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Base-Promoted Synthesis of Isoquinolines through a Tandem Reaction of 2-Methyl-arylaldehydes and Nitriles

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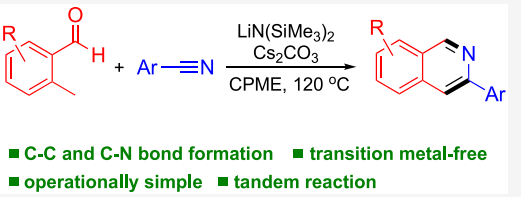
ABSTRACT: A convenient method for preparing 3-aryl isoquinolines via a base-promoted tandem reaction is presented. Simply combining commercially available 2-methyl-arylaldehydes, benzonitriles, $NaN(SiMe_3)_2$, and Cs_2CO_3 enabled the synthesis of a variety of isoquinolines (23 examples, ≤90% yield).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

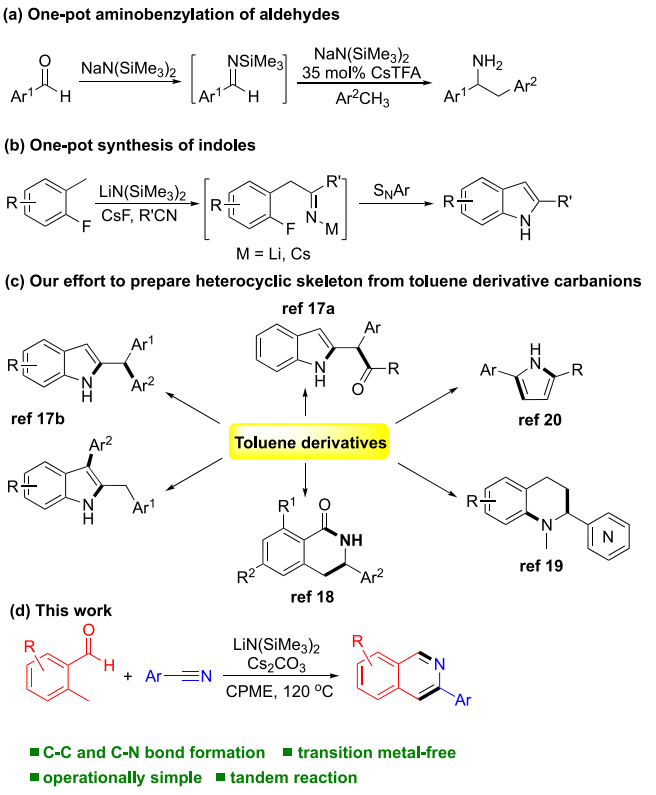


INTRODUCTION

Isoquinolines make up 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 in terms of 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 that are active in these processes form. 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

Scheme 1. Our Previous Work



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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 of the 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]

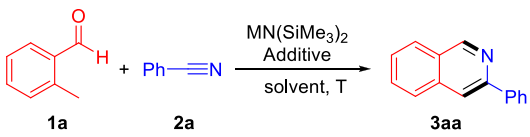
On the basis of these studies, we were interested in developing an approach to 3-arylisoquinolines. Herein, we report the efficient synthesis of 3-arylisoquinolines via the tandem reaction of 2-methyl-arylaldehydes and nitriles (Scheme 1d). Compared to the existing routes, this protocol is simple, environmentally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

RESULTS AND DISCUSSION

As a starting point, we employed 2-methylbenzaldehyde **1a** and benzonitrile **2a** in CPME (cyclopentyl methyl ether) at 100 °C. On the basis of our past studies, we employed $MN(SiMe_3)_2$ (M = Li, Na, or K) with 1.0 equiv of CsF as an additive. The yield with $LiN(SiMe_3)_2$ was higher than those of $KN(SiMe_3)_2$ and $NaN(SiMe_3)_2$ (Table 1, entries 1−3, 51% vs 31−32%). 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 and 8, respectively, 57−58%), while toluene and THF both led to the product in 44% yield (Table 1, entries 9 and 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 a 50% yield (Table 1, entry 11) and 0.3 equiv of Cs_2CO_3 generating an 18% yield (Table 1, entry 12). Increasing the amount of benzonitrile from 1.0 to 3.0 equiv was beneficial, improving the yield of **3aa** from 59% to 80% (Table 1, entries 5, 13, and 14). Notably, a 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.

The substrate scope of arylnitriles was next examined with 2-methylbenzaldehyde **1a** under the optimized conditions (Table 2). 4-*tert*-Butylbenzonitrile and 4-phenylbenzonitrile produced **3ab** and **3ac** in 70% and 69% yields, 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.

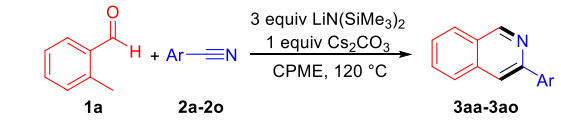
Table 1. Optimization of the Annulation Reaction[a]

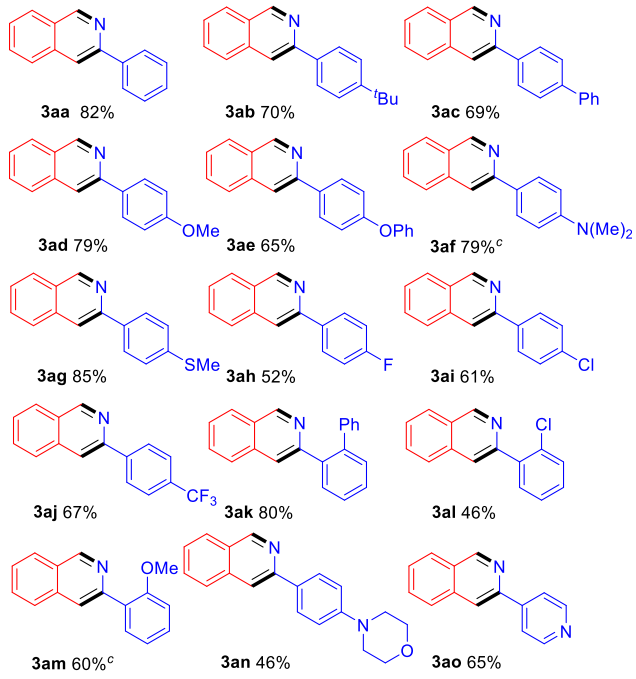


entry	solvent	M	additive	1a:2a	yield[b] (%)
1	CPME	K	CsF	1.5:1	32
2	CPME	Na	CsF	1.5:1	31
3	CPME	Li	CsF	1.5:1	51
4	CPME	Li	CsTFA	1.5:1	41
5	CPME	Li	Cs_2CO_3	1.5:1	59
6	CPME	Li	–	1.5:1	11
7	DME	Li	Cs_2CO_3	1.5:1	57
8	1,4-dioxane	Li	Cs_2CO_3	1.5:1	58
9	toluene	Li	Cs_2CO_3	1.5:1	44
10	THF	Li	Cs_2CO_3	1.5:1	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), a base (0.3 mmol), an additive (0.1 mmol), and a solvent (1 mL) at 100 °C for 12 h. [b]Isolated yields. [c]With 0.05 mmol of Cs_2CO_3. [d]With 0.03 mmol of Cs_2CO_3. [e]At 80 °C. [f]At 120 °C.

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), and CPME (1.0 mL) at 120 °C for 12 h. [b]Isolated yield. [c]Reaction conducted with 3 equiv of $NaN(SiMe_3)_2$ (2.0 mol/L in THF, 0.15 mL, 0.3 mmol), and 1 equiv of CsTFA (0.1 mmol).

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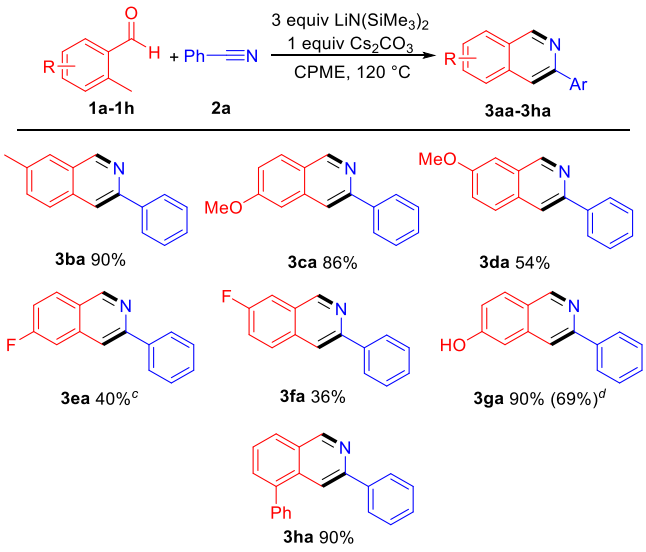
Substrates with electronegative substituents were slightly less effective (52−67% yields for **3ah**−**3aj** vs 65−85% yields for **3ad**−**3ag**). In addition, sterically hindered arylnitriles bearing electronically diverse substituents at the *ortho* positions (2-Ph, 2-Cl, or 2-OMe) were all suitable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

The scope of arylaldehydes was next explored with benzonitrile **2a** (Table 3). 2,5-Dimethylbenzaldehyde reacted with benzonitrile to give isoquinoline products **3ba** in 90% yield. For arylaldehydes bearing electron-donating substituents, the performance of 4-methoxy-2-methylbenzaldehyde was better than that of 5-methoxy-2-methylbenzaldehyde (86% yield, **3ca**, vs 54% yield, **3da**). This may be due to the electron-donating nature of the *p*-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 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 annulation product **3ga** in 90% yield. The sterically hindered 2-methylbiphenyl-3-carbaldehyde provided product **3ha** in 90% 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. Cyclization product **3ga** was isolated in 69% yield (1.22 g). The use of 4 and 5 equiv of $LiN(SiMe_3)_2$ did not improve the yield.

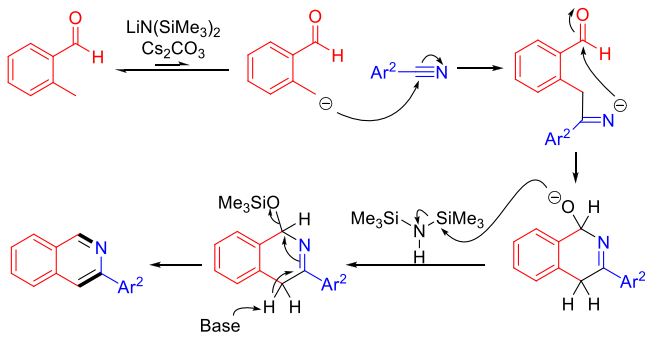
A proposed reaction pathway is shown in Scheme 2. The reaction is initiated with the reversible deprotonation of 2-methylbenzaldehyde. Next, addition of the resulting benzyl anion to the nitrile generates a metalated imine. Subsequent attack of the metalated imine on the aldehyde carbonyl leads to a cyclized intermediate. Elimination and aromatization are envisioned to be initiated by the 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.

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), and CPME (1.0 mL) at 120 °C for 12 h. [b]Isolated yield. [c]Reaction conducted with 0.5 equiv of CsTFA (0.05 mmol). [d]Reaction conducted on an 8 mmol scale.

Scheme 2. Possible Reaction Path



CONCLUSION

In conclusion, an efficient, transition metal-free method for the synthesis of 3-aryl isoquinolines is introduced. The benefits of this method include readily accessible starting materials and the formation of C−C and C−N bonds in a simple procedure. Using this method, a variety of 3-aryl isoquinoline derivatives were generated in 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 its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.4c00123.

Experimental details, additional results, and ^1H NMR, $^{13}C\{^1H\}$ NMR, and MS (HRMS) data (PDF)

FAIR data, including the primary NMR FID files, for compounds **3aa**−**3ah** (ZIP)

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Notes

The authors declare no competing financial interest.

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