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Diaminocyclopropenylidene Organocatalysts: Beyond N-Heterocyclic Carbenes**

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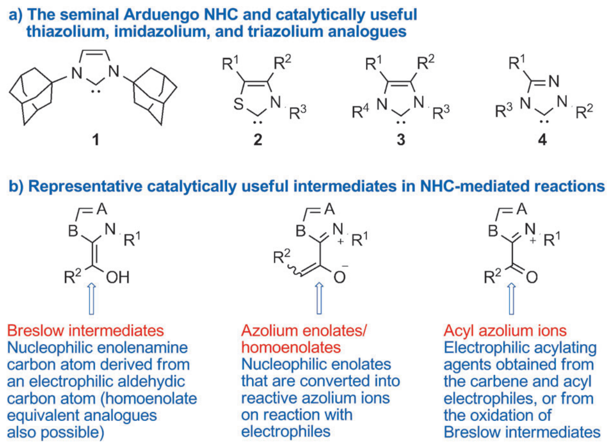
asymmetric catalysis · carbenes · cyclopropenylidenes · Stetter reaction · umpolung

In the 22 years since the seminal discovery of stable, isolable N-heterocyclic carbenes (NHCs), such as **1**, by Arduengo and co-workers,[1] these species have become invaluable to synthetic chemists, to the extent that the unique transformations that they catalyze (often with high enantio- and diastereocontrol) are widely considered to constitute a distinct subdomain of the ever-burgeoning field of organocatalysis.[2] Carbenes that are prepared from five-membered azolium precursors, such as thiazolium (**2**), imidazolium (**3**) or triazolium (**4**) salts, have dominated the field (Figure 1).


a) The seminal Arduengo NHC and catalytically useful thiazolium, imidazolium, and triazolium analogues

b) Representative catalytically useful intermediates in NHC-mediated reactions

Breslow intermediates
Nucleophilic enolenamine carbon atom derived from an electrophilic aldehydic carbon atom (homoenolate equivalent analogues also possible)

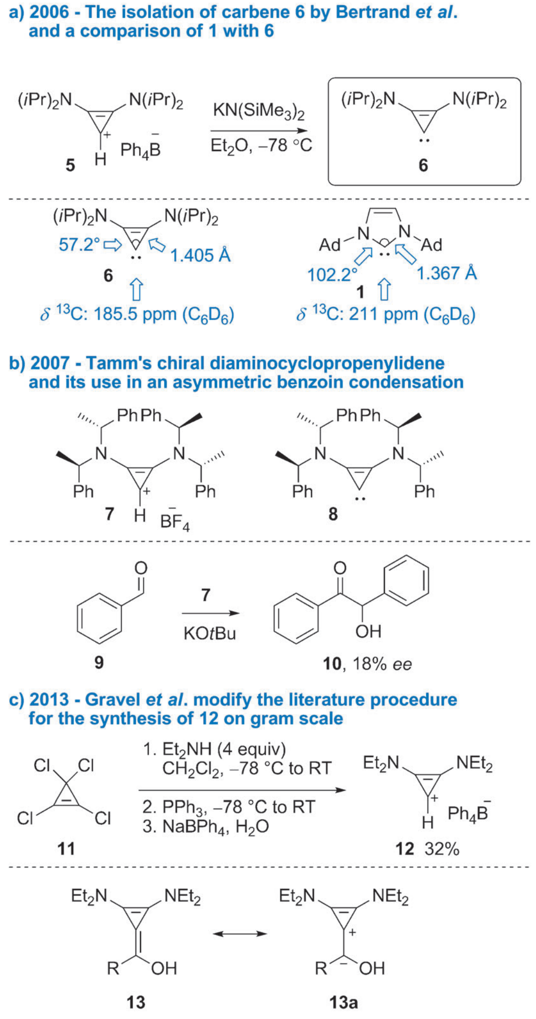
Azolium enolates/homoenolates
Nucleophilic enolates that are converted into reactive azolium ions on reaction with electrophiles

Acyl azolium ions
Electrophilic acylating agents obtained from the carbene and acyl electrophiles, or from the oxidation of Breslow intermediates

Figure 1. a) Typical NHC structures. b) Typical catalytically relevant intermediates in NHC-mediated reactions.

Much of the utility of NHCs in catalysis derives from the nucleophilicity of the carbene center and our ability to modify the steric and electronic environment of the carbene-stabilizing heteroatoms to generate reactive species, such as Breslow intermediates, azolium enolates, and acyl azolium ions, in situ.

In 2006, Bertrand et al.[3] isolated the cyclopropenylidene **6**. The carbene is highly air-sensitive, but thermally very stable, and is readily prepared by deprotonation of the corresponding cyclopropenium chloride **5** (Scheme 1 a). Most interestingly, it is devoid of stabilizing heteroatoms directly adjacent to the carbene center. Even a cursory glance at the


a) 2006 - The isolation of carbene 6 by Bertrand *et al.* and a comparison of 1 with 6

b) 2007 - Tamm's chiral diaminocyclopropenylidene and its use in an asymmetric benzoin condensation

c) 2013 - Gravel *et al.* modify the literature procedure for the synthesis of 12 on gram scale

Scheme 1. a) Synthesis of carbene **6**. b) First use of a cyclopropenylidene in (asymmetric) catalysis. c) Synthesis of the less hindered salt **12** by Gravel and Wilde. Ad = adamantyl.

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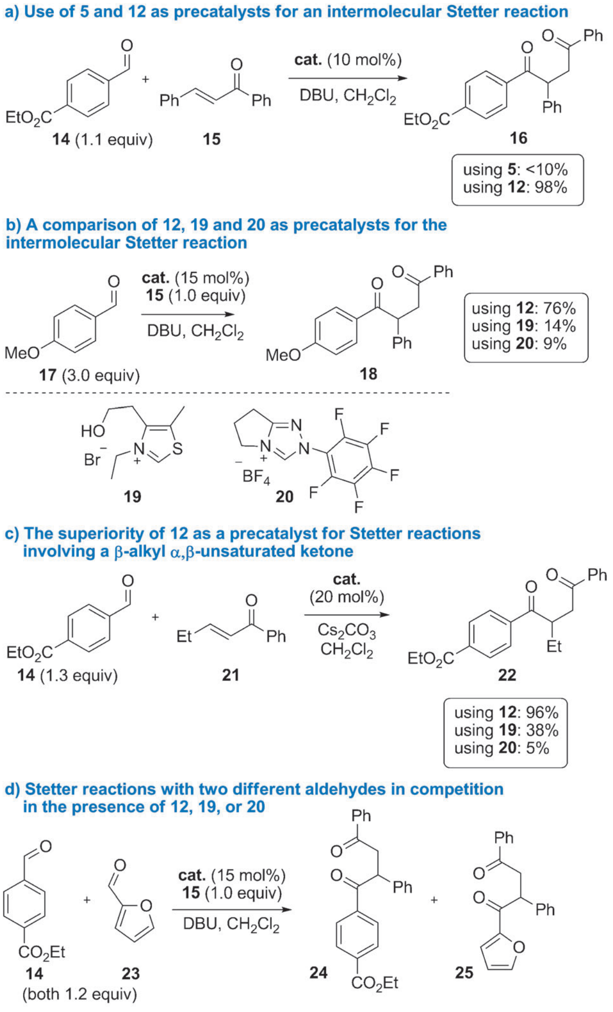
structure and ^{13}C NMR chemical shift of the carbene carbon atom reveals that this is a species with steric and electronic characteristics that are very different to those of the prototype NHC developed by Arduengo and co-workers (Scheme 1 a, right). Surprisingly, only one report that describes the use of a cyclopropenylidene as an organocatalyst has emerged since the seminal work of Bertrand and co-workers: Tamm et al.[4] demonstrated that carbene **8** could be generated from **7**, and that **7** could be used as a precatalyst for the conversion of benzaldehyde (**9**) into benzoin (**10**) in poor, yet appreciable enantiomeric excess (Scheme 1 b). No product yield or detailed reaction conditions were reported.

It is difficult to fathom why cyclopropenylidenes have been largely ignored by those (including this author) interested in organocatalysis, particularly at a time when the finer mechanistic aspects of NHC-mediated umpolung processes are receiving increased attention.[5] One could speculate that a degree of groupthink (understandable given the enormous synthetic utility of NHCs in catalysis, the scope and limitations of which have not yet been fully charted[1]) and concerns regarding the ability of diaminocyclopropenylidenes to generate Breslow-type intermediates of sufficient stability to be catalytically competent or relevant, or a combination of both, may be responsible.

Very recently, Gravel and Wilde[6] noted the potential difficulty associated with the stability of intermediates such as **13**/**13a** and synthesized both Bertrand's salt **5** and the less bulky analogue **12** using a modification of the literature procedure (Scheme 1 c).[7] These salts were then evaluated as precatalysts for the intermolecular Stetter reaction.

Whereas the sterically hindered salt **5** possessed poor activity in the reaction between the activated aldehyde **14** and chalcone (**15**), the use of the bis(diethylamino) analogue **12** allowed the formation of the adduct **16** in nearly quantitative yield (Scheme 2 a). More strikingly, when the performance of **12** was compared with that of the more traditional thiazolium- and triazolium-based precatalysts (**19** and **20**, respectively) in the reaction between **15** and the relatively electron-rich (and thus usually more recalcitrant) aldehyde **17**, the cyclopropenylidene precursor proved clearly superior (Scheme 2 b). A similar trend was observed in the reaction between **14** and the β-alkyl-substituted Michael acceptor **21** in the presence of either **12**, **19**, or **20** (Scheme 2 c).



Cat.	Comb. yield [%]	Ratio 24/25
12	99	85:15
19	80	37:63
20	85	12:88

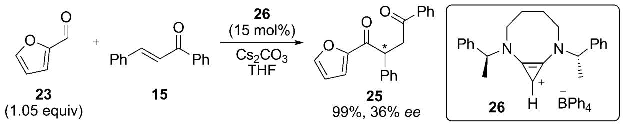
Scheme 2. a) **5** and **12** as precatalysts for the Stetter reaction. b) A comparison of **12**, **19**, and **20** as precatalysts for the Stetter reaction. c) Expansion of the reaction scope beyond chalcone. d) Competition experiments.

In a competition experiment, Gravel and Wilde then offered these three catalyst precursors a choice between equimolar amounts of two different aldehydes, namely the benzaldehyde derivative **14** and the heterocyclic aldehyde furfural (**23**), as reaction partners for chalcone (**15**) in an intermolecular Stetter process that is similar to those previously examined, to generate mixtures of adducts **24** and **25** (Scheme 2 d). The combined yield of adducts was highest in the presence of **12**, and the carbene derived from this salt also exhibited a strong preference for the formation of the Breslow intermediate derived from **14** (leading to adduct **24**). However, the NHCs derived from both **19** and **20** preferentially generated **25**, which stems from initial attack of the catalyst on the heterocyclic aldehyde **23**. The authors established that these reactions are under kinetic control and suggested that the less hindered carbene **12** is less susceptible to steric factors than either triazolium- or thiazolium-based carbenes.

There is certainly some evidence in this study to support this hypothesis; however, one would assume that additional verification is necessary, as **14** and **23** are less than perfectly matched electronically, and the steric discrepancy between them is not considerable. Nonetheless, it is clear that this is a very significant finding: The carbene derived from **12** possesses complementary predilections to standard NHCs when faced with two different aldehydes. The carbene derived from **12** is also considerably more reluctant to catalyze the formation of benzoin (a chemoselectivity problem which can bedevil the Stetter reaction and other carbene-catalyzed umpolung processes): No benzoin was observed in Stetter processes involving **12**, whereas, for example, benzoin was formed in 73 % yield in the reaction to generate **22** in the presence of the triazolium precatalyst **20** (Scheme 2c). The ability of **12** to avoid benzoin formation is likely to prove very useful to practitioners. It would be very interesting to see if this chemoselectivity can be maintained in the presence of a more hindered Michael acceptor. The issue of compatibility with enolizable, aliphatic aldehydes would also be worthy of investigation.

Gravel and Wilde also demonstrated a domino Stetter–Michael process and a considerably less efficient lactone synthesis that involves a putative homoenolate intermediate.

Finally, the synthesis and evaluation of a novel, chiral, bicyclic cyclopropenylidene was demonstrated. In their previous work (Scheme 1b), Tamm and co-workers had suggested that the low *ee* observed was a consequence of "rapid internal rotation of the chiral substituents". The more rigid precatalyst **26** presumably represents an attempt to partially circumvent this issue, and in this regard it may be considered a success; **23** and **15** underwent smooth conversion into adduct **25** in excellent yield and with 36% *ee* (Scheme 3).



Scheme 3. A bicyclic chiral diaminocyclopropenylidene as the catalyst of an asymmetric intermolecular Stetter reaction.

Although this level of enantiocontrol is moderate, it certainly is a step in the right direction and an important proof-of-concept, which will certainly stimulate further interest in these systems. More rigid designs that are able to extend the influence of the chiral information further out towards the site of asymmetric induction in the transition state of the stereocenter-forming step may prove useful.

The evidence that relatively unhindered cyclopropenylidenes are useful catalysts for intermolecular Stetter reactions is very significant, and has opened the way to developing catalyst systems that share carbene-type reactivity with NHCs, but that can behave in a very distinct fashion in C–C bond-forming reactions.

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[1] a) A. J. Arduengo III, R. L. Harlow, M. A. Kline, *J. Am. Chem. Soc.* **1991**, *113*, 361; b) A. J. Arduengo III, *Acc. Chem. Res.* **1999**, *32*, 913.

[2] For representative general reviews, see: a) D. Enders, O. Niemeier, A. Henseler, *Chem. Rev.* **2007**, *107*, 5606; b) N. Marion, S. Díez-González, S. P. Nolan, *Angew. Chem.* **2007**, *119*, 3046; *Angew. Chem. Int. Ed.* **2007**, *46*, 2988; c) J. L. Moore, T. Rovis, *Top. Curr. Chem.* **2009**, *291*, 77; d) E. M. Phillips, A. Chan, K. A. Scheidt, *Aldrichimica Acta* **2009**, *42*, 55; e) P.-C. Chiang, J. W. Bode in *N-Heterocyclic Carbenes: From Laboratory Curiosities to Efficient Synthetic Tools*, (Ed. S. Díez-González), Royal Society of Chemistry, Cambridge, **2010**, p. 339; f) C. D. Campbell, K. B. Ling, A. D. Smith in *N-Heterocyclic Carbenes in Transition Metal Catalysis and Organocatalysis*, *Vol. 32* (Ed. C. S. J. Cazin), Springer, Dordrecht, **2011**, p. 263; g) V. Nair, R. S. Menon, A. T. Biju, C. R. Sinu, R. R. Paul, A. Jose, V. Sreekumar, *Chem. Soc. Rev.* **2011**, *40*, 5336; h) A. Grossmann, D. Enders, *Angew. Chem.* **2012**, *124*, 320; *Angew. Chem. Int. Ed.* **2012**, *51*, 314; i) X. Bugaut, F. Glorius, *Chem. Soc. Rev.* **2012**, *41*, 3511.

[3] a) V. Lavallo, Y. Canac, B. Donnadieu, W. W. Schoeller, G. Bertrand, *Science* **2006**, *312*, 722; b) V. Lavallo, Y. Ishida, B. Donnadieu, G. Bertrand, *Angew. Chem.* **2006**, *118*, 6804; *Angew. Chem. Int. Ed.* **2006**, *45*, 6652.

[4] D. Holschumacher, C. G. Hrib, P. G. Jones, M. Tamm, *Chem. Commun.* **2007**, 3661.

[5] For representative recent examples, see: a) A. Berkessel, S. Elfert, V. R. Yatham, J.-M. Neudörfl, N. E. Schlörer, J. H. Teles, *Angew. Chem.* **2012**, *124*, 12537; *Angew. Chem. Int. Ed.* **2012**, *51*, 12370; b) J. Mahatthananchai, J. W. Bode, *Chem. Sci.* **2012**, *3*, 192; c) C. J. Collett, R. S. Massey, O. R. Maguire, A. S. Batsanov, A. C. O'Donoghue, A. D. Smith, *Chem. Sci.* **2013**, *4*, 1514.

[6] M. M. D. Wilde, M. Gravel, *Angew. Chem.* **2013**, *125*, 12883; *Angew. Chem. Int. Ed.* **2013**, *52*, 12651.

[7] a) Z.-I. Yoshida, Y. Tawara, *J. Am. Chem. Soc.* **1971**, *93*, 2573; b) Z.-I. Yoshida, *Top. Curr. Chem.* **1973**, *40*, 47.