Tandem Transformations of Nitriles into N-Heterocyclic Compounds by Electrophilic Trapping of Blaise Reaction Intermediates

Ju Hyun Kim,[a] Yu Sung Chun,[a] Hyunik Shin,*[b] Sang-gi Lee*[a]

[a] Department of Chemistry and Nano Science (BK21), Ewha Womans University, 120-750 Seoul, Korea

[b] Chemical Development Division, LG Life Science, Ltd/R&D, Daejeon 350-380, Korea
Fax +82(2)32774505; E-mail: sanggi@ewha.ac.kr

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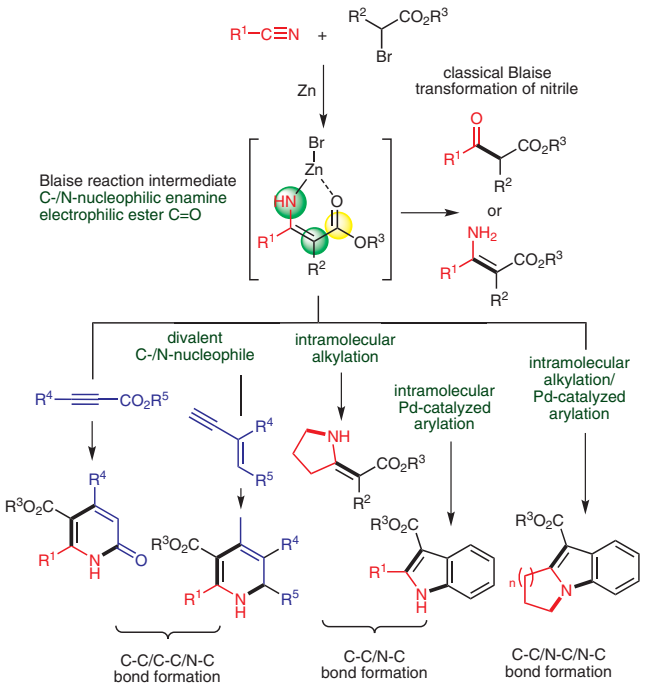
Abstract: Tandem transformations of nitriles into various N-heterocycles have been accomplished through the reaction of electrophiles with Blaise reaction intermediates formed in situ. The reaction of the Blaise reaction intermediates with propiolates gives 2-pyridones through consecutive C- and N-nucleophilic reactions. The tandem reactions of the Blaise reaction intermediate with 1,3-enynes proceed through C-nucleophilic addition followed by an electrocyclization–aromatization cascade to give pyridines. Exocyclic enamino esters can be prepared by transformations of ω-chloroalkyl nitriles through chemoselective intramolecular alkylation of the Blaise reaction intermediate. Palladium-catalyzed intramolecular arylations or copper-catalyzed intermolecular cross-coupling reactions of the Blaise reaction intermediate give a range of indole derivatives. Combinations of tandem alkylations and palladium-catalyzed couplings of the Blaise reaction intermediates of ω-chloroalkyl nitriles give N-fused indoles.

Key words: nitriles, tandem reactions, heterocycles, cyclizations, catalysis

The reaction of a Reformatsky reagent with a nitrile, known as the Blaise reaction,[1] proceeds via the zinc bromide complex of the β-enamino ester. Hydrolytic workup of this reaction intermediate under acidic or basic conditions provides the corresponding β-keto ester or β-enamino ester, respectively. These reactions are among the most classical and popular transformations of nitriles.[2] Recently, we envisioned that Blaise reaction intermediates could be considered as functionalized organozinc reagents and might serve as suitable platforms for tandem transformation of nitriles into various organic compounds. Despite the undeniable benefits of tandem reactions in minimizing the number of synthetic steps, reducing waste generation, and generating molecular complexity,[3] the development of new tandem methods for transforming nitriles via Blaise reaction intermediates remains a challenging problem.[4] The potential of the Blaise intermediate as a reagent for tandem bond-formation reactions has not previously been recognized, and before our study, no tandem transformations of nitriles by means of the Blaise reaction had been reported.

The Blaise reaction intermediate has unique features in that it combines an ambivalent C-/N-nucleophilic enamine moiety with an electrophilic ester group, permitting possible reactions with electrophiles, nucleophiles, or both. We have explored the intrinsic reactivity and C-/N-chemoselectivity of the Blaise reaction intermediate toward various electrophiles,[5] and have proved that the selectivity associated with the ambivalent C-/N-nucleophilic nature of the Blaise reaction intermediate can be utilized in tandem transformations of nitriles into various N-heterocyclic compounds (Scheme 1).[6] Electrophilic trappings of Blaise reaction intermediates with electrophiles possessing two electrophilic groups, such as propiolates or 1,3-enynes, provide a new tandem one-pot method for the synthesis of pyridones[6a] or pyridines,[6b] respectively. The chemoselective intramolecular alkylation,[6c] palladium-catalyzed arylation, and alkylation/palladium-catalyzed arylation of Blaise reaction intermediates have been investigated for the development of tandem transformations of nitriles into exocyclic enamine esters and indole derivatives.[6d] Here, we describe the scope and the limitations of these tandem transformations of nitriles into N-heterocyclic compounds through electrophilic trapping of Blaise reaction intermediates.



Scheme 1 Tandem Blaise transformations of nitriles into heterocyclic compounds

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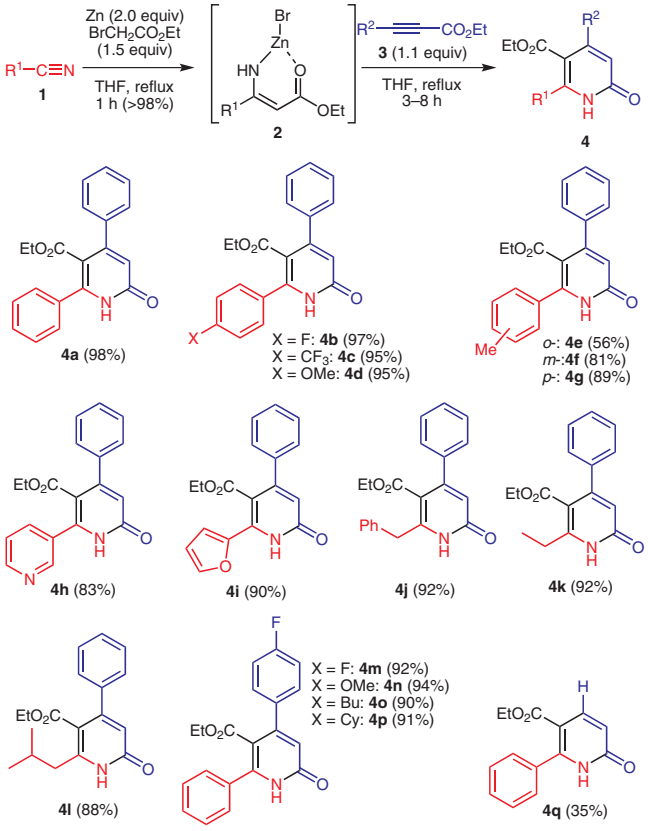
Tandem Transformation of Nitriles into 2-Pyridones

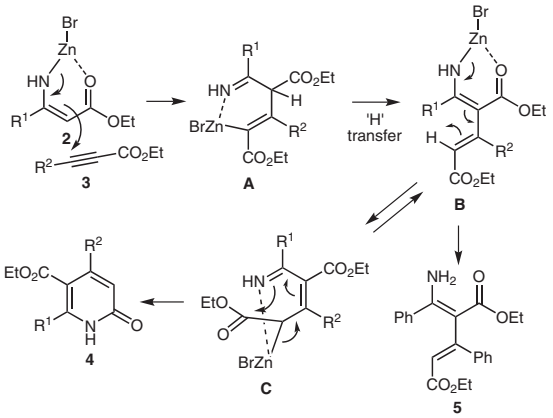
Pyridones are embedded as structural units in many natural products and biologically active compounds.[7] Although various effective methods have been developed for the synthesis of pyridone derivatives, most require multiple steps.[8] We have devised a tandem one-pot synthesis of 2-pyridone derivatives from nitriles by electrophilic trapping of Blaise reaction intermediates with propiolates as terminal electrophiles (Scheme 2).[6a] A wide range of aromatic, heteroaromatic, and aliphatic nitriles can be transformed efficiently into the corresponding 4-phenyl-2-pyridones in good-to-excellent yields (≤98%) through the tandem reaction of Blaise reaction intermediates with ethyl phenylpropiolates.



Scheme 2 Tandem transformations of nitriles into 2-pyridones

In general, the electronic properties of the nitriles did not affect their reactivity. However, sterically demanding 2-methylbenzonitrile showed a diminished reactivity, resulting in a relatively lower yield of 2-pyridone **4e** (56%). The reaction efficiency was not markedly affected by the structure of the propiolate, so that the aryl and alkyl propiolates reacted with the Blaise reaction intermediate to afford the corresponding 2-pyridones in high yields. However, under the same reaction condition, the reaction of ethyl propiolate (R^2 = H) gave a low yield (18%) of 2-pyridone **4q**, although this rose to 35% when 2.2 equivalents of propiolate were allowed to react for 24 hours. A significant amount of the β-enamino ester Blaise adduct was recovered, reflecting the ease of proton transfer from the acidic acetylenic proton to the Blaise reaction intermediate.

The formation of a 2-pyridone ring clearly demonstrated the ambivalent nucleophilic nature of the Blaise reaction intermediate **2**, as both the α-carbon and the β-nitrogen atoms can act as nucleophiles. As shown in Scheme 3, the Michael addition of the Blaise reaction intermediate to the propiolate gives the vinyl zinc bromide **A**, which isomerizes to the α-vinylated zinc bromide complex **B**, through intermolecular and/or intramolecular proton transfer of the acidic α-proton. Rearrangement of **B** to the C(sp^3)–ZnBr complex **C**, followed by intramolecular cyclization, leads to the 2-pyridone structure. Careful monitoring and quenching of the reaction in the early stage permitted the isolation of appreciable amounts of the α-vinylated β-enamino ester **5**, which supports our proposed reaction mechanism. Although, it is not possible to introduce a substituent on C3, which is a limitation of this tandem transformation, the technique still provides a rapid build-up of a wide range of pyridine derivatives that are inaccessible by other methods.

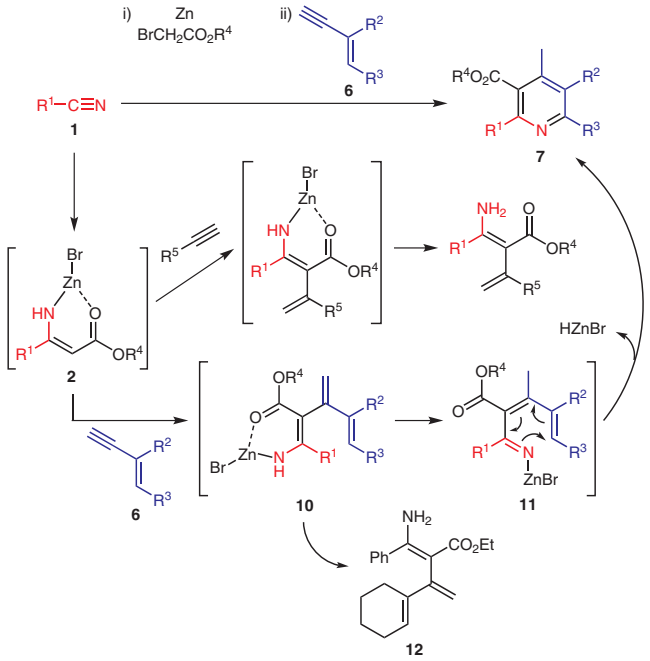


Scheme 3 Proposed reaction pathway for tandem synthesis of 2-pyridones

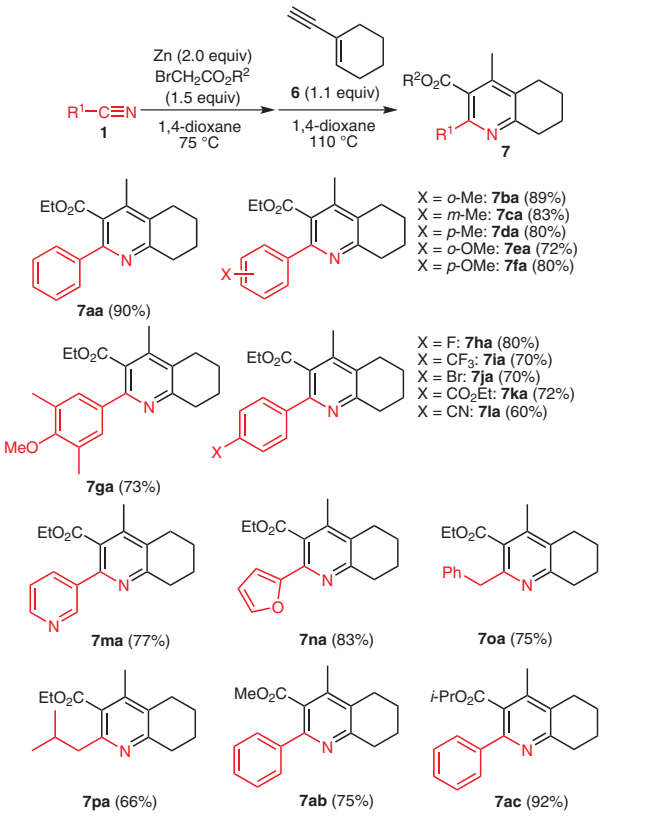
Tandem Transformation of Nitriles into Pyridines

The pyridine moiety is also an important component of various natural products, pharmaceuticals, and functional materials.[9] Consequently, the development of a new synthetic method for the construction of pyridines is always important. We have recently developed a method for the tandem transformation of nitriles into pyridines **7** through the tandem reaction of the Blaise reaction intermediate **2** with 1,3-enynes **6**.[6b] This transformation is based on the propensity of the Blaise reaction intermediate **2** to play the dual role of a carbon nucleophile and a Lewis acid in reacting with nonactivated terminal alkynes for regio- and chemoselective α-vinylation.[5c] We reasoned that if identical tandem reactions were conducted with a 1,3-enyne **6**, the resulting α-dienylated β-enaminozincate **10** might be capable of undergoing isomerization to form the N-zinc-

ated 1-azatriene **11**, which could facilitate a 6π-electrocyclization and/or cycloaddition to produce pyridines **7** after elimination of zinc hydrogen bromide (HZnBr) (Scheme 4).[10]



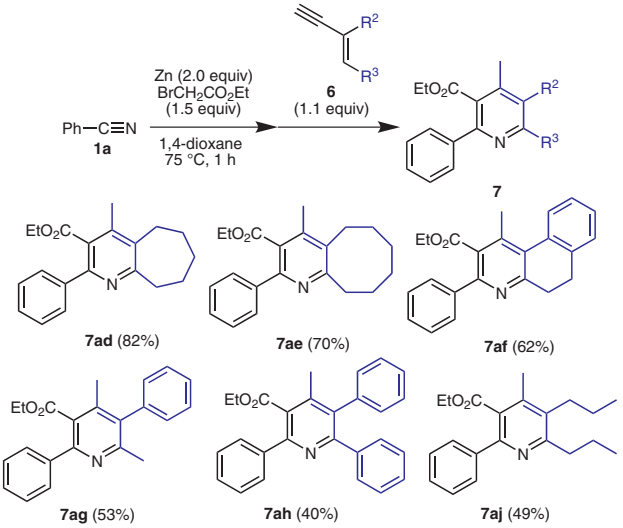
Scheme 4 Proposed reaction pathway for tandem transformation of nitriles to pyridines



Scheme 5 Tandem transformations of various nitriles to tetrahydroquinolines

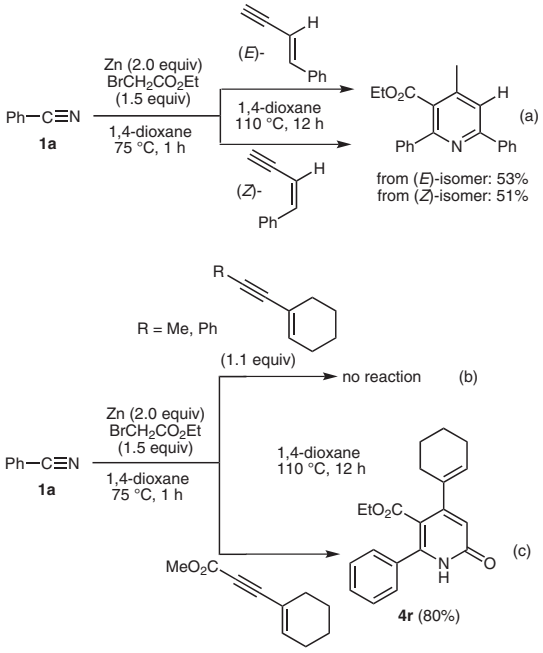
To test our hypothesis, we commenced our investigation with the Blaise reaction intermediate **2a**, formed from the reaction of benzonitrile (**1a**) with a Reformatsky reagent generated in situ from ethyl bromoacetate (1.5 equivalents) and zinc (2.0 equivalents) in tetrahydrofuran; over 96% of **1a** was converted into **2a**. The tandem reaction of **2a** with commercially available 1-ethynylcyclohexene (**6a**; 1.1 equivalents) was carried out in refluxing tetrahydrofuran for two hours to afford the tetrahydroquinoline **7aa** in 70% yield, along with the α-dienylated β-enamino ester **12** (13%). This result clearly showed that the zincated aminotriene **10** was formed as an intermediate. When the tandem reaction was carried out in 1,4-dioxane at 110 °C, the yield of **7aa** was increased to 90%. Under standard conditions, various aromatic nitriles with electron-donating or -withdrawing groups such as methyl, methoxy, halides, and ester groups were readily converted into the corresponding tetrahydroquinolines **7aa–la** in good-to-excellent yields (Scheme 5). Heteroaromatic and aliphatic nitriles were also readily converted into the corresponding tetrahydroquinoline derivatives **7ma–pa** in high yields (66–83%). The use of Reformatsky reagents with different R^2 groups did not diminish the yield, thus allowing the preparation of the 3-methyl ester **7ab** (75%) and the 3-isopropyl ester **7ac** (92%) in high yields.

This tandem transformation protocol could also be successfully applied to different types of cyclic 1,3-enynes to afford the corresponding carbacycle-fused pyridines in good yields. Acyclic 1,3-enynes with two phenyl, phenyl and methyl, phenyl and hydrogen, or two propyl substituents reacted smoothly with the Blaise reaction intermediate **2a** to give the corresponding polysubstituted pyridines. However, their yields were lower than those obtained from cyclic 1,3-enynes, which was attributed to the entropic effects (Scheme 6).



Scheme 6 Tandem transformations of benzonitrile to pyridines by using various 1,3-enynes as terminal electrophiles

Significantly, the stereochemistry of the enyne did not affect the reactivity of the reactions. Thus, tandem reactions with the enynes (*E*)-**6i** and (*Z*)-**6i** afforded the same pyridine **7ai** with almost the same yield (Scheme 7a). However, the 1,3-enynes with internal alkynes such as 1-prop-1-ynylcyclohexene and (cyclohex-1-enylethynyl)benzene were not suitable substrates for this tandem reaction (Scheme 7b). Furthermore, the tandem reaction with cyclohex-1-enyl propiolate gave the cyclohexenyl-substituted pyridine **4r** in 80% yield (Scheme 7c).

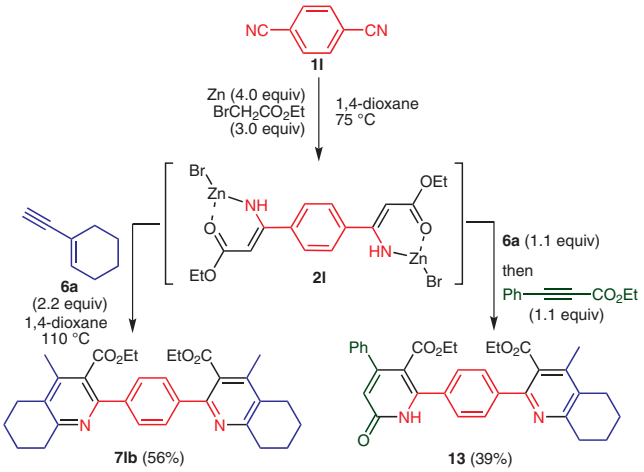


Scheme 7 (a) Pyridines from (*E*)- and (*Z*)-3-enynes; (b) and (c) limitations on tandem transformations of benzonitrile to pyridines

Finally, extension to divergent tandem reactions allowed the construction of a molecule containing both a pyridine and a pyridone ring. Both nitrile groups of terephthalonitrile can react with an excess of a Reformatsky reagent to generate the bisenaminozincate intermediate **2l**, which can subsequently react with 2.1 equivalents of **6a** to form the two pyridine rings in the bipyridyl compound **7lb** in 56% yield (Scheme 8). The chemoselectivity of the Blaise reaction intermediate **2a** towards activated alkynes and 1,3-enynes permitted divergent tandem one-pot constructions of two different heterocyclic rings, a pyridine ring and a pyridine ring, in one molecule. Thus, the bisenaminozincate **2l** reacted sequentially with the 1,3-enyne **6a** and phenylpropiolate to afford **13** in 39% yield along with bispyridine **7lb** in 15% yield (Scheme 8).

Tandem Transformation of Nitriles into Exocyclic Enamino Esters

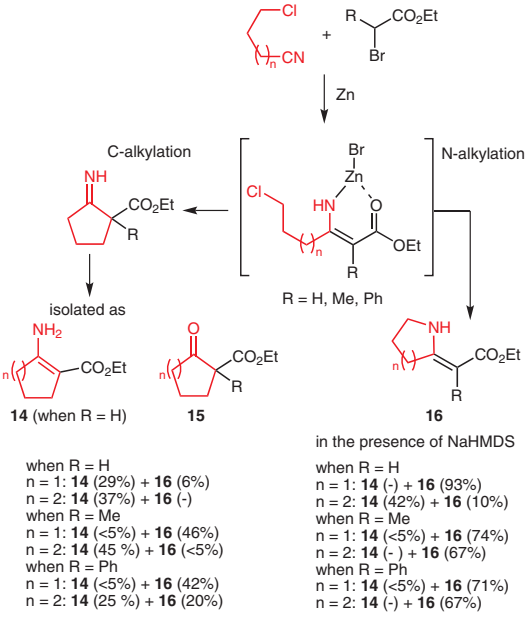
Exocyclic enamine esters are highly versatile intermediates for the synthesis of the N-heterocyclic fragments that are embedded in many useful pharmaceuticals and natural



Scheme 8 Double tandem transformation of a bisnitrile for a one-pot construction of a biheterocyclic compound

products.[11] Synthetic approaches to exocyclic enamine esters rely mainly on the use of existing N-heterocycles.[12] In contrast, construction of the N-heterocyclic moiety though intramolecular ring-closure reactions has been rarely reported, and most of them require multistep syntheses of the cyclization precursors.[13] To provide a more-general synthetic route towards exocyclic enamine esters from readily available compounds, we investigated the tandem transformation of ω-chloroalkyl nitriles into exocyclic enamine esters through chemoselective intramolecular N-alkylation of the various Blaise reaction intermediates (Scheme 9).[6c]

The reactivity and N/C selectivity of the Blaise reaction intermediate were insufficient to provide an entry to exocyclic enamine esters. The N/C cyclization selectivity is determined mainly by the substituent at the C-2 position.



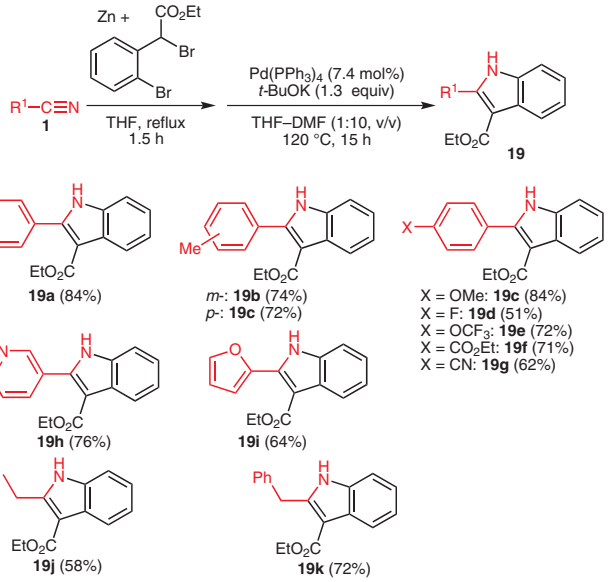
Scheme 9 The tandem transformations of ω-chloroalkyl nitriles into exocyclic compounds

Thus, Blaise reaction intermediates with no α-substituent (R^2 = H) cyclized C-selectively, whereas N-cyclization was dominant with the Blaise reaction intermediate having α-substituents ($R^2 \neq$ H). The low reactivity and poor N/C selectivity could be overcome by addition of sodium hexamethyldisilazide, which significantly enhanced the N-nucleophilicity and permitted the tandem synthesis of the exocyclic enamine esters from nitriles. In terms of the yield and the control of N/C selectivity, this modification is sufficient to permit the use of the current protocol as a general method for the construction of N-heterocyclic exocyclic enamino esters.

Tandem Transformation of Nitriles into Indoles and N-Fused Indoles

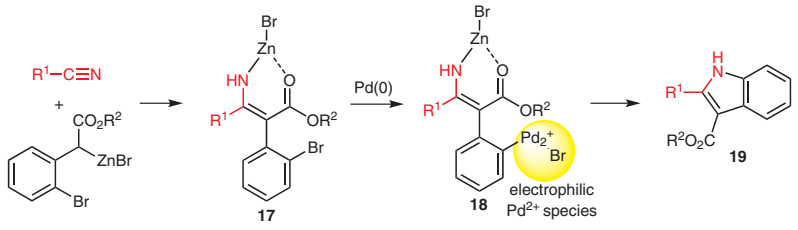
Many elegant approaches have been developed for preparing the indole ring moiety.[14] However, because most of these approaches start from anilines, arylhydrazines, or amine derivatives, the development of new methods for the synthesis of indoles from simple and readily available non-amino compounds is of great interest. In this context, we envisioned a novel tandem transformation of nitriles into indoles through palladium-catalyzed N-arylative coupling reaction of the Blaise reaction intermediate. We hypothesized that a Blaise reaction intermediate possessing an *o*-bromophenyl group at the α-carbon should undergo oxidative addition of palladium(0) to generate electrophilic an palladium(2+) species that might be trapped by the nucleophilic β-nitrogen atom to form an indole ring (Scheme 10).[6d]

On the basis of an analogy with the recently disclosed palladium-catalyzed cross couplings of Reformatsky reagents with aryl halides under base-free conditions,[15] we initially hypothesized that the nucleophilic nature of the intermediate would induce palladium-catalyzed intramolecular N-arylation in the absence of a base. However, the tandem reactions did not proceed at all in refluxing tetrahydrofuran in the presence of bis(dibenzylideneacetone)palladium/dicyclohexyl(2′,6′-dimethoxybiphenyl-2-yl)phosphine (Sphos) or tetrakis(triphenylphosphine)palladium as the catalyst. These results suggested that the nucleophilicity of the Blaise reaction intermediate might not be sufficient for the intramolecular transmetalation of the electrophilic palladium(II) species formed by oxidative addition of the *o*-bromide with palladium(0). After extensive screening of the reaction conditions, such as the type of solvent, the reaction temperature, the ligand, and the base, we found that the N-arylative trapping of the Blaise reaction intermediate **17a** (R^1 = Ph) did occur in the presence of tetrakis(triphenylphosphine)palladium (7.4 mol%) and potassium *tert*-butoxide (1.3 equiv) in 1:10 v/v tetrahydrofuran/*N*,*N*-dimethylformamide to give the corresponding indole **19a** in 84% yield (Scheme 11). Under the optimized conditions, various aromatic nitriles with electron-donating and electron-withdrawing substituents, as well as heteroaromatic nitriles and aliphatic nitriles, could be converted into the corresponding indoles **19a–k** in a one-pot manner. Although 4-fluorobenzonitrile and propionitrile were converted into the corresponding indoles **19d** and **19j** in slightly diminished yields, the electronic nature of the substituents on the aromatic nitriles did not significantly affect the reactivity. One nitrile group of terephthalonitrile could be transformed into an indole ring to afford **19g** in 62% yield.

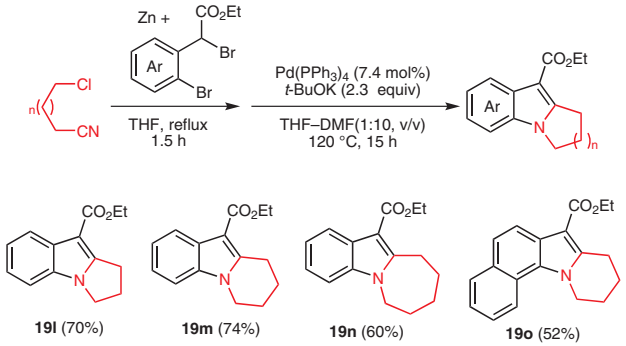


Scheme 11 Tandem transformation of nitriles into indoles

Fortunately, these reaction conditions are also useful for the tandem transformation of ω-chloroalkyl nitriles into N-fused indoles through chemoselective intramolecular N-alkylation/palladium-catalyzed N-arylation of the Blaise reaction intermediate. Trapping experiments at lower reaction temperatures suggested that the N-alkylation reaction precedes N-arylation (Scheme 12).

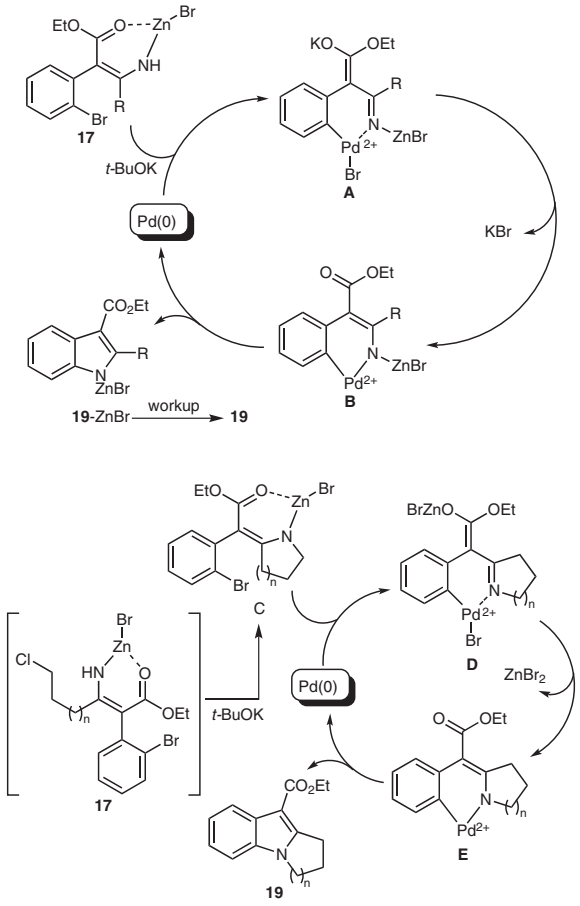


Scheme 10 Strategy for tandem transformation of nitriles into indoles through palladium-catalyzed N-arylative trapping

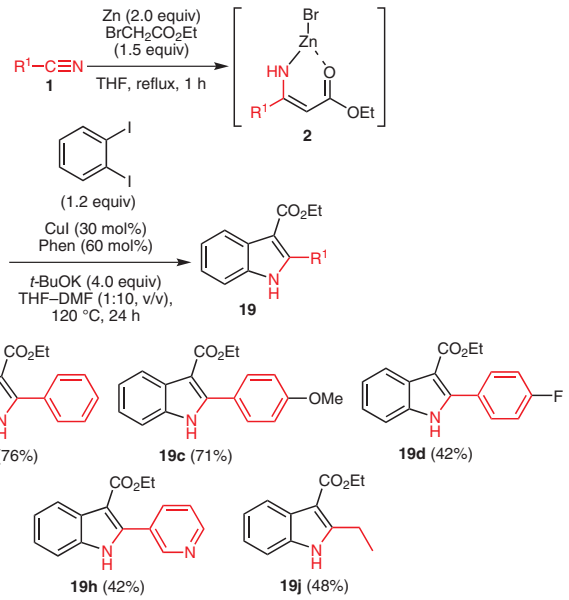


Scheme 12 Tandem transformation of ω-chloroalkyl nitriles into N-fused indoles

The possible reaction pathways for the formation of indoles and N-fused indoles are shown in Scheme 13. Deprotonation of the acidic N–H group and oxidative addition to palladium(0) gives the palladium(II) bromide complex **A**. Intramolecular transmetalation, followed by reductive elimination of the resulting palladium(II) complex **B**, regenerates palladium(0) for a subsequent catalytic cycle and forms the zinc bromide complex of indole **19**, which is subsequently converted into indole **19** after workup (Scheme 13). For the formation of N-fused indoles, the intramolecular N-alkylation of the Blaise reaction intermediate **17** proceeds in the presence of base to form **C**, which has sufficient nucleophilicity to permit intramolecular transmetalation of **D** to form **E**. Reductive elimination then gives the N-fused indole **19**.



Scheme 13 Tandem transformations of ω-chloroalkyl nitriles onto N-fused indoles

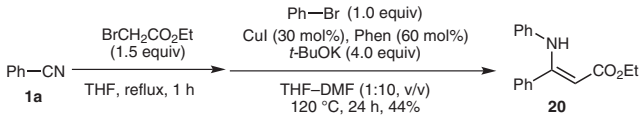


Scheme 14 Copper-catalyzed intermolecular arylative trapping of the Blaise reaction intermediate

Finally, we envisioned that the C-/N-ambivalent nucleophilic nature of the Blaise reaction intermediate might be utilized in the design of 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 intermediates with 1,2-dibromobenzene. However, in contrast to intramolecular N-arylation, palladium catalysts, such as tetrakis(triphenylphosphine)palladium or complexes of bis(dibenzylideneacetone)palladium with dicyclohexyl(2′,4′,6′-triisopropylbiphenyl-2-yl)phosphine (XPhos) or 1,1′-binaphthalene-2,2′-diylbis(diphenylphosphine) (BINAP), were ineffective for the tandem indolization reaction. However, copper(I) iodide did catalyze the tandem intermolecular C–C/C–N coupling reaction of the Blaise reaction intermediate with 1,2-dibromobenzene. After screening of a number of conditions, we carried out the tandem reaction out by using copper(I) iodide (20 mol%), phenanthroline (Phen; 40 mol%) as a ligand, and potassium *tert*-butoxide as the base in 1:10 v/v *N*,*N*-dimethylformamide–tetrahydrofuran at 120 °C for 24 hours to afford the indole **19a** in 54% yield.[16] The yield increased to 65% when the catalyst loading was increased to 30 mol% of copper(I) iodide and 60 mol% of Phen. When the same reaction was carried out with 1,2-iodobenzene, the yield of indole **19a** was further increased to 76%. Although the yields were slightly lower than those obtained from the palladium-catalyzed intermolecular arylative trapping reactions shown in Scheme 11, a wide diversity of indoles could be synthesized in moderate-to-good yields by the copper(I) iodide catalyzed intermolecular C–C/N–C coupling reactions of 1,2-di-

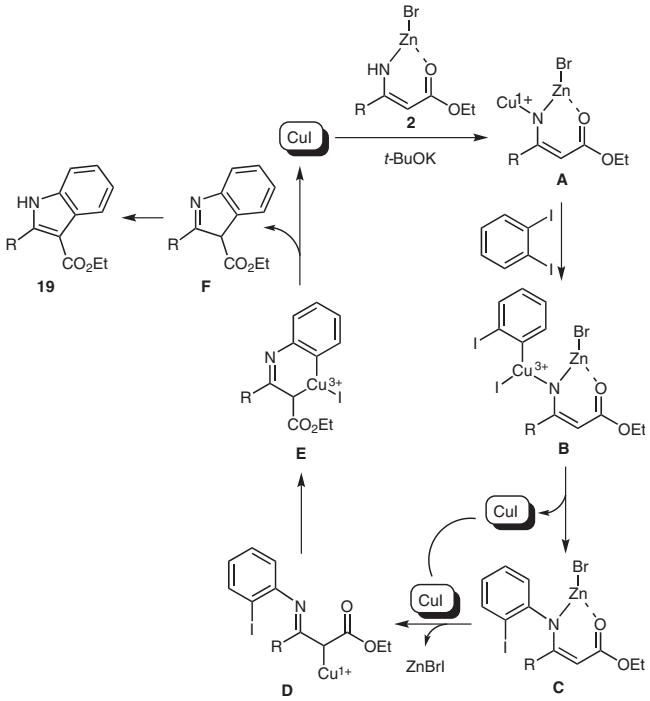
iodobenzene with the Blaise reaction intermediates (Scheme 14).

To determine the timing of the N-arylation and C-arylation reactions, we examined the the copper(I) iodide catalyzed intermolecular arylation of the Blaise reaction intermediate with bromobenzene. The N-arylated product **20** was formed exclusively in 44% yield (Scheme 15), clearly showing that the copper(I) iodide catalyzed N-arylation reaction precedes C-arylation.



Scheme 15 Chemoselective intermolecular copper-catalyzed N-arylation of Blaise reaction intermediates

Our proposed copper(I)/copper(III)-type mechanism for the copper(I) iodide catalyzed intermolecular coupling reaction of a Blaise reaction intermediate with 1,2-diiodobenzene is shown in Scheme 16.[17] The Blaise reaction intermediate reacts with copper(I) in the presence of a base to form the nitrogen-coordinated copper(I) complex **A**, which subsequently reacts with 1,2-diiodobenzene to form the copper(III)-complex **B**. Reductive elimination of copper(I) then gives the N-arylated intermediate **C**, which reacts with copper(I) at the α-carbon to form **D**. Intramolecular formation of the copper(III)-complex **E** and reductive elimination followed by isomerization of the resulting imine **F** gives the indole **19**. The regenerated copper(I) can then participate in subsequent catalytic cycles.



Scheme 16 Proposed reaction pathway for copper-catalyzed intermolecular arylative trapping of the Blaise reaction intermediate

In summary, we have developed a series of novel methods for tandem transformation of nitriles into various N-heterocycles. Electrophilic trapping of the Blaise reaction intermediate with various electrophiles through alkylation, addition, and cross-coupling reactions provides a useful tandem synthetic route to derivatives of pyrid-2-ones, pyridines, enamine esters, and indoles from the appropriate nitriles. Moreover, we have delineated the reactivity of Blaise reaction intermediates and their N/C selectivity profiles, and we have modified these to a useful extent through the inclusion of additives. These results provide a platform for future studies on applications of Blaise reaction intermediates as functionalized organozinc nucleophiles for metal-catalyzed bond-forming reactions. Further studies on the tandem transformation of nitriles with Blaise reaction intermediates are underway in our laboratory.

All reactions and manipulations were performed in an argon atmosphere using standard Schlenk techniques. Flasks were flame-dried under a stream of argon. All solvents were distilled before use and transferred by oven-dried syringes. All purchased reagents were used as received without further purification. NMR spectra were recorded at 300 MHz (^{1}H) and 75.5 MHz (^{13}C) on a Bruker Avance III 3000 spectrometer or at 250 MHz (^{1}H) and 62.9 MHz (^{13}C) on a Bruker 9503 DPX spectrometer. The chemical shifts are reported relative to TMS as an internal reference for ^{1}H NMR and to the residual solvent signal ($CDCl_3$; δ = 77.16 ppm) for ^{13}C NMR. HRMS spectra were recorded on a Micromass QTOF2-MS instrument.

Ethyl 6-Oxo-2,4-diphenyl-1,6-dihydropyridine-3-carboxylate (4a): Typical Procedure for Tandem Transformation of Nitriles into 2-Pyridones

$MeSO_3H$ (3.7 mg) in anhyd THF (4.0 mL) was added to a stirred suspension of commercial Zn dust (10 μm, 1.0 g, 15.3 mmol). The mixture was refluxed for 10 min before PhCN (0.8 mL, 7.6 mmol) was added. $BrCH_2CO_2Et$ (1.26 mL, 11.4 mmol) was then added over 1 h from a syringe pump to the refluxing mixture, and the mixture was refluxed for a further 1 h. PhC≡CCO_2Et (1.4 mL, 8.4 mmol) was added and the stirred mixture was refluxed for 3 h. The reaction was quenched with sat. aq NH_4Cl at r.t. and the mixture was extracted with EtOAc (3 × 30 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a residue that was purified by chromatography (silica gel) to give a yellow solid; yield: 2.65 g (98%); mp 208–210 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.75 (t, *J* = 7.1 Hz, 3 H), 3.80 (q, *J* = 7.2 Hz, 2 H), 6.45 (s, 1 H), 7.26–7.41(m, 5 H), 7.45–7.52 (m, 5 H), 12.21(br s, 1 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.2, 61.2, 114.3, 118.5, 127.2, 128.2, 128.4, 128.7, 128.8, 130.3, 132.9, 138.1, 147.2, 154.0, 163.7, 166.7.

Ethyl 4-Methyl-2-phenyl-5,6,7,8-tetrahydroquinoline-3-carboxylate (7aa): Typical Procedure for Tandem Transformation of Nitriles into Pyridines

A 1 M soln of $MeSO_3H$ in 1,4-dioxane (0.3 mL, 0.3 mmol) was added to a stirred suspension of commercial Zn dust (392 mg, 6.0 mmol) in 1,4-dioxane (1.2 mL) at a bath temperature of 75 °C. After 10 min, PhCN (306 μL, 3.0 mmol) was added followed, at the same temperature, by $BrCH_2CO_2Et$ (0.5 mL, 4.5 mmol), added over 1 h by using a syringe pump. The mixture was stirred for a further 1 h before 1-ethynylcyclohexene (388 μL, 3.3 mmol) and 1,4-dioxane (2.0 mL) were added and the bath temperature was raised to 110 °C. After 3 h, the mixture was cooled to r.t. and the reaction was quenched with sat. aq NH_4Cl. The mixture was neutralized with sat. aq Na_2CO_3 and extracted with EtOAc (3 × 40 mL). The combined

organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a residue that was purified by chromatography [silica gel, hexane–EtOAc (4:1)] to give a pale-yellow solid: yield: 796 mg (2.69 mmol, 90%); mp 104–106 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.98 (t, *J* = 7.2 Hz, 3 H), 1.87–1.89 (m, 4 H), 2.26 (s, 3 H), 2.70 (br s, 2 H), 2.99 (br s, 2 H), 4.09 (q, *J* = 7.2 Hz, 2 H), 7.32–7.42 (m, 3 H), 7.53–7.56 (m, 2 H).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.6, 15.8, 22.6, 22.8, 26.1, 33.4, 61.3, 127.3, 128.17, 128.23, 129.6, 140.5, 143.5, 153.2, 157.5, 169.4.

HRMS (EI): *m/z* $[M]^+$ calcd for $C_{19}H_{21}NO_2$: 295.1572; found: 295.1571.

Ethyl Pyrrolidin-2-ylideneacetate (16, R = H; n = 1): Typical Procedure for Tandem Transformation of ω-Chloroalkyl Nitriles into Exocyclic Enamine Esters

$MeSO_3H$ (6.5 mol%) was added to a suspension of Zn dust (500 mg, 7.65 mmol) in THF (1.5 mL) and the mixture was refluxed for 10 min. To the refluxing mixture was added $Cl(CH_2)_4CN$ (3.82 mmol), followed by $BrCH_2CO_2Et$ (4.97 mmol) added over 1 h from a syringe pump. The reaction was continued until all the Blaise reaction intermediate had disappeared (GC). The mixture was then cooled to 0 °C and a 1.0 M soln of NaHDMS in THF (13.37 mL, 13.37 mmol) was added. The mixture was then stirred for 5 h at r.t. before the reaction was quenched with sat. aq NH_4Cl and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by column chromatography [silica gel, hexane–EtOAc (7:1)] to give a white solid; yield: 552 mg (93%); mp 60–61 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.24 (t, *J* = 7.1 Hz, 3 H), 1.97 (tt, *J* = 7.3, 7.3 Hz, 2 H), 2.58 (t, *J* = 7.7 Hz, 2 H), 3.52 (t, *J* = 6.9 Hz, 2 H), 4.12 (q, *J* = 7.1 Hz, 2 H), 4.52 (s, 1 H), 7.93 (br s, 1 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 14.4, 21.7, 31.9, 46.7, 58.0, 76.2, 166.1, 170.3.

Ethyl 2-Phenyl-1*H*-indole-3-carboxylate (19a): Typical Procedure for Tandem Transformation of Nitriles into Indoles through Palladium-Catalyzed Intramolecular N-Arylation of the Blaise Reaction Intermediate

$MeSO_3H$ (6.5 mol%) was added to a suspension of commercial Zn dust (300 mg, 4.59 mmol) in THF (0.85 mL), and the mixture was refluxed for 10 min before PhCN (0.32 mL, 2.29 mmol) was added. 2-$BrC_6H_4CH(Br)CO_2Et$ (960 mg, 2.98 mmol) was then added over 1 h from a syringe pump and the mixture was refluxed for 1.5 h. The mixture was then cooled to r.t. before $Pd(PPh_3)_4$ (198.8 mg, 0.17 mmol), *t*-BuOK (352.0 mg, 2.98 mmol), and anhyd DMF (9.0 mL) were added. The mixture was kept for 15 h at 120 °C then cooled to r.t. The reaction was quenched with sat. aq NH_4Cl and the product was extracted with EtOAc (3 × 20 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue that was purified by column chromatography (silica gel) to give a pale yellow solid; yield: 510 mg (84%); mp 150–152 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.33 (t, *J* = 7.1 Hz, 3 H), 4.27 (q, *J* = 7.1 Hz, 2 H), 7.27–7.39 (m, 6 H), 7.59–7.63 (m, 2 H), 8.26–8.29 (m, 1 H), 9.13 (br s, 1 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 14.3, 59.8, 104.3, 111.4, 122.0, 123.1, 127.6, 128.0, 129.1, 129.6, 132.0, 135.4, 144.9, 165.8.

HRMS: *m/z* $[M + H]^+$ calcd for $C_{17}H_{16}NO_2$: 266.1181; found: 266.1178.

N-Fused Indoles 19l–o; General Procedure

$MeSO_3H$ (6.5 mol%) was added to a suspension of commercial Zn dust (300 mg, 4.59 mmol) in THF (0.9 mL) and the mixture was refluxed for 10 min. ω-Chloroalkane nitrile **7** (2.29 mmol) was then added to the refluxing mixture followed by 2-$BrC_6H_4CH(Br)CO_2Et$ (960 mg, 2.98 mmol) added over 1 h from a syringe pump. The mixture was refluxed for 1.5 h then cooled to r.t. $Pd(PPh_3)_4$ (198.8 mg, 0.17 mmol), *t*-BuOK (704 mg, 5.28 mmol), and anhyd DMF (9.0 mL) were added and the mixture was kept for 15 h at 120 °C. The mixture was then cooled to r.t. and the reaction was quenched with sat. aq NH_4Cl. The mixture was extracted with EtOAc (3 × 20 mL) and the combined organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was purified by chromatography [silica gel, hexane–EtOAc (7:1 to 5:1)] to give the N-fused indole; yield: 52–74%.

Ethyl 2-Phenyl-1*H*-indole-3-carboxylate (19a): Typical Procedure for Tandem Transformation of Nitriles into Indoles by Copper Iodide Catalyzed Intermolecular Cross-Coupling of the Blaise Reaction Intermediate

$MeSO_3H$ (6.5 mol%) was added to a suspension of commercial Zn dust (500 mg, 7.65 mmol) in THF (1.2 mL) and the mixture was refluxed for 10 min. PhCN (394 mg, 3.82 mmol) was added to the refluxing mixture, followed by $BrCH_2CO_2Et$ (958 mg, 5.73 mmol) added over 1 h by using a syringe pump. After refluxing for 1 h, the mixture was cooled to r.t. and 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) were added. The mixture was kept for 24 h at 120 °C then cooled to r.t. The reaction was quenched with sat. aq Na_2CO_3 and the product was extracted with EtOAc (3 ×100 mL). The combined organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a residue that was purified by chromatography (silica gel) to give a pale yellow solid; yield: 771mg (76%); mp 150–152 °C.

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