Organocatalysis

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Intermolecular N-Heterocyclic Carbene Catalyzed Hydroacylation of Arynes**

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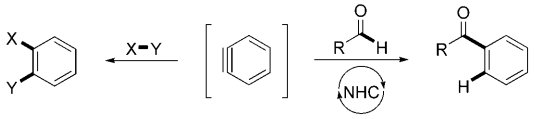
Arynes are highly reactive intermediates endowed with numerous applications in organic synthesis.[1] The introduction of 2-(trimethylsilyl)aryl triflates as mild aryne precursors led to a rapid growth of this field.[2] Arynes have been utilized extensively in transition-metal-catalyzed reactions[3] and, recently, efforts have been devoted to transition-metal-free reactions, which include the initial addition of nucleophiles to arynes and subsequent trapping with electrophiles.[4] This approach allows the formal insertion of arynes into carbon–carbon, carbon–heteroatom, and heteroatom–hydrogen bonds.[1c,5] Interestingly, the insertion of arynes into the C_{formyl}–H bond of aldehydes is unknown.[6] This reaction would not only be mechanistically interesting, but would also provide an attractive transition-metal-free synthetic strategy to a wide range of aryl ketones [Eq. (1)]. In connection with

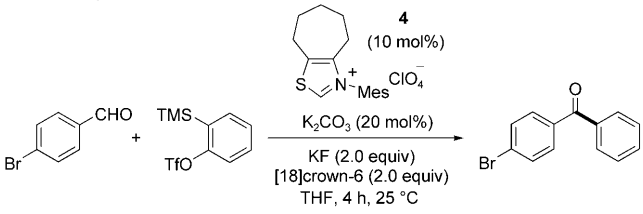


(1)

our recent success in the N-heterocyclic carbene (NHC) catalyzed[7] intramolecular hydroacylation of unactivated alkenes and alkynes,[8] we envisioned that arynes could serve as an acceptor for acyl-anion intermediates generated from aldehydes by a NHC-catalyzed umpolung reaction.[9] Herein, we report the NHC-organocatalyzed formal insertion of arynes into the C_{formyl}–H bond of aldehydes—the intermolecular hydroacylation[10] of arynes. The high levels of chemoselectivity observed in this process are especially intriguing.

Our present study commenced with the NHC-catalyzed reaction of 4-bromobenzaldehyde (**1a**) with the aryne generated in situ from 2-trimethylsilylaryl triflate (**2a**) and 2.0 equivalents each of KF and [18]crown-6. Reacting these substrates in the presence of the carbene generated from **4**[8,11] by deprotonation using K_2CO_3 resulted in the formation of 4-bromobenzophenone (**3a**) in 60% yield (based on GCMS; Table 1, entry 1). Remarkably, in contrast to this NHC, other common NHCs derived from **5**–**8** are far less effective (entries 2–5). The use of DBU and NaH as the base resulted in no conversion (entries 6 and 7), while KO*t*Bu promoted the

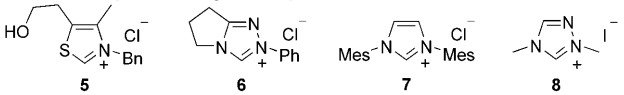
Table 1: Optimization of the reaction conditions.[a]



1a 2a 3a

Entry	Variation of the standard conditions[a]	Yield of **3a** [%][b]
1	none	60
2	**5** instead of **4**	5
3	**6** instead of **4**	4
4	**7** instead of **4**	0
5	**8** instead of **4**	12
6	DBU instead of K_2CO_3	0
7	NaH instead of K_2CO_3	0
8	KO*t*Bu instead of K_2CO_3	78
9	TBAF as the fluoride source	13
10	CsF and CH_3CN instead of KF and THF	30
11	1,4-dioxane instead of THF	27
12	DME instead of THF	49
13	10 mol% K_2CO_3 instead of 20 mol%	75
14	10 mol% KO*t*Bu instead of 20 mol% K_2CO_3	83
15	15 mol% **4** and 15 mol% K_2CO_3	90
16	15 mol% **4** and 15 mol% KO*t*Bu	98 (92)[c]

[a] Standard conditions: **1a** (0.25 mmol), **2a** (0.3 mmol), NHC·HX (10 mol%), K_2CO_3 (20 mol%), KF (0.5 mmol), [18]crown-6 (0.5 mmol), THF (1.0 mL), 25 °C, 4 h. Bn = benzyl, DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene, DME = 1,2-dimethoxyethane, Mes = 2,4,6-trimethylphenyl. [b] The yields were determined by GCMS analysis of the crude reaction mixture using mesitylene as the internal standard. [c] Yield of the isolated product is given in parentheses.



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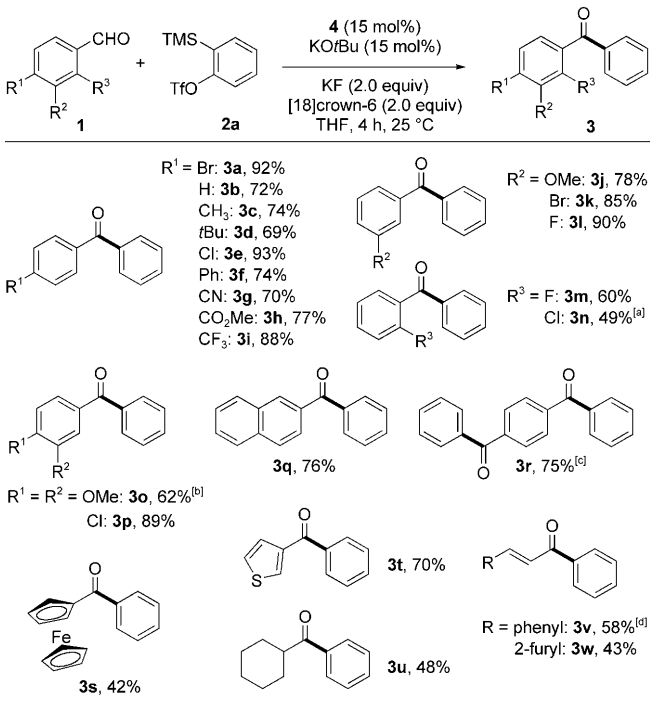
reaction more efficiently than K_2CO_3, and afforded **3a** in 78% yield (entry 8). The use of other fluoride sources such as tetrabutylammonium fluoride (TBAF) and CsF were not found to be beneficial (entries 9 and 10, respectively), and solvents other than THF were not efficient (entries 11 and 12). The use of a 1:1 ratio of **4** and the base improved the yield (entries 13 and 14). Finally, increasing the catalyst loading to 15 mol% and using 15 mol% KO*t*Bu improved the reactivity, with **3a** obtained in 92% yield (entry 16). Under optimized conditions, no products from the direct addition of either the nucleophilic NHC to the electrophilic arynes or of aldehydes to arynes[6] were observed.

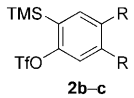
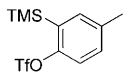
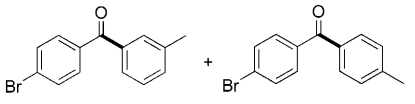
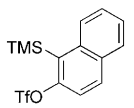
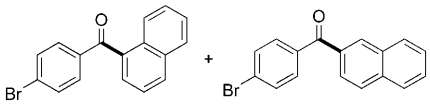
With these optimized reaction conditions in hand, we then examined the substrate scope of this novel aryne insertion reaction (Scheme 1). The unsubstituted parent system worked well, and a variety of electron-donating and electron-withdrawing groups at the 3- and 4-positions of the aromatic ring were well tolerated, and led to benzophenones in 69–93% yield (**3a–l**). As often observed in NHC organocatalysis, 2-substituted benzaldehydes result in significantly lower yields. However, gratefully, 2-fluoro- and 2-chlorobenzaldehyde still provide significant amounts of product (**3m**, **3n**), with **3n** requiring a higher reaction temperature of 60 °C. Furthermore, disubstituted aldehydes as well as 2-naphthaldehyde worked well (**3o–q**). Interestingly, the transformation of terephthalaldehyde resulted in the smooth formation of the disubstituted 1,4-dibenzoylbenzene **3r** in 75% yield. Moreover, this novel transformation is not only limited to benzophenone formation. Gratifyingly, challenging aldehydes such as ferrocenecarboxaldehyde as well as heterocyclic and aliphatic aldehydes also furnished moderate to good yields of the desired products, further expanding the scope of this aryne C–H insertion reaction (**3s–u**). In addition, α,β-unsaturated aldehydes can also be employed in this umpolung reaction, leading to the formation of α,β-unsaturated ketones in moderate yield (**3v**,**w**).

Next, we examined the effect of varying the substituents on the aryne precursor **2** (Table 2). Electronically different 4,5-disubstituted symmetrical aryne precursors **2b** and **2c**



Scheme 1. NHC-catalyzed hydroacylation of arynes: Scope of aldehydes. General conditions: **1** (0.5 mmol), **2a** (0.6 mmol), **4** (15 mol%), KO*t*Bu (15 mol%), KF (1.0 mmol), [18]crown-6 (1.0 mmol), THF (2.0 mL), 25 °C, 4 h. Yields of isolated products are given. TMS = trimethylsilyl, Tf = triflate. [a] The reaction was carried out at 60 °C. [b] The reaction mixture was stirred for 6 h. [c] 0.25 mmol scale. [d] Using 20 mol% of **4** and 20 mol% of KO*t*Bu.

Table 2: Variation of the aryne moiety.[a]

Entry	Aryne precursor	Product(s), yield [%]
1		R = Me: **9b**, 70%
2	**2b–c**	R = O(CH$_2$)O: **9c**, 77%
3	 **2d**	 **9d**, 34% **9d'**, 33%
4	 **2e**	 **9e**, 21% **9e'**, 54%

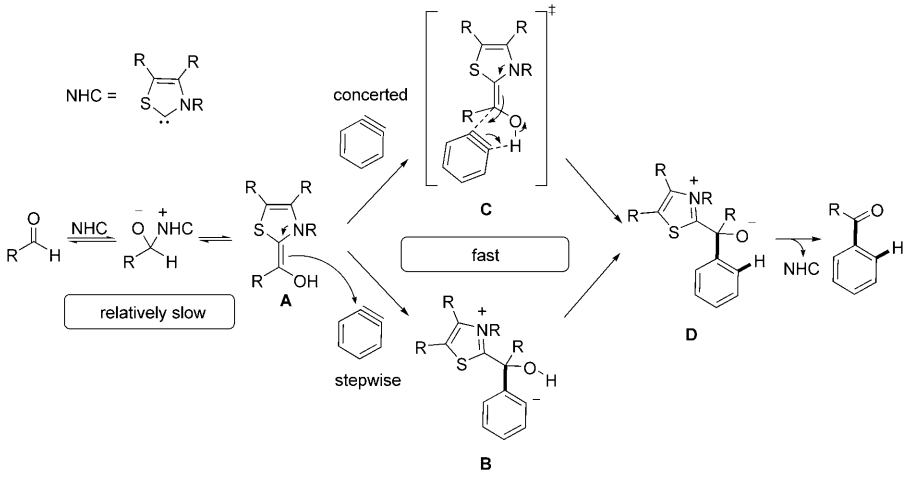
[a] General conditions: **1a** (0.5 mmol), **2** (0.6 mmol), **4** (15 mol%), KO*t*Bu (15 mol%), KF (1.0 mmol), [18]crown-6 (1.0 mmol), THF (2.0 mL), 25 °C, and 4 h. Yields of the isolated products are given.

readily afforded the benzophenones **9b** and **9c** in good yields. Additionally, the reaction of the unsymmetrical aryne generated from **2d** resulted in the formation of separable regioisomers **9d**/**9d′** in a 1:1 ratio (entry 3). Moreover, the unsymmetrical naphthalyne **2e** underwent hydroacylation to afford separable regioisomers **9e** and **9e′** in 75% overall yield (entry 4). The observed regioisomeric ratio in this case revealed the preferential attack of the Breslow intermediate at the less sterically hindered carbon atom of the aryne. Interestingly, competition experiments carried out using electronically dissimilar aryne precursors **2a** and **2c** revealed no preference for either **2a** or **2c**. Hence, it is reasonable to assume that the electronic nature of the aryne is not involved in the rate-determining step.[12]

Further insightful experiments have shed light on the mechanism of this novel transformation. Competition experiments carried out on the coupling of the unsubstituted benzyne formed from **2a** with electronically different aromatic aldehydes showed that the rate of the reaction increases in the order **1c** (4-Me) < **1b** (4-H) < **1h** (4-CO_2Me), with **1h** reacting approximately 11 times faster than **1c** under standard conditions.[12] This finding indicates that the electronic

nature of the aldehydes plays a prominent role in the rate-determining step.[13] The fact that electron-poor aldehydes react faster than the electron-rich ones seems to indicate that the electrophilicity of the aldehydes is more important than the nucleophilicity of the Breslow intermediate[14] in the aryne hydroacylation.

These observations can be summarized in a mechanistic proposal (Scheme 2). After the reversible formation of the Breslow intermediate **A**,[12,15] the in situ formed aryne can be attacked in a stepwise manner to give the alkoxide intermediate **D** via the intermediate **B**.[16] Alternatively, a concerted transition state[8,17] **C** can also be invoked in analogy to the reaction of 1,3-dipoles with arynes.[18] Both of these steps seem to be faster than the formation of the Breslow intermediate.[12] Release of the NHC catalyst closes the catalytic cycle and results in the formation of the observed ketone product.



Scheme 2. Proposed mechanism of the reaction.

In conclusion, we have developed a transition-metal-free NHC-organocatalyzed intermolecular hydroacylation of arynes to furnish benzophenones as well as α,β-unsaturated and other aryl ketones. This is the first time that NHCs have been found to be compatible with arynes, and the present study reveals an unprecedented formal insertion of arynes into C_{formyl}–H bonds under mild conditions. Further studies on the mechanistic aspects of this reaction as well as related NHC-organocatalyzed reactions are ongoing.

Experimental Section

General procedure: The thiazolium salt **4** (27.9 mg, 0.075 mmol), dry KO*t*Bu (8.4 mg, 0.075 mmol), KF (58.1 mg, 1.0 mmol), and [18]crown-6 (264.3 mg, 1.0 mmol) were added in a glove box to a flame-dried screw-capped test tube equipped with a magnetic stir bar. The aldehyde **1** (0.5 mmol) was then added to this mixture outside the glove box under argon. The mixture was dissolved in THF (2 mL) and 2-(trimethylsilyl)phenyl triflate **2a** (0.179 g, 146 μL, 0.6 mmol) was added to the stirred solution. The resultant mixture was stirred at 25 °C for 4 h. The mixture was then diluted with EtOAc (2 mL) and filtered through a pad of silica gel and eluted with EtOAc (10 mL). Evaporation of the solvent followed by column chromatography afforded the corresponding aryl ketone **3**.

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