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TITANIUM TETRAIODIDE INDUCED CYCLIZATION OF CYANOKETONES INTO 3-ARYL-1-IODOISOQUINOLINES

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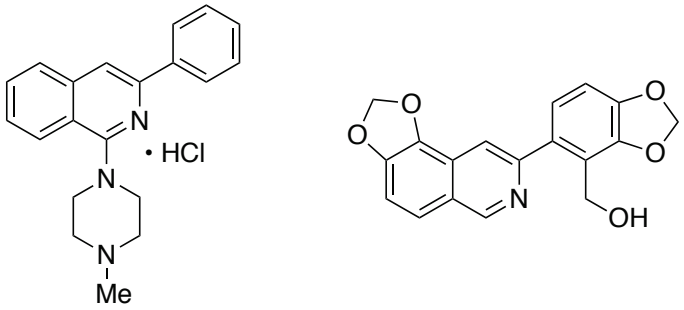
Abstract – 3-Aryl-1-iodoisoquinoline synthesis is developed using titanium tetraiodide induced cyclization of cyanoketones. The method is applied to the short step formal synthesis of CWJ-a-5 having a topoisomerase I inhibitory activity. 3-Iodo-1-phenylisoquinoline synthesis is also reported under the similar reaction conditions.

INTRODUCTION

Synthetic methods for the preparation of nitrogen-containing heterocycles are of utmost interest and importance because these structures are the key components of natural and unnatural biologically active compounds and functionalized materials. Imines and nitriles having carbon-nitrogen double or triple bonds are often used as a nitrogen source constituting nitrogen-containing heterocycles. Among several imines, alkynyl imines are some of the most useful nitrogen-containing starting materials and extensively used in the synthesis of nitrogen-containing compounds including heterocycles. We have been interested in the reactivity at the β-position of alkynyl imines as a Michael acceptor and developed efficient synthetic methods for several nitrogen-containing heterocycles such as 2-pyridones,[1] bicyclo-pyridones,[2] iminopyridines,[3] aminopyridines,[3] β-lactams,[4] and 4-quinolones.[5]

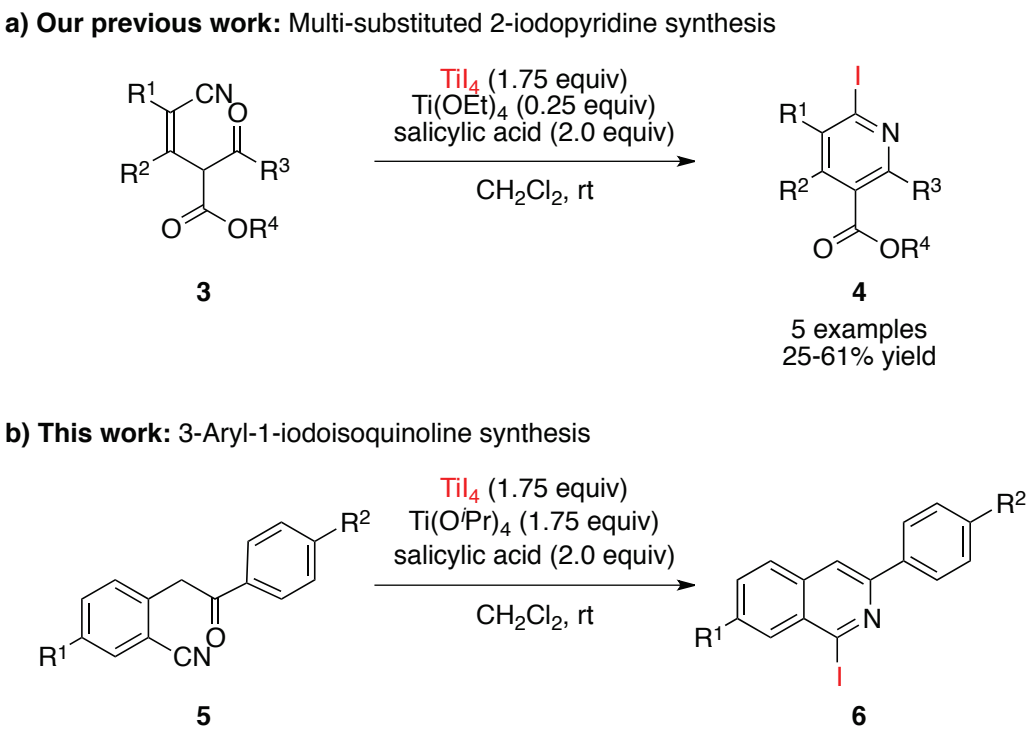
Isoquinolines and their derivatives are one of the most important nitrogen-containing compounds because they are often used as pharmaceuticals[6] and organic functional materials.[7] Bischler-Napieralski,[8] Pomeranz-Fritsch,[9] and Pictet-Spengler[10] reactions are used for the synthesis of isoquinolines as a classical method. However, these methods are often limited due to the use of harsh reaction conditions. Recently, transition metal catalyzed reactions have been developed for the preparation of isoquinoline derivatives.[11] Iodoisoquinolines are utilized as useful intermediates which are transformed into various bioactive substances because metal-halogen exchanges[12] and S_NAr reactions[13] easily occur or they are excellent starting materials for transition metal catalyzed reactions.[14] Among the isoquinoline derivatives, 3-arylisoquinolines such as CWJ-a-5 (**1**)[15] and decumbenine B (**2**)[16] are attractive compounds because

they have prominent biological activities (Figure 1). Therefore, the development of efficient synthetic methods of 3-arylisoquinolines has been highly desired.[17]



CWJ-a-5 (**1**) decumbenine B (**2**)

Figure 1. 3-Arylisoquinolines having biological activityes



Scheme 1. Titanium tetraiodide induced cyclization of cyanoketones for the syntheses of nitrogen-containing heterocycles

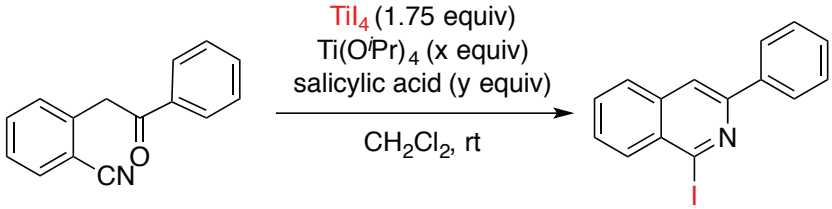
Titanium(IV) halides are extensively used in carbon-carbon bond forming reactions; for examples, Mukaiyama aldol reactions of aldehydes with silyl enol ethers, Diels–Alder reactions, and carbonyl-ene reactions as a Lewis acid. Low valent titanium halides promote reductive coupling reactions of carbonyl compounds. In most of these reactions, ligands of titanium halides are chloride or bromide.[18] Although titanium(IV) tetraiodide (TiI_4) had been used for the production of high purity metal titanium, its use was rare in organic synthesis.[19] We have focused on a mild Lewis acidity, reducing and iodination abilities of

titanium(IV) tetraiodide, and already reported several reactions such as reductive aldol,[20] Mannich-type reactions,[21] pinacol coupling reaction,[22] Prins reaction,[23] and iodoaldol reaction.[24] In 2009, we reported the synthesis of multi-substituted 2-iodopyridines (**4**) via iodination-cyclization reactions of 2-(2-cyanoalk-1-enyl)-β-ketoesters (**3**) using TiI_4 (Scheme 1a).[25] We envisioned a synthesis of isoquinolines (**6**) via iodination-cyclization reactions of benzonitrile derivatives (**5**) using TiI_4 (Scheme 1b). Herein we describe the synthesis of 3-aryl-1-iodoisoquinolines (**6**) via iodination-cyclization reactions of 2-(2-aryl-2-oxoethyl)benzonitrile derivatives (**5**) using TiI_4.[26] Moreover, to prove the utility of the method, we applied it to a short step formal synthesis of CWJ-a-5 (**1**) having a topoisomerase I inhibitory activity.

RESULTS AND DISCUSSION

Several reaction conditions were examined regarding the iodination-cyclization reaction of 2-(2-oxo-2-phenylethyl)benzonitrile (**5a**). Table 1 summarizes the results. First, the TiI_4 induced cyclization of **5a** was carried out without any additives because it was thought that the cyclization reaction would efficiently occur compared to that of a 2-iodopyridine formation due to a benzene ring-fused substrate. However, the desired 1-iodo-3-phenylisoquinoline (**6a**) was not obtained. Use of salicylic acid or $Ti(O^iPr)_4$ as a single additive was not effective (entries 2 and 3). The desired reaction proceeded in the presence of TiI_4, $Ti(O^iPr)_4$, and salicylic acid to give the desired 1-iodo-3-phenylisoquinoline (**6a**) in 21% yield (entry 4). When the amount of $Ti(O^iPr)_4$ increased, 1-iodo-3-phenylisoquinoline (**6a**) was obtained in 40% yield (entry 5).[27]

Table 1. Optimization of reaction conditions

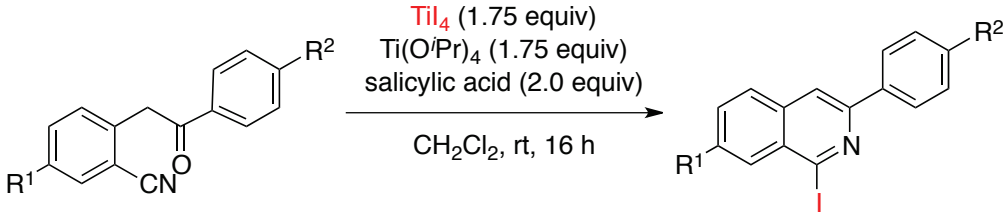


5a **6a**

Entry	$Ti(O^iPr)_4$ (equiv)	Salicylic acid (equiv)	Time (h)	Yield (%)
1	–	–	36	–
2	–	2.0	36	–
3	0.25	–	10	3
4	0.25	2.0	10	21
5	1.75	2.0	16	40

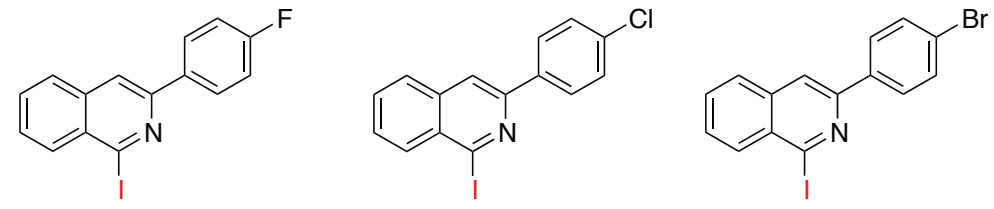
With the optimized reaction conditions in hand, several 2-(2-aryl-2-oxoethyl)benzonitrile derivatives (**5**) were subjected to the iodination-cyclization reaction. Table 2 summarizes the results. The reactions of 2-(2-aryl-2-oxoethyl)benzonitrile derivatives (**5b**-**d**) having a halogen group at the phenyl moiety afforded the 1-iodo-3-(4-halophenyl)isoquinolines (**6b**-**d**) in 35%, 33%, and 38% yields, respectively. The reaction of 2-(2-oxo-2-(*p*-tolyl)ethyl)benzonitrile (**5e**) gave 1-iodo-3-(*p*-tolyl)isoquinoline (**6e**) in low yield probably because the electrophilicity of the keto carbonyl group decreases by an electron-donating methyl group. The reactions of 2-(2-aryl-2-oxoethyl)benzonitrile derivatives (**5f**) and (**5g**) possessing a halogen group at the benzonitrile moiety afforded the 1-iodo-3-(4-halophenyl)isoquinolines (**6f**) and (**6g**) in 42% and 44% yields, respectively.

Table 2. Synthesis of several 3-aryl-1-iodoisoquinolines **(6)**

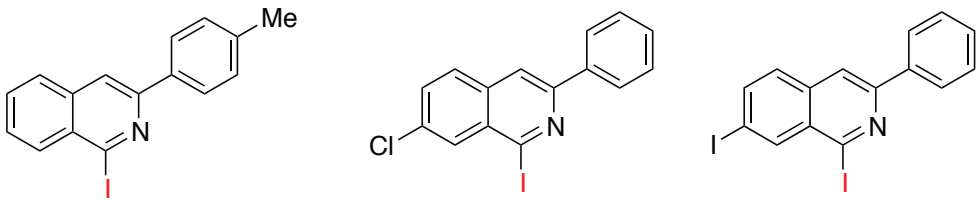


5b: R^1 = H, R^2 = F
5c: R^1 = H, R^2 = Cl
5d: R^1 = H, R^2 = Br
5e: R^1 = H, R^2 = Me
5f: R^1 = Cl, R^2 = H
5g: R^1 = I, R^2 = H

6b-6g



6b: 35% **6c**: 33% **6d**: 38%

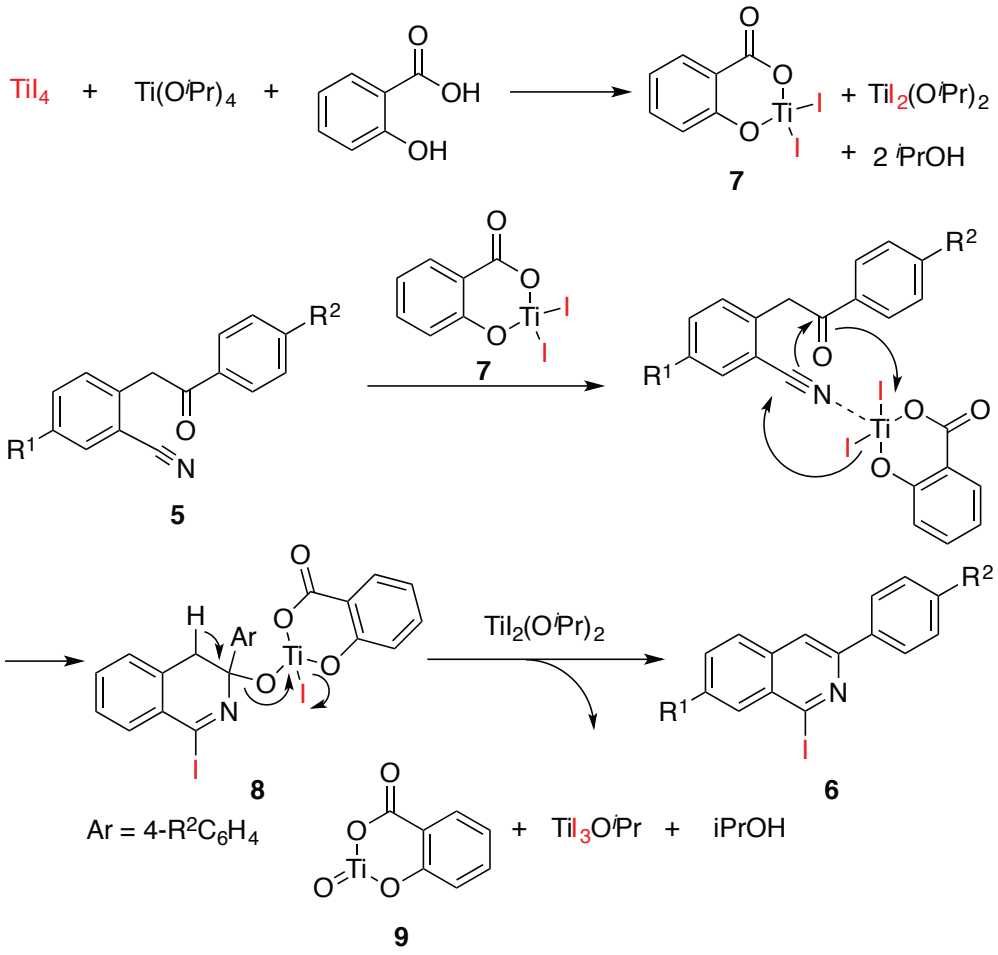


6e: 8% **6f**: 42% (54%)[a] **6g**: 44% (51%)[a]

[a] Conversion yield.

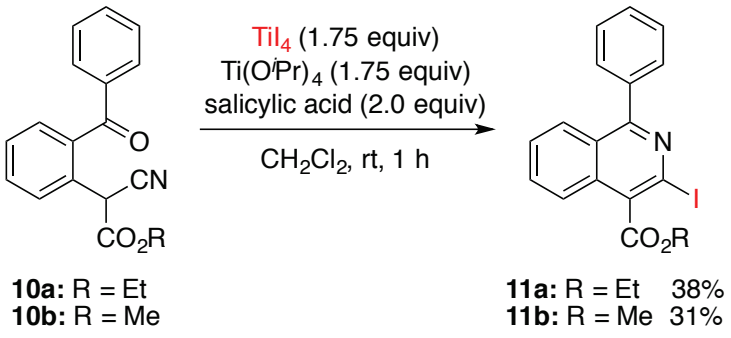
A plausible reaction mechanism for the 3-aryl-1-iodoisoquinolines (**6**) formation is shown in Scheme 2. First, TiI_4 would react with $Ti(O^iPr)_4$ and salicylic acid to form the (diiodosalicyloxy)titanium (**7**), which would coordinate to the cyano group of 2-(2-aryl-2-oxoethyl)benzonitrile derivatives (**5**). The titanium alkoxide intermediate (**8**) would be formed via a nucleophilic addition of an iodide ion to the cyano group

and the subsequent cyclization. The titanium alkoxide intermediate (**8**) would undergo aromatization via the elimination of titanium oxide (**9**) to give 3-aryl-1-iodoisoquinolines (**6**).



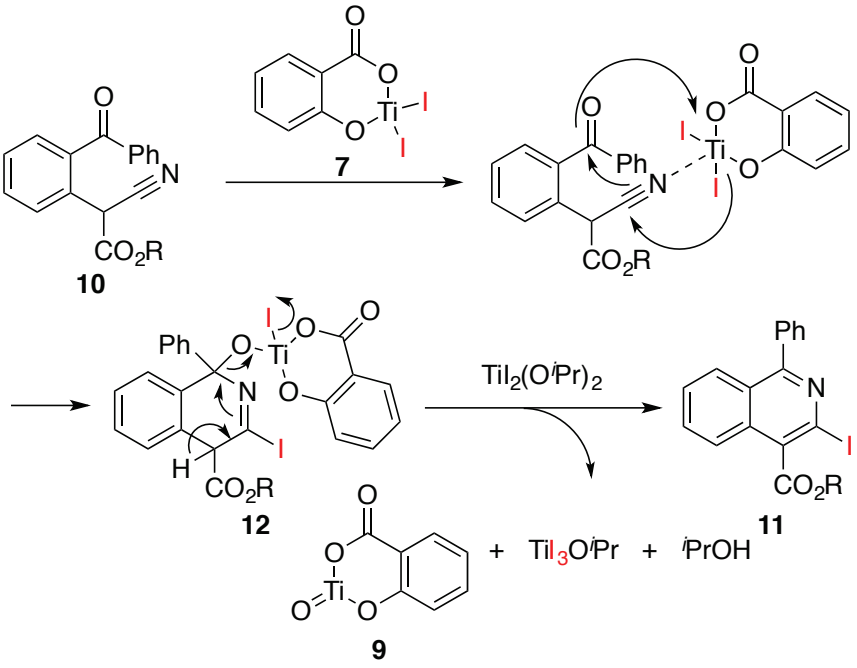
Scheme 2. Plausible reaction mechanism for the 3-aryl-1-iodoisoquinoline (**6**) formation

We next examined the iodination-cyclization reaction of alkyl 2-(2-benzoylphenyl)-2-cyanoacetates (**10**) instead of 2-(2-aryl-2-oxoethyl)benzonitrile derivatives (**5**). The reactions of (**10a**) and (**10b**) proceeded smoothly to give the desired 3-iodo-1-phenylisoquinolines (**11a**) and (**11b**) having an alkoxy carbonyl group in 38% and 31% yields, respectively (Scheme 3).[28]

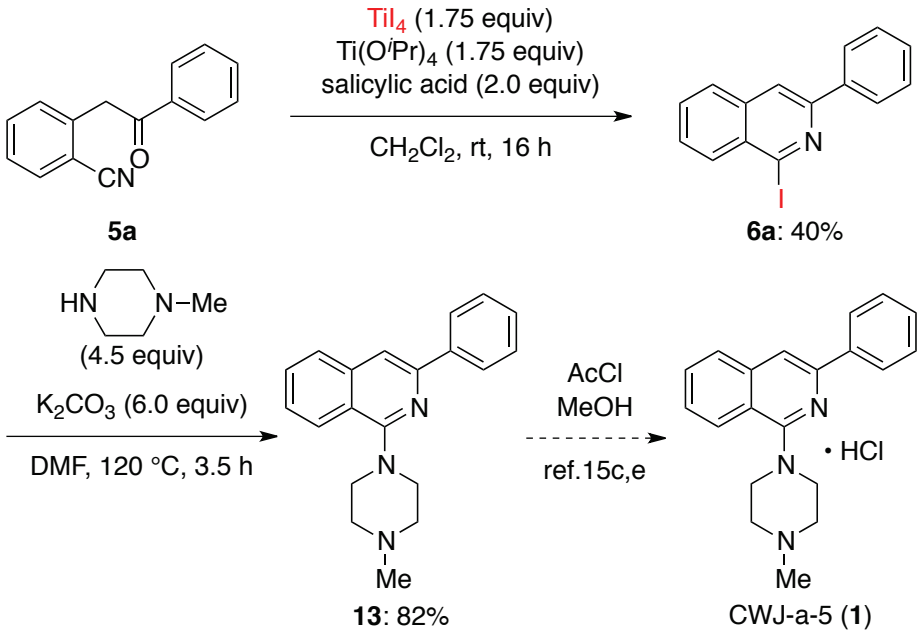


Scheme 3. Synthesis of 3-iodo-1-phenylisoquinolines (**11**)

A plausible reaction mechanism for the 3-iodo-1-phenylisoquinolines (**11**) is shown in Scheme 4. The (diiodosalicyloxy)titanium (**7**) would coordinate to the cyano group of an alkyl 2-(2-benzoylphenyl)-2-cyanoacetate (**10**). The titanium alkoxide intermediate (**12**) would be formed via a nucleophilic addition of an iodide ion to the cyano group and the subsequent cyclization. The titanium alkoxide intermediate (**12**) would undergo aromatization via the elimination of titanium oxide (**9**) to give 3-iodo-1-phenylisoquinolines (**11**).



Scheme 4. Plausible reaction mechanism for the 3-iodo-1-phenylisoquinoline (**11**) formation



Scheme 5. A short step formal synthesis of CWJ-a-5 (**1**)

As an application, we examined a short step formal synthesis of CWJ-a-5 (**1**) having a topoisomerase I inhibitory activity from 2-(2-oxo-2-phenylethyl)benzonitrile (**5a**), which is prepared from a commercially available 2-methylbenzonitrile and methyl benzoate in a single step. The S_NAr reaction of 2-(2-oxo-2-phenylethyl)benzonitrile (**6a**) with *N*-methylpiperazine proceeded smoothly to provide the 1-(4-methylpiperazin-1-yl)-3-phenylisoquinoline (**13**) in high yield (Scheme 5).[15]

CONCLUSIONS

In conclusion, we have developed a synthesis of 3-aryl-1-iodoisoquinolines (**6**) using TiI_4 induced iodination-cyclization reactions of 2-(2-aryl-2-oxoethyl)benzonitrile derivatives (**5**) as a nitrogen source and the subsequent application to the short step formal synthesis of CWJ-a-5 (**1**) has been successfully achieved. The present 3-aryl-1-iodoisoquinoline synthesis is an attractive alternative method because 2-(2-aryl-2-oxoethyl)benzonitrile derivatives (**5**) are readily prepared from the corresponding 2-methylbenzonitrile derivatives and methyl benzoate derivatives in a single step, and furthermore, an iodine substituent can be transformed into other functional groups using S_NAr reactions, transition metal catalyzed cross coupling reactions, or iodine-metal exchange reactions.

EXPERIMENTAL

General. Melting point (Mp) determinations were performed using a YAMATO MP-21 instrument and are uncorrected. Infrared spectra were recorded on a JASCO FT/IR-460 Plus spectrometer. ^{1}H NMR spectra were recorded on a JEOL ECX-400 spectrometer (400 MHz) with tetramethylsilane as an internal standard. ^{13}C NMR spectra were recorded on a JEOL ECX-400 spectrometer (100 MHz). Chemical sifts are reported in δ units, parts per million from the central peak of $CDCl_3$ (δ 77.0) as an internal reference. High resolution mass spectra (EI) were recorded on a JEOL JMS-700D mass spectrometer. 1,2-Dimethoxy ethane (DME) was distilled from CaH_2 and then cupper(I) chloride, and stored over sodium. Dimethyl sulfoxide (DMSO) was pre-dried with CaH_2, distilled from CaH_2, and stored over molecular sieves 4Å. Dichloromethane (CH_2Cl_2) was pre-dried with P_2O_5, distilled from CaH_2, and stored over molecular sieves 4Å. *N*,*N*-Dimethylformamide (DMF) was pre-dried with P_2O_5, distilled from CaH_2, and stored over molecular sieves 4Å. Purification of products was performed by column chromatography on silica gel (Kanto Chemical Co. Inc., Silica Gel 60 N (spherical, neutral)) and/or preparative TLC on silica gel (Merck Kiesel Gel GF254 or Wakogel B-5F). All reactions were carried out under an argon atmosphere.

Synthesis of cyanoketones (5)

Cyanoketones (**5a**), (**5c**), and (**5e**) were synthesized from 2-methylbenzonitrile with the corresponding methyl benzoate derivatives according to the literature method.[29]

2-(2-(4-Fluorophenyl)-2-oxoethyl)benzonitrile (5b):

A stirred slurry of sodium hydride (60% dispersion in mineral oil, 800 mg, 20.0 mmol) in DME (5.0 mL) was refluxed. 2-Methylbenzonitrile (593 mg, 5.06 mmol) and methyl 4-fluorobenzoate (1.00 g, 6.49 mmol) were added to the slurry. After a catalytic amount of MeOH was added, the mixture was refluxed for 7 h. The mixture was cooled to 0 ºC. Water (10 mL) was added to quench the reaction and then 2 M HCl (10 mL) was added. The resulting mixture was diluted with EtOAc (30 mL). The aqueous layer was extracted with EtOAc (2x30 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and filtered. The solvents were evaporated in vacuo. The crude product was purified by column chromatography on silica gel (hexane/EtOAc = 6:1 to 2:1 as an eluent) to give 2-(2-(4-fluorophenyl)-2-oxoethyl)benzonitrile (**5b**) (285 mg, 28%). White solid. Mp 88-90 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07-8.10 (m, 2H), 7.69 (d, J = 7.8 Hz, 1H), 7.56-7.60 (m, 1H), 7.38-7.42 (m, 2H), 7.16-7.20 (m, 2H), 4.52 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.8, 166.0 (d, J = 256 Hz), 138.3, 132.8, 132.6 (d, J = 2.9 Hz), 132.6, 131.0, 127.7, 117.8, 115.9 (d, J = 21.1 Hz), 113.5, 43.5. IR (KBr): 3064, 2904, 2230, 1686, 1595, 1504, 1449, 1412, 1335, 1304, 1231, 1159, 1099, 1045, 994, 895, 839, 768, 709 cm^{-1}. HRMS (EI): Calcd for $C_{15}H_{10}FNO$ 239.0746 $(M)^+$, found: 239.0742.

2-(2-(4-Bromophenyl)-2-oxoethyl)benzonitrile (5d):

A stirred slurry of sodium hydride (60% dispersion in mineral oil, 800 mg, 20.0 mmol) in DME (5.0 mL) was refluxed. 2-Methylbenzonitrile (593 mg, 5.06 mmol), methyl 4-bromobenzoate (1.40 g, 6.54 mmol), and DME (5.0 mL) were added to the slurry. After a catalytic amount of MeOH was added, the mixture was refluxed for 18 h. The mixture was cooled to 0 ºC. Water (10 mL) was added to quench the reaction and then 2 M HCl (10 mL) was added. The resulting mixture was diluted with EtOAc (30 mL). The aqueous layer was extracted with EtOAc (2x30 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and filtered. The solvents were evaporated in vacuo. The crude product was purified by column chromatography on silica gel (hexane/EtOAc = 6:1 as an eluent) to give 2-(2-(4-bromophenyl)-2-oxoethyl)benzonitrile (**5d**) (1.35 g, 89%). Light yellow solid. Mp 111-113 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90-7.93 (m, 2H), 7.69 (d, J = 7.8 Hz, 1H), 7.64-7.66 (m, 2H), 7.56-7.60 (m, 1H), 7.36-7.42 (m, 2H), 4.51 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.4, 138.1, 134.9, 132.8, 132.8, 130.9, 129.8, 128.9, 127.7, 117.8, 113.5, 43.5. IR (KBr): 3066, 3033, 2945, 2907, 2228, 1689, 1586, 1486, 1449, 1397, 1339, 1284, 1206, 1182, 1074, 994, 822, 763 cm^{-1}. HRMS (EI): Calcd for $C_{15}H_{10}BrNO$ 298.9946 $(M)^+$, found 298.9944.

5-Chloro-2-(2-oxo-2-phenylethyl)benzonitrile (5f):

A stirred slurry of sodium hydride (60% dispersion in mineral oil, 564 mg, 14.1 mmol) in DME (3.5 mL) was refluxed. 5-Chloro-2-methylbenzonitrile (534 mg, 3.52 mmol), methyl benzoate (653 mg, 4.80 mmol), and DME (3.5 mL) were added to the slurry. After a catalytic amount of MeOH was added, the

mixture was refluxed for 7 h. The mixture was cooled to 0 ºC. Water (10 mL) was added to quench the reaction and then 2 M HCl (10 mL) was added. The resulting mixture was diluted with EtOAc (30 mL). The aqueous layer was extracted with EtOAc (2x30 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and filtered. The solvents were evaporated in vacuo. The crude product was purified by recrystallization from ethanol to give 5-chloro-2-(2-oxo-2-phenylethyl)benzonitrile (**5f**) (684 mg, 76%). White solid. Mp 142-144 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03-8.05 (m, 2H), 7.60-7.66 (m, 2H), 7.49-7.56 (m, 3H), 7.32-7.34 (m, 1H), 4.52 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.8, 137.0, 136.0, 133.8, 133.6, 133.1, 132.4, 132.2, 128.9, 128.3, 116.6, 115.1, 43.0. IR (KBr): 3084, 3061, 3033, 2945, 2902, 2230, 1690, 1596, 1483, 1448, 1419, 1335, 1222, 1209, 1192, 1119, 1000, 993, 881, 849, 754 cm^{-1}. HRMS (EI): Calcd for $C_{15}H_{10}ClNO$ 255.0451 $(M)^+$, found 255.0453.

5-Iodo-2-(2-oxo-2-phenylethyl)benzonitrile (5g):

A stirred slurry of sodium hydride (60% dispersion in mineral oil, 480 mg, 12.0 mmol) in DME (3.0 mL) was refluxed. 5-Iodo-2-methylbenzonitrile (729 mg, 3.00 mmol), methyl benzoate (544 mg, 4.00 mmol), and DME (3.0 mL) were added to the slurry. After a catalytic amount of MeOH was added, the mixture was refluxed for 7 h. The mixture was cooled to 0 ºC. Water (10 mL) was added to quench the reaction and then 2 M HCl (10 mL) was added. The resulting mixture was diluted with EtOAc (30 mL). The aqueous layer was extracted with EtOAc (2x30 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, and filtered. The solvents were evaporated in vacuo. The crude product was purified by recrystallization from ethanol to give 5-iodo-2-(2-oxo-2-phenylethyl)benzonitrile (**5g**) (635 mg, 61%). Yellow white solid. Mp 134-136 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98-8.04 (m, 3H), 7.87-7.89 (m, 1H), 7.60-7.64 (m, 1H), 7.49-7.53 (m, 2H), 7.10-7.13 (m, 1H), 4.49 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.7, 141.8, 140.8, 138.1, 136.0, 133.8, 132.6, 128.8, 128.3, 116.3, 115.6, 91.7, 43.2. IR (KBr): 3097, 3056, 3033, 2951, 2884, 2230, 1688, 1594, 1479, 1448, 1416, 1385, 1332, 1204, 1110, 988, 906, 868, 837, 806, 752 cm^{-1}. HRMS (EI): Calcd for $C_{15}H_{10}INO$ 346.9807 $(M)^+$, found 346.9820.

Synthesis of cyanoketo esters (10)

Cyanoketoester (**10b**) was synthesized according the literature method.[28a]

2-(2-Benzoylphenyl)-2-cyanoacetate (10a):

A stirred mixture of 2-fluorobenzophenone (936 mg, 4.68 mmol), ethyl cyanoacetate (1.06 g, 9.40 mmol), Cs_2CO_3 (3.06 g, 9.39 mmol) in DMSO (20 mL) was heated to 130-140 ºC for 5 h. After cooling, water (20 mL) was added to quench the reaction. The mixture was filtered through a Celite pad, and extracted with EtOAc-hexane (1:4). The combined organic layers were washed with 2 M HCl and brine, dried over Na_2SO_4, and filtered. The solvents were evaporated in vacuo. The crude product was purified by column chromatography on silica gel (hexane/EtOAc/CH_2Cl_2 = 16:2:1 as an eluent) to give ethyl 2-(2-benzoylphenyl)-2-cyanoacetate (**10a**) (538 mg, 39%). Orange oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ =

7.71-7.80 (m, 3H), 7.59-7.64 (m, 2H), 7.44-7.51 (m, 4H), 5.70 (s, 1H), 4.09-4.23 (m, 2H), 1.17 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.2, 164.7, 137.2, 136.6, 133.3, 131.9, 131.2, 130.3, 130.1, 129.9, 128.4, 128.3, 115.7, 63.2, 40.1, 13.7. IR (neat): 3064, 2984, 2945, 2901, 2252, 1747, 1659, 1597, 1579, 1448, 1317, 1272, 1217, 1158, 1027, 942, 926, 767, 743, 701 cm^{-1}. HRMS (EI): Calcd for $C_{18}H_{15}NO_3$ 293.1052 $(M)^+$, found 293.1073.

General procedure for the titanium tetraiodide induced cyclization of cyanoketones (5) or cyanoketo esters (10) into aryliodoisoquinolines (6) or (11)

To a suspension of TiI_4 (195 mg, 0.35 mmol) in CH_2Cl_2 (0.65 mL) was added $Ti(O^iPr)_4$ (0.35 mL, 1.0 M in CH_2Cl_2, 0.35 mmol) at room temperature. After stirring for 10 min, salicylic acid (55.2 mg, 0.40 mmol) was added to the mixture. The mixture was stirred for another 10 min. Cyanoketone (**5**) or cyanoketo ester (**10**) (0.20 mmol) in CH_2Cl_2 (1.0 mL) was added to the resulting mixture, which was stirred at room temperature for 16 h or 1 h. The reaction mixture was quenched with phosphate buffer solution (10 mL), and EtOAc (10 mL) and 10 wt% aqueous $NaHSO_3$ (10 mL) were added successively. The mixture was filtered through a Celite pad, and extracted with EtOAc. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by preparative silica gel TLC (toluene/EtOAc = 40:1 as an eluent) to give aryliodoisoquinolines (**6**) or (**11**).

1-Iodo-3-phenylisoquinoline (6a):

Light brown solid (40%). Mp 77-78 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07-8.11 (m, 3H), 7.94 (s, 1H), 7.74 (d, J = 7.4 Hz, 1H), 7.66-7.70 (m, 1H), 7.60-7.63 (m, 1H), 7.46-7.50 (m, 2H), 7.38-7.43 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.8, 137.8, 136.9, 132.8, 131.1, 131.0, 129.0 128.8, 128.6, 127.6, 127.4, 126.8, 116.7. IR (KBr): 3058, 3020, 1618, 1589, 1553, 1483, 1436, 1354, 1306, 1250, 1202, 1149, 1025, 955, 924, 885, 853, 818, 777, 766, 749, 718, 697, 674, 646 cm^{-1}. HRMS (EI): Calcd for $C_{15}H_{10}$IN-I 204.0813 $(M\text{-}I)^+$, found 204.0815.

3-(4-Fluorophenyl)-1-iodoisoquinoline (6b):

Light brown solid (35%). Mp 97-99 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05-8.10 (m 3H), 7.89 (s, 1H), 7.74 (d, J = 7.3 Hz, 1H), 7.67-7.71 (m, 1H), 7.60-7.64 (m, 1H), 7.13-7.19 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.5 (d, J = 249 Hz), 150.7, 136.9, 134.0 (d, J = 2.9 Hz), 132.9, 131.2, 130.9, 128.7, 128.6 (d, J = 8.6 Hz), 127.5, 127.4, 116.4, 115.7 (d, J = 22.1 Hz). IR (KBr): 3068, 3050, 1599, 1583, 1554, 1511, 1482, 1442, 1307, 1247, 1233, 1202, 1159, 1149, 954, 884, 859, 832, 771, 746, 722, 697 cm^{-1}. HRMS (EI): Calcd for $C_{15}H_9$FIN 348.9764 $(M)^+$, found 348.9778.

3-(4-Chlorophenyl)-1-iodoisoquinoline (6c):

Light brown solid (33%). Mp 119-121 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (d, J = 8.3 Hz, 1H), 8.03-8.06 (m, 2H), 7.93 (s, 1H), 7.76 (d, J = 7.3 Hz, 1H), 7.69-7.73 (m, 1H), 7.62-7.66 (m, 1H), 7.43-7.47 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.5, 136.8, 136.3, 135.1, 132.9, 131.3, 131.1, 129.0, 128.9,

128.1, 127.6, 127.5, 116.7. IR (KBr): 3052, 1617, 1552, 1497, 1307, 1248, 1094, 1010, 953, 833, 816, 772, 753, 716, 675 cm^{-1}. HRMS (EI): Calcd for $C_{15}H_9ClIN$-I 238.0424 $(M-I)^+$, found 238.0436.

3-(4-Bromophenyl)-1-iodoisoquinoline (6d):

Yellow orange solid (38%). Mp 141-143 ºC. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.09 (d, J = 8.2 Hz, 1H), 7.96-7.99 (m, 2H), 7.93 (s, 1H), 7.75 (d, J = 7.8 Hz, 1H), 7.68-7.73 (m, 1H), 7.62-7.66 (m, 1H), 7.58-7.62 ppm (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.5, 136.8, 136.7, 132.9, 131.9, 131.3, 131.1, 128.9, 128.4, 127.6, 127.6, 123.4, 116.7. IR (KBr): 3055, 1617, 1589, 1553, 1495, 1440, 1305, 1248, 1204, 1150, 1076, 1007, 954, 886, 853, 832, 772, 754, 745, 713, 664 cm^{-1}. HRMS (EI): Calcd for $C_{15}H_9BrIN$-I 281.9918 $(M-I)^+$, found 281.9920.

1-Iodo-3-(*p*-tolyl)isoquinoline (6e):

Light brown solid (8%). Mp 91-92 ºC. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.09 (d, J = 8.2 Hz, 1H), 8.01 (d, J = 8.3 Hz, 2H), 7.93 (s, 1H), 7.75 (d, J = 7.8 Hz, 1H), 7.67-7.71 (m, 1H), 7.60-7.64 (m, 1H), 7.29 (d, J = 8.2 Hz, 2H), 2.42 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.9, 139.0, 137.0, 135.1, 132.9, 131.0, 130.9, 129.5, 128.4, 127.5, 127.4, 126.7, 116.6, 21.3. IR (KBr): 3034, 2958, 2913, 2857, 1618, 1589, 1553, 1516, 1440, 1306, 1248, 1151, 955, 875, 831, 823, 816, 788, 772, 752, 715, 697, 672 cm^{-1}. HRMS (EI): Calcd for $C_{16}H_{12}IN$ 345.0014 $(M)^+$, found 345.0020.

7-Chloro-1-iodo-3-phenylisoquinoline (6f):

White solid [42% (54% conversion yield on the basis of 22% of the recovered starting cyanoketone **5f**)]. Mp 104-105 ºC. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.06-8.09 (m, 3H), 7.90 (s, 1H), 7.69 (d, J = 8.7 Hz, 1H), 7.60 (dd, J = 1.9, 10.7 Hz, 1H), 7.39-7.50 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.1, 137.4, 135.1, 134.2, 132.1, 131.7, 131.6, 129.3, 129.2, 128.8, 126.8, 125.5, 116.2. IR (KBr): 3060, 3030, 1574, 1543, 1498, 1470, 1347, 1290, 1248, 1176, 1085, 966, 883, 872, 826, 816, 771, 757, 695, 661 cm^{-1}. HRMS (EI): Calcd for $C_{15}H_9ClIN$ 364.9468 $(M)^+$, found 364.9480.

1,7-Diiodo-3-phenylisoquinoline (6g):

White solid [44% (51% conversion yield on the basis of 13% of the recovered starting cyanoketone **5g**)]. Mp 153-154 ºC. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.48 (s, 1H), 8.05-8.10 (m, 2H), 7.89-7.93 (m, 2H), 7.40-7.51 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.3, 141.5, 139.8, 137.4, 135.7, 132.1, 129.3, 128.9, 128.9, 126.7, 125.1, 116.3, 93.8. IR (KBr): 3063, 3027, 1570, 1536, 1497, 1344, 1290, 1248, 1175, 960, 883, 857, 813, 740, 694 cm^{-1}. HRMS (EI): Calcd for $C_{15}H_9I_2N$ 456.8824 $(M)^+$, found 456.8847.

Ethyl 3-iodo-1-phenylisoquinoline-4-carboxylate (11a):

White solid (38%). Mp 131-132 ºC. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.08 (d, J = 8.2 Hz, 1H), 7.79 (d, J = 8.7 Hz, 1H), 7.70-7.75 (m, 1H), 7.63-7.66 (m, 2H), 7.56-7.60 (m, 1H), 7.51-7.53 (m, 3H), 4.60 (q, J = 7.3 Hz, 2H), 1.51 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.7, 162.3, 137.7, 134.5, 132.1, 131.6, 130.0, 129.3, 128.4, 128.1, 128.0, 125.3, 123.9, 108.2, 62.5, 14.1. IR (KBr): 3061, 2983, 2898,

1712, 1614, 1569, 1521, 1496, 1471, 1444, 1382, 1349, 1254, 1204, 1160, 1143, 1099, 1074, 1040, 1008, 872, 766, 760, 715, 703, 668, 643 cm^{-1}. HRMS (EI): Calcd for $C_{18}H_{14}INO_2$-I 276.1025 $(M-I)^+$, found 276.1014.

Methyl 3-iodo-1-phenylisoquinoline-4-carboxylate (11b):

White solid (31%). Mp 140-142 ºC. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.08 (d, J = 8.7 Hz, 1H), 7.78 (d, J = 8.3 Hz, 1H), 7.70-7.75 (m, 1H), 7.65-7.68 (m, 2H), 7.57-7.61 (m, 1H), 7.51-7.51 (m, 3H), 4.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.2, 162.4, 137.7, 134.6, 132.1, 131.6, 130.1, 129.4, 128.4, 128.1, 128.1, 125.2, 123.9, 108.3, 53.2. IR (KBr): 3061, 2947, 2848, 1727, 1611, 1568, 1526, 1501, 1446, 1386, 1349, 1257, 1205, 1145, 1102, 1023, 921, 842, 798, 779, 714, 698, 671 cm^{-1}. HRMS (EI): Calcd for $C_{17}H_{12}INO_2$ 388.9913 $(M)^+$, found 388 9901.

Short step formal synthesis of CWJ-a-5 (1)

To a suspension of 1-iodo-3-phenylisoquinoline (**6a**) (26.7 mg, 0.0806 mmol) and K_2CO_3 (33.4 mg, 0.242 mmol) in DMF (2.0 mL) was added *N*-methylpiperazine (18.1 mg, 0.181 mmol) at room temperature. The mixture was stirred at 120 ºC for 2 h. After cooling, K_2CO_3 (33.4 mg, 0.242 mmol) and *N*-methylpiperazine (18.1 mg, 0.181 mmol) were added to the mixture, which was stirred at 120 ºC for more 2 h. The reaction mixture was cooled to room temperature and then quenched with water (10 mL). The mixture was extracted with CH_2Cl_2 (3x10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by preparative silica gel TLC (EtOAc as an eluent) to give 1-(4-methylpiperazin-1-yl)-3-phenylisoquinoline (**13**)[30] (20.0 mg, 82%). Light yellow solid. Mp 74-76 ºC. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.16-8.18 (m, 2H), 8.07 (d, J = 8.7 Hz, 1H), 7.79 (d, J = 8.2 Hz, 1H), 7.70 (s, 1H), 7.56-7.60 (m, 1H), 7.45-7.49 (m, 3H), 7.35-7.39 (m, 1H), 3.59 (t, J = 4.6 Hz, 4H), 2.72 (t, J = 4.6 Hz, 4H), 2.42 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.6, 148.3, 139.7, 139.1, 129.6, 128.5, 128.2, 127.6, 126.6, 125.7, 125.5, 120.6, 111.1, 55.3, 51.1, 46.3. IR (KBr): 3060, 2969, 2834, 2796, 2766, 2741, 1618, 1562, 1500, 1456, 1412, 1370, 1345, 1305, 1287, 1269, 1202, 1148, 1075, 1029, 1009, 943, 920, 877, 849, 837, 798, 772, 752, 695, 678 cm^{-1}. HRMS (EI): Calcd for $C_{20}H_{21}N_3$ 303.1736 $(M)^+$, found 303.1723.

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