Base-promoted synthesis of isoquinolines through a tandem reaction of 2-methyl-arylaldehydes and nitriles

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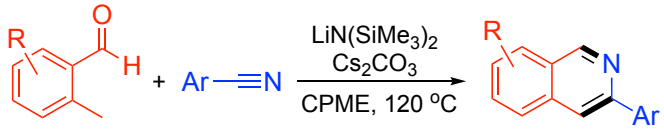
Supporting Information Placeholder



■ **C-C and C-N bond formation** ■ **transition metal-free**
■ **operationally simple** ■ **tandem reaction**

ABSTRACT: A convenient method to prepare 3-aryl isoquinolines *via* a base-promoted tandem reaction is presented. Simply combining commercially available 2-methyl-arylaldehydes, benzonitriles, $NaN(SiMe_3)_2$, and Cs_2CO_3 enabled the synthesis of a variety of isoquinolines (23 examples, up to 90% yield). Among the syntheses of isoquinolines, the transition metal-free method described here is straightforward, practical, and operationally simple.

INTRODUCTION

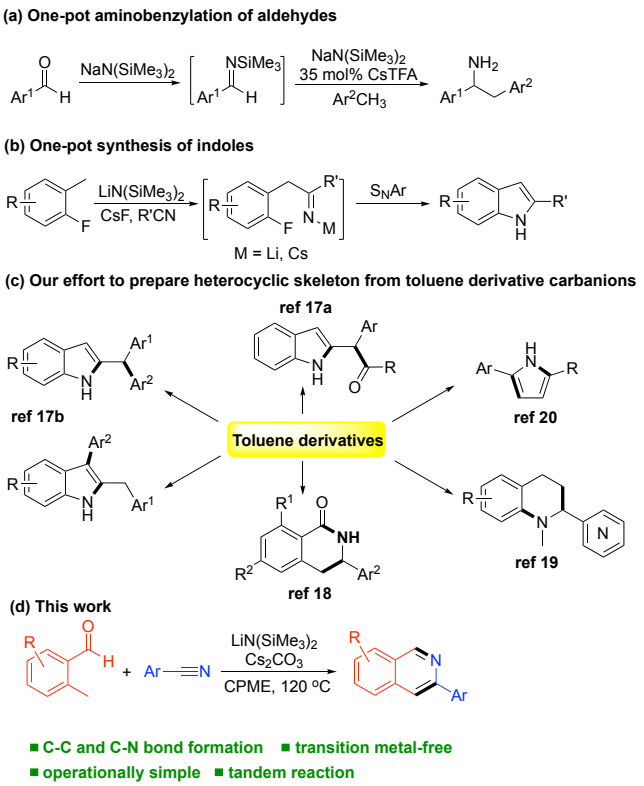
Isoquinolines are an important class of heterocycles found in numerous natural products[1] and bioactive molecules with antitumor,[2] anti-inflammatory,[3] antimalarial,[4] and cardiovascular[5] properties. They are also valuable building blocks in advanced functional materials[6] and used in enantioenriched ligands for asymmetric catalysis.[7] Consequently, numerous synthetic strategies have been devoted to the synthesis of these privileged heterocycles. Arguably, the most popular route for the synthesis of isoquinolines is the annulation of 2-alkynylbenzyl azides with transition metal catalysts, including Pd, Ag, Au, Co, Cu, Ni, etc.[8] Recent years have also witnessed several transition metal-catalyzed annulation reactions of 2-alkylnyl aromatic imines[9] and oximes[10] as viable alternatives. Other methods such as C–H functionalization,[11] dehydrogenation of *N*-heterocycles,[10a] and tandem processes[12] have also been reported. Despite great advances made in this area, challenging issues associated with catalyst toxicity,[2] the requirement of complex functionalized substrates,[13] and poor chemoselectivities plague some methods.[14] The development of more efficient approaches for the synthesis of isoquinolines, especially starting from readily available substrates, remains desirable.

Our team has a long-standing interest in the functionalization of benzylic carbanions toward the preparation of valuable heterocyclic compounds. This line of research employs cation-π interactions to aid in the deprotonation of the weakly acidic toluene derivatives ($pK_a = 43$ in DMSO). For the reversible deprotonation of toluene derivatives, we employ silyl amide bases, $MN(SiMe_3)_2$, in the presence of Cs^+ salts. We hypothesize that under the reaction conditions, $CsN(SiMe_3)_2$ or related heterobimetallic bases form that are active in these processes. Some recent examples of our approach include the one-pot aminobenzylation of aldehydes with toluene derivatives (Scheme 1a)[15] and a convergent synthesis of indoles from benzonitriles and fluorotoluenes (Scheme 1b).[16] We also introduced a series of

tandem processes for the synthesis of more functionalized indoles,[17] 3,4-dihydroisoquinolones,[18] 2-azaaryl tetrahydroquinolines,[19] and 2,5-disubstituted pyrroles[20] involving the functionalization of benzylic or propargylic C–H bonds under basic conditions (Scheme 1c). Other impressive examples on functionalization of toluene derivatives were developed by Kobayashi and co-workers, who introduced an asymmetric addition of toluene-derived benzyl groups to imines.[21] The groups of Guan[22] and Gandhi[23] have also introduced methods for the functionalization of toluenes. Wang and Ma outlined the synthesis of isoquinolone derivatives from 2-methylaryl aldehydes and benzonitriles.[24]

Based on these studies, we were interested in developing an approach to 3-arylisoquinolines. Herein we report the efficient synthesis of 3-arylisoquinolines *via* tandem reaction of 2-methyl-arylaldehydes and nitriles (Scheme 1d). Compared to the existing routes, this protocol is simple, environmentally friendly, and atom economical. During the final stages of this work, a closely related study was published by the Wang group in this journal.[25]

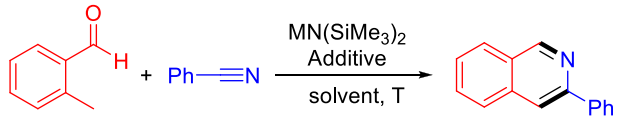
Scheme 1. Our Previous Work.



RESULTS AND DISCUSSION

As a starting point, we employed 2-methylbenzaldehyde **1a** and benzonitrile **2a** in CPME (cyclopentyl methyl ether) at 100 °C. Based on our past studies, we employed $MN(SiMe_3)_2$ (M = Li, Na, K) with 1.0 equiv of CsF as additive. $LiN(SiMe_3)_2$ showed higher yield than $KN(SiMe_3)_2$ and $NaN(SiMe_3)_2$ (Table 1, entries 1–3, 51% *vs*. 31–32% yield). Screening of the cesium salts indicated that Cs_2CO_3 was the best choice, giving isoquinoline product **3aa** in 59% yield (Table 1, entry 5). CsTFA exhibited inferior performance (Table 1, entry 4, 41% yield) and only 11% yield of the product was obtained without Cs^+ additives (Table 1, entry 6). Solvent screening with DME, 1,4-dioxane, toluene, and THF indicated that reactions in DME and 1,4-dioxane exhibited similar yields (Table 1, entries 7–8, 57–58%), while toluene and THF both led to the product in 44% yield (Table 1, entries 9–10). In contrast, the isoquinoline product was not observed with other solvents, such as dichloromethane, DMSO, and DMF. These did not match the yield with CPME, which was used in the remainder of the study. Decreasing the amount of Cs_2CO_3 was detrimental to the reaction with 0.5 equiv. of Cs_2CO_3 providing 50% yield (Table 1, entry 11) and 0.3 equiv. of Cs_2CO_3 generating 18% yield (Table 1, entry 12). Increasing the amount of benzonitrile from 1.0 to 1.5 equiv. was beneficial, improving the yield of **3aa** from 59% to 80% (Table 1, entries 5, 13, and 14). Notably, high temperature was essential. The isoquinoline product was isolated in 71% yield at 80 °C and 82% isolated yield at 120 °C. Overall, the optimized reaction conditions are those in entry 16 and were carried forward to explore the substrate scope.

Table 1. Annulation Reaction Optimization[a]



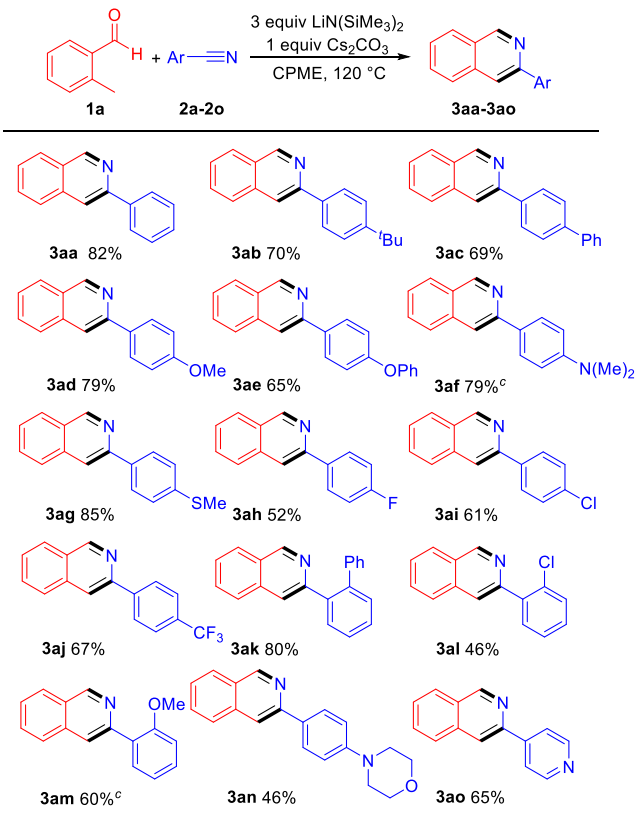
Entry	Solvent	M	Additive	1a:2a	Yield[b]
1	CPME	K	CsF	1.5:1	32
2	CPME	Na	CsF	1.5:1	31
3	CPME	Li	CsF	1.5:1	51
4	CPME	Li	CsTFA	1.5:1	41
5	CPME	Li	Cs_2CO_3	1.5:1	59
6	CPME	Li	–	1.5:1	11
7	DME	Li	Cs_2CO_3	1.5:1	57
8	1,4-Dioxane	Li	Cs_2CO_3	1.5:1	58
9	Toluene	Li	Cs_2CO_3	1.5:1	44
10	THF	Li	Cs_2CO_3	1.5:1	44
11[c]	CPME	Li	Cs_2CO_3	1.5:1	50
12[d]	CPME	Li	Cs_2CO_3	1.5:1	18
13	CPME	Li	Cs_2CO_3	1:2	65
14	CPME	Li	Cs_2CO_3	1:3	80
15[e]	CPME	Li	Cs_2CO_3	1:3	71
16[f]	CPME	Li	Cs_2CO_3	1:3	82

[a]Reactions were conducted with **1a** (0.1 mmol), **2a** (0.15 mmol), base (0.3 mmol), additive (0.1 mmol), solvent (1 mL), 100 °C, 12 h. [b]Isolated yields. [c]0.05 mmol of Cs_2CO_3. [d]0.03 mmol of Cs_2CO_3. [e]80 °C. [f]120 °C.

The substrate scope of arylnitriles was next examined with 2-methylbenzaldehyde **1a** under optimized conditions (Table 2). 4-*tert*-Butylbenzonitrile and 4-phenylbenzonitrile produced **3ab** and **3ac** in 70% and 69% yield, respectively. Benzonitriles bearing electronically diverse substituents, including electron-donating (4-OMe, **3ad;** 4-OPh, **3ae**; 4-NMe_2, **3af**; 4-SMe, **3ag**) and electronegative or electron-withdrawing groups (4-F, **3ah**; 4-Cl, **3ai**; 4-CF_3, **3aj**) gave the annulation products. Substrates

with electronegative substituents were slightly less effective (52–67% yields for **3ah**–**3aj** *vs.* 65–85% yields for **3ad**–**3ag**). In addition, sterically hindered arylnitriles bearing electronically-diverse substituents at the *ortho*-positions (2-Ph, 2-Cl, 2-OMe) were all suitable in this transformation, providing the corresponding products (**3ak**–**3am**) in 46–80% yields. A benzonitrile possessing a 4-morpholino group furnished the isoquinoline product **3an** in 46% yield. 4-Cyanopyridine was an appropriate substrate, affording the desired product **3ao** in 65% yield.

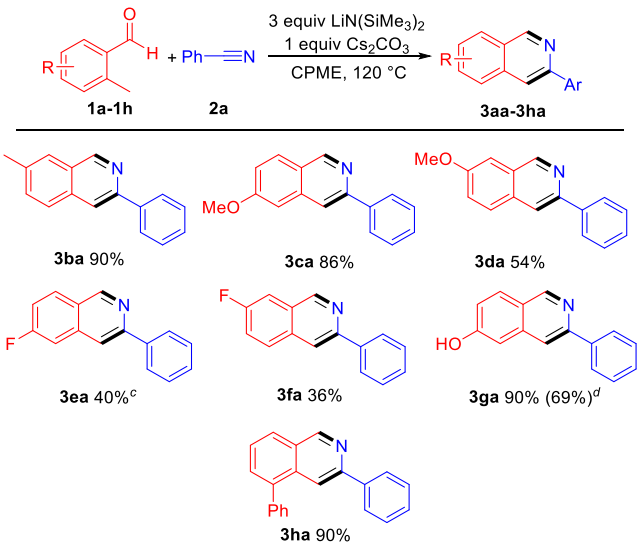
Table 2. Scope of Arylnitriles in the Synthesis of Isoquinolines [a,b]



[a]Reaction conditions: **1a** (0.1 mmol), arylnitrile (0.3 mmol), $LiN(SiMe_3)_2$ (1.0 mol/L in THF, 0.3 mL, 0.3 mmol), Cs_2CO_3 (0.1 mmol), CPME (1.0 mL), 120 °C, 12 h. [b]Isolated yield. [c]Reaction conducted with 6 equiv of arylnitrile (0.6 mmol).

The scope of arylaldehydes was next explored with benzonitrile **2a** (Table 3). 2,5-Dimethylbenzaldehyde reacted with benzonitrile to give the isoquinoline products **3ba** in 90% yield. For arylaldehydes bearing electron-donating substituents, 4-methoxy-2-methylbenzaldehyde showed better performance than 5-methoxy-2-methylbenzaldehyde (86% yield, **3ca** *vs.* 54% yield, **3da**). This may be due to the electron-donating nature of the para-methoxy group, which will decrease the acidity of the methyl group. Substrates possessing fluoro groups, such as 4-fluoro-2-methylbenzaldehyde and 5-fluoro-2-methylbenzaldehyde, showed lower conversions, affording the products **3ea** and **3fa** in 40% and 36% yields, respectively. A possible side reaction with these aryl fluorides is *via* elimination to generate benzynes, which decompose under the reaction conditions. Interestingly, 4-hydroxy-2-methylbenzaldehyde readily reacted with benzonitrile to furnish the annulation product **3ga** in 90% yield. The sterically hindered 2-methylbiphenyl-3-carbaldehyde provided the product **3ha** in 61% yield. To illustrate the scalability of this method, we conducted the reaction of 4-hydroxy-2-methylbenzaldehyde (**1g**) and benzonitrile (**2a**) on a 8 mmol scale. The cyclization product **3ga** was isolated in 69% yield (1.22 g). Use of 4 and 5 equiv of $LiN(SiMe^3)_2$ did not improve the yield.

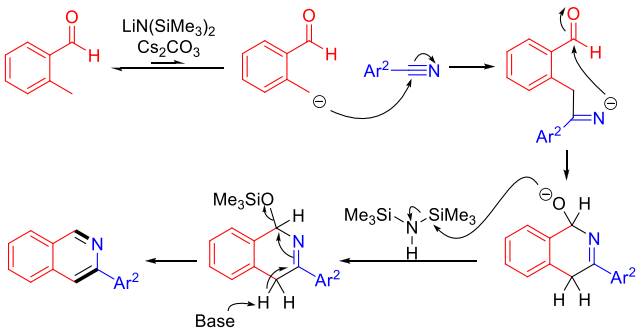
Table 3. Scope of 2-methyl-arylaldehydes [a,b]



[a]Reaction conditions: 2-methyl-arylaldehyde (0.1 mmol), **2a** (0.3 mmol), $LiN(SiMe_3)_2$ (1.0 mol/L in THF, 0.3 mL, 0.3 mmol), Cs_2CO_3 (0.1 mmol), CPME (1.0 mL), 120 °C, 12 h. [b]Isolated yield. [c]Reaction conducted with 0.5 equiv of CsTFA (0.05 mmol). [d]Reaction conducted on 8 mmol scale.

A proposed reaction pathway is shown in Scheme 2. The reaction is initiated with the reversible deprotonation of 2-methylbenzaldehyde. Next, addition of the resulting benzyl anion to the nitrile generates a metalated imine. Subsequent attack of the metalated imine on the aldehyde carbonyl leads to a cyclized intermediate. Elimination and aromatization is envisioned to be initiated by transfer of a silyl group from the conjugate acid of the base to the alkoxy group of the tetrahedral intermediate. Finally, $MN(SiMe_3)_2$ (M = Li or Cs) promoted elimination of $-OSiMe_3$ furnishes the 3-aryl isoquinoline product.

Scheme 2. Possible Reaction Path.



CONCLUSION

In conclusion, an efficient, transition metal-free method for the synthesis of 3-aryl isoquinolines is introduced. Benefits of this method include readily accessible starting materials and C–C and C–N bond-formations in a simple procedure. Using this method a variety of 3-aryl isoquinoline derivatives were generated with 36–90% yields. Considering 3-aryl isoquinolines are valuable molecular scaffolds, which are common in natural products and pharmaceuticals, we envision that this protocol will be of interest in medicinal chemistry.

■ EXPERIMENTAL SECTION

See the Supporting Information for the Experimental Section.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published and online Supporting Information

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details, additional results, ^{1}H NMR, ^{13}C{^{1}H} NMR, and MS (HRMS) data (PDF). FAIR Data is available as Supporting Information for Publication and includes the primary NMR FID files for compounds **3aa-3ah**.

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Author Contributions

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript. / ‡SS and JM contributed equally.

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