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N-Heterocyclic Carbene-Catalyzed Cross-Coupling of Aromatic Aldehydes with Activated Alkyl Halides

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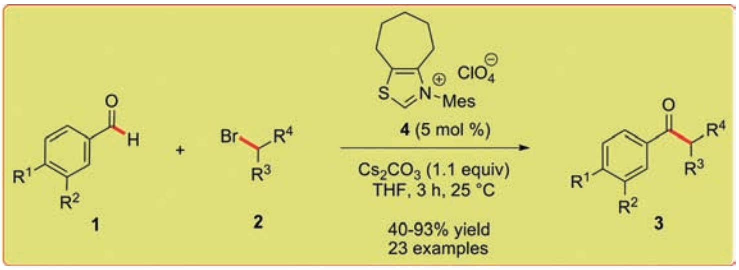
ABSTRACT



N-Heterocyclic carbene-catalyzed umpolung of aldehydes followed by their interception with diarylbromomethanes has been reported. This conceptually novel transition-metal-free cross-coupling of aldehydes with alkyl halides works well at low catalyst loadings and under mild reaction conditions leading to the formation of diaryl acetophenone derivatives in good yields. In addition, α-halo ketones and esters can also be used as aldehyde reaction partners.

N-Heterocyclic carbenes (NHCs)[1] have found widespread applications as versatile ligands in transition-metal catalysis[2] and as organocatalysts in their own right.[3] NHC-organocatalyzed umpolung reactions of aldehydes can lead to the formation of nucleophilic acyl anion intermediates, which can react with various electrophiles, like aldehydes and ketones,[4] imines,[5] and activated, polarized $C{=}C$ double bonds.[6] Intriguingly, however, whereas the NHC-catalyzed

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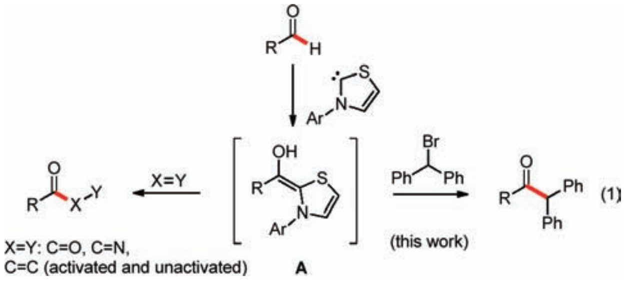
10.1021/ol102626p

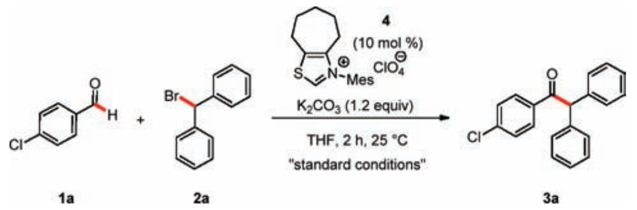
generation of the Breslow intermediate (**A**)[7] and its subsequent interception with sp^2-carbon centered electrophiles are well documented,[3] the analogous reaction with sp^3-carbon-centered electrophiles is extremely rare,[8] and the NHC-catalyzed umpolung addition of aldehydes to diarylbromomethane derivatives are, to the best of our knowledge, unknown (Scheme 1).[9] Very recently, the NHC-*mediated* alkylation of aromatic aldehydes with benzyl halides was reported by Du, Deng, et al.[8a] Herein, we report the NHC-*catalyzed* umpolung of aldehydes, followed by their alkylation using alkyl halides, leading to the formation of acetophenone derivatives.

Scheme 1. NHC-Catalyzed Umpolung of Aldehydes



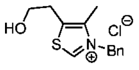
Our present study commenced with the exposure of 4-chlorobenzaldehyde **1a** and (bromomethylene)dibenzene **2a** with thiazolium salt **4**[10] and 1.2 equiv of K_2CO_3 in THF. To our delight, a facile reaction occurred leading to the formation of diphenylethanone derivative **3a** in excellent yield (based on ^1H NMR analysis of the crude product, Table 1, entry 1). This NHC has been designed by us for the dual NHC/Pd catalysis,[10a] which we recently applied successfully in the hydroacylation of unactivated alkenes,[11a] alkynes,[11b] arynes,[11c] and formaldehyde.[11,12] Remarkably, in contrast to this NHC, other common NHCs derived from **5**−**8** are far less effective (entries 2−5).[13] The use of bases such as DBU, Et_3N, and KO*t*-Bu furnished reduced yield of the product (entries 6−8), but Cs_2CO_3 maintained the reactivity, affording **3a** in excellent yield (entry 9). The use of other solvents such as 1,4-dioxane, DME, or Et_2O was not found to be beneficial (entries 10−12). Additionally, the reaction carried out using catalytic amounts of base considerably reduced the yield of product (entry 13) indicating that excess of base is needed for excellent conversion. Finally, reducing the catalyst loading to 5 mol % of **4** and 1.1 equiv of Cs_2CO_3 maintained the reactivity, affording product **3a** in 93% isolated yield (entry 15).

Table 1. Optimization of the Reaction Conditions[a]



entry	variation of the standard conditions[a]	yield of **3a**[b] (%)
1	none	99
2	**5** instead of **4**	5
3	**6** instead of **4**	45
4	**7** instead of **4**	0
5	**8** instead of **4**	0
6	DBU instead of K_2CO_3	80
7	Et_3N instead of K_2CO_3	16
8	KO*t*-Bu instead of K_2CO_3	22
9	Cs_2CO_3 instead of K_2CO_3	99
10	1,4-dioxane instead of THF	52
11	DME instead of THF	87
12	Et_2O instead of THF	2
13	0.2 equiv of K_2CO_3 instead of 1.2 equiv K_2CO_3	28
14	0.05 equiv **4** and 1.1 equiv of K_2CO_3, 3 h	82
15	**0.05 equiv 4 and 1.1 equiv of Cs_2CO_3, 3 h**	**98 (93)**[c]

[a] Standard conditions: 1 (0.25 mmol), NHC•HX (10 mol %), K_2CO_3 (1.2 equiv), THF (2.5 mL), rt and 2 h. [b] The yields were determined by ^1H NMR analysis of crude products using CH_2Br_2 as the internal standard. [c] Isolated yield in parentheses.



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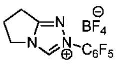

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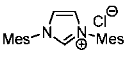

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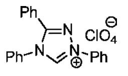

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With these optimized reaction conditions in hand, we examined the substrate scope of this NHC-organocatalyzed umpolung/alkylation reaction (Scheme 2). The parent system worked well, and a variety of electron-withdrawing and electron-donating groups at the 4-position of the ring are well tolerated, leading to the formation of alkylated products in 62−93% (**3a**−**g**) although electron-rich substrates needed higher catalyst loading for efficient conversion. Moreover, 3-substituted aldehydes and disubstituted aldehydes resulted in the smooth conversion to the product (**3h**−**l**). Interestingly, the transformation of terephthalaldehyde resulted in the formation of dialkylated product in 63% yield. Furthermore, this novel alkylation reaction of aldehydes is not only limited

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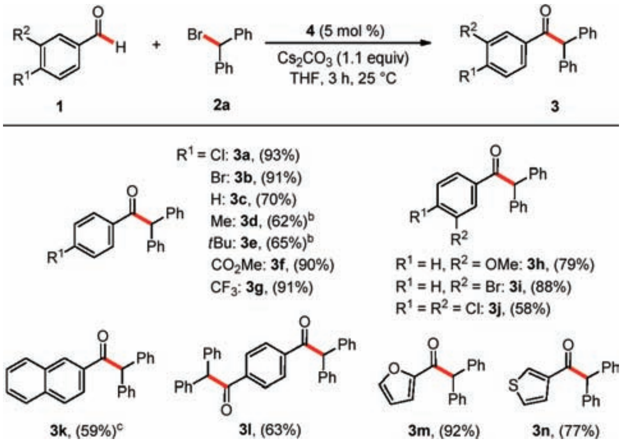
(13) For details, see the Supporting Information.

Scheme 2. NHC-Catalyzed Alkylation of Aldehydes: Variation of the Aldehyde Moiety[a]

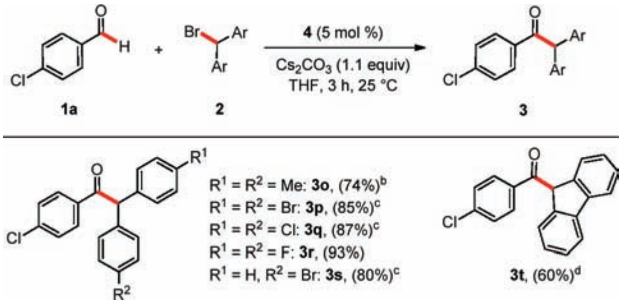


[a] General conditions: **1** (1.0 mmol), **2a** (1.0 mmol), **4** (5 mol %), Cs_2CO_3 (1.1 mmol), THF (10 mL), 25 °C, and 3 h. [b] Using 20 mol % of **4** and 1.4 equiv of Cs_2CO_3. [c] Reaction was run for 24 h.

to the formation of triphenylethanones. Gratifyingly, heterocyclic aldehydes also worked well leading to the formation of the desired products (**3m**,**n**) in good to excellent yields. It is important to note, however, that in preliminary experiments aliphatic aldehydes and 2-substituted benzaldehydes failed to undergo this transformation under the standard reaction conditions.

In view of these interesting results, we further investigated the scope of the reaction using various differently substituted diarylbromomethanes (Scheme 3). Gratifyingly, both electron-withdrawing and electron-donating groups at the 4- and 4′-position of the aromatic ring of **2** are well tolerated, leading to the formation of versatile α,α-diaryl acetophenone derivatives amenable for further functional group manipulations[14] in 74−95% yield (**3o**−**s**). Interestingly, the cyclic 9-bromofluorene also afforded the desired product in 60% yield.

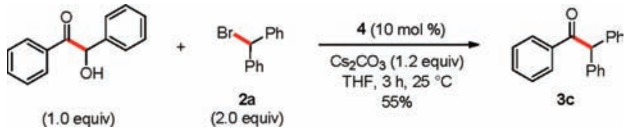
Scheme 3. Variation of Diaryl Bromomethane Moiety[a]



[a] General conditions: **1** (1.0 mmol), **2a** (1.0 mmol), **4** (5 mol %), Cs_2CO_3 (1.1 mmol), THF (10 mL), 25 °C, and 3 h. [b] Starting material **2o** contained small amounts of an impurity. [c] Reaction was run for 24 h. [d] ^{1}H NMR yield of the product.

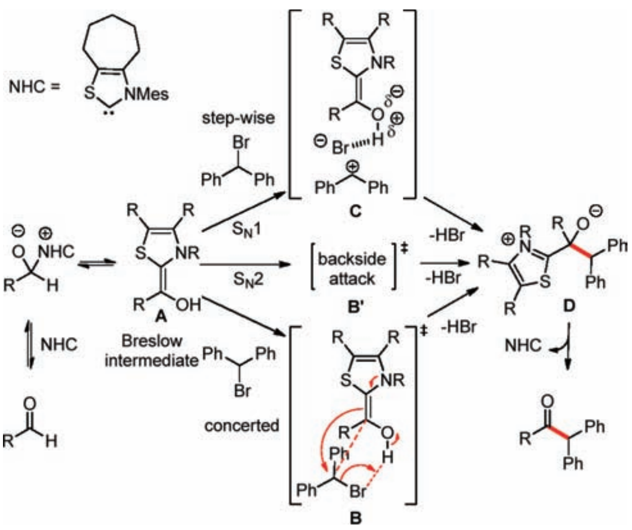
Based on the widely accepted mechanistic proposal for the benzoin and Stetter reaction,[5c,15] we envisaged using benzoin as a masked aldehyde equivalent. Treatment of benzoin with **2a** employing 10 mol % of **4** and 1.2 equiv of Cs_2CO_3 furnished 1,2,2-triphenylethanone **3c** in 55% yield, indicating the reversibility of the formation of Breslow intermediate under the present reaction conditions (Scheme 4).

Scheme 4. Reaction Using Benzoin Instead of Benzaldehyde



A mechanistic rationale for the reaction may be advanced along the following lines (Scheme 5). Following the reversible formation of Breslow intermediate **A**, the nucleophilic enaminol can attack the diaryl bromomethane in a concerted fashion via the five-membered transition state **B** or via a backside attack (**B′**) resembling the S_N2 displacement to furnish the alkoxide intermediate **D**. Alternatively, a stepwise S_N1 pathway involving the formation of a diphenylmethyl carbonium ion can also be invoked (intermediate **C**), where the carbonium ion will be eventually attacked by **A** leading to alkoxide **D**. Liberation of NHC from **D** completes the catalytic cycle and results in the formation of the diaryl acetophenone derivatives.

Scheme 5. Possible Mechanistic Pathways



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(14) See, for example: (a) Popielarz, R.; Arnold, D. R. *J. Am. Chem. Soc.* **1990**, *112*, 3068. (b) Churruca, F.; SanMartin, R.; Carril, M.; Urtiaga, M. K.; Solans, X.; Tellitu, I.; Domínguez, E. *J. Org. Chem.* **2005**, *70*, 3178.

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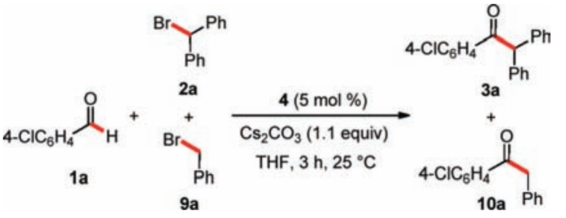
Further insightful experiments seem to favor the stepwise pathway. Reactions carried out using benzyl bromide **9a** as the electrophile in the alkylation reaction did not furnish any alkylated product, although **9a** is known as powerful electrophile in S_N2-type reactions (Table 2, entry 2).[16] In competition experiments carried out using **2a** and **9a**, the product **3a** was observed in 66% yield, and no alkylated product derived from **9a** was observed (entry 3). Thus, the absence of reactivity of **9a** is not due to catalyst deactivation, since the formation of 66% of **3a** clearly demonstrated that the catalyst maintained reactivity.[13]

Table 2. Electrophile Competition Experiments

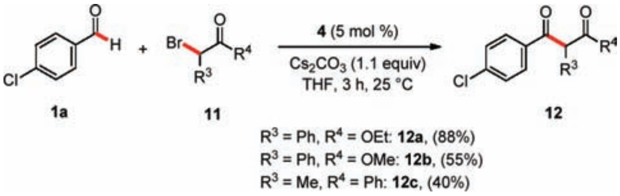


entry	**2a** (equiv)	**9a** (equiv)	yield of **3a**^{a} (%)	yield of **10a**^{a} (%)
1	1	0	98	0
2	0	1	0	0
3	1	1	66	0

^{a} The yields were determined by ^{1}H NMR analysis of crude products using CH_2Br_2 as the internal standard.

Furthermore, this novel NHC-catalyzed alkylation of aldehydes via the umpolung strategy is not limited to diarylbromomethane derivatives. In addition, α-bromo esters and an α-bromo ketone were also successfully employed as the electrophilic coupling partner leading to the formation of β-keto esters and β-diketone in moderate to good yields (Scheme 6).

Scheme 6. Utility of α-Bromo Esters and α-Bromo Ketone



In conclusion, we have uncovered a transition-metal-free NHC-organocatalyzed alkylation reaction of aldehydes via the umpolung of aldehydes leading to the formation of acetophenone, β-diketone, and β-keto ester derivatives. Considering the widespread application of NHCs in organocatalysis, the present methodology represents a rare case of the addition of Breslow intermediate to sp^3-carbon centered electrophiles. Further studies should be directed toward improved understanding of the mechanism, expanding the scope, and developing asymmetric variants of this transformation.

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Supporting Information Available: Experimental procedures and full spectroscopic data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[16] For more details, see the Supporting Information of ref 9.