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Benzylic aroylation of toluenes with unactivated tertiary benzamides promoted by directed *ortho*-lithiation

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The deprotonative functionalization of toluenes, for their weak acidity, generally needs strong bases, thus leading to the requirement of harsh conditions and the generation of by-products. Direct nucleophilic acyl substitution reaction of amides with organometallic reagents could provide an ideal solution for ketone synthesis. However, the inert amides and highly reactive organometallic reagents bring great challenges for an efficient and selective synthetic approach. Herein, we reported an lithium diisopropylamide (LDA)-promoted benzylic aroylation of toluenes with unactivated tertiary benzamides, providing a direct and efficient synthesis of various aryl benzyl ketones. This process features a kinetic deprotonative functionalization of toluenes with a readily available base LDA. Mechanism studies revealed that the directed *ortho*-lithiation of the tertiary benzamide with LDA promoted the benzylic kinetic deprotonation of toluene and triggered the nucleophilic acyl substitution reaction with the amide.

toluene, aroylation, unactivated tertiary benzamides, directed *ortho*-lithiation, nucleophilic acyl substitution reaction

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1 Introduction

Toluene, a simple and readily available feedstock chemical, has been widely used as a versatile building block in organic synthesis. The homolytic cleavage of the benzylic C–H bonds was extensively explored for diverse transformations [1,2]. These reactions, however, always suffered from an excessive amount of oxidants. The direct benzylic deprotonation of toluene could provide a benzyl carbanion, which acts as a crucial intermediate for further various nucleophilic reactions. However, for the weak acidity of toluene ($pK_a = 43$ in tetrahydrofuran (THF)) [3,4], the benzylic deprotonation needs bases even stronger than simple alkyl lithiums, usually the combination of alkyl lithiums and activators such as *N*,*N*,*N*',*N*'-tetramethylethane (TMEDA) and *t*-BuOK [5–14]. For example, O'Shea and co-workers [12–14] reported the regioselective benzylic metalation of toluene using a mixed-metal amide composed of *t*-BuOK, *n*-BuLi, and 2,2,6,6,-tetramethylpiperidine (Scheme 1a). With potassium amide or potassium alkyl catalysts, Kobayashi and co-workers [15,16] recently reported the catalytic addition of toluenes to imines and alkenes (Scheme 1b). With the combined catalysts of alkali amides and cesium salts, Walsh and co-workers [17–19] realized the addition of toluenes to aldimines and nitriles to synthesize amines and indoles (Scheme 1b). The coordination of the phenyl ring with a metal could activate the benzylic C–H bond, resulting in the deprotonation with relatively weak bases.

Takemoto, Matsuzaka and co-workers [20] reported the first catalytic dehydrative condensation of the benzylic C−H bonds of toluenes with aromatic aldehydes *via* the benzylic deprotonation-functionalization of an η^6-coordinated toluenes with a ruthenium complex. With the toluenes coordinated with $Cr(CO)_3$, Walsh and co-workers [21–23]

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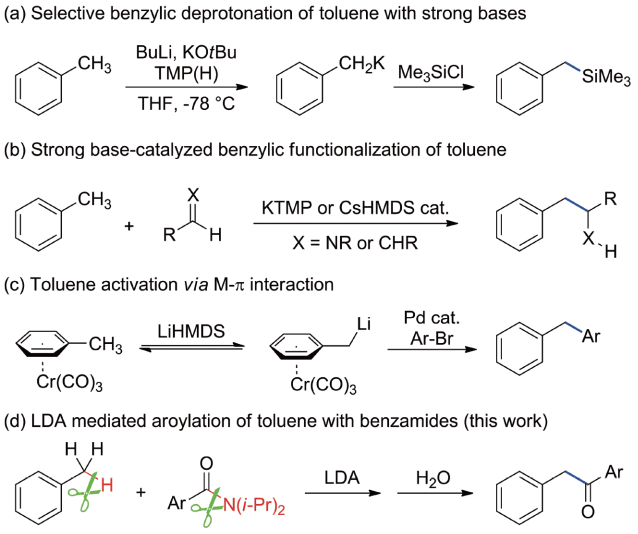


Scheme 1 Deprotonative functionalization of benzylic C–H bond of toluenes (color online).

achieved the palladium-catalyzed allylation and arylation reactions under weak base conditions (Scheme 1c). Recently, they further reported the arylation of simple toluenes with NIXANTPHOS-ligated palladium or nickel complex. The key factor was proposed to be the η^6-coordination with a main group element, enabling toluene to be deprotonated with the relatively weak bases such as $KN(SiMe_3)_2$ and $NaN(SiMe_3)_2$ [24,25]. Despite these developments, the deprotonative functionalization of toluene generally needed strong bases, or the relatively weak bases but with transition metal catalysts. The direct deprotonative functionalization of toluene simply with relatively weak bases still leaves a great challenge.

The transformation of the inert amide groups is a significant challenge in synthetic chemistry for their decreased electrophilicity and the enhanced C–N bond energy originating from the resonance stability. The reactions between amides and strongly nucleophilic organolithium or organomagnesium reagents could take place but usually under harsh conditions to prevent possible side reactions. To overcome these challenges, various activated amides including chelating amides [26,27], electron-deficient amides [28–30] and structurally distorted amides [31–34] were particularly designed for the nucleophilic acyl substitution reactions [35]. With the *in-situ* amide activation strategies, the direct transformations of secondary and tertiary amides with Grignard reagents were recently achieved by Charette and Huang [36–39], respectively. The highly electrophilic nitrilium intermediates generated from secondary amides and Tf_2O were reactive enough to readily undergo the reaction with arenes and alkenes to afford ketone products [40–45]. The less reactive organozinc and organoboron compounds are conducive to avoid side reactions. However, the reactions of amides with less reactive organometallic reagents always needed transition metal catalysts [46–50]. Despite that, the major drawback of the nucleophilic acyl substitution reaction of amides is the use of organometallic reagents, which was always synthesized from organohalides or *via* deprotonation under strong base conditions. Herein, we reported an lithium diisopropylamide (LDA)-promoted benzylic aroylation of toluenes with unactivated tertiary benzamides, providing an ideal pathway for the synthesis of aryl benzyl ketones (Scheme 1d).

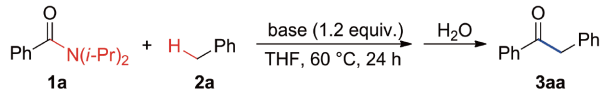
2 Results and discussion

In our former work about base-catalyzed C–H bond alkylation reactions, we found that some relatively weak base catalysts would not undergo the complete deprotonation of a weakly acidic C–H bond to afford a stable carbanion intermediate, but construct a deprotonative equilibration [51–54]. The reactive carbanion intermediate formed but in a low concentration, which would help to avoid side reactions and achieve the reaction selectively. The observation of the kinetic deprotonative functionalization reactions inspired us to investigate the nucleophilic acyl substitution reaction of toluene under a relatively weak base condition. We firstly examined several bases in the reaction between toluene and *N*,*N*-diisopropyl benzamide at 60 °C in THF (Table 1).

Alkali bis(trimethylsilyl)amides failed to give the desired ketone product (entries 1–3). LDA and LiTMP could smoothly drive on the nucleophilic acyl substitution reaction and give the benzyl phenyl ketone product **3aa** in good yields (entries 4 and 5). It is worthy of noting that neither LDA nor LiTMP could deprotonate benzylic C–H bond of toluene for their weak basicity. For the first time LDA or LiTMP, the relatively weaker bases than alkyl lithiums, achieved the deprotonation of benzylic C–H bond of toluene and the following nucleophilic acyl substitution reaction with benzamides. Even more basic $TMSCH_2Li$ and *n*-BuLi were also subjected into the reaction. The amide was completely consumed; however, the product was obtained in low yields of 18% and 14%, suggesting that some side reactions took place possibly because of the strong reactivity of the alkyl lithium reagents (entries 6 and 7). When 3 equiv. of toluene was used, the reaction completed in 12 h and the product was obtained in a high yield of 91% (entry 8). We tested the reaction with different amount of LDA and found it to be a stoichiometric reaction. To demonstrate the reliability, we carried out a gram-scale reaction and obtained the product in 88% yield (1.04 g, for more condition screening, see Supporting Information online).

Various substituted toluenes were then allowed to react with amide **1a** under present conditions, and the benzoylation products were obtained in good to high yields (Scheme

Table 1 Base promoted benzylic benzoylation of toluene [a)]



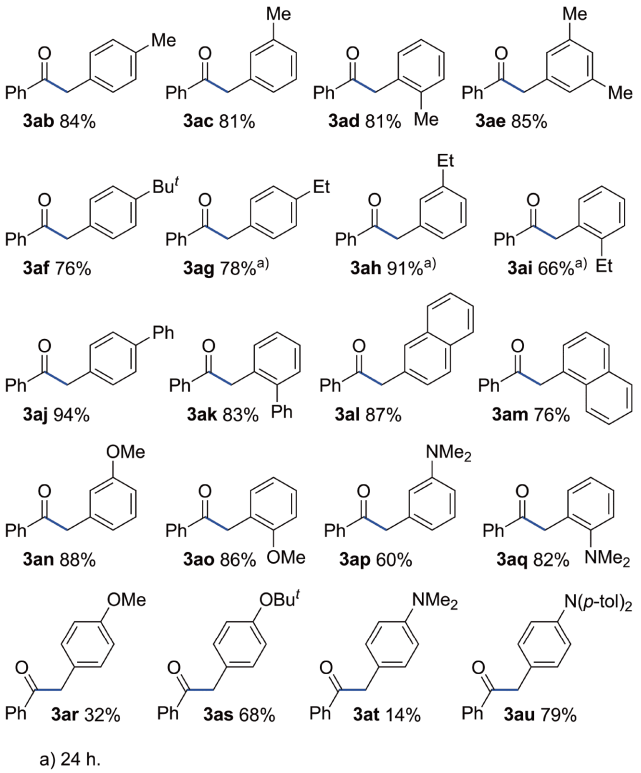
1a **2a** **3aa**

entry	base	**1a** Conv. (%) [b)]	**3aa** yield (%) [b)]
1	LiHMDS	16	< 5
2	NaHMDS	5	< 5
3	KHMDS	7	< 5
4	LDA	99	83
5	LiTMP	100	78
6	$TMSCH_2Li$	100	18
7	*n*-BuLi [c)]	99	14
8 [d)]	LDA	97	92 (91)

a) Reaction conditions: tertiary benzamide **1a** (0.4 mmol), toluene **2a** (0.8 mmol), and base (0.48 mmol) in THF (1.0 mL) at 60 °C for 24 h. HMDS: bis(trimethylsilyl)-amide; LiTMP: lithium 2,2,6,6-tetramethylpiperidide. b) gas mass (GC) yields with *n*-tridecane as an internal standard, isolated yield in parenthesis. c) 2.5 M in hexane. d) Toluene (1.2 mmol), 12 h.

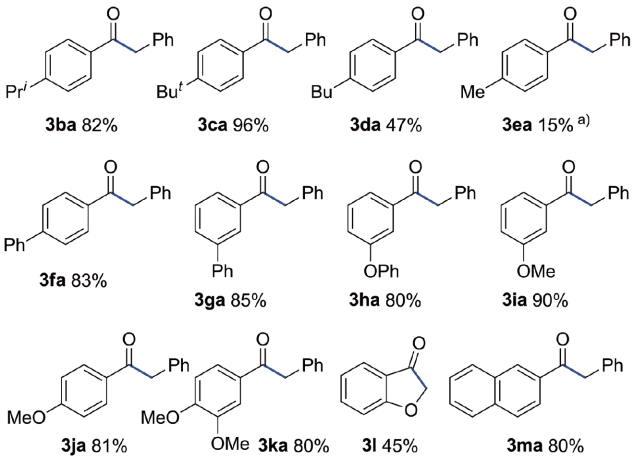
2). It is interesting to note that the benzoylation of ethyl toluenes takes place selectively on the methyl group (**3ag**–**3ai**). Ethylbenzene did undergo the benzoylation but gave the product in a low yield of 19% under the same conditions (see Supporting Information online). *Ortho*-substituted toluenes gave the benzoylation products in moderate to good yields (**3ai**, **3ak** and **3am**) which was lower than that of *para*-substituted toluenes (**3ag**, **3aj** and **3al**), suggesting that the steric hindrance from toluenes would affect the benzoylation reaction but not so significantly. *Ortho*- and *meta*-methoxy toluenes smoothly underwent the benzoylation to give the products in good yields (**3an** and **3ao**). *Para*-methoxy toluene, however, under the same conditions gave a low yield of 32% (**3ar**). *N*,*N*,2-trimethylaniline and *N*,*N*,3-trimethylaniline gave the products in 82% and 60% yields, respectively, while *N*,*N*,4-trimethylaniline gave benzoylation product **3at** in 14% yield. The toluenes with sterically bulky *tert*-butoxyl and diarylamino groups on the *para*-position, however, smoothly afforded the product in good yields (**3as** 68% yield and **3au** 79% yield). These results hinted that the coordination groups near the methyl group of toluenes would be helpful for the benzoylation reactions, while the coordination groups on the *para*-position would inhibit the reactions. The methoxyl and amino groups on the *meta*-position could possibly work as an electron-withdrawing group to facilitate the benzylic benzoylation reactions.

Several benzamides were examined in the reaction with toluene. However, only the steric bulkier *N*,*N*-diisopropyl and *N*,*N*-dicyclohexyl benzamides gave satisfactory yields. *N*,*N*-dimethyl and *N*,*N*-diethyl benzamides did undergo the benzylation reaction but the product was obtained in low yields (see Supporting Information online). We then further investigated the scope of substituted *N*,*N*-diisopropyl benzamides (Scheme 3). 4-Isopropyl benzamide **1b** and 4-*tert*-butyl benzamide **1c** successfully gave the acyl substitution products in good to high yields (**3ba** and **3ca**). However, 4-butyl benzamide **1d** and 4-methyl benzamide **1e** just yielded the corresponding products in much lower yields (**3da** 47% and **3ea** 15%). The reason for their low yields could be the side reactions of the alkyl groups on the benzamides. For an example of 4-methyl benzamide **1e**, the methyl groups of amide and the substitution product (**3ea**) could further undergo the aroylation reactions (see Supporting Information online). Phenyl, phenoxyl and methoxyl benzamides were also suitable substrates to give the substitution products in good to high yields (**3fa**–**3ka**). 2-Methoxyl benzamide **1l** did not react with toluene but underwent the aroylation reaction on its own methoxyl group to give benzofuran-3(2*H*)-one (**3l**) in 45% yield. 2-Naphthamide **1m** reacted with toluene smoothly to afford the desired product in 80% yield (**3ma**). 1-Naphthamide, however, gave the product in a low yield of 8%. In addition, the tertiary benzamide bearing a phenyl group on 2-position failed to react with toluene. These significant reactivity difference revealed that the steric hindrance from benzamides would greatly inhibit the aroylation reaction. Fluorobenzamides, 3-furanyl, and 3-thienyl amide were also tested but failed to undergo the nucleophilic acyl substitution reaction of toluene.



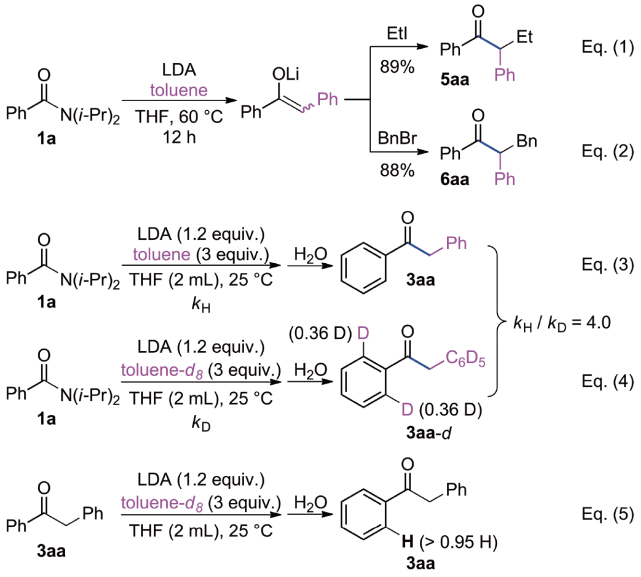
Scheme 2 Scope of toluenes. Conditions: tertiary benzamide **1a** (0.6 mmol), **2** (1.8 mmol), LDA (0.72 mmol), THF (1 mL), 60 °C, 12 h. (color online).

The deprotonation of toluene with LDA is the key step of



a) Aroylation product of amide **1e** and ketone product **3ea** were found as by-products (34% and 29%, respectively).

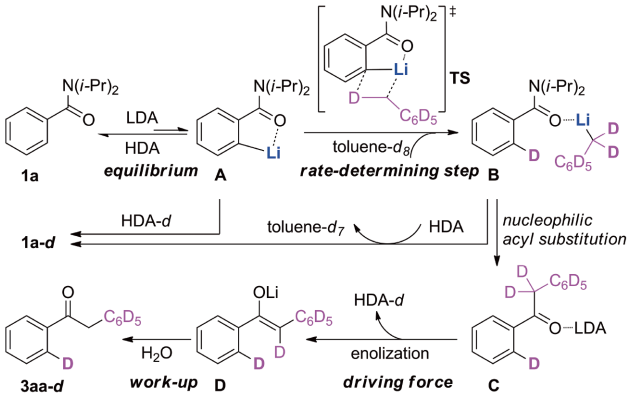
Scheme 3 Scope of amides. Conditions: tertiary benzamide **1** (0.6 mmol), toluene **2a** (1.8 mmol), LDA (0.72 mmol), THF (1 mL), 60 °C, 12 h (color online).



Scheme 4 Control experiments (color online).

acyl substitution reaction with the tertiary benzamide, and it is also of our greatest concern. The direct deprotonation of toluene with LDA in THF, as expected, did not take place. Thus, the amide should also play a very important role in the deprotonation process. The acyl substitution reaction between the amide and benzyl lithium should generate benzyl phenyl ketone (deoxybenzoin) and a new LDA. The α-H of the ketone, for its acidity, would easily undergo the deprotonation reaction with LDA. This easy enolization could provide the driving force for the entire reaction. To demonstrate the formation of an enolate, we carried out the reaction and quenched it with ethyl iodide or benzyl bromide rather than water. As expected, further α-alkylation products were obtained in high yields of 89% and 88%, respectively (Scheme 4, Eqs. (1) and (2)). After getting the thermodynamics validity, we further tried to find dynamics probability about the deprotonation of toluene with LDA. We compared the reaction of the amide with toluene and toluene-d_8 exactly under the same conditions at 25 °C. We monitored the reactions, measured the initiating reaction rates and found out a remarkable primary kinetic isotope effects (KIE = 4.0, Eqs. (3) and (4)), suggesting that the cleavage of the benzylic C–H bond of toluene could be the rate-determining step. More importantly, we found the reaction with toluene-d_8 gave the product with 0.72 deuterium incorporation on the *ortho*-position of carbonyl group (**3aa**-*d*), which revealed that the *ortho*-C–H bond of tertiary benzamide was involved in the reaction. Early quench of this reaction recovered the reactant amide **1a**-*d* with deuterium incorporation (0.64 D). The reaction with large excess of toluene-d_8 (15 equiv.) gave the product with even higher deuterium incorporation (1.02 D, see the Supporting Information online). To find out when the *ortho*-deuteration took place, we carried out the reaction of the ketone product **3aa** and toluene-d_8 and found no any deuterium scrambling product, which excluded the deuteration of the ketone product. Thus, it is very possible that the *ortho*-deprotonation of the tertiary benzamide took place firstly to generate an aryl lithium intermediate, which underwent the deuteration reaction with toluene-d_8 before the benzoylation reaction. The intermediate **A** was prepared *via* the deprotonation of amide with *t*-BuLi and isolated as a dimmer complex, which could undergo the reaction with toluene to give the benzylation product **3aa**. We further measured the kinetic data through initial-rate methods. The reaction was found to be first order in the amide, first order in LDA, first order in toluene, and minus one order in HDA, suggesting a deprotonation equilibrium of the amide and a rate-determining deprotonation of toluene (see Supporting Information online).

On the basis of the results described above, we proposed a possible pathway for the benzoylation of toluene-d_8 as shown in Scheme 5. The deprotonation equilibrium between the tertiary benzamide (pK_a = 37.8 in THF) and LDA (HDA: pK_a = 35.7 in THF) provides *ortho*-lithiation intermediate **A** in low concentration [55–62], which would undergo the σ-bond metathesis reaction with toluene-d_8 *via* a four-membered ring transition state (**TS**). The σ-bond metathesis reaction generates a benzyl lithium intermediate coordinating with the deuterated tertiary benzamide (**B**), which would easily undergo the nucleophilic acyl substitution reaction to give the ketone intermediate (**C**) and LDA. The easy acid-base reaction between the ketone and LDA could provide the driving force of the reaction and give an enolate intermediate **D** [63,64]. After quenched with water, the protonation of the enolate **D** in the work-up process finally afforded the product. The protonation of intermediate **B** with HDA could



Scheme 5 A plausible reaction pathway. For clarity, intermediate **A** was showed in its monomer rather than a possible dimer structure (color online).

also take place to give deuterated amide **1a**-*d* and deuterium-diluted toluene, resulting in the product with deuterium-diluted *ortho*-C–H bond.

3 Conclusions

In summary, we have developed a benzylic aroylation reaction of toluenes with benzamides, which provides a direct and efficient strategy for the synthesis of aryl benzyl ketones. This reaction features a kinetic deprotonative functionalization of toluenes with a relatively weak base LDA, which was actually not basic enough to produce thermodynamically stable carbanion intermediates from either toluene or the tertiary benzamide. Preliminary mechanism studies revealed that the benzylic C–H bond activation of toluene was promoted by the directed *ortho*-lithiation of the tertiary benzamide. In virtue of the driving force provided by the enolization of the ketone product, the deprotonation equilibrium provided a reactive *ortho*-lithiation intermediate, which could undergo the kinetics deprotonation of toluene and trigger the following nucleophilic acyl substitution reaction. The low concentration of the reactive intermediates arising from the deprotonation equilibrium of the relatively weak base LDA could be the key factor for restraining side reactions and improving the selectivity. Further applications based on this unique process are currently ongoing in our group.

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Conflict of interest The authors declare no conflict of interest.

Supporting information The supporting information is available online at http://chem.scichina.com and http://link.springer.com/journal/11426. The supporting materials are published as submitted, without typesetting or editing. The responsibility for scientific accuracy and content remains entirely with the authors.

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