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Bis(amino)cyclopropenylidenes as Organocatalysts for Acyl Anion and Extended Umpolung Reactions**

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The use of N-heterocyclic carbenes (NHCs) as organocatalysts has gained considerable attention in recent years because of their unique properties and modes of reactivity.[1] In addition to their use as acyl anion equivalents in the reversal of reactivity (umpolung) of aldehydes,[2] they have also been utilized in the extended umpolung of α-functionalized aldehydes,[3] in the umpolung of activated olefins,[4] and as nucleophilic catalysts.[5] As a result of this versatility, significant effort has gone into the design of NHC catalysts that are tailored to particular reactions and reaction types. To date, the most commonly used precatalysts all feature a five-membered nitrogen-containing heterocyclic core, as present in 2-thiazolium, 1,2,4-triazolium, imidazolium, and imidazolinium salts. The usefulness of each of these NHC families is now well established and new substitution patterns are constantly being introduced to improve or modulate reactivity. Although many studies have shown the catalytic properties of NHCs to be greatly influenced by often subtle steric and electronic effects, the search for new properties and complementary reactivity would benefit from the introduction of entirely new catalytic architectures.[6]

The bis(amino)cyclopropenium motif, which was first explored in the 1970s,[7–9] received renewed attention in 2006 when Bertrand and co-workers successfully characterized by X-ray crystallography the free carbene bis(diisopropylamino)cyclopropenylidene (*i*PrBAC) derived from bis(amino)cyclopropenium salt **1** (Figure 1).[10] The thermal stability of this carbene stands in contrast to the NHCs derived from commonly used thiazolium and triazolium salts,

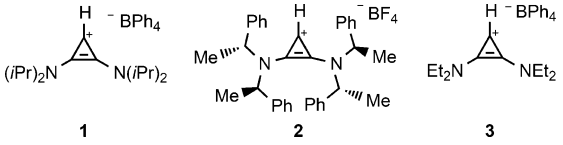

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Figure 1. Bis(amino)cyclopropenium salts.

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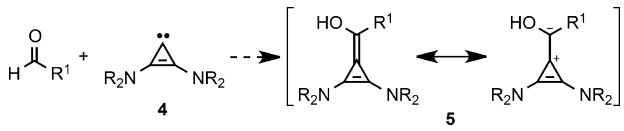
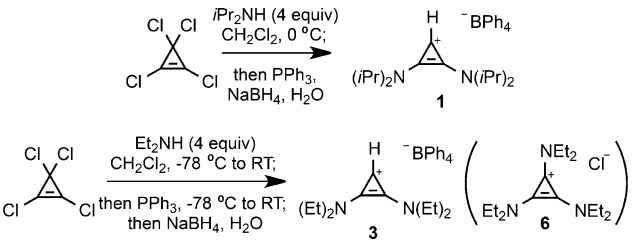
which have proven elusive toward isolation and characterization.[11] This stability is due not only to the bulky isopropyl substituents, but also to the electron-donating nitrogen substituents, the π-aromatic character of the singlet state, and to a significant degree of σ-aromaticity.[12] Thus, even sterically unhindered BACs (such as **4**) may have a sufficient lifetime in solution to participate in organocatalytic reactions (Scheme 1). Despite the apparent improbability of BACs



Scheme 1. Formation of an enolamine between a BAC and an aldehyde.

forming the required strained enolamine (**5**),[13] the possibility of using carbene catalysts that are readily accessible and less sterically hindered than commonly used 1,2,4-triazolium salts prompted this study. To our knowledge, there is no report on the use of BACs as organocatalysts apart from a brief mention by Tamm and co-workers, who used the hindered chiral BAC **2** in a benzoin reaction.[14] Herein, we describe our preliminary results on the use of BACs in representative umpolung reactions. As detailed below, differences between the reactivity of these carbenes and those derived from thiazolium and triazolium salts are striking and should spur further investigations.

The bis(amino)cyclopropenium salt *i*PrBAC·HBPh$_4$ (**1**) was prepared from commercial tetrachlorocyclopropene according to a known procedure (Scheme 2).[10a] Preparation and isolation of the less hindered salt EtBAC·HBPh$_4$ (**3**) proved more difficult because the procedure reported by Yoshida[8a,b] afforded mainly tris(diethylamino)cyclopropenium chloride (**6**)[15] and only small amounts of **3**, the purification of which failed. Addition of the amine at −78 °C in the first step was found to be necessary to minimize

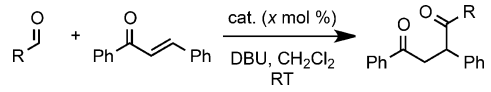


Scheme 2. Preparation of bis(amino)cyclopropenium salts **1** and **3**.

the trisubstitution of tetrachlorocyclopropene. The recrystallization of **3** was also more difficult than that of **1**, and it was found that the use of methanol effectively removed all phosphorus-containing by-products while selectively providing **3** in a fine crystalline form. This modified one-pot procedure reliably provides 30–40% yield of **3** on a gram scale.

The catalytic properties of **1** and **3** were first examined by using the intermolecular Stetter reaction.[16] Various aldehydes were reacted with *trans*-chalcone, the latter being a useful benchmark because it has been used in a number of reported Stetter reactions. A preliminary base screening showed that the use of tertiary amines does not lead to any reaction, presumably because the precatalysts are not deprotonated under these conditions. However, both DBU and cesium carbonate proved highly effective in precatalyst activation. The large difference in catalytic efficiency between **1** and the less hindered **3** became readily apparent upon reaction with methyl *p*-formylbenzoate (Table 1, entries 1–3).

Table 1: Stetter reaction using precatalysts **1** and **3**.[a]

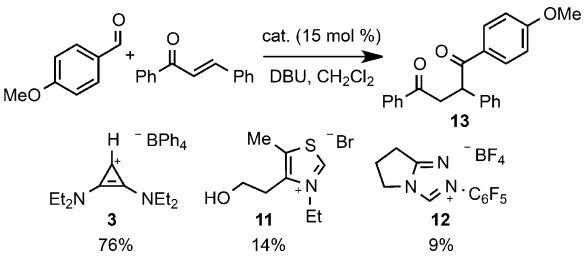


Entry	R	Catalyst	Cat. loading (*x*)	Product	Yield [%][b]
1	*p*-$CO_2MeC_6H_4$	**1**	10	**7**	< 10[c]
2	*p*-$CO_2MeC_6H_4$	**1**	30	**7**	24
3	*p*-$CO_2MeC_6H_4$	**3**	10	**7**	98
4	2-furyl	**3**	10	**8**	99
5	*m*-$MeOC_6H_4$	**3**	10	**9**	72
6	C_6H_5	**3**	20	**10**	65

[a] All reactions were run with 1–1.7 equiv of aldehyde. Reactions in entries 1,3, and 4 were run for 1.5-3 hrs. Reactions in entries 2, 5, and 6 were run for 16 h. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene. [b] Yield of isolated pure product. [c] Product not isolated.

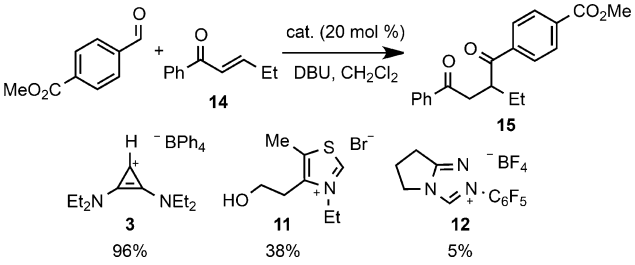
Indeed, only small amounts of the Stetter product were obtained using **1**, even at a loading of 30 mol% and after an extended reaction time. By contrast, the product was obtained in nearly quantitative yield using 10 mol% of **3**. This result highlights the importance of steric hindrance in this family of catalysts, as well as the necessity to prepare unhindered ones through a reliable route. Other aromatic and heteroaromatic aldehydes could be used successfully in Stetter reactions catalyzed by **3** (Table 1, entries 4–6). Interestingly, and in contrast to analogous reactions using thiazolium and triazolium salts, the formation of benzoin products during the course of the reaction was not observed.[17]

Stetter reactions involving particularly challenging substrates were then performed using **3** as the catalyst, and compared to reactions using the commonly employed salts **11** and **12**. Bis(amino)cyclopropenium salt **3** efficiently catalyzes the Stetter reaction of even electron-rich aldehydes such as *p*-methoxybenzaldehyde (Scheme 3). The use of electron-rich aldehyde substrates represents an ongoing challenge in various NHC-catalyzed processes. This often-encountered difficulty is illustrated by the poor yields obtained through the



Scheme 3. Stetter reaction of *p*-methoxybenzaldehyde employing different carbene precursors. Yields of **13** are given for each of the three catalysts (**3**, **11**, and **12**).

use of thiazolium salt **11** or triazolium salt **12** under otherwise identical conditions. The use of simple β-alkyl substituted ketone acceptors in the Stetter reaction also represents a significant challenge. The more electrophilic β-alkyl nitroolefins[18] and alkylidene malonates[17b,19] have been employed, but these acceptors do not provide direct access to the ubiquitous and useful 1,4-diketone motif. Gratifyingly, the Stetter reaction between methyl *p*-formylbenzoate and enone **14** provided an excellent yield of the addition product under the catalysis of bis(amino)cyclopropenium salt **3** (Scheme 4). By contrast, the use of thiazolium salt **11** or

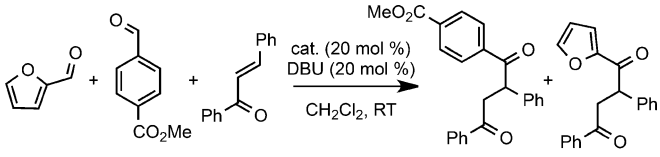


Scheme 4. Stetter reaction of an alkyl-substituted acceptor employing different carbene precursors. Yields of **15** are given for each of the three catalysts (**3**, **11**, and **12**).

triazolium salt **12** only afforded slow and incomplete conversion to the Stetter product. In the case of triazolium **12**, the competing benzoin product was obtained in 73% yield. In the reactions catalyzed by **3** (Schemes 3 and 4), the mixture remained remarkably clean throughout, consisting essentially of product, catalyst, and unreacted starting material. In line with with previous results using **3**, and in contrast to reactions using catalysts **11** and **12**, no competing benzoin by-products were observed.

The reactivity of thiazolium- and triazolium-based catalysts is known to be affected by the bulkiness of the aldehyde reactant.[18c,20] By contrast, the unhindered nature of the reactive carbene center in EtBAC may make it relatively less susceptible to steric factors. To test this hypothesis, competition reactions were performed between furfural and methyl 4-formylbenzoate in the presence of *trans*-chalcone (Table 2). As anticipated, the use of EtBAC·$HBPh_4$ (**3**) as precatalyst led preferentially to Stetter product **7**, formed from the more hindered but more electron-poor methyl 4-formylbenzoate.

Table 2: Aldehyde competition reaction.

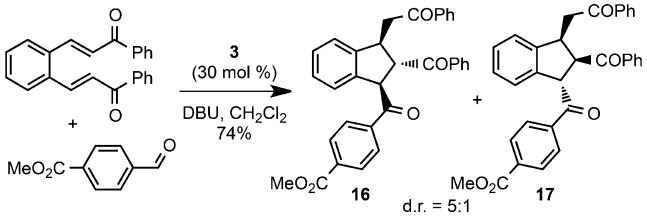


Entry	Catalyst	Product ratio **7**/**8**[a]	Combined yield [%][b]
1	**3**	85:15	99
2	**11**	37:63	80
3	**12**	12:88	85

[a] Determined by ^{1}H NMR spectroscopy on the crude reaction mixture. [b] Isolated as a mixture of Stetter products **7** and **8**.

In comparison, the use of thiazolium **11** or triazolium **12** favored Stetter product **8**, formed from the less hindered furfural. Control experiments show that these reactions are under kinetic control (see the Supporting Information).

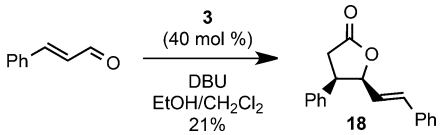
The success of the EtBAC-catalyzed Stetter reaction can be transposed to our previously disclosed domino Stetter–Michael reaction, as shown in Scheme 5.[17c,21] The preferred



Scheme 5. Domino Stetter–Michael reaction.

formation of the all-*trans* diastereomer **16** is presumably the result of thermodynamic control under the basic reaction conditions.

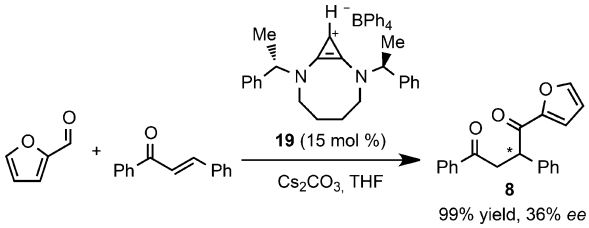
In addition to their ability to catalytically form acyl anion equivalents as demonstrated in the Stetter reaction, BACs can also display homoenolate-type reactivity in the presence of enals. Indeed, when cinnamaldehyde was left to react with catalytic amounts of **3** under basic conditions, *cis*-lactone **18** was formed through extended umpolung (Scheme 6).[22]



Scheme 6. Lactone formation through homoenolate reactivity.

Although the yield of this unoptimized transformation is modest, the ability of catalyst **3** to mediate both acyl anion equivalent and homoenolate reactions is remarkable.

Given the straightforward and modular synthesis of BAC precatalysts, we decided to highlight this aspect through the rapid preparation of a chiral analogue. To this end, catalyst **19** was prepared in a single step from a chiral diamine[23] (see the Supporting Information). This catalyst was then tested in an enantioselective Stetter reaction between furfural and chalcone, for which excellent yield and moderate enantioselectivity were achieved (Scheme 7). Enantioselective Stetter reactions involving unsaturated ketones have been notoriously difficult to accomplish with a high degree of enantioselectivity using chiral triazolium salts.[17a,24] Current efforts are thus aimed at designing more rigid BAC catalysts that can better provide facial selectivity in the Stetter reaction of enones.



Scheme 7. Enantioselective Stetter reaction.

In summary, BACs have been shown to be a viable and effective family of catalysts for both acyl anion and extended umpolung transformations. Stetter reactions involving notoriously unreactive substrates can be mediated with high efficiency using BACs compared with their NHC counterparts. The short and modular nature of BAC synthesis lends itself well to the rapid preparation of a diverse set of precatalysts. The design of BACs with varying electronic properties as well as various chiral scaffolds for enantioselective applications is currently underway.

Experimental Section

Bis(diethylamino)cyclopropenium tetraphenylborate **3**: Diethylamine (2.36 mL, 22.5 mmol) was added dropwise to a solution of tetrachlorocyclopropene (0.690 mL, 5.64 mmol) in dichloromethane (100 mL) at −78 °C under nitrogen. The reaction mixture was warmed to room temperature over 3 h, then cooled back to −78 °C. Triphenylphosphine (1.48 g, 5.64 mmol) was then quickly added and the mixture was warmed to room temperature. Distilled water (20 mL) was added and the two-phase mixture was stirred vigorously for 16 h. Sodium tetraphenylborate (1.93 g, 5.64 mmol) was then added and the reaction was transferred to a separatory funnel with dichloromethane. The organic layer was washed with 0.5 M HCl, saturated aqueous $NaHCO_3$, and H_2O, and then dried over Na_2SO_4 and concentrated in vacuo. The resulting crude oil was purified by recrystallization first from methanol/water, then from CH_2Cl_2/Et_2O. The title compound was obtained as a white solid (920 mg, 32 %). M.p. 132–133 °C; ^{1}H NMR (500 MHz, $CHCl_3$): $\delta = 7.51$ (br s, 8H), 7.03 (t, $J = 7.1$ Hz, 8H), 6.86 (t, $J = 7.1$ Hz, 4H), 4.46 (br s, 1H), 3.20 (q, $J = 7.5$ Hz, 4H), 3.10 (q, $J = 7.5$, 4H), 1.21 (t, $J = 7.5$, 6H), 1.11 ppm (t, $J = 7.5$, 6H); ^{13}C NMR (125 MHz, $CHCl_3$): $\delta = 164.4$ (C-B, q, $^1J_{CB} = 49$ Hz), 136.2, 135.4, 125.9 (C-B, q, $^2J_{CB} = 2.8$ Hz), 122.0, 98.2, 48.1, 46.9, 14.2, 12.9 ppm; FTIR (KBr thin film): $\tilde{\nu}_{max} = 3108$, 3053, 2984, 1895, 1589 cm^{-1}; HRMS (ESI +): *m/z:* calcd for $C_{11}H_{21}N_2^+$ $[M]^+$: 181.1699; found: 181.1703.

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