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Diamidocarbenes as versatile and reversible [2 + 1] cycloaddition reagents

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We describe the synthesis of a variety of cyclopropanes and epoxides by combining a readily accessible and isolable *N*,*N*′-diamidocarbene with a range of structurally and electronically diverse olefins and aldehydes, including electron-rich derivatives. Surprisingly, the cyclopropanation and epoxidation reactions were discovered to be rapid and thermally reversible at relatively low temperatures, two features often desired for applications that utilize dynamic covalent chemistry. In addition, a diamidocyclopropane derivative prepared via this method was hydrolysed successfully to form the corresponding linear carboxylic acid in a metal- and carbon monoxide-free hydrocarboxylation reaction. As such, diamidocarbenes are expected to find utility in the synthesis of cyclopropanes, epoxides and their derivatives, as well as in dynamic covalent chemistry applications.

Highly strained rings, particularly cyclopropanes and epoxides, enjoy extraordinary utility in a broad range of synthetic[1–3] and biological[4,5] applications. Moreover, from a fundamental perspective, these compounds attract interest for their unique structural and bonding characteristics[6,7]. An efficient method for the synthesis of three-membered carbocycles and oxacycles involves metal-mediated delivery of a carbene to an olefin or aldehyde[8,9]; however, free carbenes have also been employed successfully[10–12]. Although most free carbenes used in [2 + 1] cycloadditions are generated *in situ*, the use of isolable derivatives as starting materials is particularly attractive as they offer avenues to streamline the synthetic procedure, aid in the discovery of novel transformations and provide opportunities to probe deeper into the mechanism and structure of reactive organic species[13,14]. Unfortunately, [2 + 1] cycloadditions that involve isolable carbenes remain extremely rare.

The first example of an isolable free carbene capable of participating in cyclopropanation and epoxidation reactions was the phosphinosilylcarbene **I** (Fig. 1)[15,16], which was reported by Bertrand and co-workers in 1989. Since then, the acyclic alkylamino **II** (in 2004) and diamino[3]ferrocenophane[17] (**III**) (in 2010) carbenes were found to display similar cyclopropanation reactivities[18,19]. The chemistry displayed by the latter was particularly surprising, as *N*-heterocyclic carbenes investigated previously[20–23] yielded exocyclic olefins rather than cyclopropane products[24]. Regardless, the cycloaddition chemistry displayed by **I**–**III** was restricted to electron-deficient olefins[16,18,19,25–27] and aldehydes[16,28–30], and until now isolable carbenes have not been shown to engage in [2 + 1] cycloadditions with electron-rich olefins[20].

Recently, we reported that diamidocarbenes (DACs)[31–38], which can be prepared in two high-yielding steps from a 1,3-disubstituted formamidine and malonyl dichloride, exhibit a wide range of nucleophilic and electrophilic characteristics. For example, akin to nucleophilic carbenes, they were found to condense with CS_2 and ligate to various transition metals[31,34,37,38]. However, they were also found to undergo transformations typical of more electrophilic carbenes, such as ammonia activation[34], C–H insertions[31], reversible coupling with carbon monoxide[31,34,37] and irreversible coupling with isonitriles[33,34,37]. Given this unique reactivity profile and their reduced singlet–triplet gap[33], we reasoned that DACs would be excellent candidates for participating in [2 + 1] cycloadditions. Moreover, the carbene carbon in DACs is in the same oxidation state as the carbon atom in carbon monoxide and bears amides that should be susceptible to hydrolysis. As such, we predicted that DACs could also serve as a masked equivalent of CO (a molecule that does not readily undergo [2 + 1] cycloaddition chemistry) for use in accessing synthetically versatile cyclopropanone derivatives or other carbonyl-containing compounds. Indeed, as described below, we found that isolable DAC **1** not only effected a broad range of cyclopropanation and epoxidation reactions that involved electron-deficient as well as electron-rich olefins and aldehydes, but also that many of these reactions were thermally reversible. Additionally, we found that hydrolysis of a diamidocyclopropane derivative afforded the corresponding linear carboxylic acid via a metal- and carbon monoxide-free hydrocarboxylation, which presumably occurred through a cyclopropanone intermediate[39,40]. During the course of our studies, we also discovered an unprecedented formal [4 + 1] cycloaddition between **1** and α,β-unsaturated ketones, which provided rapid access to a new class of dihydrofurans.

Results and discussion

Given that known, isolable carbenes react with electron-deficient olefins[16,18,19,25–27], our initial efforts focused on studying the cycloaddition chemistry of readily accessible **1** with methyl acrylate. Stirring equimolar quantities of **1** and methyl acrylate for two hours in benzene ($[\mathbf{1}]_0 = 0.29$ M) at ambient temperature, followed by the removal of the solvent and washing with cold hexanes, afforded a white solid in 98% yield (Table 1). ^{1}H NMR analysis of this material revealed diagnostic signals at $\delta = 0.96$, 1.63 and 2.01 ppm (C_6D_6) consistent with the structure of cyclopropane **2a**. To explore the scope of this cyclopropanation chemistry, a

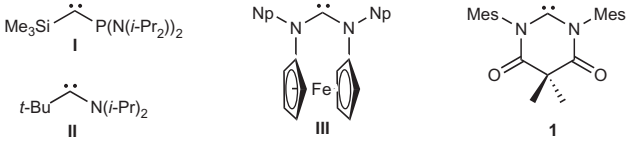

Figure 1 | Examples of isolable carbenes that may be used as [2 + 1] cycloaddition reagents. Np = neopentyl, Mes = 2,4,6-trimethylphenyl.

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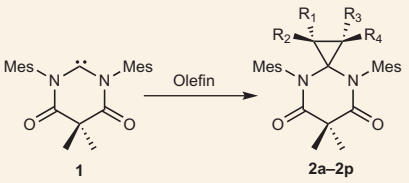
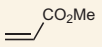
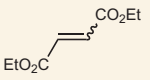
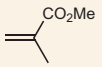
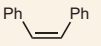
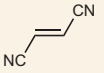
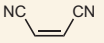
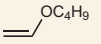
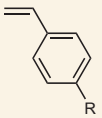
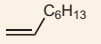
Table 1 | Summary of cyclopropanations of DAC 1 with various olefins.*



1 2a–2p

Olefin	Product (isolated yield†)	Olefin	Product (isolated yield†)
	**2a** (98%)		**2j** (93%, *trans*)
	**2b** (92%)		**2k** (39%, *trans*)§
	**2c** (96%)		**2l** (52%, *trans*)
	**2d** (92%)		**2m** (45%, *cis*)
	2e R = CF_3 (71%)‡		**2n** (53%)§
	**2f** R = Cl (82%)‡		**2o** (43%, *exo*)‖
	2g R = F (74%)‡		**2p** (47%)§
	2h R = H (90%)‡ **2i** R = OMe (76%)‡		

* In general, the cycloaddition reactions were performed using equimolar concentrations of **1** and the olefin indicated in C_6H_6 for two hours at ambient temperature except where noted. †Isolated yield of the corresponding cyclopropane product. Where applicable, the stereochemistry of the cyclopropane product is indicated in parentheses. ‡The reaction was performed at 60 °C for 16 hours. §The reaction was performed neat at 100 °C for two hours. ‖The reaction was performed neat at 120 °C for two hours.

variety of 1-substituted and 1,1-disubstituted olefins were treated with **1** (Table 1). In general, equimolar concentrations of **1** and an olefin were subjected to the reaction conditions and purification procedure described above. Using this method, the reaction of **1** with methyl methacrylate, acrylonitrile or methacrylonitrile afforded the expected cyclopropane products **2b**–**2d** in excellent yield (92–96%). Likewise, styrene and a variety of its *p*-substituted derivatives, including a relatively electron-rich derivative (*p*-methoxystyrene), were cyclopropanated readily by **1**, although a slightly elevated temperature (60 °C) was required to obtain a high yield of the corresponding products **2e**–**2i** (71–90%). Cyclopropane formation was determined unequivocally for **2e** by single-crystal X-ray diffraction analysis (Fig. 2a).

Next, we turned our attention towards evaluating the ability of **1** to cyclopropanate 1,2-disubstituted olefins. The reaction of equimolar quantities of diethyl maleate or diethyl fumarate with **1** was found to proceed at ambient temperature in C_6H_6 and exclusively afforded the same product (**2j**), as determined by ^{1}H NMR spectroscopy, and in identical yield (93%, Fig. 3a). X-ray diffraction analysis of a single crystal obtained from the reaction of **1** and diethyl maleate revealed that **2j** was the *trans*-diastereomer (see Supplementary Fig. S9). Although elevated temperatures (100–120 °C for two hours) were required, similar results were obtained when **1** was treated with *cis*- or *trans*-stilbene, which both formed *trans*-**2k** as the exclusive product, albeit in modest yield (up to 39%). In contrast, treatment of **1** with one equivalent of an 87:13 molar mixture of maleonitrile:fumaronitrile, prepared via the method of Linstead and Whalley[41], at ambient temperature for one hour afforded an 87:13 ratio of the respective *cis*:*trans* products (**2m**:**2l**), as determined by NMR spectroscopy (C_6D_6). The structure of the *cis*-diastereomer was confirmed subsequently by single-crystal X-ray diffraction analysis (Fig. 2b). Whereas the retention of stereochemistry in the formation of **2m** was consistent with a concerted mechanism[42–44], the rapid closure of a transient 1,3-dipole cannot be ruled out. In contrast, formation of the *trans*-diastereomeric cyclopropanes **2j** and **2k** from their respective *cis*-olefins is in accord with a stepwise process that involves a 1,3-dipole intermediate capable of bond rotation prior to ring closure. Collectively, these results are similar to those observed with cycloheptatrienylidene, a carbene that must be generated *in situ* via photolysis or thermolysis of the sodium salt of tropone tosylhydrazone[45,46].

Building on the aforementioned cyclopropanation of *p*-methoxystyrene, subsequent efforts were directed towards evaluating the ability of **1** to cyclopropanate electron-rich alkenes. Heating **1** ($[\mathbf{1}]_0 = 0.4$ M) in neat *n*-butyl vinyl ether (19 equiv.) to 100 °C for two hours followed by purification of the reaction mixture using silica-gel column chromatography afforded a white solid in 53% yield. The structure of this product was consistent with that of **2n**, as determined by a heteronuclear correlation NMR experiment, in which the ^{1}H signals observed at $\delta = 3.49$ (1H) and

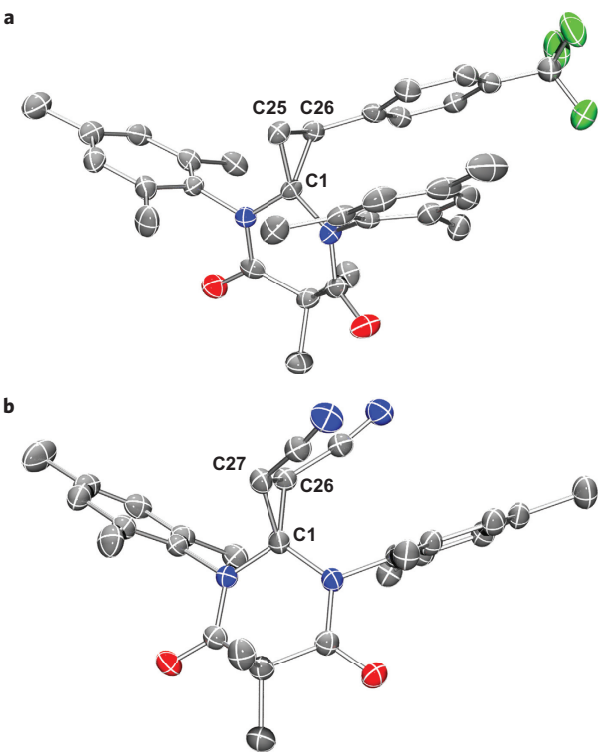


Figure 2 | X-ray structures of the [2 + 1] cycloaddition products 2e and 2m. **a**, ORTEP diagram of **2e** with thermal ellipsoids drawn at 50% probability and H atoms omitted for clarity. Selected distances and angles: C1–C25, 1.497(6) Å; C1–C26, 1.551(6) Å; C25–C26, 1.501(6) Å; C25–C1–C26, 59.0(3)°; C25–C26–C1, 58.7(3)°; C1–C25–C26, 62.3(3)°. **b**, ORTEP diagram of **2m** with thermal ellipsoids drawn at 50% probability and H atoms omitted for clarity. Selected distances and angles: C1–C26, 1.518(3) Å; C1–C27, 1.560(3) Å; C26–C27, 1.536(3) Å; C26–C1–C27, 59.85(12)°; C26–C27–C1, 58.73(12)°; C1–C26–C27, 61.42(12)°.

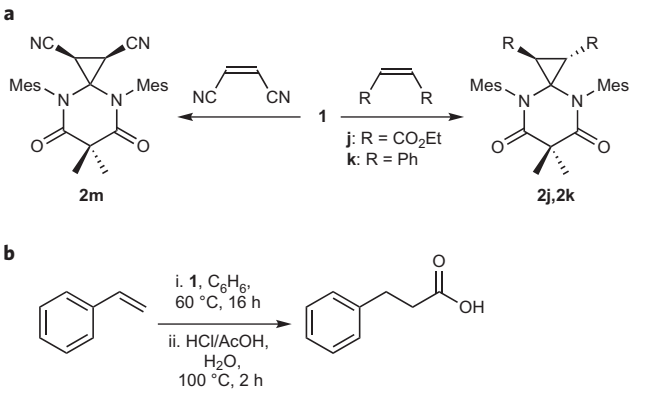


Figure 3 | Stereospecificity of the [2 + 1] cycloaddition with 1 and the formation of a linear carboxylic acid. a, Treatment of **1** with maleonitrile afforded the *cis*-1,2-disubstituted cyclopropane **2m**; in contrast, the *trans*-1,2-disubstituted cyclopropanes **2j** and **2k** were obtained when **1** was treated with diethyl maleate or *cis*-stilbene, respectively. Although the former is consistent with a concerted mechanism, the latter examples may reflect a stepwise cycloaddition process. Conditions for **2j** and **2m**: room temperature (r.t.), two hours, C_6H_6. Conditions for **2k**: 100 °C, two hours, neat. **b**, Treatment of styrene with **1** followed by hydrolysis of the cyclopropane product (that is, **2h**) under acidic conditions afforded hydrocinnamic acid in 56% isolated yield (unoptimized).

0.84 ppm (2H) (C_6D_6) were correlated with the ^{13}C signals found at 59.37 and 15.33 ppm, respectively. Similarly, cyclopropanes **2o** and **2p** were obtained in 43–47% yield by heating **1** for two hours in neat norbornene (120 °C) or 1-octene (100 °C), respectively. NMR spectroscopy and X-ray crystallography identified the structure of **2o** as the *exo*-isomer (see Supplementary Fig. S11).

Having discovered that DAC **1** was capable of cyclopropanating electronically diverse alkenes, a number of trisubstituted olefins were examined next, primarily to clarify the role of sterics. The introduction of **1** to methyl-3-methyl-2-butenoate, a functionalized olefin that features a disubstituted β-carbon, resulted in no reaction, even at elevated temperatures (up to 100 °C). Hence, attack of the carbene lone pair at the β-position in substituted olefins may be pivotal in the cyclopropanation mechanism and inhibited by steric bulk. In light of this result, we reasoned that a 1,1,2-trisubstituted olefin, such as methyl angelate, should be more prone to cyclopropanation. Although <20% of the cyclopropanated product formed when an equimolar mixture of methyl angelate and **1** was heated at 60 °C for 16 hours in C_6D_6, a 56:44 ratio of methyl tiglate:methyl angelate was observed by ^1H NMR spectroscopy (see Supplementary Fig. S1). As a control experiment, methyl angelate was heated to 100 °C for 24 hours (in the absence of **1**), which resulted in less than 2% isomerization. Collectively, these data are consistent with a reversible interaction between **1** and methyl angelate, which enables scrambling of the olefin's stereochemistry (see below for additional discussion).

Bearing in mind that the carbene centre in **1** is in the same oxidation state as the carbon atom in carbon monoxide, we reasoned that the hydrolysis of the *N*,*N*′-diamidocyclopropanes described above would afford the corresponding cyclopropanones and/or their derivatives. To test this hypothesis, **2h** was treated with CH_3CO_2H/HCl. After two hours at 100 °C, hydrocinnamic acid was obtained in 56% isolated yield (unoptimized). Moreover, similar results were obtained when the two-step cyclopropanation/hydrolysis reaction was performed in a single reaction vessel (Fig. 3b). Considering that *N*,*N*′-dimesityl-2,2-dimethylmalonamide and its partially hydrolysed derivative 3-(mesitylamino)-2,2-dimethyl-3-oxopropanoic acid were isolated as by-products from this reaction, we believe that the hydrolysis of **2h** affords a cyclopropanone intermediate that readily adds water and rearranges to give the corresponding propionic acid under aqueous conditions[39]. Regardless, the DAC effectively enabled a formal anti-Markovnikov hydrocarboxylation of an alkene to a linear

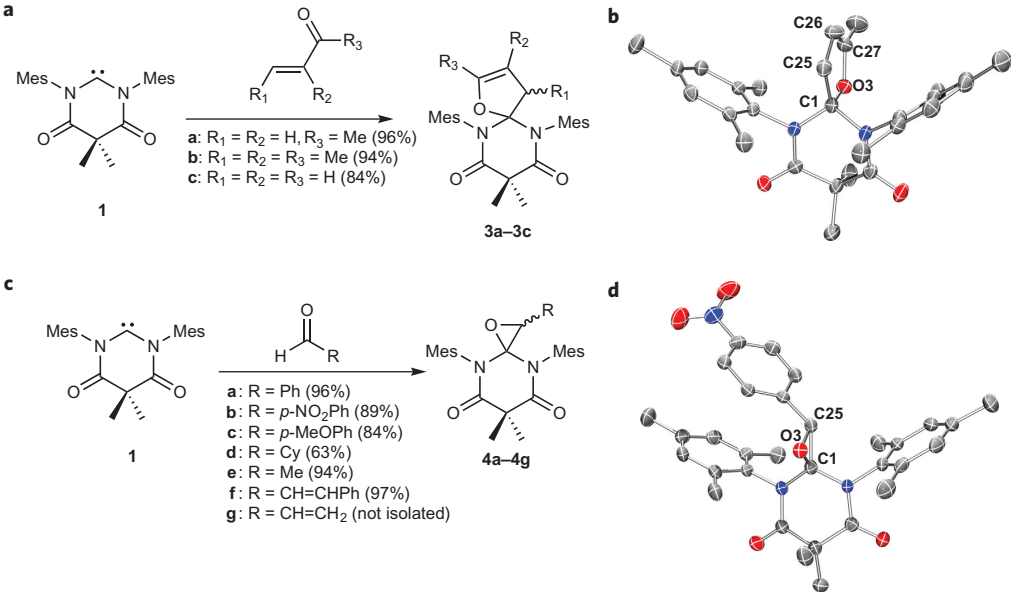


Figure 4 | Formal [4 + 1] cycloadditions of DAC 1 with α,β-unsaturated ketones and acrolein and [2 + 1] cycloadditions with aldehydes. a, Unlike the other olefins studied, the addition of **1** to α,β-unsaturated ketones and acrolein afforded dihydrofuran derivatives rather than cyclopropanes. Conditions for **3a** and **3b**: r.t., two hours, C_6H_6. Conditions for **3c**: 60 °C, 12 hours, C_6H_6. **b**, ORTEP diagram of **3a** with thermal ellipsoids drawn at 50% probability and H atoms omitted for clarity. Selected distances: C1–C25, 1.543(3) Å; C25–C26, 1.486(3) Å; C26–C27, 1.307(3) Å; C27–O3, 1.386(2) Å; O3–C1, 1.460(2) Å. **c**, Combining **1** with a variety of aldehydes afforded the corresponding epoxides in good to excellent yields. Conditions: r.t., 2–24 h, C_6H_6. **d**, ORTEP diagram of **4b** with thermal ellipsoids drawn at 50% probability and H atoms omitted for clarity. Selected distances and angles: C1–O3, 1.442(3) Å; C1–C25, 1.481(3) Å; O3–C25, 1.450(3) Å; O3–C1–C25, 59.45(13)°; C1–O3–C25, 61.61(14)°; O3–C25–C1, 58.94(13)°.

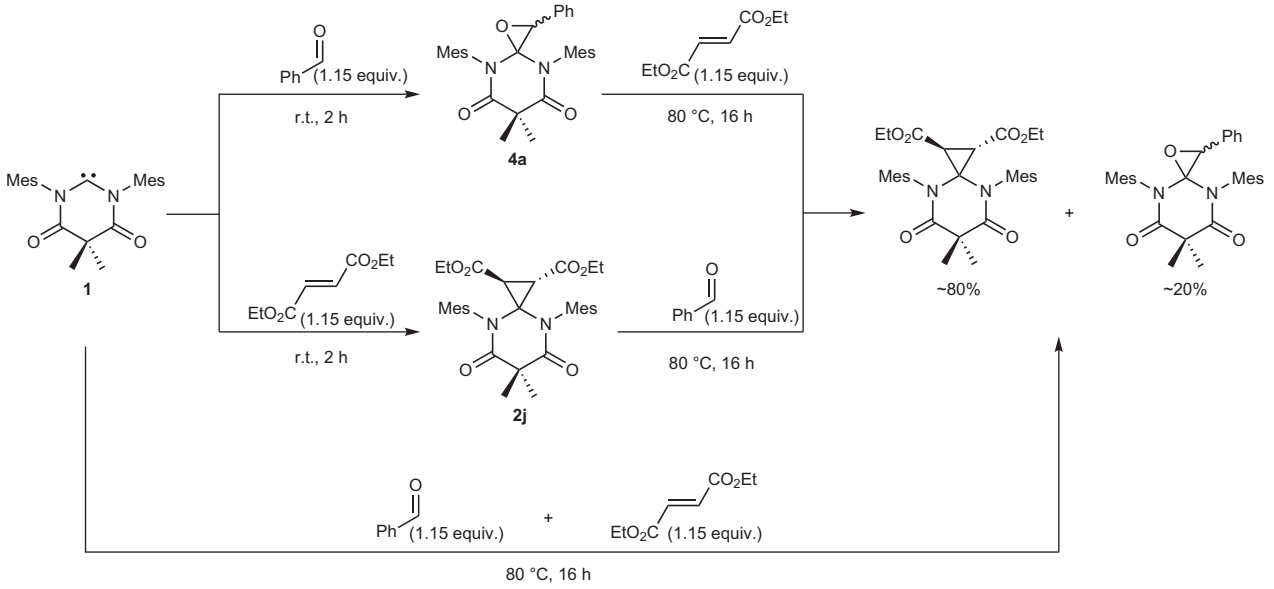


Figure 5 | Reversible [2 + 1] cycloadditions involving 1. Treatment of **1** with 1.15:1.15 equiv. of benzaldehyde:diethyl fumarate, **2j** with 1.15 equiv. benzaldehyde or **4a** with 1.15 equiv. diethyl fumarate afforded the same product mixture. Conditions: 80 °C, 16 hours, C_6D_6.

carboxylic acid, an industrially useful process that typically requires transition metals and/or high pressures of carbon monoxide[40].

To further expand the utility of the cyclopropanation chemistry described above and considering the central role of cyclopropyl ketones in the synthesis of furans[1], α,β-unsaturated ketones were also explored as potential cycloaddition partners for DAC **1**. Treatment of **1** with an equimolar quantity of methyl vinyl ketone in benzene at ambient temperature for two hours followed by removal of the solvent and washing of the residue with cold hexanes afforded a white solid in 96% yield. The lack of a ν_{CO} peak assignable to a ketone moiety in the infrared spectrum (KBr) and a signal indicative of a shielded olefinic proton ($\delta = 3.50$ ppm (C_6D_6)) in the ^{1}H NMR spectrum of the product were consistent with the formation of dihydrofuran **3a** (Fig. 4a). The structural assignment of this compound was later confirmed by X-ray crystallography (Fig. 4b). Formally a [4 + 1] cycloaddition, the aforementioned transformation is unprecedented and may occur via the Michael addition of **1** with the α,β-unsaturated ketone followed by ring closure or via a 1,3-rearrangement of a [2 + 1] cycloadduct intermediate. Analogous results were obtained with 3-methyl-3-penten-2-one (which afforded a 93% yield of **3b**), although no reaction was observed with 4-methyl-3-penten-2-one, even at 100 °C, presumably because of steric inhibition.

Subsequent attention shifted towards exploring the potential of **1** to react with aldehydes. As shown in Fig. 4c, stirring benzaldehyde with an equimolar quantity of **1** in C_6H_6 at ambient temperature for two hours followed by washing the crude product with cold hexanes afforded **4a** in 96% yield. The structure of **4a** was supported by the disappearance of the ^{1}H NMR signal assigned to an aldehyde moiety ($\delta = 9.63$ ppm) and the appearance of a new signal diagnostic of an epoxide at $\delta = 4.03$ ppm (C_6D_6). Analogous results were obtained with electron-deficient and electron-rich derivatives of benzaldehyde (**4b** and **4c**, 84–89% yield); the structure of **4b** was confirmed by X-ray crystallography (Fig. 4d). Likewise, similar reactivity was observed with the aliphatic derivatives cyclohexanecarboxaldehyde and acetaldehyde, which afforded the epoxides **4d** and **4e** in 63% and 94% yield, respectively. Reflecting the chemoselectivity of DACs towards aldehydes versus olefins, exposure of **1** to cinnamaldehyde under similar conditions afforded the epoxide **4f** in 97% yield. Similarly, treatment of **1** with acrolein in benzene at ambient temperature for 16 hours yielded epoxide **4g** as the major product and furan **3c** as the minor product (5:1), as determined by ^{1}H NMR spectroscopy. However, heating to 60 °C for 12 hours or stirring this mixture for two weeks at ambient temperature in solution afforded **3c** as the sole product, which was isolated subsequently in 84% yield (Fig. 4a,c). Thus far, attempts to hydrolyse the diamidooxiranes have resulted in a range of products and further investigation is underway.

Although the conversion of **4g** into **3c** requires cleavage of the epoxide C–C bond[47], a retro epoxidation reaction followed by Michael addition would facilitate the formation of the observed product. To probe for such a retro [2 + 1] cycloaddition, a series of exchange reactions was performed. Heating a mixture of **4a** and diethyl fumarate (1.15 equiv.) to 80 °C in a sealed vial for 16 hours followed by NMR analysis revealed an 83:17 mixture of **2j**:**4a** (Fig. 5). Similarly, heating a mixture of **2j** and benzaldehyde (1.15 equiv.) afforded the same ratio of the products after the same amount of time. Although a 5:95 ratio of **2j**:**4a** was observed after mixing diethyl fumarate, benzaldehyde and **1** (1.15:1.15:1) for 30 minutes at ambient temperature, an 80:20 ratio of **2j**:**4a** was obtained on heating this mixture to 80 °C for 16 hours. Collectively, these results indicate that the cyclopropane and epoxide cycloadducts of **1** are capable of undergoing formal retro [2 + 1] cycloaddition reactions under mild conditions. Additionally, heating **2j** to 100 °C in C_7D_8 resulted in the liberation of diethyl fumarate as determined by variable-temperature NMR spectroscopy, although the free carbene **1** was not observed because of a competitive intramolecular C–H insertion process that is facilitated at elevated temperatures[31]. To the best of our knowledge, these are the first examples of thermally reversible [2 + 1] cycloadditions that involve an isolable carbene[48].

Conclusion

In summary, we report that DAC **1** is capable of participating in [2 + 1] cycloadditions with a wide range of olefins and aldehydes, including electron-rich derivatives. Structural and mechanistic studies support a stepwise addition process, although a *cis*-cyclopropane was observed when maleonitrile was used as the starting material, which suggests to us that some cycloadditions may be concerted. Whereas the ability of isolable carbenes to engage in [2 + 1] cycloaddition chemistry had been limited in scope (that is, restricted to electron-deficient olefins), the results reported

herein effectively expand the utility of carbenes in the construction of three-membered carbocycles and oxacycles. Additionally, **1** was found to undergo an unprecedented, formal [4 + 1] cycloaddition with α,β-unsaturated ketones to afford dihydrofuran derivatives rapidly. In light of the broad scope of olefins and aldehydes, and recalling that the DAC was constructed from readily accessible and modular formamidine and malonyl precursors, we envision that many derivatives of these cycloaddition partners will be accessible using the methodology described above. Furthermore, hydrolysis of the diamidocarbene cyclopropane **2h** afforded hydrocinnamic acid, a linear carboxylic acid, via a formal metal- and carbon monoxide-free hydrocarboxylation of styrene. Additional efforts to explore the utility of DACs in synthesis and as masked carbon-monoxide equivalents are in progress.

Beyond their synthetic utility, DACs were also found to enable the first examples of reversible [2 + 1] cycloaddition reactions that proceed rapidly at relatively low temperatures, an advantage over many other dynamic covalent reactions. This surprising discovery is expected to initiate new fundamental studies and expand the applications of stable carbenes to include uses as protecting groups for olefins or aldehydes, or as latent sources of reactive intermediates. Akin to other reversible cycloadditions, such as the Diels–Alder reaction, reversible [2 + 1] cycloaddition processes also hold promise for use as the basis of structurally dynamic materials and reversible covalent inhibitors, and to facilitate applications that utilize dynamic combinatorial libraries (for example, sensor discovery and development)[49,50].

Methods

Detailed descriptions of experimental, spectroscopic and crystallographic methods and results are provided in the Supplementary Information.

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C.W.B. and J.P.M. conceived and designed the experiments, and co-wrote the paper. J.P.M. performed the experiments and analysed the data. Both authors discussed the results and commented on the manuscript.

Additional information
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