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Aza-Morita–Baylis–Hillman reactions catalyzed by a cyclopropenylidene†

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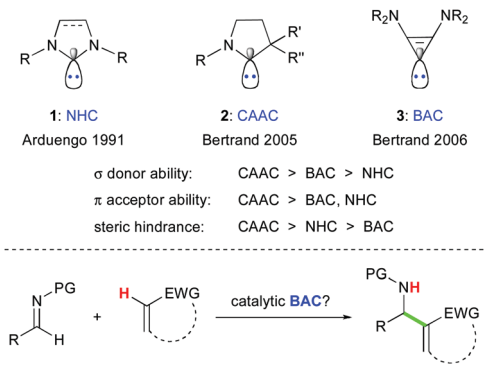
Catalysis using a bis(dialkylamino)cyclopropenylidene (BAC) has been developed, which relies on a formal *umpolung* activation of Michael acceptor pro-nucleophiles. Various aza-Morita–Baylis–Hillman reactions between aromatic, heteroaromatic, or aliphatic imines and acyclic or cyclic α,β-unsaturated ketones and carboxylic acid derivatives have been catalyzed by a BAC under mild conditions. Functionalities such as unprotected amino and hydroxy groups have been tolerated. The catalyst loading was decreased to 1 mol% without loss of activity. The BAC catalyst was shown to be substantially more active than a cyclic (alkyl)(amino) carbene (CAAC), *N*-heterocyclic carbenes (NHCs), and *P*- or *N*-centered Lewis bases.

Since the isolation of the first carbene species over 25 years ago,[1] *N*-heterocyclic carbenes [NHCs (**1**)] have proved to be extremely versatile in both inorganic and organic chemistry (Scheme 1). Due to their unique electronic and steric properties as well as structural flexibility,[2] σ donors **1** have been shown to stabilize elements in their low-oxidation state,[3] and to act as ligands in metal catalysis.[4] In addition, NHCs have proved to be unique Lewis bases for catalytic *umpolung* of aldehydes and Michael acceptors,[5] as well as Lewis acidic pro-nucleophiles.[6] Moreover, NHCs have been critical components in dual catalysis with acid or Pd redox co-catalysts.[7]

In order to further develop the field of carbene catalysis, it is important to increasingly explore the potential of non-NHC carbenes.[8] In this context, Bertrand *et al.* have recently discovered distinct species that can be isolated, cyclic (alkyl)(amino)carbenes [CAACs (**2**)][9] and bis(dialkylamino)cyclopropenylidenes [BACs (**3**);[10] Scheme 1]. CAACs (**2**) have to be synthesized in a multi-step sequence;[9] the N–C–N motif of **1** has been replaced by an N–C–C unit bearing a quaternary carbon atom adjacent to the carbene centre, which renders CAACs both more sterically demanding and stable than NHCs.[9a] In addition, CAACs have been shown to display both stronger σ donor[9a] and π acceptor[11] abilities than NHCs.[8a,12b] While CAACs have been used as ligands in stoichiometric[12] and catalytic[9a,13] metal complex applications, CAAC organocatalysis has not been reported yet. BACs (**3**) bear a carbocyclic core; these unique and stable carbenes can be synthesized in a straightforward two-step protocol.[10a] Due to the distance of the bulky dialkylamino groups to the carbene centre, BACs have been considered the least sterically hindered carbenes.[12b,14b] Moreover, BACs have been shown to be stronger σ donors[14b] than NHCs, whereas the π acceptor ability[11] has been described as comparable to NHCs. BACs have been sporadically used as ligands in stoichiometric metal complexes,[14] as well as in Ni catalysis.[15]



Scheme 1 Properties of NHC, CAAC, and BAC – proposed BAC catalysis.

In our program exploiting low-oxidation main group elements in catalysis, we have become interested in examining BACs (**3**) as we anticipated a distinct reactivity profile due to their strong σ donor ability *and* unique non-sterically demanding shape compared to carbene types **1** and **2**.[8] To date, sporadic BAC organocatalysis has been reported for the *umpolung* of aldehydes.[16] Inspired by a recently published NHC catalysis,[17] we have examined aza-Morita–Baylis–Hillman (aza-MBH) reactions[18] between various imines and acyclic or cyclic Michael acceptors (PG = *N*-protecting group; EWG = electron-withdrawing group; Scheme 1). The aza-MBH reaction is one of the most important C–C bond formations

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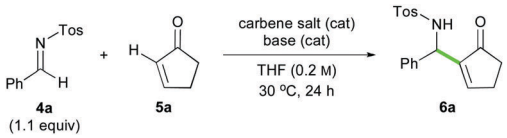
due to its atom economy and high synthetic value.[18] Typically, amine or phosphine catalysts[18,19] form a zwitterionic enolate through conjugate addition to a Michael acceptor; the *in situ* generated nucleophile undergoes subsequent addition to an imine, followed by proton transfer and regeneration of the Lewis base catalyst.[18c] In certain cases, an acid co-catalyst has been shown to facilitate C–C bond formation, which has proved to be critical for asymmetric catalysis; the acid may be included in the Lewis base catalyst,[20] or may act as a separate co-catalyst.[21] Although various catalyst systems have been developed, a general aza-MBH reaction with low catalyst loading and mild conditions for a broad variety of electrophiles *and* pro-nucleophiles has remained a challenge.[18–21] We report here rare BAC-catalyzed C–C bond formations, which rely on a formal *umpolung* activation of Michael acceptor pro-nucleophiles.

In an initial experiment, cyclopropenylidene **3a** was generated *in situ* from its bench-stable salt **3a**·HBF_4 and a potassium amide[10a] (Scheme 2). In order to confirm the formation of Lewis base **3a**, the latter was reacted with a Lewis acid, triethyl borane, to form a donor–acceptor complex, **3a**·BEt_3 (Scheme 2). This reaction was monitored by ^{11}B NMR spectroscopy (see ESI†): the signal at 87 ppm (BEt_3) was cleanly converted to a peak at −13 ppm, which is consistent with the formation of a boron–ate complex involving a carbene.[22] In this context, $KN(SiMe_3)_2$ was reacted in a control experiment with BEt_3 to form a boron–ate complex that displays a distinct chemical shift (δ = −1.7 ppm). To the best of our knowledge, **3a**·BEt_3 represents the first example of a boron–ate complex involving a BAC. Next, the *in situ* generated carbene **3a** (10 mol%) was used to trigger an aza-MBH reaction between benzaldehyde-derived *N*-tosyl imine **4a** (1.1 equiv.) and cyclopentenone (**5a**) in THF (Scheme 2). Adduct **6a** was obtained in 26% yield, which confirmed that a catalyst turnover was possible although the reaction conditions had to be optimized.

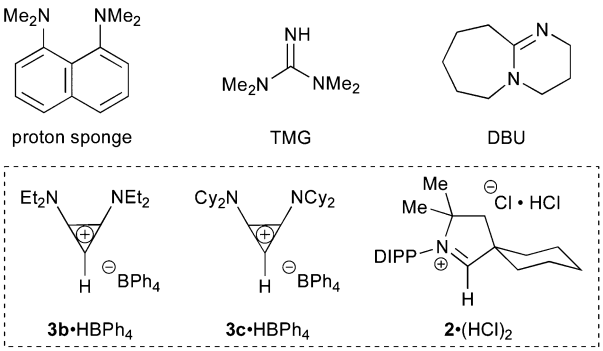
Hence, a base screening[14a] was carried out (Table 1). In contrast to the initial carbene catalysis (entry 1), the control reaction with $KN(SiMe_3)_2$ alone failed to give product **6a** (entry 2). The use of other alkali metal amides or alkoxides did not improve the initial result (entries 3–8). Among alkali metal carbonates, the use of the cesium base gave **6a** in the highest yield (57%; entry 12). The use of metal-free organobases revealed that DBU was the best co-catalyst (79% yield; entry 15); a control experiment with DBU alone failed

Table 1 Screening of bases and carbene salts[a]

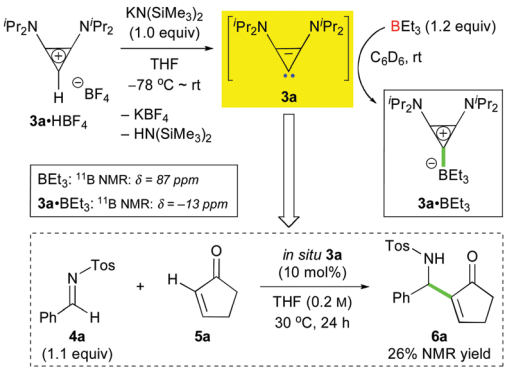


Entry	Carbene salt [mol%]	Base [mol%]	Yield[a] [%]
1	**3a**·HBF_4 [10]	$KN(SiMe_3)_2$ [10]	26
2	—	$KN(SiMe_3)_2$ [10]	NR[b]
3	**3a**·HBF_4 [10]	$NaN(SiMe_3)_2$ [10]	17
4	**3a**·HBF_4 [10]	$LiN(SiMe_3)_2$ [10]	10
5	**3a**·HBF_4 [10]	LiN^iPr_2 [10]	12
6	**3a**·HBF_4 [10]	LiTMP [10]	33
7	**3a**·HBF_4 [10]	NaO^tBu [10]	NR[b]
8	**3a**·HBF_4 [10]	KO^tBu [10]	24
9	**3a**·HBF_4 [10]	Li_2CO_3 [10]	NR[b]
10	**3a**·HBF_4 [10]	Na_2CO_3 [10]	26
11	**3a**·HBF_4 [10]	K_2CO_3 [10]	36
12	**3a**·HBF_4 [10]	Cs_2CO_3 [10]	57
13	**3a**·HBF_4 [10]	Proton sponge [10]	NR[b]
14	**3a**·HBF_4 [10]	TMG [10]	60
15	**3a**·HBF_4 [10]	DBU [10]	79
16	—	DBU [10]	NR[b]
17[c]	**3a**·HBF_4 [5]	DBU [5]	94
18[c]	**3b**·$HBPh_4$ [5]	DBU [5]	34
19[c]	**3c**·$HBPh_4$ [5]	DBU [5]	26
20[c]	**2**·$(HCl)_2$ [5]	DBU [5]	NR[b]
21[d]	**3a**·HBF_4 [1]	DBU [1]	90

TMP = 2,2,6,6-tetramethylpiperidide; TMG = 1,1,3,3-tetramethylguanidine; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; DIPP = 2,6-diisopropylphenyl



[a] Yields have been determined by ^1H NMR analysis of a reaction aliquot *vs.* Bn_2O. [b] NR = no reaction; product **6a** was not detectable – only unreacted **4a** and **5a** were detected (^1H NMR analysis of a reaction aliquot). [c] THF (0.3 M), 30 °C, 30 h. [d] THF (0.3 M), 30 °C, 72 h. Solvent screening (conditions in entry 15) – dioxane, dimethoxyethane, toluene, ethyl acetate: 50–65%; Et_2O, ^{t}BuOMe, $C_6H_5CF_3$, MeCN: 24–46%; in our hands, chlorinated aliphatic solvents have not been tolerated.



Scheme 2 Initial experiments with *in situ* generated BAC **3a**.

to give **6a** (entry 16). At 5 mol% loading using DBU as a base, the activity of various carbene salts was examined; the use of BAC precursor **3a**·HBF_4 gave product **6a** in 94% yield, and proved to be substantially more active than its BAC analogues **3b**·$HBPh_4$ and **3c**·$HBPh_4$ as well as CAAC salt **2**·$(HCl)_2$ (entries 17–20).[14a] Remarkably, even at 1 mol% loading the combined use of **3a**·HBF_4 and DBU gave product **6a** in 90% yield (entry 21). This C–C bond formation represents the first BAC catalysis with **3a**.[16] In addition, this formal *umpolung* activation of a Michael acceptor is clearly distinct from the reported BAC catalysis, which has triggered *umpolung* of aldehydes.[16] It is noted that NHCs and conventional aza-MBH catalysts, such as *N*- or *P*-centered Lewis bases, proved to

be significantly less reactive (see ESI†). Preliminary stoichiometric experiments using *in situ* formed carbene **3a** and imine **4a** or Michael acceptor **5a** failed to give conclusive data regarding initial adduct formation; we assume a classic aza-Morita–Baylis–Hillman mechanism.[18c]

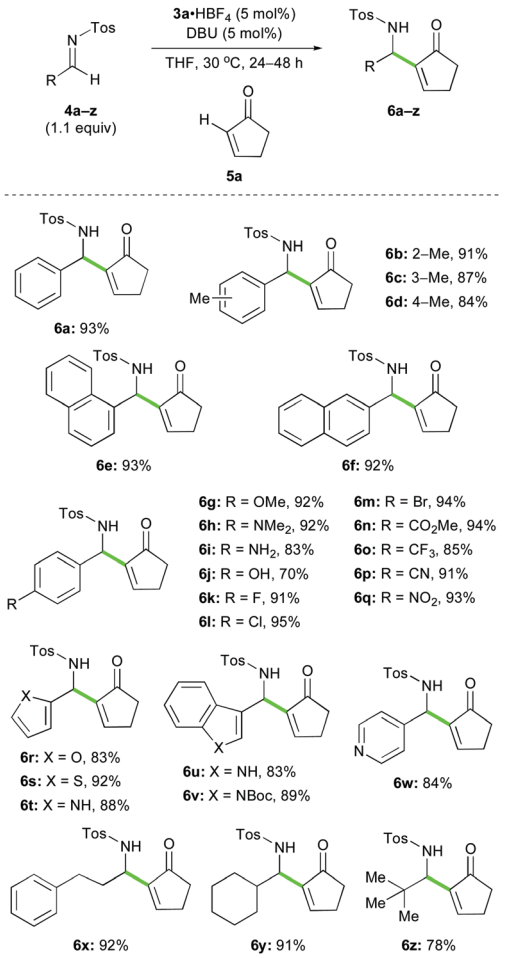
Next, the imine scope was examined by using cyclopentenone (**5a**) as pro-nucleophile in the presence of *in situ* formed cyclopropenylidene **3a** (5 mol%) at 30 °C (Table 2). The use of various aromatic imines proved to be effective resulting in the formation of products **6a–q** in 70–95% isolated yields. It is noted that *o*-, *m*-, and *p*-substitution as well as electron-donation and -withdrawal were tolerated. Likewise, accessible functionalities include amino, hydroxy, ester, cyano, and nitro groups (**h–j**, **n**, **p–q**). In addition, various heterocyclic imines with distinct electron demand proved to be excellent substrates giving products **6r–w** in 83–92% isolated yields. It is noted that primary, secondary, and tertiary aliphatic imines were converted to products **6x–z** in 78–92% isolated yields.

Furthermore, the scope of Michael acceptors was examined by using imine **4a** as electrophile; here, a catalyst system composed of **3b**·HBPh$_4$ and DBU at 40 °C proved to be most effective (10 mol%; Table 3). Various Michael acceptors were shown to be compatible with the *in situ* formed cyclopropenylidene catalyst under mild conditions. Cyclic *and acyclic* α,β-unsaturated ketones were converted to products **6ab–ae** in 90–95% isolated yields. Various α,β-unsaturated carboxylic acid derivatives have reacted in an aza-MBH fashion as well: esters, amides, and a nitrile were α-alkylated to give adducts **6af–aj** in 74–96% isolated yields. This BAC-triggered regioselectivity contrasts NHC-induced β-alkylation[23] of the same type of pro-nucleophiles in the absence[23a,c,d] or the presence[23b] of an imine. This distinct BAC catalysis has proved to go far beyond the reported NHC catalysis in terms of efficiency and scope.[17]

Finally, the potential for asymmetric BAC catalysis was demonstrated by using Gravel's enantiopure carbene precursor **3d**·HBPh$_4$[16a] (Scheme 3).

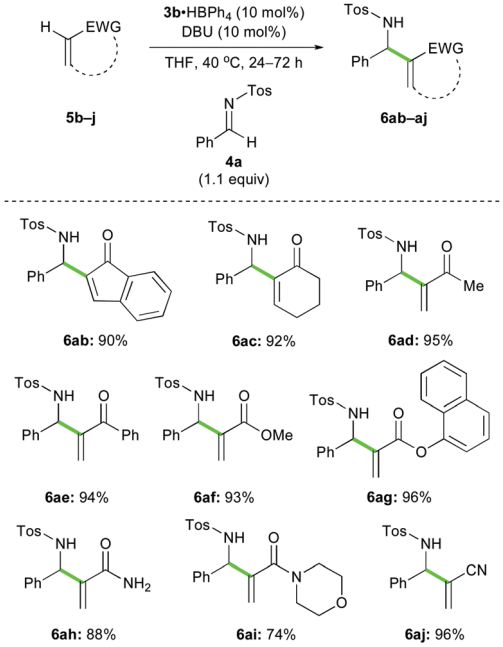
In summary, a rare BAC catalysis has been uncovered, which is clearly distinct from related catalyses.[16,17] Aza-MBH reactions between aromatic, heteroaromatic, or aliphatic imines and acyclic or cyclic α,β-unsaturated ketones and carboxylic acid derivatives

Table 2 Scope of imines[a]

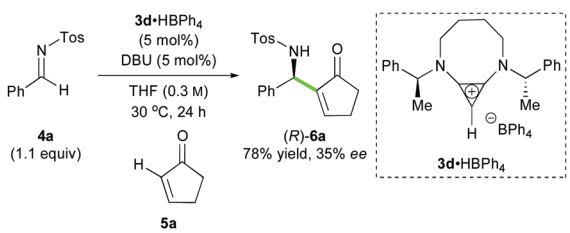


[a] Yields refer to isolated products **6a–z**, after purification by preparative thin-layer chromatography (PTLC) on silica gel.

Table 3 Scope of Michael acceptors[a]



[a] Yields refer to isolated products **6ab-aj**, after purification by preparative thin-layer chromatography (PTLC) on silica gel.



Scheme 3 Asymmetric induction with the enantiopure BAC precursor **3d**·HBPh$_4$.

have proceeded under mild conditions. Important functionalities such as unprotected amino and hydroxy groups have been tolerated. The catalyst loading was decreased to 1 mol% without loss of activity. The BAC catalyst was shown to be substantially more active than a CAAC, NHCs, and *P*- or *N*-centered Lewis bases. This novel cyclopropenylidene chemistry is expected to impact on carbene-catalyzed reactions, and our current investigations are focused on the development of highly asymmetric BAC catalysis.

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