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Novel Synthesis of Cinnolines and 1-Aminoindolines via Cu-Catalyzed Intramolecular N-Arylation of Hydrazines and Hydrazones Prepared from 3-Haloaryl-3-hydroxy-2-diazopropanoates

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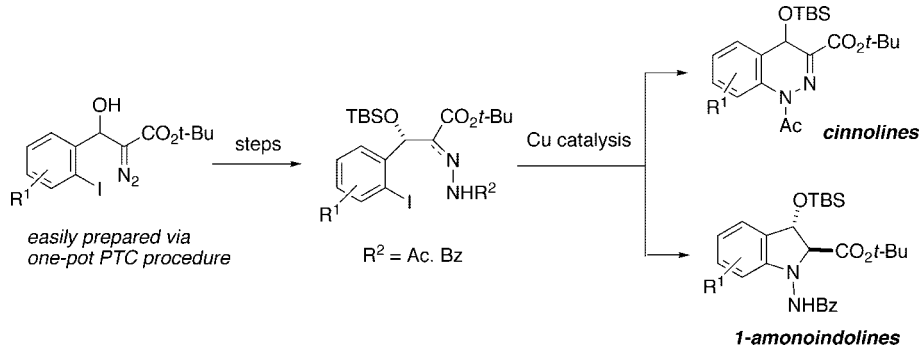

A new and facile access to cinnolines, dihydrocinnolines, and 1-aminoindolines was established by use of diazo functionalities. The hydrazines and hydrazones as cyclization precursors derived from 3-haloaryl-3-hydroxy-2-diazopropanoates, which are prepared by one-pot procedure utilizing phase-transfer catalysis, are successfully converted to the corresponding nitrogen heterocycle by Cu-catalyzed N-arylation. Furthermore, analysis of UV spectra proved that 4-oxo-3-carboxylates predominantly exist not as 4-hydroxycinnoline (enol form) but as cinnolone (keto form).

Introduction

Cinnoline[1a] and 1-aminoindoline[1b] are important skeletons that are found in natural products and pharmaceuticals (Figure 1) and thus are potential candidates for biologically important molecules.[1c] The development of their facile synthesis has been an important issue.

The cinnoline scaffold can be an attractive structural template in agriculture, biology, and medicine. In fact, over the past few years cinnoline derivatives have been patented as agrochemical and pharmaceutical drugs.[2] They can also be used in organic nonlinear optics (NLO) materials by utilizing a polarized heteroaromatic π-system.[3] With respect to the synthesis of cinnoline-3-carboxylic acid derivatives, although three representative methods have been reported, they have been used in only limited appications. For example, strongly acidic media is necessary to generate a diazonium salt in a typical von Richter synthesis,[4] and regiocontrolled cyclization is still difficult in Barber synthesis.[5] Furthermore, intramolecular aromatic substitution sometimes requires the protection of hydrazones to

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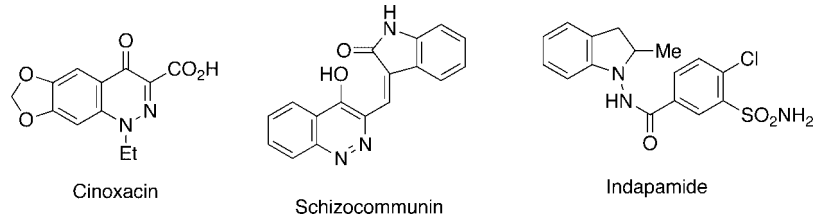
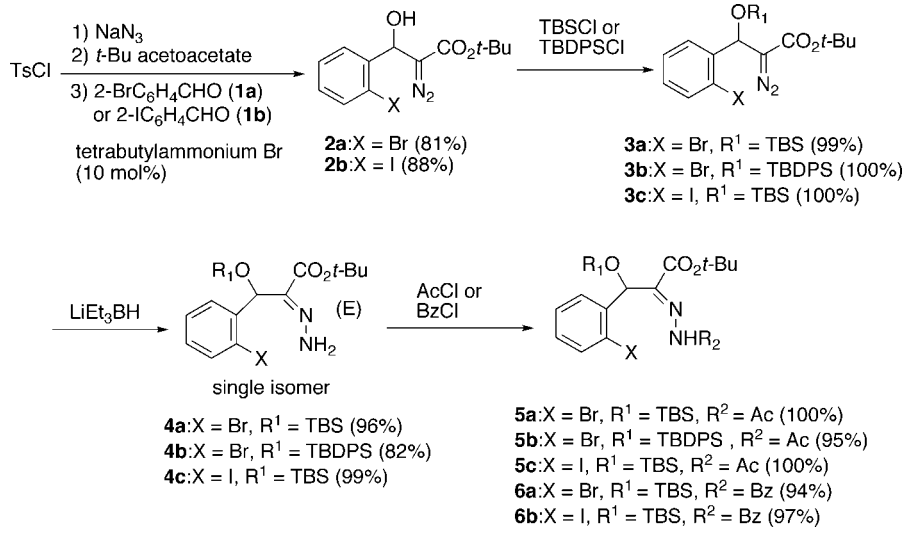


FIGURE 1

SCHEME 1. Synthesis of Hydrazones

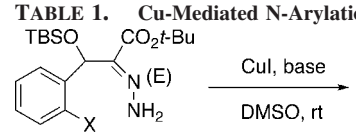


avoid a Wolff−Kishner-type process.[6] To overcome these disadvantages, we planned to develop a general synthetic method to produce a cinnoline skeleton using 3-haloaryl-3-hydroxy-2-diazopropanoates,[7] which have been shown to be useful building blocks for the synthesis of nitrogen-containing molecules.[8] Furthermore, we describe a facile synthesis of 1-aminoindolines by a similar strategy.

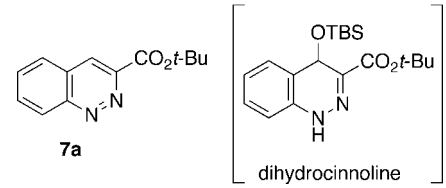
Initially, we prepared some hydrazones **5** and **6** as cyclization precursors for the synthesis of cinnolines and dihydrocinnolines (Scheme 1). An aldol-type reaction of 2-bromo or 2-iodobenzaldehydes **1** with tosyl chloride in a one-pot synthesis gave **2** in respective yields of 81% and 88% using our procedure that has been reported previously.[8] After conversion to silyl ethers **3**, stereoselective reduction of diazo group by $LiEt_3BH$ gave (*E*)-**4**. The stereochemistry of (*E*)-hydrazone was previously determined by X-ray analysis of phenylderivatives.[8b] Subsequent acylation of terminal nitrogens with acid chlorides gave the substrates **5** and **6** for cyclization in reasonable yields.

With the substrates in hand, we first attempted a palladium-catalyzed N-arylation using **4a** by Buchwald's procedure;[9] however, the reaction resulted in the formation of a complex mixture. Next we studied Cu-mediated cyclization,[10] as shown in Table 1. The reaction of **4a** in the presence of an excess amount of CuI with CsOAc in DMSO[10b] at room temperature gave cinnoline **7a** in 30% yield (entry 1). Iodide **4c** was more reactive and converted to **7a** within 10 min in quantitative yield (entry 2). This cyclization proceeded under catalytic conditions with a longer reaction time in 86% yield (entry 3). This

TABLE 1. Cu-Mediated N-Arylation of 4



4a: X = Br
4c: X = I



entry	4	CuI (mol %)	base (equiv)	time	yield of **7a** (%)
1	**4a**	200	CsOAc (5)	15 h	30
2	**4c**	200	CsOAc (5)	10 min	quant
3	**4c**	10	CsOAc (5)	9 h	86
4	**4c**	200	NaOAc (1.1)	2 h	quant

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SCHEME 2. One-Pot Synthesis of 7a

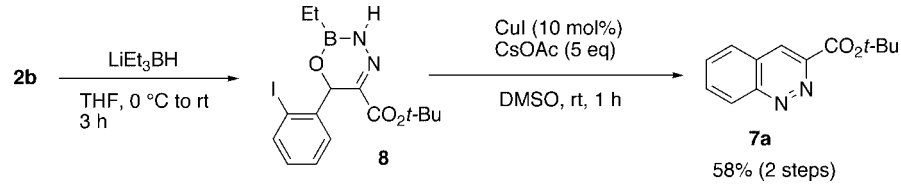
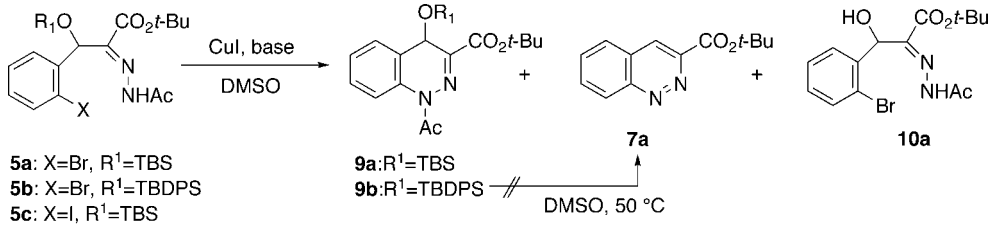
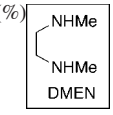


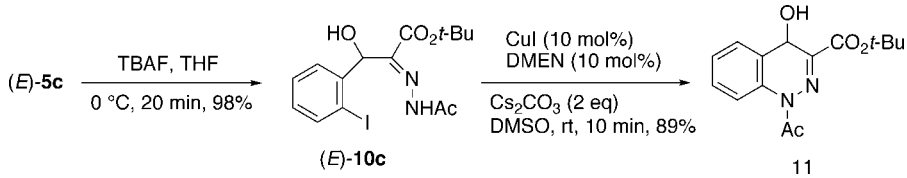
TABLE 2. Cu-Mediated N-Arylation of 5a−c



DMEN (%) 

entry	5	CuI (mol %)	DMEN (%)	base (equiv)	conditions	9 (%)	yield of 7a (%)	10a (%)
1	**5a**	200		CsOAc (5)	rt, 3 h	**9a**: 15	0	70
2	**5b**	200		CsOAc (5)	50 °C, 8 h	**9b**: 28	38	0
3	**5b**	200		NaOAc (5)	50 °C, 19 h	**9b**: 53	40	0
4	**5b**	200		NaOAc (1.1)	50 °C, 19 h	**9b**: 65	25	0
5	**5c**	10		Cs_2CO_3 (2)	rt, 1 h	**9a**: quant	0	0
6	**5c**	10	10	Cs_2CO_3 (2)	rt, 10 min	**9a**: 93	0	0

SCHEME 3. Preparation and Reaction of (*E*)-10c

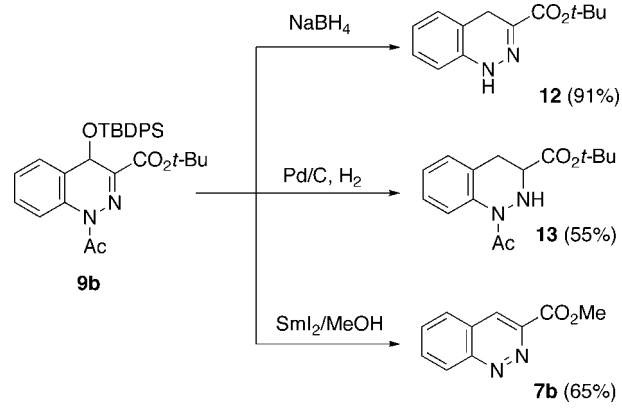


aromatization seemed to be caused by the elimination of a silanol from dihydrocinnoline under basic conditions. When a weaker base (NaOAc) was used, only a trace amount of dihydrocinnoline was observed and **7a** was obtained in almost quantitative yield (entry 4).

Dihydrooxadiazaborine **8**, which is readily available by the reduction of **2b**, was also applicable for cyclization. Thus, treatment of **2b** with $LiEt_3BH$ followed by cyclization successfully gave **7a** in 58% yield in two steps (Scheme 2).

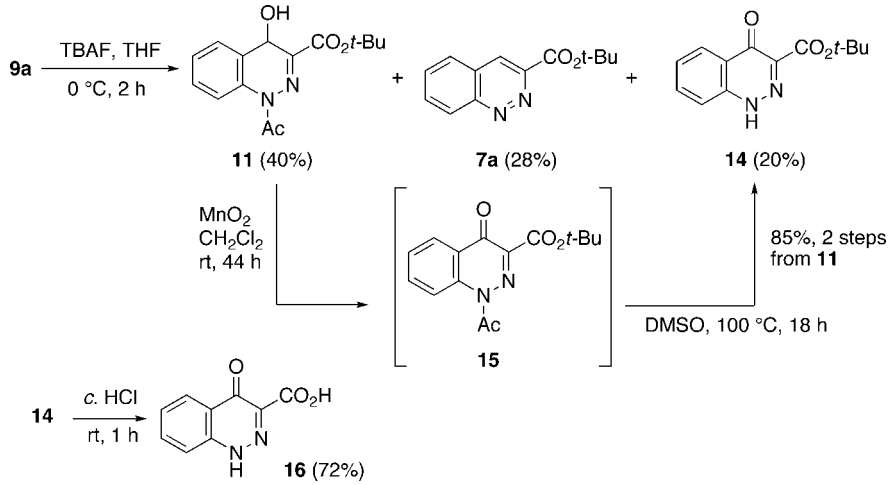
Because the lower electron density on the terminal nitrogen might prevent the elimination of silanol, we next investigated N-acylated substrates **5a−c** to obtain dihydrocinnolines. The Cu-mediated cyclization of **5a** with CsOAc at room temperature gave **9a** in 15% yield without any significant aromatization, although deprotection of the TBS group proceeded to give **10a** in 70% yield (Table 2, entry 1). To minimize this desilylation, a TBDPS ether **5b** was chosen for further studies at 50 °C. The reaction of **5b** gave cyclized products **9b** and **7a** in respective yields of 28% and 38% without formation of **10a** (entry 2). Because **9b** did not give **7a** at 50 °C in DMSO under neutral conditions, a weaker base such as sodium acetate (5 equiv) was used next. As expected, **9b** was obtained as a major product in 53% yield, and using a reduced amount of base (1.1 equiv) was more effective to give **9b** in 65% yield together with **7a** in 25% yield (entries 3 and 4). The reaction using **5c** with Cs_2CO_3 at room temperature was quite efficient to give **9a** in quantitative yield even in a catalytic system without any aromatization or deprotection (entry 5). This reaction was accelerated by diamine ligand:[10c] the addition of *N*,*N*′-dimethylethylenediamine (DMEN, 10 mol %) gave **9a** as a sole product in 93% yield within 10 min (entry 6).

SCHEME 4. Reduction of 9b



The (*E*)-stereochemistry of **5** is found to be quite important because the (*Z*)-isomer of **5c**, easily prepared from (*E*)-**4c**, gave a complex mixture under optimized conditions.[11] We also found that silyl protection is not necessary for this Cu-catalyzed

SCHEME 5. Transformation of 9a to 4-Oxo Derivatives



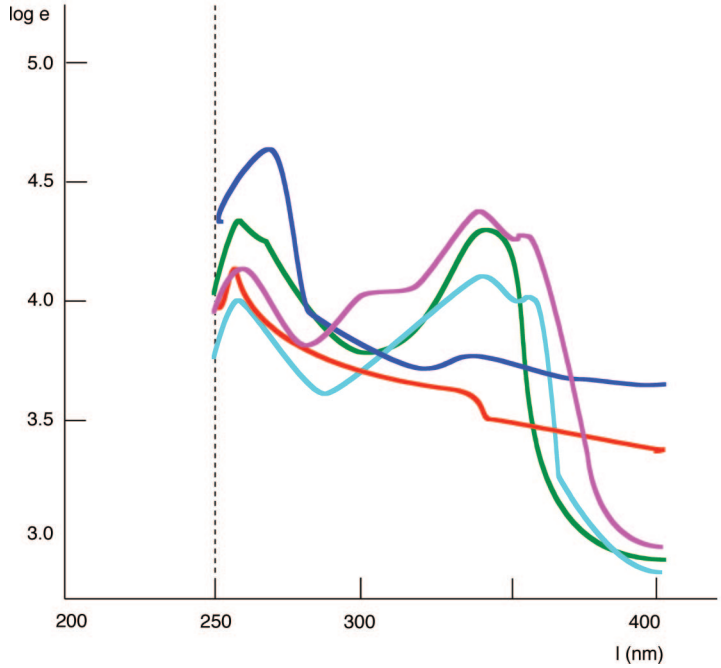
cyclization. For example, OH-free substrate **10c**, prepared from (*E*)-**5c** with TBAF, was smoothly converted to **11** in 89% yield (Scheme 3).

After succeeding in Cu-catalyzed cyclization to cinnolines, we next investigated the further transformation of **9b** with various reducing agents to expand its synthetic utility (Scheme 4). The reaction using $NaBH_4$ proceeded with deacetylation and deoxygenation to give **12** in 91% yield. Hydrogenation promoted not only reduction of the C═N bond but also deoxygenation to give **13** in 55% yield. Treatment with SmI_2 resulted in aromatization via deacetylative deoxygenation (**7b**: 65%).

Because 4-oxo derivatives such as cinoxacin, which shows good antibacterial against Gram-negative bacteria,[6a] seem to be useful, we next attempted the transformation of **9a** to **16** (Scheme 5). Treatment of **8a** with TBAF gave the three products **11**, **7a**, and **14**. Compound **11** was then converted to **14** via oxidation using MnO_2 and aromatization under thermal conditions (85%, 2 steps). The following acid treatment gave **16** in 72% yield, and its structure was determined by the comparison to the reported analytical data,[5d] which suggests a keto form (cinnolone) does exist predominantly.

To confirm the structure of the other related compounds, we next analyzed the UV spectra of cinnoline **7a,b** and **14**−**16** in DMSO. As expected, a different UV pattern was observed: the former shows one strong λ_{max} around 260 nm and the latter has two strong signals in both 260 and 340 nm, respectively (Figure 2). These results strongly suggest not cinnnoline but the cinnnolone form is favored in **14**−**16**. Caliculation (HF/3-21G level with Spartan 06) also suggest that both 4-keto-cinnolone calboxylic acid and calboxylate are more stable than the corresponding enol form, due to the hydrogen bonding between carboxylic proton and keto carbonyl group. The NMR analysis also indicates the latter does exist as a keto form[12] (see Supporting Information).

We next studied the synthesis of 1-aminoindolines, which are also important pharmacophores in medicinal chemistry.[1b]



Compound.	lmax nm (log e)
CO2t-Bu, N, N, 7a	256 (4.17), 329 (3.69)
MeO, MeO, CO2t-Bu, N, N, 7b	265 (4.65), 336 (3.77)
O, CO2t-Bu, N, N, Ac, 15	257 (4.41), 268 (4.37) 341 (4.40)
O, CO2t-Bu, N, N, H, 14	257 (4.14), 300 (4.03) 339 (4.35), 354 (4.28)
O, CO2H, N, N, H, 16	257 (4.00), 341 (4.15) 356 (4.04)

FIGURE 2. UV spectra in DMSO for **7a,b** and **14**−**16**.

SCHEME 6. Stereocontrolled Synthesis of 18a

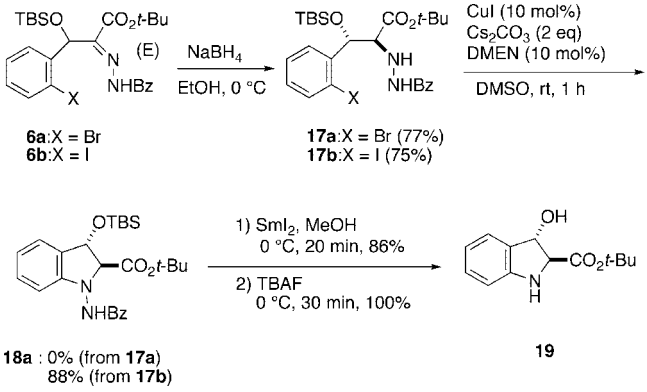
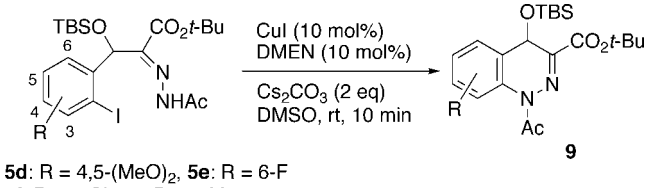


TABLE 3. Intramolecular N-Arylation of 5d−g



5d: R = 4,5-(MeO)$_2$, **5e**: R = 6-F
5f: R = 4-Cl, **5g**: R = 3-Me

entry	5	yield (%)
1	**5d**	**9d**: 61[a]
2	**5e**	**9e**: quant
3	**5f**	**9f**: quant
4	**5g**	**9g**: 58

[a] **9d** is partially aromatized upon silica gel column chromatography to give **7d** (38%).

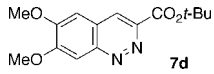
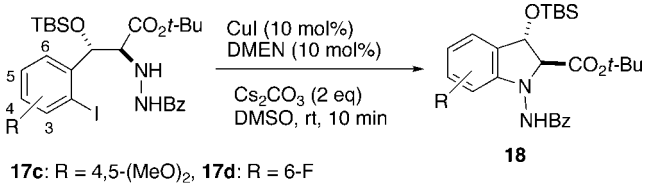


TABLE 4. Intramolecular N-Arylation of 17c−f



17c: R = 4,5-(MeO)$_2$, **17d**: R = 6-F
17e: R = 4-Cl, **17f**: R = 3-Me

entry	17	yield (%)
1	**17c**	**18c**: 70
2	**17d**	**18d**: 71
3	**17e**	**18e**: 71
4	**17f**	**18f**: 29

The most widely used method for synthesizing 1-aminoindolines is a multistep synthesis via N-amination of the corresponding indolines or indoles.[13] Indoline formation by nucleophilic attack of the internal nitrogens of hydrazines should be achieved by Cu-catalyzed N-arylation. Particularly, 3-hydroxyindoline-2-carboxylates are expected to be attractive building blocks as conformationally fixed phenylalanine equivalents.[14] The synthesis is shown in Scheme 6; stereoselective reduction of (*E*)-**6a,b** gave **17a,b** as *anti*-isomers, exclusively.[15] Although the cyclization using **17a** with CuI under the optimized conditions (CuI, DMEN, Cs_2CO_3, DMSO, rt) was unsuccessful, **17b** was quite reactive to give **18a** within 1 h in 88% yield. Cleavage of the N−N bond by SmI_2[16] followed by deprotection of a TBS group with TBAF gave **19** in 86% yield.

To confirm the generality of these methods, four types of hydrazones **5d−g** and hydrazines **17c−f** were prepared from the corresponding aldol adducts. First, we applied the intramolecular N-arylation of **5** under the optimized conditions (Table 3). Change in the electronic nature of the substituents on benzene ring did not affect the efficiency in this cyclization (entries 1−3). Even in the case of sterically hindered substrate such as **5g**, the reaction gave **9g** in 58% yield (entry 4).

Similar investigation using **17c−e** revealed that 1-aminoindolines were obtained in good yield (entries 1−3). However, **17f**, which has a substituent at the 3-position, prevented cyclization to give **18f** in low yield (entry 4). These results are summarized in Table 4.

In summary, we have demonstrated that both hydrazones and hydrazines are useful precursors for the facile synthesis of cinnoline, dihydrocinnoline, and 1-aminoindoline derivatives by Cu-catalyzed intramolecular N-arylation. Further application of this protocol to natural product synthesis is currently under investigation.

Experimental Section

Typical Procedure for Cu-Catalyzed N-Arylation. Synthesis of 9a (Table 2, entry 6). A test tube was charged with **5c** (53.2 mg, 0.10 mmol), CuI (1.9 mg, 0.01 mmol), and Cs_2CO_3 (65.2 mg, 0.20 mmol). The tube was evacuated and backfilled with argon. To the mixture were added dried DMSO (0.5 mL) and *N*,*N*′-dimethylethylenediamine (DMEN, 1.1 μL, 0.01 mmol). The reaction mixture was stirred at room temperature for 10 min. The resulting mixture was filtered through a pad of silica gel, eluting with Et_2O. The filtrate was concentrated, and the residue was purified by flash column chromatography (*n*-hexane/AcOEt = 20:1) to give **9a** (37.4 mg, 93%) as a colorless oil. IR (neat) ν: 2931, 1718 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.03 (s, 3H), 0.09 (s, 3H), 0.73 (s, 9H), 1.59 (s, 9H), 2.66 (s, 3H), 5.68 (s, 1H), 7.27−7.43 (m, 3H), 8.55 (d, 1H, J = 8.4 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 173.3, 162.3, 140.7, 134.5, 129.0, 128.9, 126.2, 123.8, 119.5, 82.4, 58.6, 28.0, 25.5, 23.9, 18.0, −4.4. LRMS (FAB) *m*/*z*: 443 (M + K). HRMS (FAB) calcd for $C_{21}H_{32}N_2O_4SiK$ 443.1768, found 443.1735.

Synthesis of 18a (Scheme 6). A test tube was charged with **17b** (49.0 mg, 0.08 mmol), CuI (1.6 mg, 0.008 mmol), and Cs_2CO_3 (53.5 mg, 0.16 mmol). The tube was evacuated and backfilled with argon. To the mixture were added dried DMSO (0.4 mL) and *N*,*N*′-dimethylethylenediamine (0.9 μL, 0.008 mmol). The reaction mixture was stirred at room temperature for 1 h. To the resulting mixture were added AcOEt (5 mL) and ammoniacal solution of NaCl (10 mL). The mixture was stirred vigorously to dissolve the precipitate and then extracted with AcOEt (10 mL × 3). The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Flash column chromatography (*n*-hexane/AcOEt = 15:1) gave **18a** (34.0 mg, 88%) as a colorless amorphous solid. IR (neat) ν: 3285, 2929, 2857, 1725, 1660, 834

(11) Sakamoto reported that both *E*- and *Z*-isomer hydrazones successfully cyclized to give indazole via intramolecular N-arylation under Pd catalysis; see: Inamoto, K.; Katsuno, M.; Yoshino, T.; Suzuki, I.; Hiroya, K.; Sakamoto, T. *Chem. Lett.* **2004**, *33*, 1026–1027. Our result using the *Z*-isomer is described in Supporting Information.

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(14) Collot, V.; Schmitt, M.; Marwah, P.; Bourguignon, J. *Heterocycles* **1999**, *51*, 2823–2847.

(15) The stereochemistry of **17a,b** was determined by conversion to *tert*-butyl 2-(*N*-benzoylhydrazino)-3-phenyl-3-(*tert*-butyldimethylsilyloxy)propionate by dehalogenation (*s*-BuLi/THF,−78 °C, 1 h); see ref 8b.

(16) Burk, M. J.; Feaster, J. E. *J. Am. Chem. Soc.* **1992**, *114*, 6266–6267.

cm^{-1}. ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 0.17 (s, 3H), 0.22 (s, 3H), 0.94 (s, 9H), 1.48 (s, 9H), 4.41 (d, 1H, J = 4.0 Hz), 5.48 (d, 1H, J = 4.0 Hz), 6.74 (d, 1H, J = 8.4 Hz), 6.92 (dd, 1H, J = 7.6, 7.6 Hz), 7.23−7.56 (m, 5H), 7.83 (d, 2H, J = 7.8 Hz), 8.04 (s, 1H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ: 169.9, 166.6, 149.4, 132.7, 132.0, 129.6, 128.7, 127.9, 127.1, 124.9, 121.3, 109.5, 82.6, 76.6, 74.6, 28.0, 25.8, 18.0, −4.3. LRMS (FAB) *m*/*z*: 507 (M + K). HRMS (FAB) calcd for $C_{26}H_{36}N_2O_4SiK$ 507.2081, found 507.2078.

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Supporting Information Available: General experimental procedures, ^{1}H and ^{13}C NMR spectra, charactrization data for new compounds of **2**-**14** and **16**−**19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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