One-pot aminobenzylolation of aldehydes with toluenes

Zhiting Wang¹, Zhipeng Zheng², Xinyu Xu¹, Jianyou Mao¹ & Patrick J. Walsh¹,²

Amines are fundamental motifs in bioactive natural products and pharmaceuticals. Using simple toluene derivatives, a one-pot aminobenzylolation of aldehydes is introduced that provides rapid access to amines. Simply combining benzaldehydes, toluenes, NaN(SiMe₃)₂, and additive Cs(O₂CCF₃) (0.35 equiv.) generates a diverse array of 1,2-diarylethylamine derivatives (36 examples, 56–98% yield). Furthermore, suitably functionalized 1,2-diarylethylamines were transformed into 2-aryl-substituted indoline derivatives via Buchwald–Hartwig amination. It is proposed that the successful deprotonation of toluene by MN(SiMe₃)₂ is facilitated by cation–π interactions between the arene and the group(I) cation that acidify the benzylic C–Hs.
Toluene and xylenes are large volume, inexpensive commodity chemicals commonly used as solvents on industrial scale. As such, there are no better feedstocks for the preparation of more elaborate, high-value organic molecules with applications in pharmaceutical sciences, agrochemicals, and materials chemistry. To fully exploit these feedstocks, efficient and economical methods for the selective functionalization of the benzylic C–Hs are required. Recent advances along these lines have been considerable, although many rely on highly reactive stoichiometric oxidants or directing groups to facilitate these transformations. Related to this strategy, Stahl and Liu have recently developed mild methods to generate diarylmethanes via copper-catalyzed arylation of toluene and its derivatives with arylboronic acids. Palladium-promoted toluene functionalization strategies also hold promise.

We have been interested in the functionalization of very weakly acidic (pKₐ up to ~34) benzylic C–Hs of arenes and heteroarenes via deprotonative cross-coupling processes (DCCP). Substrates for DCCP include allyl benzenes (Fig. 2a), diarylmethanes, triarylmethanes, and benzylic sulfonamides among others. The success of DCCP relies partly on reversible deprotonation of the benzylic C–Hs of the pronucleophile. For deactivated toluene derivatives, however, we conjectured that the high pKₐ values (~43 in DMSO) of the benzylic C–Hs were far beyond the reach of MN(SiMe₃)₂ bases [M = alkali metal, pKₐ = 26 for HN(SiMe₃)₂ in THF]. Thus, to address this long-standing challenge, we have activated the arenes with stoichiometric transition metals by forming (p^6-toluenecr(CO)₃ complexes. The benzylic C–H of (p^6-toluenecr(CO)₃ exhibit increased acidity and are reversibly deprotonated with LiN(SiMe₃)₂, enabling functionalization (Fig. 2b). The group of Matsuzaka improved upon this approach with a ruthenium-sulfonamide-based catalyst for in situ deprotonation of toluene and dehydrative condensation with aldehydes to generate (E)-stilbenes.

As a valuable complement, Schneider developed a method for functionalization of allyl benzene (pKₐ = 34.25) catalyzed by NaN(SiMe₃)₂ (Fig. 2d). Benzyl functionalization of more acidic alkylazaarenes (pKₐ = 35 for 4-methyl pyridine) catalyzed by KN(SiMe₃)₂ with N,N-dimethylcinnamamide by Kobayashi and co-workers also represents an advance. More recently, Guan reported a KN(SiMe₃)₂-catalyzed C–H bond addition of alkylpyridines to simple styrenes (Fig. 2f). During the revision process, Bronsted base-catalyzed benzylic C–H bond functionalizations of toluenes and diarylmethanes were reported by Kobayashi and Guan, respectively. Important early contributions involved additions of 2-methyl pyridine (Fig. 2g), and Grignard reagents (Fig. 2h) to in situ generated N-(trimethylsilyl)imines were developed by Giles and Harr, respectively.

The results in Fig. 2b–h, as well as our recent work on the use of cation–π interactions to direct C–H functionalization reactions, inspired us to wonder if cation–π interactions between toluene and earth-abundant alkali metals derived from MN(SiMe₃)₂ (M = Li, Na, K, Cs) would increase the acidity of the benzylic C–Hs sufficiently to allow reversible deprotonation under relatively mild conditions. If indeed such an equilibrium could be established, which would undoubtedly lie very far to the side of toluene, would it be possible to trap the fleeting benzylic organometallic with an electrophile before rapid quenching with the conjugate acid of the base [HN(SiMe₃)₂]? Finally, if benzylic organometallic species could be generated from toluene and its derivatives, would it be possible to transform them into high-value building blocks of interest to the pharmaceutical industry?

Herein, we report a successful tandem C–C and C–N bond-forming reaction for the one-pot chemoselective aminobenzyla-
ction of aldehydes with toluene derivatives (Fig. 2i). This method enables rapid access to a variety of 1,2-diphenylethylamine derivatives that are important building blocks in natural products and potent drugs and pharmaceuticals. We have been interested in the functionalization of very weakly acidic (pKₐ up to ~34) benzylic C–Hs of arenes and heteroarenes via deprotonative cross-coupling processes. Related to this strategy, Stahl and Liu have recently developed mild methods to generate diarylmethanes via copper-catalyzed arylation of toluene and its derivatives with arylboronic acids. Palladium-promoted toluene functionalization strategies also hold promise.

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As a valuable complement, Schneider developed a method for functionalization of allyl benzene (pKₐ = 34.25) catalyzed by NaN(SiMe₃)₂ (Fig. 2d). Benzyl functionalization of more acidic alkylazaarenes (pKₐ = 35 for 4-methyl pyridine) catalyzed by KN(SiMe₃)₂ with N,N-dimethylcinnamamide by Kobayashi and co-workers also represents an advance. More recently, Guan reported a KN(SiMe₃)₂-catalyzed C–H bond addition of alkylpyridines to simple styrenes (Fig. 2f). During the revision process, Bronsted base-catalyzed benzylic C–H bond functionalizations of toluenes and diarylmethanes were reported by Kobayashi and Guan, respectively. Important early contributions involved additions of 2-methyl pyridine (Fig. 2g), and Grignard reagents (Fig. 2h) to in situ generated N-(trimethylsilyl)imines were developed by Giles and Harr, respectively.

The results in Fig. 2b–h, as well as our recent work on the use of cation–π interactions to direct C–H functionalization reactions, inspired us to wonder if cation–π interactions between toluene and earth-abundant alkali metals derived from MN(SiMe₃)₂ (M = Li, Na, K, Cs) would increase the acidity of the benzylic C–Hs sufficiently to allow reversible deprotonation under relatively mild conditions. If indeed such an equilibrium could be established, which would undoubtedly lie very far to the side of toluene, would it be possible to trap the fleeting benzylic organometallic with an electrophile before rapid quenching with the conjugate acid of the base [HN(SiMe₃)₂]? Finally, if benzylic organometallic species could be generated from toluene and its derivatives, would it be possible to transform them into high-value building blocks of interest to the pharmaceutical industry?

Results

Preliminary reaction optimization. Initial screens were conducted with benzaldehyde (1a) in toluene (2a) with three different bases [LiN(SiMe₃)₂, NaN(SiMe₃)₂, and KN(SiMe₃)₂] at 110 °C for 12 h (Table 1, entries 1–3, AY = assay yield, determined by ¹H NMR of unpurified reaction mixtures). NaN(SiMe₃)₂ failed to give the desired product 3aa (entry 1), although it is known to react with benzaldehyde to generate aldmine. This screen led to the identification of NaN(SiMe₃)₂ as a promising base, affording the product 3aa in 47% assay yield (entry 2). It is known that K⁺ forms the stronger cation–π interactions in solution in the series Li⁺, Na⁺, and K⁺ among others, however, under our conditions the potassium amide was not as successful as NaN(SiMe₃)₂ (entry 3 vs. 2). This may be because KN(SiMe₃)₂ is less efficient in the formation of the aldmine. We were also interested in examining the use of CsN(SiMe₃)₂. Unfortunately, this base is not widely available commercially like its lighter analog CsN(SiMe₃)₂ is not widely available commercially like its lighter analog CsN(SiMe₃)₂. It can be prepared, of course, but this would make the methods that require its use less attractive. O’Hara and co-workers found that CsN(SiMe₃)₂ could be generated by mixing NaN(SiMe₃)₂ with CsX (X = Cl, Br, or I). Furthermore, combining CsN(SiMe₃)₂ with equimolar NaN(SiMe₃)₂ led to formation of a sodium–cesium amide polymer [toluene·CsNa(N(SiMe₃)₂)₂]₃. It is noteworthy that the toluene in this structure forms a cation–π complex with the Cs⁺ [Cs⁺···toluene(centroid) = 3.339 Å]. Such cation–π interactions are often found in the structures of organometallic complexes.

On the basis of the structures in these reports, we examined a variety of cesium salts with commercially available NaN(SiMe₃)₂ in 1:1 ratio (entries 4–13). This screen led to the identification of NaN(SiMe₃)₂ and CsTFA (TFA = trifluoroacetate) as the best combination, generating 3aa in 92% AY (entry 13). Other cesium salts either did not promote the transformation (CsF, Cs₂CO₃, CsCl, CsOAc, entries 4–7) or gave low yields of 3aa (Cs₂SO₄, CsClO₄, EtCOOCs, CsBr, CsI, entries 8–12). Upon decreasing the amounts of both base and CsTFA [2 equiv. NaN(SiMe₃)₂ and 0.35 equiv. CsTFA], the AY of 3aa remained high (95%, entry 15). Further lowering the CsTFA to 0.2 equiv, however, led to a slight decrease in assay yield (89%, entry 16). The reactivity decreased significantly when catalytic MN(SiMe₃)₂ was used (41%, entry 17).
20 mol %). We wanted to determine if the combination of MN (SiMe3)2 (M = Li, K) and CsTFA could affect the reactivity under the conditions of entry 15, so we reexamined LiN(SiMe3)2 and KN(SiMe3)2 with CsTFA (35 mol%). In the presence of CsTFA, the difference between LiN(SiMe3)2 and NaN(SiMe3)2 was negligible (entry 15 vs 18). KN(SiMe3)2, however, still gave low assay yield (entry 19). We also examined the impact of temperature on the reactivity under the conditions of entry 15. As the temperature was decreased from 110 to 30 °C, the reactivity decreased dramatically at 30 °C affording the desired product in 67% yield (entry 22). At this point, the nature of the active base and even the amount of Cs in solution remained desired product in 67% yield (entry 22). Our optimized reaction conditions for the one-pot aminobenzylation of benzaldehyde are 2 equiv. of the subject of future work. Our optimized reaction conditions for the one-pot aminobenzylation of benzaldehyde are 2 equiv. of NaN(SiMe3)2, 1 mL toluene, and 35 mol% CsTFA at 110 °C for 12 h.

**Scope of aldehydes.** With the optimized reaction conditions in hand, we next examined the scope of aldehydes in the aminobenzylation with toluene (Table 2). In addition to the parent benzaldehyde (1a), a variety of aryl and heteroaryl aldehydes were successfully employed. Benzyldiazides bearing electron-donating groups, such as 4-t-Bu, 4-methyl, 4-methoxy, and 4-N,N-dime-thylamino, exhibited very good reactivity, producing 3ba–3ea in 70–88% yield. Benzaldehydes possessing halogens are also good coupling partners even at 40 °C. 4-Fluoro-, 4-chloro-, and 4-bromobenzaldehydes afforded the corresponding products in 90%, 98%, and 83% yield, respectively (3fa–3ha). Likewise, 2-bromo (3ia, 95%) and 2-chloro (3ja, 98%) benzaldehydes were very good substrates. Of course, these products could potentially be further functionalized through cross-coupling reactions. Substrates with extended π-systems, such as 1- and 2-naphthyl aldehydes, furnished products in 92–94% yield (3ka and 3la).

In general, benzaldehyde derivatives bearing additional functional groups and heteroatoms were well tolerated. Nitriles are known to undergo nucleophilic additions with organometallic reagents. Under our aminobenzylation conditions, however, 4-cyano benzaldehyde afforded the desired product (3ma) in 70% yield with high chemoselectivity. Considering that, fluorinated compounds are extremely important in medicinal chemistry, we examined fluorinated benzaldehydes. Both 4-trifluoromethyl- and 4-trifluoromethoxy benzaldehydes were excellent substrates, affording 3na and 3oa in 97% and 90% yield, respectively. Benzaldehydes containing 4-SMe, 4-Ph, and 4-OPh groups rendered the products in 88–93% yield (3pa–3ra). The silyl-ether containing product (3sa, 77%) could be accessed via this protocol. Heterocyclic amines exhibit various bioactivities. Amines containing indole, pyridine, pyrrole, and quinoline groups could be prepared with our approach, as exemplified by Benzaldehydes possessing halogens are also good coupling partners even at 40 °C. 4-Fluoro-, 4-chloro-, and 4-bromobenzaldehydes afforded the corresponding products in 90%, 98%, and 83% yield, respectively (3fa–3ha). Likewise, 2-bromo (3ia, 95%) and 2-chloro (3ja, 98%) benzaldehydes were very good substrates. Of course, these products could potentially be further functionalized through cross-coupling reactions. Substrates with extended π-systems, such as 1- and 2-naphthyl aldehydes, furnished products in 92–94% yield (3ka and 3la).

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the generation of 3ta–3xa in 66–97% yield. Cinnamaldehyde was a competent partner under our conditions, as exemplified by the synthesis of allylic amine 3ya in 56% yield.

**Scope of toluene derivatives.** Next, the substrate scope of toluene derivatives was examined in the aminobenzylation of benzaldehyde (1a) (Table 3). Toluene bearing electron-donating groups, such as 4-Pr (2b), 4-O2Me (2c), and 2-O2Me (2d), provided the corresponding products in 78%, 66%, and 77% yield, respectively. It is noteworthy that the methyl of p-cymene (2b) undergoes reaction with high chemoselectivity. 4-Chlorotolene (2e) exhibited reduced reactivity, furnishing 3ae in 66% yield at 40 °C. In contrast, 2-chloro- and 2-bromotoluenes exhibited good reactivity, giving the desired products (3af and 3ag) in 86% and 85% yield, respectively. For polymethyl-substituted toluenes (2h–2k), excellent chemoselectivity was observed, affording the products (3ah–3ak) in 81–96% yield. It is noteworthy that mesitylene was an outstanding substrate (96% yield, 3ak). π-Extended 1-methynaphthalene was also a good substrate, affording 3ai in 88% yield.

**Reaction pathway.** Based on the results above, we propose a reaction pathway for this one-pot aminobenzylation process. First, the NaN(SiMe3)2 reacts with the aldehyde to form the intermediate adduct A, followed by an aza-Peterson olefination to afford the N-(trimethylsilyl)limine B, which was not isolated but reacted directly in this one-pot process. In the presence of NaN(SiMe3)2 and CsTFA, the toluene derivative was reversibly deprotonated to generate an η1- or η3-bound metal complex C and C′. The deprotonated toluene derivative then attacks the in-situ-generated aldimine B to give the aminobenzylated product 3 after workup (Fig. 3).

**Further transformations.** For a method to be useful, it must be scalable. To test the scalability of the aminobenzylation, 5 mmol of benzaldehyde (0.53 g) was reacted with 2-bromotoluene (2g) (Fig. 4a). An 81% yield of 3ag was obtained. Additionally, a column-free process for direct synthesis of hydrochloride salt of 3aa was explored. Under the optimized conditions, the salt 3′aa was obtained in 78% yield (Fig. 4b). To further demonstrate the synthetic potential of the aminobenzylation, the product derived from 2-bromotoluene, NaN(SiMe3)2, and benzaldehydes 1a, 1n, 1q, and 1v were readily converted into valuable 2-aryl-substituted indoline derivatives using a Buchwald–Hartwig amination in 81–90% yield (Fig. 4c). N-Substituted 2-arylindoline derivatives are used to treat estrogen-deficiency diseases. Furthermore, the parent 1,2-diphenylethylamine was easily converted to a diverse array of biologically active compounds (Fig. 4d).

**Discussion.** We have advanced a general method for the activation and functionalization of inexpensive toluene feedstocks at the benzylic position via a one-pot aminobenzylation of aldehydes. The reaction takes place without added transition metal catalysts and does not employ preformed main group organometallic reagents. By employing readily available benzaldehydes, commodity toluene derivatives, NaN(SiMe3)2, and substoichiometric CsTFA a diverse array of valuable and biologically active 1,2-...
### Table 2 Scope of aldehydes

| R          | 1a–1x | 2a   | 3aa–3xa |
|------------|-------|------|---------|
|            | 0.2 mmol | 2 mL |         |

**Reaction Conditions:**
- 2 equiv NaN(SiMe3)2
- 35 mol % CsTFA
- 110 °C, 12 h

| Product   | Yield (%) |
|-----------|-----------|
| 3aa       | (92%)     |
| 3ba       | (88%)     |
| 3ca       | (70%)     |
| 3da       | (86%)     |
| 3ea       | (79%)     |
| 3f         | (90%)     |
| 3g         | (98%)†    |
| 3h         | (83%)†    |
| 3i         | (95%)†    |
| 3j         | (98%)†    |
| 3k         | (94%)†    |
| 3l         | (92%)†    |
| 3m         | (70%)     |
| 3n         | (97%)†    |
| 3o         | (85%)     |
| 3p         | (88%)     |
| 3q         | (93%)†    |
| 3r         | (92%)     |
| 3s         | (77%)     |
| 3t         | (80%)     |
| 3u         | (84%)     |
| 3v         | (75%)     |
| 3w         | (97%)†    |
| 3x         | (66%)     |
| 3y         | (56%)     |

*Isolated yields
†Reaction conducted at 40 °C

### Table 3 Scope of toluene derivatives

| R          | 1a | 2b–l | 3ab–3al |
|------------|----|------|---------|
|            | 0.2 mmol | 1 mL |         |

**Reaction Conditions:**
- 2 equiv NaN(SiMe3)2
- 35 mol % CsTFA
- Cyclohexane (1 mL)
- 110 °C, 12 h

| Product   | Yield (%) |
|-----------|-----------|
| 3ab       | (78%)     |
| 3ac       | (66%)†    |
| 3ad       | (77%)     |
| 3ae       | (66%)†§   |
| 3af       | (86%)     |
| 3ag       | (85%)     |
| 3ah       | (82%)     |
| 3ai       | (84%)     |
| 3aj       | (81%)     |
| 3ak       | (96%)     |
| 3al       | (88%)§    |

*Isolated yields
†Reaction conducted in 1 mL 4-methylanisole
‡Reaction conducted in 1 mL 4-chlorotoluene
§Reaction conducted at 40 °C
**Fig. 3** Possible reaction pathway for the aminobenzylation. In situ imine formation provides aldimine B while NaN(SiMe₃)₂/CsTFA-mediated benzylic deprotonation generates transient organometallic C. Intermediate C is trapped by B to furnish intermediate D. Workup then affords the desired amine product 3.

**a** Grame-scale synthesis of 3ag

\[
\text{RHN(SiMe₃)₂} + \text{BrPh} \rightarrow \text{NH₂PhR} \quad (\text{2 equiv NaN(SiMe₃)₂, 100 °C, 12 h})
\]

1a (5 mmol) + 2g (50 mL) → 3ag (81% yield, 1.12 g)

**b** Column-free preparation of hydrochloride salt of 3aa

\[
\text{RHN(SiMe₃)₂} + \text{BrPh} \rightarrow \text{NH₂PhR} \quad (\text{2 equiv NaN(SiMe₃)₂, 100 °C, 12 h})
\]

1a (0.2 mmol) + 2a (2 mL) → 3'aa (78% yield)

**c** Further transformation for the synthesis of 2-substituted indoline

1 mmol

R = H, 1a
R = 4-OCF₃, 1n
R = 4-Ph, 1q
R = 4-(2-pyridyl), 1v

3ag 82% yield
3ng 73% yield
3qg 84% yield
3vg 88% yield

**d** Synthesis of biologically active compounds

5b NPDPA

(1) Acetone
(2) NaBH₄, EtOH 73%

5a NEDPA

Bromoethane DMF 75%

1,5-Dibromopentane K₂CO₃, CH₃CN 81%

5c Lefetamine

Formaldehyde Formic acid reflux 51%

5d Diphenidine

**Fig. 4** Gram scale and further transformations. **a** Scale up of aminobenzylation. **b** Column-free synthesis of the hydrochloride salt of the amine product. **c** Synthesis of indolines via Buchwald–Hartwig amination. **d** Synthesis of bioactive compounds.
diarylethylamine derivatives were conveniently synthesized. The N-alkylated analogs of our diarylethylamines are used as opioid analgesics. Additionally, this one-pot aminobenzylation exhibits remarkable chemoselectivity and excellent functional group tolerance. Suitably substituted aldehyde aminobenzylations products were readily transformed into pharmaceutically relevant 2-aryl-substituted indoline derivatives via Buchwald–Hartwig amination.

We ascribe the success of our aminobenzylation of aldehydes to cation–π interactions between the π-electrons of the tolune derivative and Na and/or Cs centers. We hypothesize that this interaction acidifies the benzylic C–H bonds, facilitating deprotonation by moderate bases, MN(SiMe3)2. Because of its simplicity and potential to produce valuable bioactive building blocks in a single step, we anticipate that this aminobenzylation reaction will find applications in medicinal chemistry.

Methods

General procedure A. To an oven-dried microwave vial equipped with a stir bar under argon atmosphere inside a glove box was added Na[N(SiMe3)2] (73.2 mg, 0.40 mmol), cesium trifluoroacetate (CsTFA) (17.2 mg, 0.07 mmol), and toluene (2 mL). Then, the corresponding aldehyde (0.20 mmol) was added via syringe. The microwave vial was sealed with a cap and removed from the glove box. The reaction mixture was heated to 110 °C in an oil bath and stirred for 12 h. The sealed vial was cooled to room temperature, opened to air, and then five drops of water were added. The reaction mixture was passed through a short pad of silica, washed with an additional 6 mL of ethyl acetate (3 × 2 mL), and the combined solutions were concentrated in vacuo. The crude material was loaded onto a column of silica gel for purification of the amine.

General procedure B. To an oven-dried microwave vial equipped with a stir bar under argon atmosphere inside a glove box was added Na[N(SiMe3)2] (73.2 mg, 0.40 mmol), CsTFA (17.2 mg, 0.07 mmol), and cyclohexane (1 mL). Then, the corresponding aldehyde (0.20 mmol) was added via syringe. The microwave vial was sealed with a cap and removed from the glove box. The reaction mixture was heated to 110 °C in an oil bath and stirred for 12 h. The sealed vial was cooled to room temperature, opened to air, and then five drops of water were added. The reaction mixture was passed through a short pad of silica, washed with additional 6 mL of ethyl acetate (3 × 2 mL), and the combined solutions were concentrated in vacuo. The crude material was loaded onto a column of silica gel for purification of the amine.

Data availability

The authors declare that the data supporting the findings of this study are available within the article and its Supplementary Information files.

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Author contributions

Z.W., X.X., Z.Z., and J.M. performed the experiments and analyzed the data. J.M. and P.J.W. conceived the project and wrote the manuscript. All authors discussed the results and commented on the manuscript.

Additional information

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