Tandem One-Pot Construction of Indoles via Palladium and Copper-Catalyzed Coupling Reactions of the Blaise Reaction Intermediate

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Abstract: The palladium-catalyzed intramolecular N-arylation of the Blaise reaction intermediate, formed by reaction of nitriles with an in situ generated Reformatsky reagent from ethyl α-bromo-α-(2-bromophenyl)acetate and zinc, afforded indoles in good yields. Extension of this approach to the chemoselective intramolecular N-alkylation/palladium-catalyzed N-arylation of the Blaise reaction intermediate, having ω-chloroalkyl appendages, provided a novel route for the tandem one-pot synthesis of N-fused indole derivatives. In contrast, the intermolecular coupling reaction of the Blaise reaction intermediates with 1,2-dihalobenzene did not proceed in the presence of a palladium catalyst, but proceeded in the presence of copper(I) iodide as the catalyst and resulted in indoles.

Key words: tandem reaction, Blaise reaction, palladium, copper, coupling, indoles

1 Introduction

Indoles are an iconic component of numerous natural products and potent pharmaceutical drugs.[1] Although a large number of methodologies for the construction or structural modifications of the indole scaffold are available,[2] straightforward preparation of structurally diverse indoles remains an important subject in synthetic chemistry.[3] In recent years, transition-metal-catalyzed methods, in particular on palladium-catalyzed C–C or C–C/C–N coupling processes, have proved to be especially useful.[4] Figure 1 schematically presents some of these palladium-catalyzed coupling strategies: (a) intermolecular coupling of *o*-haloanilines with alkynes (known as Larock indole synthesis),[5] (b) coupling of anilines with alkynes involving C–H activation,[6] (c) C–C/Suzuki and C–N/Heck sequences of *o*-amino-β,b-dihalostyrenes,[7] (d) C–N/C–N bond-forming reactions of *o*-halostyrenes with primary amines,[8] (e) C–N/C–C coupling of 1,2-dihaloarenes with imines,[9] (f) intramolecular C–C couplings of *N*-aryl b-enaminocarbonyls involving C–H activation,[10] and (g) cyclization of *o*-alkynylanilines.[11] However, most of these approaches rely on the use of anilines or amines as nitrogen sources, and, therefore, the development of new methods for the synthesis of indole derivatives from readily available non-amino compounds is a subject of interest. The value of these methods would be greatly enhanced if the reactions were run in tandem, as this would minimize the synthetic steps and waste generation.[12] We herein report tandem one-pot approaches for the syntheses of indoles and N-fused indoles using the Blaise reaction intermediate, formed from readily available nitriles and Reformatsky reagents (Scheme 1).

Due to their functional group tolerance, the use of organozinc reagents has gained particular attention in the development of tandem reactions.[13] However, methods for the construction of the indole moiety using organozinc reagents are rather limited. To the best of our knowledge, the reaction of alkylzinc reagents with aryldiazonium tetrafluoroborates, disclosed recently by Knochel et al., is the only precedent for indole synthesis using organozinc reagents.[14] We recently recognized the Blaise reaction intermediate, a zinc bromide complex of a β-enamino ester,[15] as a polyfunctionalized organozinc that combines

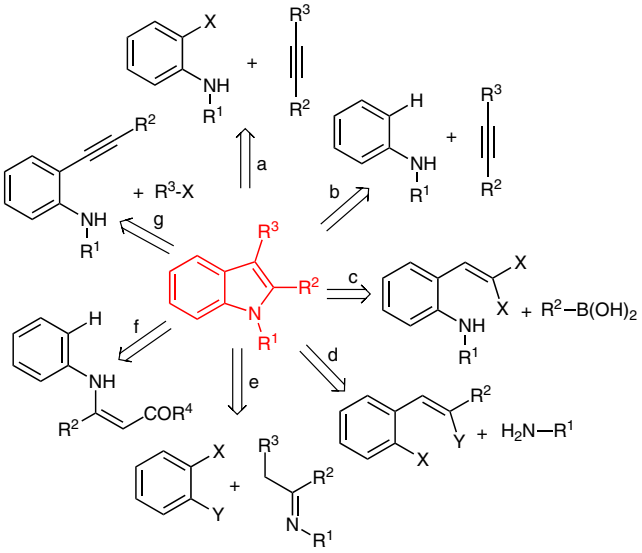

Figure 1 The relevant strategies for palladium-catalyzed indole synthesis

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the C/N-divalent nucleophilic enamine with the electrophilic α,β-unsaturated ester. In recent years, we have explored the latent potential of the Blaise reaction intermediate as a reagent of choice for tandem bond formation reactions.[16] Along this line, considering the well-developed palladium-catalyzed coupling reaction of organozinc reagents with aryl halides,[17] we became interested in the palladium-catalyzed intramolecular N-arylation of the Blaise reaction intermediate for the construction of the indole moiety. In our previous communication, we reported the feasibility of this new approach in constructing the indole skeleton [Scheme 1, (a) and (b)].[18] In this article, we described details of this tandem one-pot synthesis of indole and N-fused indoles. In addition, the intermolecular N–C/C–C coupling of the Blaise reaction intermediate with 1,2-dihaloarenes has also been investigated as an alternative approach for tandem one-pot synthesis of indoles [Scheme 1, (c)].

2 Results and Discussion

2.1 Palladium-Catalyzed Intramolecular C–N Coupling of the Blaise Reaction

Palladium-catalyzed cross-coupling reactions of organozinc reagents with aryl halides have been extensively investigated. However, all of them involve C–C couplings. Moreover, the reactivity of the Blaise reaction intermediate in palladium-catalyzed coupling reactions has not been explored to date. To investigate the reactivity of the Blaise reaction intermediate under palladium-catalyzed intramolecular coupling conditions, the intermediate **3a** was prepared by the reaction of benzonitrile (**1a**) with a Reformatsky reagent, generated in situ from ethyl α-bromo-α-(2-bromophenyl)acetate (**2a**) and zinc. Based on the recently disclosed palladium-catalyzed cross-couplings of the Reformatsky reagents with aryl halides under base-free conditions,[19] we initially anticipated that the palladium-catalyzed intramolecular C–N coupling of **3a** would be possible in the absence of a base. However, the tandem C–N coupling reactions of **3a**, using palladium catalysts such as $Pd(PPh_3)_4$ (7.4 mol%) and $Pd(dba)_2$ (5 mol%)/SPhos (10 mol%) [SPhos: 2-(dicyclohexylphosphino)-2′,6′-dimethoxybiphenyl],[20] did not proceed at all (Table 1, entries 1–3). These results suggest that the nucleophilicity of the Blaise reaction intermediate **3a** may not be sufficiently high for intramolecular transmetalation of the Pd^{2+} species, formed by oxidative addition of the 2-bromo group with Pd(0). In order to increase the nucleophilicity of the Blaise reaction intermediate, we added 2.0 equivalents of a non-nucleophilic base, sodium hexamethyldisilazanide, which resulted in the formation of the desired indole **4a** in 30% yield with $Pd(PPh_3)_4$ as the catalyst (entry 4) and a 47% yield with $Pd(dba)_2$/SPhos (entry 5). Encouraged by these results, we screened mono- and bisphosphine ligands (entries 6–11). Unfortunately, the intramolecular C–N coupling of **3a** occurred much less effectively with the palladium catalysts ligated by sterically congested XPhos [2-(dicyclohexylphosphino)-2′,4′,6′-triisopropylbiphenyl][21] (entry 6), simple tricyclohexylphosphine (entry 7), Feringa's *rac*-phosphoamidate ligand L-**X** (entry 8),[22] *rac*-BINAP (entry 9),[23] XanPhos (entry 10),[24] and bisphosphine ligand L-**Y**, which has been

Biographical Sketches

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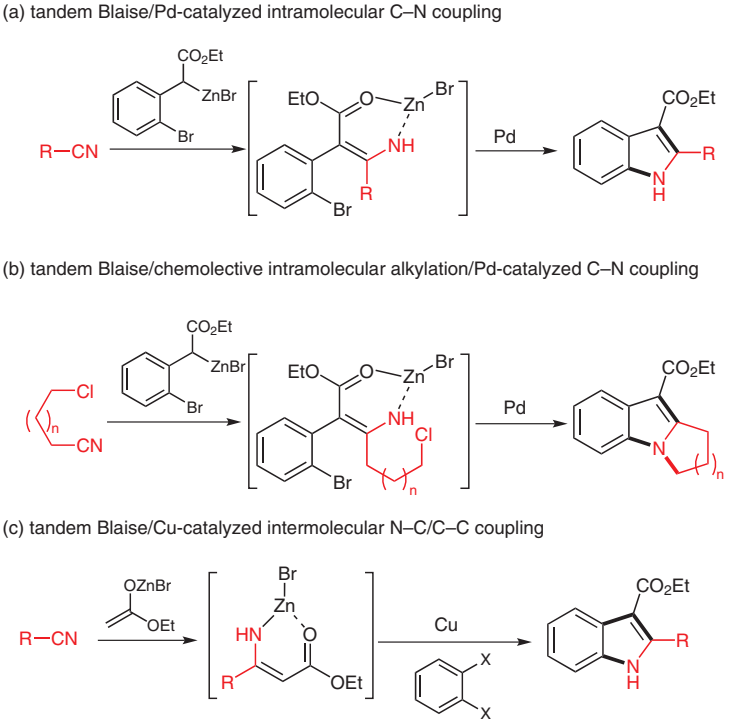
Prof. Dr. Sang-gi Lee received his B.S. from Kyungpook National University (1982) and his M.S. from the Korea Advanced Institute of Science and Technology (1985). He worked, for five years, at the Korea Institute of Science and Technology (KIST) as a Research Scientist (1985–1990) and received his Ph.D. from the University of Missouri-Columbia (1994). From 1994, he worked at KIST as a Principal Research Scientist and Director of the Medicinal Research Center. In 2006, he moved to Ewha Womans University as a professor. He received the Chang Sea Hee Academic Award from the Organic Division in the Korean Chemical Society (2005). He served as a vice president in Korean Chemical Society and the Korean Society of Organic Synthesis. His research interests are developments of new catalytic reactions, tandem reactions, and applications of ionic liquids and ionic liquid-nano hybrid materials in catalysis and functional materials.



Scheme 1 Methods for tandem one-pot synthesis of indoles using the Blaise reaction intermediate

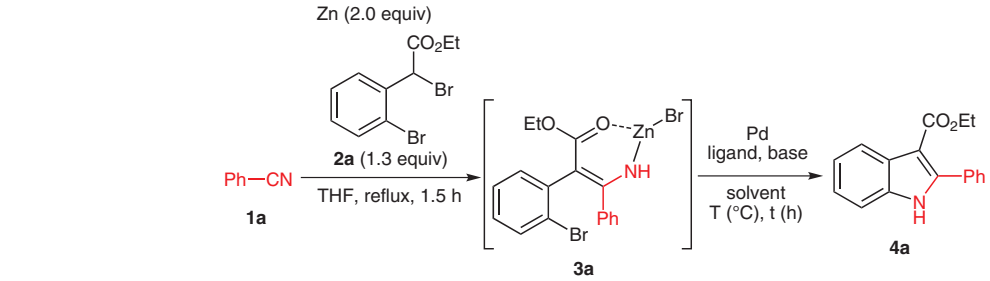
used as a chiral ligand in our previous work on rhodium-catalyzed asymmetric hydrogenation (entry 11).[25] We next investigated the effect of a base on the intramolecular coupling of **3a** using $Pd(dba)_2$/SPhos in toluene. As shown in entries 12–14, no indole **4a** was formed from the reaction with potassium *tert*-butoxide, potassium carbonate, or cesium carbonate as the base, which may be largely due to low solubility of these bases in toluene. Finally, we found that the intramolecular C–N coupling of the Blaise reaction intermediate **3a** proceeded smoothly by employing 2.0 equivalents of *tert*-butyllithium as the base (conditions A) to afford the desired indole **4a** in 74% yield (entry 15).

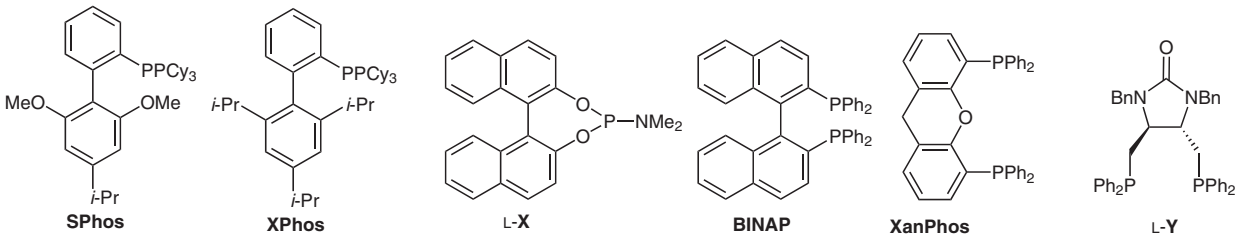
Initially, we considered that conditions A could be the optimal reaction condition to conduct the intramolecular N-arylative coupling of the Blaise reaction intermediate, and we investigated the generality of this tandem reaction with various nitriles. As shown in Table 2, the 3-methyl- (**1b**) and 4-methyl benzonitriles (**1c**) afforded the corresponding indoles **4b**,**c** in good yields under conditions A (entries 2 and 3). Disappointingly, the tandem reactions with the Blaise reaction intermediates **3d** and **3e**, prepared from the electron-withdrawing group substituted 4-(trifluoromethyl)benzonitrile (**1d**) and heteroaromatic furan-2-carbonitrile (**1e**) dramatically decreased the yield of indoles **4d**,**e** (entries 4 and 5). Moreover, reactions with alkanenitriles become more problematic, and thus, from the tandem reaction with the Blaise reaction intermediate, formed from phenylacetonitrile (**1f**), the indole **4f** was only detected by TLC, which may due to the deprotonation of the benzylic proton with the strong base, causing serious side reactions (entry 6).

To overcome the substrate limitation of conditions A, we attempted to re-optimize the reaction conditions with $Pd(PPh_3)_4$ (Table 1, entry 4). Changing the solvent to a polar solvent such as *N*,*N*-dimethylformamide and dimethyl sulfoxide substantially improved yields (entries 16 and 17). The yield was increased twofold when the base was changed to potassium *tert*-butoxide resulting in **4a** in 68% yield (entry 18). However, the yield decreased as the amount of base increased (entry 19). To our delight, the amount of base decreased to 1.3 equivalents, the indole **4a** was formed with 84% yield (entry 20) (conditions B).

Under these re-optimized conditions B, the indoles **4a**–**f** could be synthesized in good yields (Table 2, entries 1–6). Both aliphatic and aromatic nitriles with electron-withdrawing and -donating groups could also be converted into the corresponding indoles **4a**–**l** in moderate to good yields. The possible reaction pathway for the formation of indoles **4** via palladium-catalyzed intramolecular N-arylation of the Blaise reaction intermediate **3** is depicted in Scheme 2. The arylpalladium(II) bromide complex **A**, formed by oxidative addition of **3** to Pd(0), may be coordinated with the nitrogen atom of the iminoenolate, which can be generated by deprotonation of the acidic N–H proton with the base, potassium *tert*-butoxide. Intramolecular transmetalation, and reductive elimination of the resulting Pd(II) complex **B** could regenerate Pd(0) for further catalytic cycles, and the zinc bromide complex of indole **4**-ZnBr, which can then be converted into **4** after workup.

Table 1 Condition Optimization for Intramolecular Palladium-Catalyzed Arylative C–N Coupling of the Blaise Reaction Intermediate for Tandem One-Pot Synthesis of Indoles

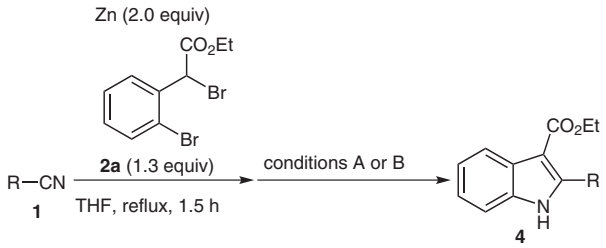




Entry	Pd	Ligand	Base	Solvent	Temp (°C)	Time (h)	Yield[b] (%)
1	$Pd(PPh_3)_4$	–	–	THF	65	48	–
2	$Pd(PPh_3)_4$	–	–	DMF	120	48	–
3	$Pd(dba)_2$	SPhos	–	THF	65	48	–
4	$Pd(PPh_3)_4$	–	NaHMDS	toluene	110	24	30
5	$Pd(dba)_2$	SPhos	NaHMDS	toluene	110	48	47
6	$Pd(dba)_2$	XPhos	NaHMDS	toluene	110	48	39
7	$Pd(dba)_2$	Cy_3P	NaHMDS	toluene	110	48	21
8	$Pd(dba)_2$	L-**X**	NaHMDS	toluene	110	48	<5
9	$Pd(dba)_2$	BINAP	NaHMDS	toluene	110	48	<5
10	$Pd(dba)_2$	XanPhos	NaHMDS	toluene	110	48	20
11	$Pd(dba)_2$	L-**Y**	NaHMDS	toluene	110	48	<5
12	$Pd(dba)_2$	SPhos	*t*-BuOK	toluene	110	48	–
13	$Pd(dba)_2$	SPhos	K_2CO_3	toluene	110	48	–
14	$Pd(dba)_2$	SPhos	$CsCO_3$	toluene	110	48	–
15	$Pd(dba)_2$	SPhos	*t*-BuLi	toluene	110	48	74
16	$Pd(PPh_3)_4$	–	NaHMDS	DMF	120	24	31
17	$Pd(PPh_3)_4$	–	NaHMDS	DMSO	120	24	60
18	$Pd(PPh_3)_4$	–	*t*-BuOK	DMF	120	24	68
19[c]	$Pd(PPh_3)_4$	–	*t*-BuOK	DMF	120	24	52
20[d]	$Pd(PPh_3)_4$	–	*t*-BuOK	DMF	120	15	84

[a] Conditions: acetate **2a** (1.3 equiv) was added over 1 h to a soln of **1a** (2.29 mmol) and Zn (2.0 equiv) in THF (0.9 mL) at reflux. After 1.5 h reflux, the Pd catalyst [$Pd(PPh_3)_4$ (7.4 mol%) or $Pd(dba)_2$ (5 mol%)/ligand (10 mol%)], solvent (THF–solvent, 1:10), and base (2.0 equiv) were added at r.t.
[b] Isolated yield by column chromatography.
[c] Reaction with *t*-BuOK (3.0 equiv).
[d] Reaction with *t*-BuOK (1.3 equiv).

Table 2 Tandem One-Pot Synthesis of Indoles via Palladium-Catalyzed Intramolecular N-Arylation of the Blaise Reaction Intermediate **3**[a]



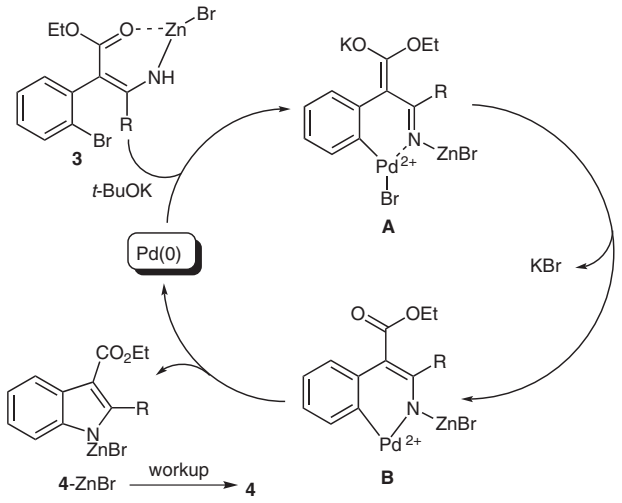
conditions A: $Pd(dba)_2$ (5 mol%), SPhos (10 mol%), *t*-BuLi (2.0 equiv) THF–toluene (1:10), 110 °C, 48 h
conditions B: $Pd(PPh_3)_4$ (7.4 mol%), *t*-BuOK (1.3 equiv) THF–DMF (1:10), 120 °C, 15 h

Entry	Conditions A or B	Nitrile **1**	R	Product **4**	Yield[b] (%)
1	A	**1a**	Ph	**4a**	74
	B				84
2	A	**1b**	3-MeC_6H_4	**4b**	71
	B				74
3	A	**1c**	4-MeC_6H_4	**4c**	78
	B				72
4	A	**1d**	3-$(F_3C)C_6H_4$	**4d**	29
	B				72
5	A	**1e**	2-furyl	**4e**	37
	B				64
6	A	**1f**	Bn	**4f**	<5
	B				72
7	B	**1g**	4-$MeOC_6H_4$	**4g**	84
8	B	**1h**	4-FC_6H_4	**4h**	51
9	B	**1i**	4-$EtO_2CC_6H_4$	**4i**	71
10	B	**1j**	4-NCC_6H_4	**4j**	62
11	B	**1k**	3-pyridyl	**4k**	76
12	B	**1l**	Et	**4l**	58

[a] Conditions: acetate **2a** (1.3 equiv) was added over 1 h to a soln of **1** (2.29 mmol) and Zn (2.0 equiv) in THF (0.9 mL) at reflux. After 1.5 h reflux, the Pd catalyst [$Pd(PPh_3)_4$ (7.4 mol%) or $Pd(dba)_2$ (5 mol%)/ligand (10 mol%)], solvent (for conditions A: THF–toluene, 1:10,; for Conditions B: THF–DMF, 1:10), and base [for Conditions A; *t*-BuLi (2.0 equiv), for conditions B: *t*-BuOK (1.3 equiv)] were added at r.t.
[b] Isolated yield by column chromatography.

2.2 Chemoselective Intramolecular N-Alkylation/Palladium-Catalyzed C–N Coupling Reaction of the Blaise Reaction

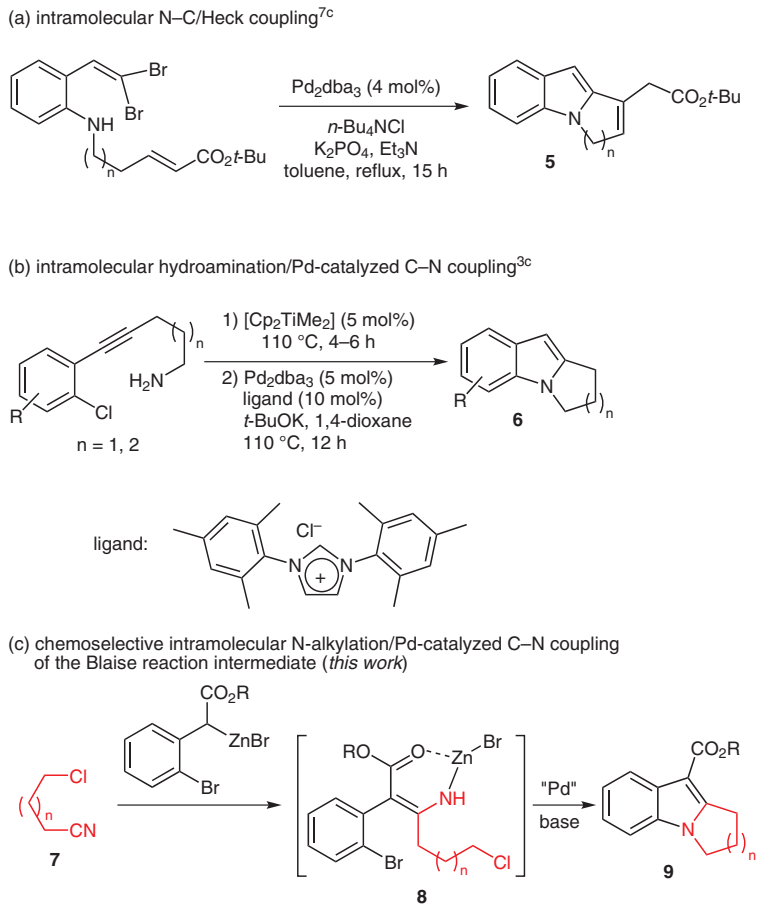
N-Fused indoles are indole derivatives and have also biological importance.[26] Although different strategies have been developed for the synthesis of N-fused indoles, most of them rely on alkyl chain elongation and ring closure on an existing indole platform.[27] Moreover, methods for palladium-catalyzed one-pot construction of N-fused indole



Scheme 2 The possible reaction pathway for the formation of indole **4** via palladium-catalyzed intramolecular N-arylation of the Blaise reaction intermediate **3**

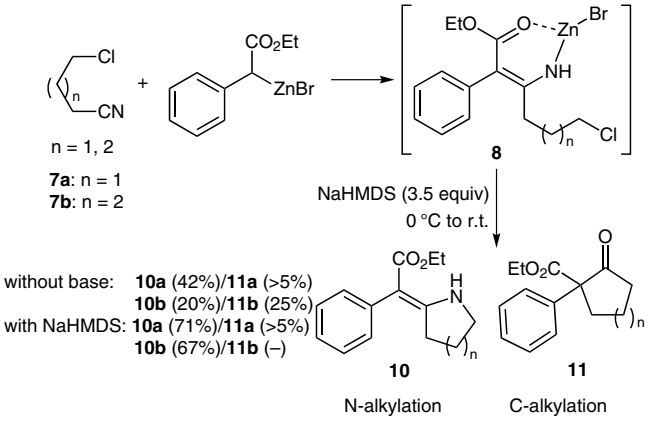
moieties are limited. For examples, Lautens and co-workers reported that palladium-catalyzed intramolecular tandem C–N/Heck coupling reactions of *o*-amino-β,β-dihalostyrenes afforded N-fused indole derivatives **5** [Scheme 3, (a)].[7c] Doye and co-workers also developed a method for the one-pot synthesis of N-fused indoles **6** through the tandem titanium-catalyzed hydroamination of alkynes/palladium-catalyzed N-arylation [Scheme 3 (b)].[3c] However, these strategies required a multistep synthesis of the substrates. We envisioned that the intramolecular N-alkylation/palladium-catalyzed N-arylation of the Blaise reaction intermediate **8**, formed by reaction of ω-haloalkanenitriles **7** with a Reformatsky reagent, could provide a new one-pot route to N-fused indoles **9** [Scheme 3 (c)].

Due to the divalent C-/N-nucleophilicity of the Blaise reaction intermediate, success of this tandem approach to N-fused indoles **9** could be largely determined by the chemoselectivity of the intramolecular alkylation of the intermediate **8** having the ω-haloalkyl appendage. Moreover, the reaction conditions should also be applicable to palladium-catalyzed intramolecular arylation. Hence, the intramolecular alkylation reactivity and selectivity of the Blaise intermediates **8a** and **8b**, having ω-chloroalkyl appendages, were investigated (Scheme 4). It was found that selectivity was largely dependent on tether length. Thus, the intermediate **8a** (n = 1) exhibited N-alkylation selectivity providing **10a** in 42% yield. However, both C-alkylated and N-alkylated products **10b** (20%) and **11b** (25%) were formed from the intermediate **8b** (n = 2). Fortunately, the addition of sodium hexamethyldisilazanide (3.5 equiv) dramatically increased not only chemoselectivity, but also reactivity, and the N-alkylated exocyclic enamino esters **10a** and **10b** could be isolated in 71% and 67% yields, respectively. Only small amounts of C-cyclized products **11a** and **11b** were detected (Scheme 4).[28] We applied these reaction conditions to the Blaise reaction intermediates, formed from ω-chloroalkanenitriles **7a–c** and



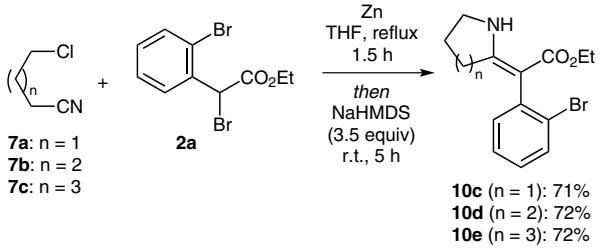
Scheme 3 Methods for palladium-catalyzed one-pot synthesis of N-fused indoles

ethyl α-bromo-α-(2-bromophenyl)acetate (**2a**), which resulted in the formation of the corresponding N-alkylated exocyclic enamino esters **10c–e** in 71–72% yields (Scheme 5).



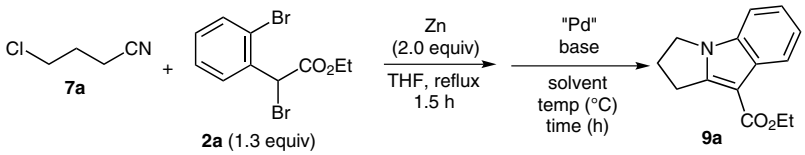
Scheme 4 Chemoselective intramolecular N-alkylation of the Blaise reaction intermediate formed from ω-chloroalkanenitriles

Based on these results, we carried out the tandem one-pot construction of the N-fused indole moiety using $Pd(PPh_3)_4$ as the catalyst and sodium hexamethyldisilazanide as the base (Table 3). However, after 24 hours reflux, only trace amounts of the N-fused indole **9a** could be detected by TLC, and only the N-cyclized *exo*-enamino ester **10c** was isolated in 60% yield (entry 1). When the reaction was carried out in tetrahydrofuran–*N*,*N*-dimethylformamide (1:10) at 120 °C for 48 hours, the desired **9a** was formed in 51% yield (entry 2). Fortunately, when the Blaise reaction intermediate was subjected to the same reaction conditions used for the synthesis of indoles **4**, $Pd(PPh_3)_4$ (7.4 mol%), and potassium *tert*-butoxide (1.3 equiv) (conditions B), the yield of **9a** increased to 62% (entry 3). By using 2.3 equivalents of potassium *tert*-butoxide, the yield further increased to 70% (entry 4). However, a lower yield of **9a** was formed under all the other conditions examined (entries 5–8). It is noteworthy that when the tandem reaction was carried out at a lower temperature (80 °C), only the N-alkylated product **10c** was



Scheme 5 Tandem one-pot synthesis of exocyclic enamino esters **10c–e**

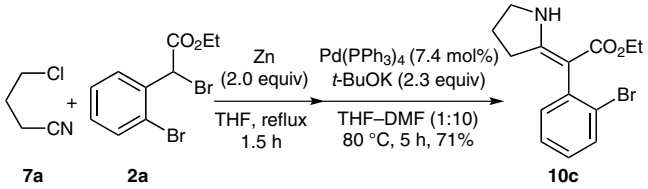
Table 3 Condition Optimizations for the Tandem Blaise/Intramolecular N-Alkylation/Palladium-Catalyzed C–N Coupling for One-Pot Synthesis of N-Fused Indoles[a]



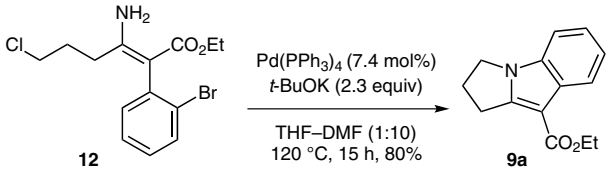
Entry	Pd	Base	Solvent	Temp (°C)	Time (h)	Yield (%) of **9a**
1	$Pd(PPh_3)_4$	NaHMDS	THF	reflux	48	<5
2	$Pd(PPh_3)_4$	NaHMDS	DMF	120	48	51
3	$Pd(PPh_3)_4$	*t*-BuOK	DMF	120	15	62
4	$Pd(PPh_3)_4$	*t*-BuOK	DMF	120	15	70
5	$Pd(dba)_2$/SPhos	NaHMDS	toluene	110	48	48
6	$Pd(dba)_2$/SPhos	*t*-BuLi	toluene	110	24	38
7	$Pd(dba)_2$/SPhos	*t*-BuOK	toluene	110	24	63
8	$Pd(dba)_2$/SPhos	*t*-BuOK	DMF	120	24	49

[a] Conditions: acetate **2a** (1.3 equiv) was added over 1 h to a soln of **1a** (2.29 mmol) and Zn (2.0 equiv) in THF (0.9 mL) at reflux. After 1.5 h reflux, the Pd catalyst [$Pd(PPh_3)_4$ (7.4 mol%) or $Pd(dba)_2$ (5 mol%)/ligand (10 mol%)], solvent (THF–solvent, 1:10), and base (1.3 equiv) were added at r.t.
[b] Isolated yield by column chromatography.

isolated in 71% yield (Scheme 6). This result clearly indicated that under these reaction conditions, the intramolecular N-alkylation reaction proceeded prior to the N-arylation with high chemoselectivity. Moreover, the isolated Blaise reaction products **12** could also be converted into the corresponding N-fused indole **9a** in 80% yield (Scheme 7).



Scheme 6 Selective formation of **10c** at low temperature



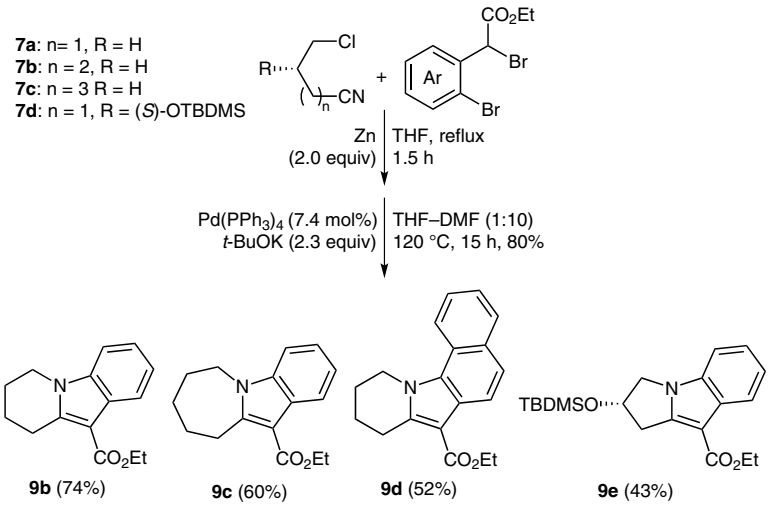
Scheme 7 Synthesis of **9a** from the Blaise reaction product **12**

The generality of the tandem chemoselective N-alkylation/palladium-catalyzed N-arylation reactions has been proven by the synthesis of six- and seven-membered N-fused indoles **9b** (74%) and **9c** (60%). By using the Reformatsky reagent, generated from ethyl α-bromo-α-(1-bromonaphthalen-2-yl)acetate, the tetrahydrobenzopyridoindole **9d** was also synthesized from **7b** in 52% yield. From the chiral epichlorohydrin-derived nitrile **7d**, the chiral N-fused indole **9e** could be synthesized in 43% yield, which would be a useful intermediate for the synthesis of bioactive mitomycin derivatives (Scheme 8).[29]

The proposed reaction pathway for the formation of N-fused indoles **9** is depicted in Scheme 9. Under the reaction condition, the chemoselective intramolecular N-alkylation reaction of Blaise reaction intermediate **8** having the ω-chloroalkyl appendage occurred first. Then, the resulting zinc bromide complex **C** may have enough nucleophilicity for the intramolecular transmetalation of the aryl–Pd(II)–Br **D**, formed by oxidative addition of Pd(0), to afford the Pd(II) complex **E**, which then produce the N-fused indoles **9** by reductive elimination.

2.3 Copper-Catalyzed Intermolecular N–C/C–C Coupling Reaction of the Blaise Reaction Intermediate with 1,2-Dihaloarenes

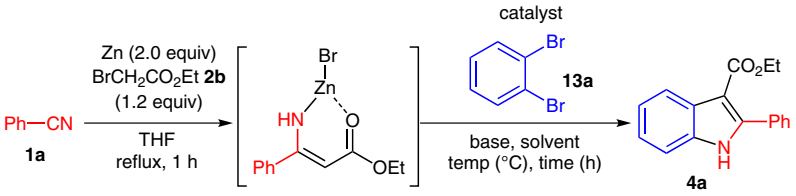
Finally, we envisioned that the C-/N-ambivalent nucleophilic nature of the Blaise reaction intermediate might be employed to design metal-catalyzed intermolecular C–C/N–C couplings with 1,2-dihaloarenes. Therefore, we decided to investigate the tandem indolization reaction of the Blaise reaction intermediate, formed by reaction of benzonitrile (**1a**) with a Reformatsky reagent, generated in situ from ethyl bromoacetate (**2b**) and zinc, with 1,2-dibromobenzene (**13a**). However, it was found that in contrast to intramolecular N-arylation, the Pd catalysts such as $Pd(PPh_3)_4$, $Pd(dba)_2$/XPhos, $Pd(dba)_2$/BINAP were not effective for the tandem indolization reaction (Table 4, entries 1–5). Instead, we found that the copper(I) iodide



Scheme 8 Tandem one-pot synthesis of N-fused indoles **9b–e**

can catalyze the tandem intermolecular C–C/C–N coupling reaction of the Blaise reaction intermediate with 1,2-dibromobenzene (**13a**). After screening a number of conditions, the tandem reaction could be carried out by employing copper(I) iodide (20 mol%), phenanthroline (Phen, 40 mol%) as a ligand, and potassium *tert*-butoxide as the base in *N*,*N*-dimethylformamide (THF–DMF, 1:10) at 120 °C for 24 hours to afford the indole **4a** in 54% yield (entry 9).[30] The yield of **4a** increased to 65% with increase in the catalyst loading to 30 mol% of copper(I) iodide and

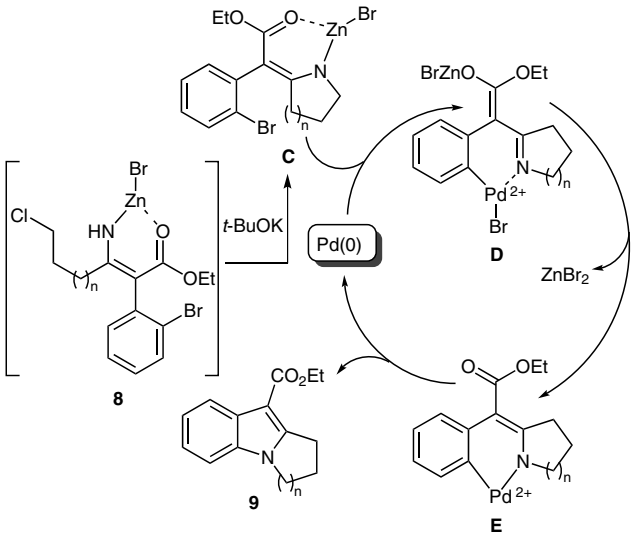
Table 4 Condition Optimization for Intermolecular Coupling of the Blaise Reaction Intermediate with 1,2-Dibromobenzene (**13a**)



Entry	Catalyst	Base	Solvent	Temp (°C)	Time (h)	Yield (%) of **4a**
1[a]	$Pd(dba)_2$/XPhos	*t*-BuONa	1,4-dioxane	reflux	24	–
2[a]	$Pd(dba)_2$/XPhos	*t*-BuONa	DMF	120	24	–
3[a]	$Pd(dba)_2$/SPhos	*t*-BuONa	1,4-dioxane	reflux	24	–
4[a]	$Pd(PPh_3)_4$	*t*-BuONa	DMF	120	24	–
5[a]	$Pd(dba)_2$/Binap	*t*-BuONa	DMF	120	24	<5
6[b]	CuI/2,2′-bipyridyl	Cs_2CO_3	DMF	120	24	27
7[b]	CuI/2,2′-bipyridyl	*t*-BuOK	DMF	120	24	37
8[b]	CuI/Phen	*t*-BuOK	DMF	120	24	43
9[b,c]	CuI/Phen	*t*-BuOK	DMF	120	24	54
10[d]	CuI/Phen	*t*-BuOK	DMF	120	24	65
11[d,e]	CuI/Phen	*t*-BuOK	DMF	120	24	76

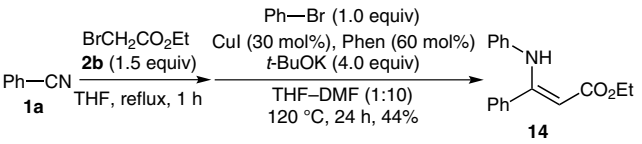
[a] Conditions: ethyl bromoacetate (**2b**, 1.5 equiv) was added over 1 h to a soln of **1a** (3.82 mmol) and Zn (2.0 equiv) in THF (1.2 mL) at reflux. After 1.0 h reflux, the Pd catalyst [$Pd(PPh_3)_4$ (7.5 mol%) or $Pd(dba)_2$ (5.0 mol%)/ligand (10 mol%)], solvent (THF–solvent, 1:10), base (3.5 equiv) and 1,2-dibromobenzene (**13a**, 1.2 equiv) were added at r.t. The reaction was continued for 24 h at 120 °C.
[b] Reaction was carried out with the copper catalyst [CuI (20 mol%)/ligand (40 mol%)], solvent (THF–solvent, 1:10), base (3.5 equiv), and 1,2-dibromobenzene (**13a**, 1.2 equiv).
[c] Reaction with base (4.0 equiv).
[d] Reaction was carried out with CuI (30 mol%)/Phen (60 mol%) and base (4.0 equiv).
[e] Reaction with 1,2-diiodobenzene (**13b**).

60 mol% of Phen (entry 10). When the same reaction was carried out using 1,2-iodobenzene, the yield of indole **4a** further increased to 76% (entry 11). The copper(I) iodide catalyzed intermolecular C–C/N–C coupling reactions of the 1,2-dibromobenzene (**13a**) and 1,2-diiodobenzene (**13b**) with the Blaise reaction intermediates, formed from aromatic **1g** and **1h**, heteroaromatic **1k**, alkanenitriles **1l**, could afford the corresponding indoles **4** in low to good yields (Table 5).



Scheme 9 Proposed reaction pathway for the formation of N-fused indoles **9**

In order to determine which of the N-arylation and C-arylation occurred first, the copper(I) iodide catalyzed intermolecular arylation of the Blaise reaction intermediate with bromobenzene was carried out, and we found that only the N-arylated product **14** was formed in 44% yield (Scheme 10). This result clearly indicated that the copper(I) iodide catalyzed N-arylation reaction occurred prior to C-arylation. The proposed Cu(I)/Cu(III)-type mechanism for copper(I) iodide catalyzed intermolecular coupling reaction of the Blaise reaction intermediate with 1,3-diiodobenzene (**13b**) is depicted in Scheme 11.[31] The Blaise reaction intermediate may have reacted with Cu(I) in the presence of a base to form the nitrogen coordinated Cu(I) complex **F**, which then reacted with 1,2-diiodobenzene (**13b**) to form Cu(III) complex **G**. Reductive elimination of Cu(I) could afford the N-arylated intermediate **H**, which then reacted with Cu(I) again at α-carbon to form **I**. Intramolecular formation of the Cu(III) complex **J**, and reductive elimination, followed by isomerization of the resulting imine **K** could afford the indole **4**. The regenerated Cu(I) can be used for next catalytic cycles.

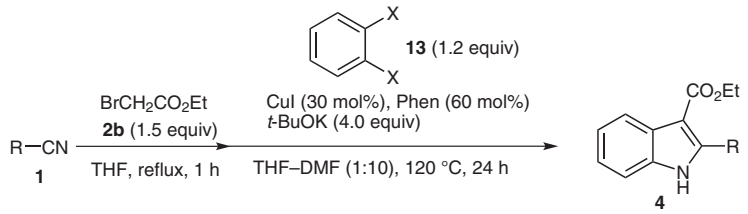


Scheme 10 Chemoselective intermolecular N-arylation of the Blaise reaction intermediate

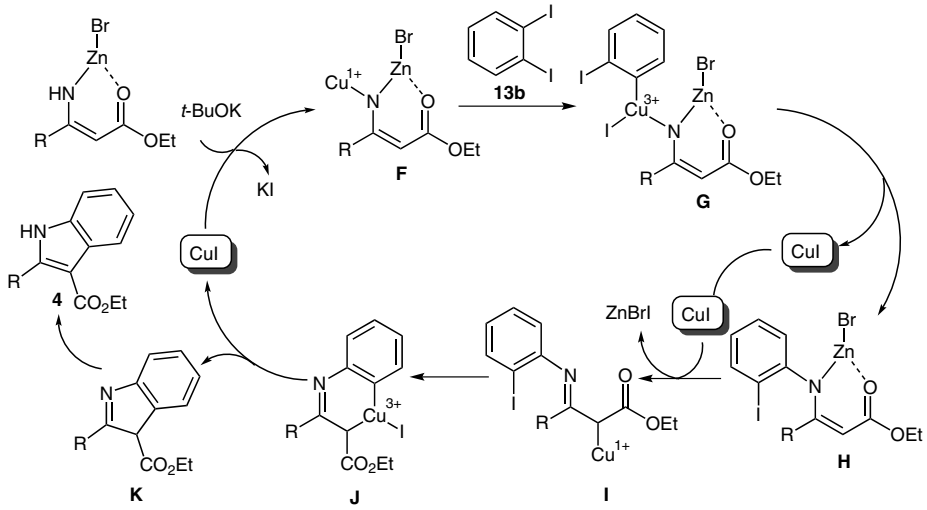
3 Conclusion

In summary, we have developed a novel tandem one-pot method for the synthesis of indoles through the palladium-catalyzed intramolecular N-arylative trapping of the Blaise reaction intermediates. Extension of this strategy to

Table 5 Tandem One-Pot Synthesis of Indoles via Copper-Catalyzed Intermolecular N–C/C–C Coupling of the Blaise Reaction Intermediate with 1,2-Dihaloarenes



Entry	Nitrile **1**	Dihalobenzene **13**	X	R	Product	Yield (%)
1	**1a**	**13a**	Br	Ph	**4a**	65
		13b	I			76
2	**1g**	**13a**	Br	4-$MeOC_6H_4$	**4g**	51
		13b	I			71
3	**1h**	**13a**	Br	4-FC_6H_4	**4h**	13
		13b	I			42
4	**1k**	**13a**	Br	3-pyridyl	**4k**	31
		13b	I			42
5	**1l**	**13a**	Br	Et	**4l**	8
		13b	I			48



Scheme 11 Proposed mechanism for the copper(I) iodide catalyzed intermolecular coupling of the Blaise reaction intermediate with 1,2-diiodobenzene (**13b**)

chemoselective intramolecular N-alkylation/palladium-catalyzed N-arylation of the Blaise reaction intermediates having an ω-chloroalkyl appendage provides a new route for tandem one-pot synthesis of N-fused indole derivatives. It has also been demonstrated that the copper-catalyzed intermolecular N–C/C–C coupling of the Blaise reaction intermediate with 1,2-dihaloarenes could be an alternative approach for tandem one-pot synthesis of indoles. Our future efforts are devoted to combining the Blaise reaction intermediate with transition-metal-catalyzed reactions for the development of new tandem catalytic reactions.

All reactions and manipulations were performed in an argon atmosphere using standard Schlenk techniques. Flasks were flame-dried under a stream of argon. All solvent were distilled prior to use and transferred by oven-dried syringe. All purchased reagents were used as received without further purification. Ethyl α-bromo-α-(2-bromophenyl)acetate (**2a**), ethyl α-bromo-α-(1-bromonaphthalen-2-yl)acetate,[32] and (3*S*)-3-(*tert*-butyldimethylsiloxy)-4-chlorobutanenitrile (**7d**)[33] were synthesized according to reported procedures. The chemical shifts were relative to TMS (as an internal reference) for ^{1}H NMR and the residual solvent signal ($CDCl_3$; δ = 77.16 ppm).

Tandem One-Pot Synthesis of Indoles 4 via Palladium-Catalyzed Intramolecular N-Arylation of the Blaise Reaction Intermediate; General Procedure

To a stirred suspension of commercial Zn dust (300 mg, 4.59 mmol) in THF (0.9 mL) was added MsOH (6.5 mol%), and the mixture was refluxed for 10 min. While maintaining reflux temperature, nitrile **1** (2.29 mmol) was added in one portion. Ethyl α-bromo-α-(2-bromophenyl)acetate (**2a**, 960 mg, 2.98 mmol) was added over 1 h by syringe pump. After 1.5 h reflux, the mixture was cooled to r.t. To the mixture was added $Pd(PPh_3)_4$ (198.8 mg, 0.17 mmol), *t*-BuOK (352.0 mg, 2.98 mmol), and anhyd DMF (9.0 mL). After 15 h at 120 °C, the mixture was cooled to r.t., quenched with sat. aq NH_4Cl, and the product was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (anhyd Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane–EtOAc, 7:1 to 3:1) to afford **4** in 51–84% yields.[18]

Chemoselective Intramolecular N-Alkylation of the Blaise Reaction Intermediate for Tandem One-Pot Synthesis of 10c–e; General Procedure

To a suspension of Zn dust (500 mg, 7.65 mmol) was added MsOH (6.5 mol%) in THF (1.5 mL), and the mixture was refluxed for 10 min. While maintaining reflux, chloroalkyl nitrile **7** (3.82 mmol) was added in one portion, and then ethyl α-bromo-α-(2-bromophenyl)acetate (**2a**, 4.97 mmol) was added over 1 h using a syringe pump. To this mixture was added a 1 M NaHMDS in THF (13.37 mmol) at 0 °C. The mixture was stirred for 5 h at r.t., quenched by the addition of sat. aq NH_4Cl, and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (anhyd Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was then purified by column chromatography (silica gel, *n*-hexane–EtOAc, 7:1) to afford the corresponding N-cyclized product **10c–e** in 71–72% yields.

Ethyl (2-Bromophenyl)pyrrolidin-2-ylideneacetate (10c)

Prepared from 4-chlorobutyronitrile (**7a**, 396 mg, 3.82 mmol), chromatography (*n*-hexane–EtOAc, 7:1); white solid; yield: 842 mg (71%); mp 52–54 °C.

^{1}H NMR (300 MHz, $CDCl_3$): d = 1.14 (t, *J* = 7.1 Hz, 3 H), 1.87–1.97 (m, 2 H), 2.20–2.39 (m, 2 H), 3.54–3.66 (m, 2 H), 4.02 (dq, *J* = 10.8, 7.1 Hz, 1 H), 4.15 (dq, *J* = 10.8, 7.1 Hz, 1 H), 7.06–7.12 (m, 1 H), 7.19–7.27 (m, 2 H), 7.57–7.60 (m, 1 H), 8.41 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): d = 14.8, 22.1, 32.0, 47.6, 59.0, 93.0, 127.2, 128.1, 132.3, 133.6, 139.4, 165.4, 169.1.

HRMS: *m*/*z* $[M - OEt]^+$ calcd for $C_{12}H_{11}BrNO$: 264.0024; found: 264.0022.

Ethyl (2-Bromophenyl)piperidin-2-ylideneacetate (10d)

Prepared from 5-chlorovaleronitrile (**7b**, 449 mg, 3.82 mmol), chromatography (*n*-hexane–EtOAc, 10:1 to 7:1) as a viscous yellow oil; yield: 892 mg (72%).

^{1}H NMR (500 MHz, $CDCl_3$): d = 1.11 (td, *J* = 7.1 Hz, 1.5 Hz, 3 H), 1.60 (m, 2 H), 1.71–1.77 (m, 2 H), 1.95–2.06 (m, 2 H), 3.34–3.43 (m, 2 H), 3.94–4.00 (m, 1 H), 4.07–4.14 (m, 1 H), 7.07–7.11 (m, 1 H), 7.17–7.19 (m, 1 H), 7.23–7.26 (m, 1 H), 7.58–7.59 (m, 1 H), 9.69 (br s, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): d = 14.7, 19.9, 22.4, 27.3, 41.5, 58.8, 94.9, 127.2, 128.05, 128.7, 132.3, 134.16, 139.25, 161.1, 169.4.

HRMS: *m/z* [M + H]$^+$ calcd for $C_{15}H_{19}BrNO_2$: 324.0599; found: 324.0601.

Ethyl (2-Bromophenyl)azepan-2-ylideneacetate (10e)

Prepared from 6-chlorohexanenitrile (**7c**, 503 mg, 3.82 mmol), chromatography (*n*-hexane–EtOAc, 10:1 to 5:1) as a viscous yellow oil; yield: 931 mg (72%).

^{1}H NMR (250MHz, $CDCl_3$): d = 1.13 (t, *J* = 7.1 Hz, 3 H), 1.27–1.35 (m, 2 H), 1.40–1.53 (m, 2 H), 1.56–1.67 (m, 2 H), 1.83–1.95 (m, 1 H), 1.99–2.11 (m, 1 H), 3.43 (t, *J* = 6.6 Hz, 2 H), 4.00 (dq, *J* = 10.8 Hz, 7.1 Hz, 1 H), 4.16 (dq, *J* = 10.8 Hz, 7.1 Hz, 1 H), 7.10–7.17 (m, 1 H), 7.19–7.23 (m, 1 H), 7.25–7.31 (m, 1 H), 7.61 (dd, *J* = 7.9 Hz, 1.1 Hz, 1 H).

^{13}C NMR (63 MHz, $CDCl_3$): d = 14.6, 26.5, 26.7, 32.1, 34.0, 44.8, 59.3, 98.4, 127.15, 128.3, 128.4, 132.4, 133.8, 138.9, 161.4, 169.4.

HRMS: *m/z* [M + H]$^+$ calcd for $C_{16}H_{21}BrNO_2$: 338.0756; found: 338.0754.

Ethyl (*Z*)-3-Amino-2-(2-bromophenyl)-6-chlorohex-2-enoate (12)

To a stirred suspension of commercial Zn dust (500 mg, 7.65 mmol) in THF (1.2 mL) was added MsOH (6.5 mol%), and the mixture was refluxed for 10 min. While maintaining reflux temperature, 4-chlorobutyronitrile (**7a**, 396 mg, 3.82 mmol) was added in one portion, and then ethyl α-bromo-α-(2-bromophenyl)acetate (**2a**, 4.97 mmol) was added over 1 h using a syringe pump. After 10 min reflux, the mixture was cooled to r.t., quenched with sat. aq NH_4Cl, and the product was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (anhyd Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, *n*-hexane–EtOAc, 10:1 to 7:1) to afford **12** as a colorless liquid; yield: 1.16 g (88%).

^{1}H NMR (250 MHz, $CDCl_3$): d = 1.13 (t, *J* = 7.1 Hz, 3 H), 1.81–1.90 (m, 2 H), 2.01–2.26 (m, 2 H), 3.48–3.54 (m, 2 H), 4.00 (dq, *J* = 10.8 Hz, 7.1 Hz, 1 H), 4.17 (dq, *J* = 10.8 Hz, 7.1 Hz, 1 H), 7.10–7.32 (m, 3 H), 7.60 (dd, *J* = 7.9 Hz, 1.1 Hz, 1 H).

^{13}C NMR (63 MHz, $CDCl_3$): d = 14.5, 30.3, 31.5, 44.3, 59.4, 98.9, 127.3, 128.4, 128.5, 132.5, 133.7, 138.7, 160.0, 169.3.

Tandem One-Pot Synthesis of N-Fused Indoles 9; General Procedure

To a stirred suspension of commercial Zn dust (300 mg, 4.59 mmol) in THF (0.9 mL) was added MsOH (6.5 mol%), and the mixture was refluxed for 10 min. While maintaining reflux temperature, ω-chloroalkanenitrile **7** (2.29 mmol) was added in one portion. Ethyl α-bromo-α-(2-bromophenyl)acetate (960 mg, 2.98 mmol) was added over 1 h by using syringe pump. After 1.5 h reflux, the mixture was cooled to r.t. To the mixture were added $Pd(PPh_3)_4$ (198.8 mg, 0.17 mmol), *t*-BuOK (704 mg, 5.28 mmol) and anhyd DMF (9.0 mL). After 15 h at 120 °C, the mixture was cooled to r.t., quenched with sat. aq NH_4Cl, and the product was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (anhyd Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, *n*-hexane–EtOAc, 7:1 to 5:1) to afford **9** in 43–74% yields.[18]

Ethyl (2*S*)-2-(*tert*-Butyldimethylsiloxy)-2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indole-9-carboxylate (9e)

Prepared from (3*S*)-3-(*tert*-butyldimethylsiloxy)-4-chlorobutanenitrile (**7d**, 894 mg, 3.82 mmol), chromatography (*n*-hexane–EtOAc, 20:1 to 7:1) as a white solid; yield: 591 mg (43%); mp 104–106 °C.

^{1}H NMR (250 MHz, $CDCl_3$): d = 0.18 (s, 6 H), 0.95 (s, 9 H), 1.45 (t, *J* = 7.1 Hz, 3 H), 3.19 (dd, *J* = 17.8 Hz, 4.1 Hz, 1 H), 3.54 (dd, *J* = 17.8 Hz, 6.9 Hz, 1 H), 3.89 (dd, *J* = 10.7 Hz, 3.9 Hz, 1 H), 4.19 (dd, *J* = 10.7 Hz, 6.3 Hz, 1 H), 4.40 (q, *J* = 7.1 Hz, 2 H), 5.04–5.10 (m, 1 H), 7.18–7.27 (m, 3 H), 8.13–8.16 (m, 1 H).

^{13}C NMR (63 MHz, $CDCl_3$): d = –4.8, –4.7, 14.7, 18.1, 25.8, 37.1, 53.4, 59.4, 74.1, 100.1, 109.8, 121.5, 121.6, 121.8, 130.3, 132.9, 150.2, 165.5.

HRMS: *m/z* [M + H]$^+$ calcd for $C_{20}H_{30}NO_3Si$: 360.1995; found: 360.1997.

CuI-Catalyzed Cross-Coupling of the Blaise Reaction Intermediate; General Procedure

To a stirred suspension of commercial Zn dust (500 mg, 7.65 mmol) in THF (1.2 mL) was added MsOH (6.5 mol%), and the mixture was refluxed for 10 min. While maintaining reflux temperature, nitrile **1** (3.82 mmol) was added in one portion, and then ethyl bromoacetate (**2b**, 958 mg, 5.73 mmol) was added over 1 h by using syringe pump. After 1 h at reflux, the mixture was cooled to r.t. To the mixture was added CuI (218 mg, 1.15 mmol), 1,10-phenanthroline (418 mg, 2.29 mmol), *t*-BuOK (1.72 g, 15.29 mmol), 1,2-dibromobenzene (1.08 g, 4.59 mmol), and anhyd DMF (12.0 mL). After 24 h reaction at 120 °C, the mixture was cooled to r.t., quenched with sat. aq Na_2CO_3, and the product was extracted with EtOAc (3 × 100 mL). The combined organic layers were dried (anhyd Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, *n*-hexane–EtOAc, 7:1 to 5:1) to afford **4** in 8–76% yields.[18]

Ethyl 3-Phenyl-3-(phenylamino)prop-2-enoate (14)

[$C_{17}H_{17}NO_2$: 53256-22-7]

Prepared from benzonitrile (**1a**, 394 mg, 3.82 mmol) with bromobenzene (720 mg, 4.59 mmol), chromatography (*n*-hexane–EtOAc, 20:1) as a yellow solid; yield: 450 mg (44%); mp 66–67 °C.

^{1}H NMR (300 MHz, $CDCl_3$): d = 1.31 (t, *J* = 7.1 Hz, 3 H), 4.20 (q, *J* = 7.1 Hz, 2 H), 4.99 (s, 1 H), 6.66 (d, *J* = 7.8 Hz, 2 H), 6.89 (t, *J* = 7.3 Hz, 1 H), 7.02–7.10 (m, 2 H), 7.24–7.37 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): d = 14.6, 59.4, 91.3, 122.3, 123.1, 128.3, 128.5, 128.7, 129.5, 136.1, 140.5, 159.2, 170.2.

Acknowledgment

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