496, 1230, 1105 cm^{-1}; HR-MS (EI): m/z = 322.1684, calcd for $C_{20}H_{22}N_2O_2$: 322.1681.

Ethyl 6-methoxy-2-(3-methoxyphenyl)-2*H*-indazole-3-carboxylate (4f): yield: 39.2 mg (60%); R_f = 0.20 (Et_2O:CH_2Cl_2:hexane = 1:1:20); white solid; mp 95–97 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96 (dd, J = 9.1 Hz, 0.6 Hz, 1H), 7.40 (td, J = 7.7 Hz, 1.1 Hz, 1H), 7.09–7.01 (m, 5H), 4.35 (q, J = 7.1 Hz, 2H), 3.90 (s, 3H), 3.85 (s, 3H), 1.34 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 159.8, 159.5, 159.4, 149.6, 142.1, 129.3, 125.3, 122.4, 120.6, 119.8, 118.9, 115.3, 112.2, 95.4, 61.2, 55.6, 55.4, 14.3; IR (film): ν = 2997, 2832, 1719, 1501, 1316, 1218 cm^{-1}; HR-MS (EI): m/z = 326.1267, calcd. for $C_{18}H_{18}N_2O_4$: 326.1267.

Ethyl 6-chloro-2-(3-chlorophenyl)-2*H*-indazole-3-carboxylate (4g): yield: 49.5 mg (74%); R_f = 0.20 (Et_2O:CH_2Cl_2:hexane = 1:1:20); ivory solid; mp 159–161 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (d, J = 9.0 Hz, 1H), 7.82 (d, J = 0.9 Hz, 1H), 7.55 (t, J = 1.7 Hz, 1H), 7.52 (dt, J = 7.7 Hz, 1.7 Hz, 1H), 7.47 (t, J = 7.7 Hz, 1H), 7.42 (dt, J = 7.8 Hz, 1.7 Hz, 1H), 7.30 (dd, J = 9.0 Hz, 1.6 Hz, 1H), 4.38 (q, J = 7.1 Hz, 2H), 1.35 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 159.0, 148.8, 141.6, 134.5, 133.5, 129.9, 129.7, 127.4, 126.9, 125.8, 124.8, 123.1, 122.5, 117.6, 61.6, 14.2; IR (film): ν = 2987, 2918, 1721, 1484, 1172, 781 cm^{-1}; HR-MS (EI): m/z = 334.0274, calcd. for $C_{16}H_{12}Cl_2N_2O_2$: 334.0276.

Ethyl 5-chloro-2-(4-chlorophenyl)-2*H*-indazole-3-carboxylate (4h): yield: 43.8 mg (65%); R_f = 0.20 (Et_2O:CH_2Cl_2:hexane = 1:1:20); yellow solid; mp 184–186 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (dd, J = 2.0 Hz, 0.7 Hz, 1H), 7.78 (dd, J = 9.1 Hz, 0.7 Hz, 1H), 7.50 (d, J = 9.0 Hz, 2H), 7.47 (d, J = 9.0 Hz, 2H), 7.37 (dd, J = 9.1 Hz, 2.0 Hz, 1H), 4.39 (q, J = 7.1 Hz, 2H), 1.39 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 159.1, 147.0, 139.2, 135.7, 131.9, 129.03, 128.99, 127.7, 124.9, 124.6, 120.6, 120.2, 61.6, 14.4; IR (film): ν = 2987, 2918, 1716, 1498, 1124, 771 cm^{-1}; HR-MS (EI): m/z = 334.0274, calcd. for $C_{16}H_{12}Cl_2N_2O_2$: 334.0276.

Ethyl 6-bromo-2-(3-bromophenyl)-2*H*-indazole-3-carboxylate (4i): yield: 56.7 mg (67%); R_f = 0.20 (Et_2O:CH_2Cl_2:hexane = 1:1:20); pink solid; mp 148–150 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (dd, J = 1.6 Hz, 0.7 Hz, 1H), 7.99 (dd, J = 9.0 Hz, 0.7 Hz, 1H), 7.70 (t, J = 1.8 Hz, 1H), 7.67 (ddd, J = 7.9 Hz, 1.9 Hz, 1.2 Hz, 1H), 7.47 (ddd, J = 8.0 Hz, 2.0 Hz, 1.2 Hz, 1H), 7.42 (dd, J = 9.0 Hz, 1.6 Hz, 1H), 7.40 (t, J = 7.9 Hz, 1H), 4.38 (q, J = 7.1 Hz, 2H), 1.35 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 159.0, 149.3, 141.7, 132.8, 130.0, 129.8, 129.7, 125.9, 125.3, 123.2, 122.8, 122.1, 121.6, 121.0, 61.7, 14.3; IR (film): ν = 3095, 2987, 1716, 1484, 1124, 678 cm^{-1}; HR-MS (EI): m/z = 621.9264, calcd. for $C_{16}H_{12}Br_2N_2O_2$: 421.9266.

Ethyl 2-(*o*-tolyl)-2*H*-indazole-3-carboxylate (4j): yield: 49.0 mg (87%); R_f = 0.20 (Et_2O:CH_2Cl_2:hexane = 1:1:20); yellow solid; mp 114–116 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, J = 8.4 Hz, 1H), 7.52 (s, 5H), 7.27–7.23 (m, 1H), 7.17 (dt, J = 7.0 Hz, 1.1 Hz, 1H), 4.34 (q, J = 7.1 Hz, 2H), 2.69 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 159.7, 148.8, 141.3, 129.4, 128.9, 128.7, 126.6, 126.2, 125.9, 125.4, 124.0, 119.0, 61.1, 17.0, 14.2; IR (film): ν = 3008, 2975, 1724, 1463, 1240, 1105 cm^{-1}; HR-MS (EI): m/z = 280.1212, calcd for $C_{17}H_{16}N_2O_2$: 280.1212.

Ethyl 2-(*m*-tolyl)-2*H*-indazole-3-carboxylate (4k): yield: 50.4 mg (90%); R_f = 0.30 (Et_2O:CH_2Cl_2:hexane = 1:1:20); white solid; mp 78–80 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (dt, J = 8.5 Hz, 1.0 Hz, 1H), 7.86 (dt, J = 8.6 Hz, 1.0 Hz, 1H), 7.44–7.29 (m, 6H), 4.36 (q, J = 7.1 Hz, 2H), 2.45 (s, 3H), 1.35 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 159.6, 148.5, 141.0, 138.9, 130.2, 128.5, 127.1, 126.9, 125.5, 125.2, 124.0, 123.6, 121.7, 118.7, 61.2, 21.4, 14.3; IR (film): ν = 3060, 2981, 1721, 1466, 1294, 1112 cm^{-1}; HR-MS (EI): m/z = 280.1214, calcd. for $C_{17}H_{16}N_2O_2$: 280.1212.

Ethyl 2-(*p*-tolyl)-2*H*-indazole-3-carboxylate (4l): yield: 45.2 mg (81%); R_f = 0.30 (Et_2O:CH_2Cl_2:hexane = 1:1:20); white solid; mp 100–102 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (dt, J = 8.4 Hz, 1.0 Hz, 1H), 7.85 (dt, J = 8.7 Hz, 1.0 Hz, 1H), 7.43–7.40 (m, 3H), 7.36–7.31 (m, 3H), 7.36–7.31 (m, 3H), 4.37 (q, J = 7.1 Hz, 2H), 2.46 (s, 3H), 1.37 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ = 159.7, 148.4, 139.5, 138.6, 129.3, 127.1, 126.1, 125.5, 125.1, 124.0, 121.7, 118.7, 61.2, 21.5, 14.3; IR (film): ν = 3044, 2984, 1718,

1457, 1290, 1118 cm^{-1}; HR-MS (EI): m/z = 280.1210, calcd. for $C_{17}H_{16}N_2O_2$: 280.1212.

Ethyl 2-(3,5-dimethylphenyl)-2*H*-indazole-3-carboxylate (4m): yield: 50.2 mg (85%); R_f = 0.30 (Et_2O:CH_2Cl_2:hexane = 1:1:20); white solid; mp 72–74 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.11 (dt, J = 8.4 Hz, 1.1 Hz, 1H), 7.84 (dt, J = 8.6 Hz, 1.0 Hz, 1H), 7.41 (ddd, J = 8.5 Hz, 6.8 Hz, 1.3 Hz, 1H), 7.34 (ddd, J = 8.4 Hz, 6.7 Hz, 1.0 Hz, 1H), 7.14 (d, J = 0.6 Hz, 1H), 7.13 (d, J = 0.6 Hz, 2H), 4.37 (q, J = 7.1 Hz, 2H), 2.39 (s, 6H), 1.36 (t, J = 7.1, Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 159.6, 148.4, 140.9, 138.5, 131.1, 127.1, 125.5, 125.1, 124.1, 124.0, 121.6, 118.7, 61.1, 21.4, 14.3; IR (film): ν = 3014, 2924, 1721, 1477, 1303, 1072 cm^{-1}; HR-MS (EI): m/z = 294.1364, calcd. for $C_{18}H_{18}N_2O_2$: 294.1368.

Ethyl 2-(3-chlorophenyl)-2*H*-indazole-3-carboxylate (4n): yield: 31.0 mg (53%); R_f = 0.20 (Et_2O:CH_2Cl_2:hexane = 1:1:20); pink solid; mp 120–122 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.12 (dt, J = 8.5 Hz, 1.1 Hz, 1H), 7.84 (dt, J = 8.6 Hz, 0.9 Hz, 1H), 7.57–7.56 (m, 1H), 7.51 (dt, J = 7.1 Hz, 2.1 Hz, 1H), 7.48–7.42 (m, 3H), 7.36 (ddd, J = 8.4 Hz, 6.8 Hz, 1.0 Hz, 1H), 4.39 (q, J = 7.1 Hz, 2H), 1.37 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 159.4, 148.7, 141.9, 134.4, 129.6, 127.5, 127.0, 125.9, 125.3, 124.9, 124.2, 121.7, 118.7, 61.4, 14.3; IR (film): ν = 3068, 2981, 1710, 1482, 1129, 776 cm^{-1}; HR-MS (EI): m/z = 300.0667, calcd. for $C_{16}H_{13}ClN_2O_2$: 300.0666.

Ethyl 2-(4-chlorophenyl)-2*H*-indazole-3-carboxylate (4o): yield: 40.1 mg (67%); R_f = 0.20 (Et_2O:CH_2Cl_2:hexane = 1:1:20); white solid; mp 139–141 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.11 (dt, J = 8.5 Hz, 1.0 Hz, 1H), 7.84 (dt, J = 8.7 Hz, 1.0 Hz, 1H), 7.52–7.47 (m, 2H), 7.43 (ddd, J = 8.4 Hz, 6.9 Hz, 1.3 Hz, 1H), 7.36 (ddd, J = 8.2 Hz, 6.9 Hz, 1.1 Hz, 1H), 4.39 (q, J = 7.1 Hz, 2H), 1.39 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 159.6, 148.7, 139.5, 135.5, 129.0, 127.8, 127.5, 125.9, 125.2, 124.1, 121.7, 118.7, 61.4, 14.3; IR (film): ν = 3048, 2978, 1713, 1493, 1124, 752 cm^{-1}; HR-MS (EI): m/z = 300.0664, calcd. for $C_{16}H_{13}ClN_2O_2$: 300.0666.

Ethyl 2-(3-bromophenyl)-2*H*-indazole-3-carboxylate (4p): yield: 53.4 mg (77%); R_f = 0.30 (Et_2O:CH_2Cl_2:hexane = 1:1:20); ivory solid; mp 121–123 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.12 (dt, J = 8.4 Hz, 1.1 Hz, 1H), 7.84 (dt, J = 8.6 Hz, 1.0 Hz, 1H), 7.72 (t, J = 1.9 Hz, 1H), 7.66 (ddd, J = 8.0 Hz, 1.9 Hz, 1.1 Hz, 1H), 7.49 (ddd, J = 8.0 Hz, 2.0 Hz, 1.1 Hz, 1H), 7.46–7.34 (m, 3H) 4.39 (q, J = 7.1 Hz, 2H), 1.37 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 159.7, 148.7, 142.0, 132.5, 129.9, 129.8, 127.5, 125.9, 125.4, 125.3, 124.2, 122.0, 121.7, 118.7, 61.4, 14.3; IR (film): ν = 3071, 2981, 1713, 1480, 1287, 684 cm^{-1}; HR-MS (EI): m/z = 344.0158, calcd. for $C_{16}H_{13}BrN_2O_2$: 344.0160.

Ethyl 2-(4-bromophenyl)-2*H*-indazole-3-carboxylate (4q): yield: 60.3 mg (87%); (R_f = 0.20 (Et_2O:CH_2Cl_2:hexane = 1:1:20); white solid; mp 136–138 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.11 (dt, J = 8.5 Hz, 1.1 Hz, 1H), 7.84 (dt, J = 8.6 Hz, 1.0 Hz, 1H), 7.66 (d, J = 8.8 Hz, 2H), 7.45–7.40 (m, 3H) 7.36 (ddd, J = 8.4 Hz, 6.7 Hz, 1.0 Hz, 1H), 4.39 (q, J = 7.1 Hz, 2H), 1.39 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 159.6, 148.7, 140.0, 131.9, 128.1, 127.5, 126.0, 125.1, 124.1, 123.6, 122.0, 118.7, 61.4, 14.3; IR (film): ν = 3048, 2978, 1713, 1493, 1290, 665 cm^{-1}; HR-MS (EI): m/z = 344.0162, calcd. for $C_{16}H_{13}BrN_2O_2$: 344.0160.

Ethyl 2-(3-acetylphenyl)-2*H*-indazole-3-carboxylate (4r): yield: 47.0 mg (76%); R_f = 0.20 (Et_2O:CH_2Cl_2:hexane = 1:1:20); ivory solid; mp 112–114 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.14–8.13 (m, 2H), 8.12 (t, J = 1.2 Hz, 1H), 7.86 (dt, J = 8.6 Hz, 1.0 Hz, 1H), 7.75 (ddd, J = 7.9 Hz, 2.1 Hz, 1.2 Hz, 1H), 7.65 (t, J = 8.1 Hz, 1H), 7.45 (ddd, J = 8.4 Hz, 6.9 Hz, 1.4 Hz, 1H), 7.38 (ddd, J = 8.4 Hz, 6.7 Hz, 1.0 Hz, 1H), 4.38 (q, J = 7.1 Hz, 2H), 2.66 (s, 3H), 1.37 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 196.8, 159.5, 148.7, 141.2, 137.6, 131.0, 129.1, 129.0, 127.5, 126.5, 125.9, 125.2, 124.1, 121.7, 118.7, 61.4, 26.9, 14.3; IR (film): 3075, 2981, 1718, 1688, 1484, 1292 cm^{-1}; HR-MS (EI): m/z = 308.1163, calcd. for $C_{18}H_{16}N_2O_3$: 308.1161.

Ethyl 2-[4-(ethoxycarbonyl)phenyl]-2*H*-indazole-3-carboxylate (4s): yield: 48.0 mg (71%); R_f = 0.40 (Et_2O:CH_2Cl_2:hexane = 1:1:20); ivory solid; mp 119–121 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.22 (d, J = 8.7 Hz, 2H), 8.12 (dt, J = 8.5 Hz, 1.1 Hz, 1H), 7.86 (dt, J = 8.6 Hz, 1.0 Hz, 1H), 7.63 (d, J = 8.7 Hz, 2H), 7.44 (ddd, J = 8.6 Hz, 6.7 Hz, 1.2 Hz, 1H), 7.37 (ddd, J = 8.5 Hz, 6.7 Hz, 1.0 Hz, 1H), 4.43 (q, J = 6.8 Hz, 2H), 4.38 (q, J = 6.8 Hz, 2H), 1.43 (t, J = 7.1 Hz, 3H), 1.37 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 165.8, 159.5, 148.8, 144.4, 131.3, 130.1, 127.5, 126.5, 126.0, 125.3, 124.2, 121.7, 118.7, 61.5, 61.4, 14.5, 14.3; IR (film): ν = 3051, 2975, 1718, 1457, 1294, 1127 cm^{-1}; HR-MS (EI): m/z = 338.1269, calcd. for $C_{19}H_{18}N_2O_4$: 338.1267.

Diethyl 2-(3-chlorophenyl)-2*H*-indazole-3,5-carboxylate (4t): yield: 46.6 mg (63%); R_f = 0.20 (Et_2O:CH_2Cl_2:hexane = 1:1:20); yellow solid; mp 157–159 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.92 (dd, J = 1.5 Hz, 0.9 Hz, 1H), 8.05 (dd, J = 9.1 Hz, 1.6 Hz, 1H), 7.85 (dd, J = 9.1 Hz, 0.9 Hz, 1H), 7.58 (td, J = 1.8 Hz, 0.4 Hz, 1H), 7.54 (dt, J = 7.4 Hz, 1.9 Hz, 1H), 7.50–7.44 (m, 2H), 4.45 (q, J = 7.1 Hz, 2H), 4.42 (q, J = 7.1 Hz, 2H), 1.45 (t, J = 7.1 Hz, 3H), 1.40 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 166.6, 158.9, 149.7, 141.5, 134.5, 130.0, 129.8, 127.9, 127.4, 127.2, 126.9, 125.9, 124.8, 123.3, 118.6, 61.8, 61.4, 14.5, 14.2; IR (film): ν = 2987, 1710, 1466, 1230, 1102, 762 cm^{-1}; HR-MS (EI): m/z = 372.0877, calcd. for $C_{19}H_{17}ClN_2O_4$: 372.0877.

Diethyl 2-(4-bromophenyl)-2*H*-indazole-3,5-dicarboxylate (4u): yield: 50.0 mg (60%); R_f = 0.20 (Et_2O:CH_2Cl_2:hexane = 1:1:20); white solid; mp 164–166 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.90 (dd, J = 1.5 Hz, 0.9 Hz, 1H), 8.05 (dd, J = 9.1 Hz, 1.6 Hz, 1H), 7.85 (dd, J = 9.1 Hz, 0.9 Hz, 1H), 7.68 (d, J = 8.8 Hz, 2H), 7.43 (d, J = 8.9 Hz, 2H), 4.45 (q, J = 7.1 Hz, 2H), 4.42 (q, J = 7.1 Hz, 2H), 1.45 (t, J = 7.1 Hz, 3H), 1.41 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ = 166.6, 159.0, 149.7, 139.6, 132.0, 128.0, 127.8, 127.3, 127.1, 125.9, 123.9, 123.3, 118.6, 61.8, 61.4, 14.5, 14.2; IR (film): ν = 2981, 1716, 1463, 1290, 1099, 684 cm^{-1}; HR-MS (EI): m/z = 416.0374, calcd. for $C_{19}H_{17}BrN_2O_4$: 416.0372.

Ethyl 2-(3-bromophenyl)-5-(trifluoromethyl)-2*H*-indazole-3-carboxylate (4v): yield: 58.3 mg (71%); R_f = 0.20 (Et_2O:CH_2Cl_2:hexane = 1:1:20); pink solid; mp 168–170 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.47 (t, J = 0.8 Hz, 1H), 7.95 (dt, J = 9.1 Hz, 0.8 Hz, 1H), 7.72 (t, J = 1.8 Hz, 1H), 7.70 (ddd, J = 8.0 Hz, 1.7 Hz, 1.4 Hz, 1H), 7.60 (dd, J = 9.1 Hz, 1.7 Hz, 1H), 7.49 (ddd, J = 8.0 Hz, 2.0 Hz, 1.2 Hz, 1H), 7.43 (t, J = 7.9 Hz, 1H), 4.41 (q, J = 7.1 Hz, 2H), 1.38 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ =

158.7, 148.9, 141.5, 133.0, 130.0, 129.7, 127.8 (q, J_{CF}= 32.0 Hz), 127.1, 125.2, 124.4 (q, $J_{C,F}$=272.2 Hz), 123.5 (q, $J_{C,F}$=2.9 Hz), 122.7, 122.2, 120.6 (q, $J_{C,F}$=5.0 Hz), 119.9, 61.9, 14.2; IR (film): ν=2989, 1713, 1482, 1262, 1112, 678 cm^{-1}; HR-MS (EI): m/z=412.0034, calcd. for $C_{17}H_{12}BrF_3N_2O_2$: 412.0034.

Ethyl 2-[4-(ethoxycarbonyl)phenyl]-5(trifluoromethyl)-2*H*-indazole-3-carboxylate (4w): yield: 38.9 mg (48%); R_f= 0.20 (Et_2O:CH_2Cl_2:hexane=1:1:20); brown solid; mp 133–135 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.47 (s, 1H), 8.24 (d, J=8.7 Hz, 2H), 7.96 (dt, J=9.0 Hz, 0.7 Hz, 1H), 7.63 (d, J=8.7 Hz, 2H), 7.60 (dd, J=9.0 Hz, 1.6 Hz, 1H), 4.44 (q, J=7.1 Hz, 2H), 4.41 (q, J=7.1 Hz, 2H), 1.44 (t, J=7.1 Hz, 3H), 1.38 (t, J=7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ=165.6, 158.8, 149.0, 143.9, 131.8, 130.3, 127.8 (q, $J_{C,F}$=31.9 Hz), 127.1, 126.5, 124.4 (q, $J_{C,F}$=272.2 Hz), 123.6 (q, $J_{C,F}$=2.9 Hz), 122.8, 120.7 (q, $J_{C,F}$=4.9 Hz), 120.0, 62.0, 61.6, 14.5, 14.3; IR (film): ν=2987, 1721, 1463, 1317, 1107, 1067 cm^{-1}; HR-MS (EI): m/z=40 6.1143, calcd. for $C_{20}H_{17}F_3N_2O_4$: 406.1140.

Ethyl 5,7-dimethyl-2-(*o*-tolyl)-2*H*-indazole-3-carboxylate (4x): yield: 49.2 mg (80%); R_f=0.30 (Et_2O:CH_2Cl_2:hexane= 1:1:20); white solid; mp 77–79 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.71 (s, 1H), 7.44–7.40 (m, 1H), 7.35–7.28 (m, 3H), 7.04 (t, J=1.4 Hz, 1H), 4.29 (q, J=7.1 Hz, 2H), 2.65 (s, 3H), 2.48 (d, J=0.8 Hz, 3H), 2.06 (s, 3H), 1.26 (t, J= 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ=159.6, 147.9, 141.0, 135.8, 135.1, 130.6, 129.6, 129.1, 128.6, 127.1, 126.4, 125.2, 123.8, 117.2, 60.9, 22.3, 17.2, 17.1, 14.2; IR (film): ν=3062, 2978, 1716, 1498, 1278, 1099 cm^{-1}; HR-MS (EI): m/z=308.1526, calcd. for $C_{19}H_{20}N_2O_2$: 308.1525.

Ethyl 2-(4-bromophenyl)-5,7-dimethyl-2*H*-indazole-3-carboxylate (4y): yield: 59.8 mg (80%); R_f=0.30 (Et_2O:CH_2Cl_2:hexane=1:1:20); white solid; mp 167–169 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.66 (s, 1H), 7.64 (d, J= 8.6 Hz, 2H), 7.40 (d, J=8.6 Hz, 2H), 7.26 (s, 1H), 4.36 (q, J=7.1 Hz, 2H), 2.63 (s, 3H), 2.47 (s, 3H), 1.36 (t, J=7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ=159.9, 148.1, 140.3, 136.2, 131.9, 129.4, 128.5, 128.3, 124.6, 124.5, 123.3, 117.2, 61.2, 22.3, 16.9, 14.4; IR (film): ν=3011, 2978, 1710, 1493, 1275, 662 cm^{-1}; HR-MS (EI): m/z=372.0469, calcd. for $C_{18}H_{17}BrN_2O_2$: 372.0473.

Synthetic Procedure of 4-(2*H*-Indazol-2-yl)morpholines

To a long test tube were added 2-iodoarytriazene (**1**) (0.2 mmol), $Pd(PPh_3)_4$ (11.5 mg, 5.0 mol%) and NaOH (24.0 mg, 0.6 mmol) in EtOH (0.4 mL) at room temperature under N_2. Subsequently, ethyl diazoacetoacetate (**2**) (62.5 mg, 0.4 mmol) in EtOH (0.4 mL) was added dropwise into the long test tube and the resulting mixture was stirred at room temperature for 2 h under N_2. After 2 h, the resulting mixture was heated at 70 °C for 2 h. After evaporation of the solvents under vacuum, the crude product was purified by column chromatography on silica gel to give the corresponding of 4-(2*H*-indazol-2-yl)morpholine derivatives.

Ethyl 2-morpholino-2*H*-indazole-3-carboxylate (6a): yield: 40.0 mg (73%); R_f=0.40 (Et_2O:CH_2Cl_2:hexane= 1:1:20); yellow solid; mp 64–66 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.01 (dt, J=8.4 Hz, 1.0 Hz, 1H), 7.76 (dt, J= 8.6 Hz, 0.9 Hz, 1H), 7.38 (ddd, J=8.6 Hz, 6.8 Hz, 1.2 Hz, 1H), 7.30 (ddd, J=8.3 Hz, 6.9 Hz, 1.0 Hz, 1H), 4.49 (q, J= 7.1 Hz, 2H), 3.99 (t, J=4.7 Hz, 4H) 3.46 (t, J=4.4 Hz, 4H) 1.50 (t, J=7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ=158.9, 144.9, 126.6, 125.2, 122.1, 121.6, 121.4, 118.2, 66.9, 61.1, 55.8, 14.6; IR (film): ν=2981, 2854, 1724, 1463, 1265, 1082 cm^{-1}; HR-MS (EI): m/z=275.1267, calcd. for $C_{14}H_{17}N_3O_3$: 275.1270.

Diethyl 2-morpholino-2*H*-indazole-3,5-dicarboxylate (6b): yield: 49.3 mg (71%); R_f=0.30 (Et_2O:CH_2Cl_2:hexane= 1:1:20); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.80 (dd, J=1.5 Hz, 0.9 Hz, 1H), 8.80 (dd, J=9.0 Hz, 1.6 Hz, 1H), 7.77 (dd, J=9.0 Hz, 0.8 Hz, 1H), 4.53 (q, J=7.1 Hz, 2H), 4.42 (q, J=7.1 Hz, 2H), 4.00 (t, J=4.6 Hz, 4H), 3.47 (dd, J=5.1 Hz, 3.7 Hz, 3H), 1.53 (t, J=7.1 Hz, 3H), 1.44 (t, J=7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ=166.7, 158.3, 146.1, 127.1, 126.5, 125.5, 123.5, 121.2, 118.0, 66.8, 61.5, 61.2, 55.8, 14.4; IR (film): ν=2981, 1716, 1468, 1273, 1224, 1102 cm^{-1}; HR-MS (EI): m/z=347.1483, calcd. for $C_{17}H_{21}N_3O_5$: 347.1481.

Ethyl 2-morpholino-5-(trifluoromethyl)-2*H*-indazole-3-carboxylate (6c): yield: 36.4 mg (53%); R_f=0.40 (Et_2O: CH_2Cl_2:hexane=1:1:20); white solid; mp 80–82 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.36 (t, J=0.8 Hz, 1H), 7.86 (dt, J= 9.0 Hz, 0.8 Hz, 1H), 7.55 (dd, J=9.0 Hz, 1.6 Hz, 1H), 4.52 (q, J=7.1 Hz, 2H), 4.52 (q, J=7.1 Hz, 2H), 4.00 (t, J= 7.1 Hz, 4H), 3.47 (dd, J=5.0 Hz, 3.8 Hz, 4H), 1.51 (t, J= 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ=158.2, 145.3, 127.1 (q, $J_{C,F}$=32.0 Hz), 124.5 (q, $J_{C,F}$=272.4 Hz), 123.4, 122.6 (q, $J_{C,F}$=3.0 Hz), 120.8, 120.3 (q, $J_{C,F}$=4.9 Hz), 119.3, 66.8, 61.6, 55.9, 14.5; IR (film): ν=2861, 1729, 1488, 1311, 1107, 1088 cm^{-1}; HR-MS (EI): m/z=343.1144, calcd. for $C_{15}H_{16}F_3N_3O_3$: 343.1144.

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