ARTICLE

Zn/F Carbenoids: Preparation, Structures, Stability, and Application to Nucleophilic Monofluoroalkylation

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Carbenoids have been important reactive intermediates in organic synthesis. Thus, numerous investigations have focused on carbenoids with diverse M/X (M = metal, X = leaving group) combinations. However, there have been limited studies on Zn/F carbenoids, despite their potential as nucleophilic monofluoroalkylating reagents. Here, we present the results of comprehensive studies on Zn/F carbenoids. These carbenoids can be generated at ambient temperature through the oxidative addition of 1-fluoro-1-haloalkanes. At 23 ℃, they exhibit a half-life of several hours, which is a more than 10^6-fold increase compared to that of Li/F carbenoids. This increased stability facilitated various NMR analyses, which revealed for the first time their solution-state structure and their decomposition mechanism. In the presence of CuCN•2LiCl, Zn/F carbenoids efficiently couple with various electrophiles, demonstrating broad functional group compatibility at ambient temperature and enabling facile access to diverse functionalized monofluoroalkanes.

Introduction

Carbenoids play a crucial role as reactive intermediates in organic synthesis. The simultaneous existence of a C—X bond (X = leaving group) and a C—M bond (M = s- or p-block metal) at a single carbon atom imparts nucleophilic and electrophilic properties to the carbenoid (Figure 1. a).[1–3] From the viewpoint of synthetic organic chemistry, Zn/X carbenoids (X = I, Br, OR) hold particular significance due to their stability and broad functional group tolerance. Typically serving as carbene equivalents or electrophiles, they have proven valuable in cyclopropanation[4] and homologation reactions[5] (Figure 1. b). Investigations of Zn/X carbenoids have unveiled insights into their stability, structures, and reactivity as well as the effects of additives and solvents, significantly expanding their synthetic applicability.[6,7] In sharp contrast, Zn/F carbenoids surprisingly remain largely unexplored.[8] Highly fluorinated alkylzinc species like trifluoromethylzinc[9] and difluoromethylzinc[10-12] species are known. However, the varying number of halogen atoms and the alkyl substituents on the α-carbon can significantly influence the nature of carbenoids,[1,2] emphasizing the importance of investigating ordinal Zn/F carbenoids (α-monofluoroalkylzinc).

M/F carbenoids are widely acknowledged as highly unstable species.[13,14] Consequently, in-depth examinations and practical applications of M/F carbenoids have been severely constrained (Figure 1. c). In 2014, Mitzel and co-workers successfully isolated LiC_2F_5 (**A**), noting its explosive potential and the imperative need for storage below − 60.8 ℃ .[13a] α-Fluoroalkyllithium (**B**) is also extremely unstable; its residual time in a flow microreactor is only 13 ms even at −60 ℃.[14d] Thus, for the of use **B** as a monofluoroalkylating reagent, employing either the internal quenching method or a flow microreactor under cryogenic conditions is essential.[14a,14c,14d,14e] Due to their inherent instability, detailed structural studies on Li/F carbenoids **B** have not been carried out. As stable M/F carbenoids, Gessener and co-workers reported carbenoids **C**, which have two anion-stabilizing substituents on their α-carbon.[13b] Carbenoids **C** displayed notable stability; however, their synthetic application remains unexplored.

We envisioned that Zn/F carbenoids would exhibit greater stability than Li/F carbenoids[15] due to the attenuated reactivity of C—Zn bonds compared to that of C—Li bonds. Additionally, we anticipated that, contrary to Zn/I carbenoids, Zn/F carbenoids would serve as potent nucleophilic monofluoroalkylating reagents owing to the lower leaving ability of fluorine ion.[16] In this study, we carried out comprehensive investigations of Zn/F carbenoids (Figure 1, d). We observed that Zn/F carbenoids can be readily formed through the oxidative addition of 1-fluoro-1-haloalkanes at ambient temperature. Their half-lives extend to *several hours at 23 ℃* (>10^6-times longer than those of the corresponding Li/F carbenoids). The enhanced stability facilitated detailed NMR analyses of Zn/F carbenoids, revealing insights into their stability, structures, and decomposition pathways. Benefiting from this improved stability, Zn/F carbenoids can be used for nucleophilic monofluoroalkylation around ambient temperature with broad functional group compatibility, offering a convenient approach to a diverse array of functionalized monofluoroalkanes.

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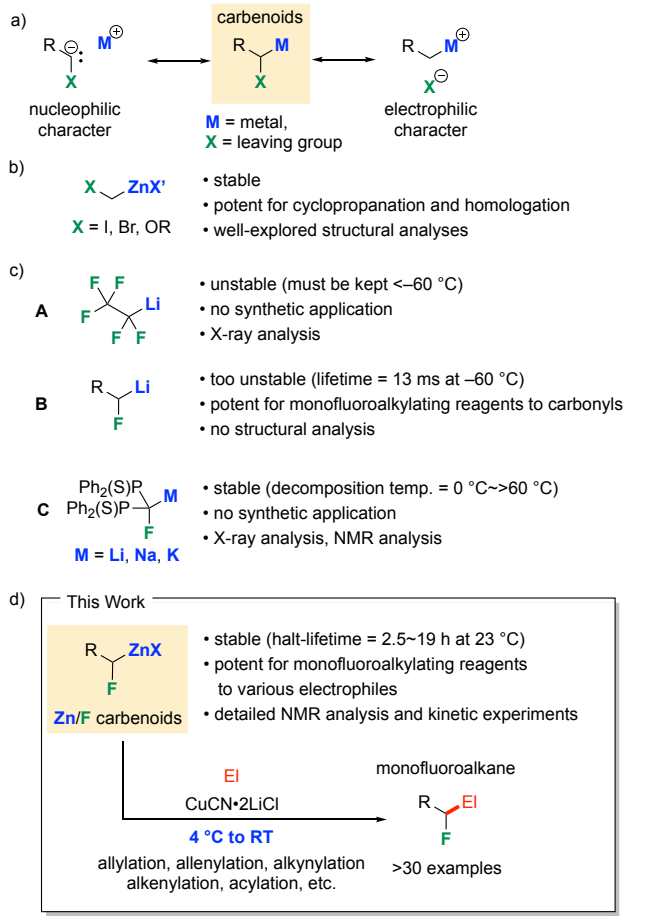


Figure 1. Carbenoids. a) Structure and ambiphilic nature of carbenoids. b) Zn/X (X = I, Br, OR) carbenoids as well-studied carbenoids. c) Reported examples of M/F carbenoids. d) This work: Comprehensive studies on Zn/F carbenoids

Results and Discussion

Preparation of Zn/F carbenoids.

We initially developed a procedure for synthesizing Zn/F carbenoids **2**. Our choice to synthesize Zn/F carbenoids **2** via oxidative addition of 1-halo-1-fluoroalkanes **1** to metallic zinc was based on the following considerations: 1) The iodine-zinc exchange method often necessitates the use of catalytic amounts of Cu or Pd reagents, complicating the detailed analysis of the pure properties of **2**. 2) The lithium-zinc transmetalation method requires the preparation of the corresponding organolithium, requiring the use of highly unstable Li/F carbenoids.

Oxidative addition of 1-halo-1-fluoroalkane **1a-I** to metallic zinc in THF-d_8 was examined, and the reaction was monitored using ^{1}H and ^{19}F NMR spectroscopy (Figure 2, a). We observed the conversion of **1a-I** to **2a-I**. However, **2a-I** appeared as a transient species and rapidly degraded to **4a** and other minor species, including fluoroalkane **3a**, within 2 hours at 23 ℃. After several trials, we found that using DMF was the best choice in terms of the rate of the oxidative addition and the lifetime of Zn/F carbenoids **2**. In DMF-d_7, the oxidative addition of **1a-I** to metallic zinc smoothly took place to give **2a-I** quantitatively (Figure 2, b). We also confirmed that >95% of **2a-I** remained after 2 hours at 23 ℃. Under the established conditions, various alkyl-substituted 1-iodo-1-fluoroalkanes **1b-I**–**1f-I** efficiently reacted with zinc quantitatively yielding **2b-I**–**2f-I** (Figure 2, c). Alkyl-substituted 1-bromo-1-fluoroalkanes **1a-Br** exhibited significantly lower activity in oxidative addition to zinc, while aryl-substituted **1g-Br** smoothly reacted with zinc to produce **2g-Br**. This phenomenon was attributed to the weakened C—Br bond of **1g-Br** due to hyperconjugation from the π-orbital of the aromatic ring to the anti-bonding C—Br orbital. Notably, terminal olefin (**2d-I**), ether (**2e-I**), sulfonamide (**2f-I**), and ester (**2g-Br**) are compatible with α-fluoroalkylzinc moiety.

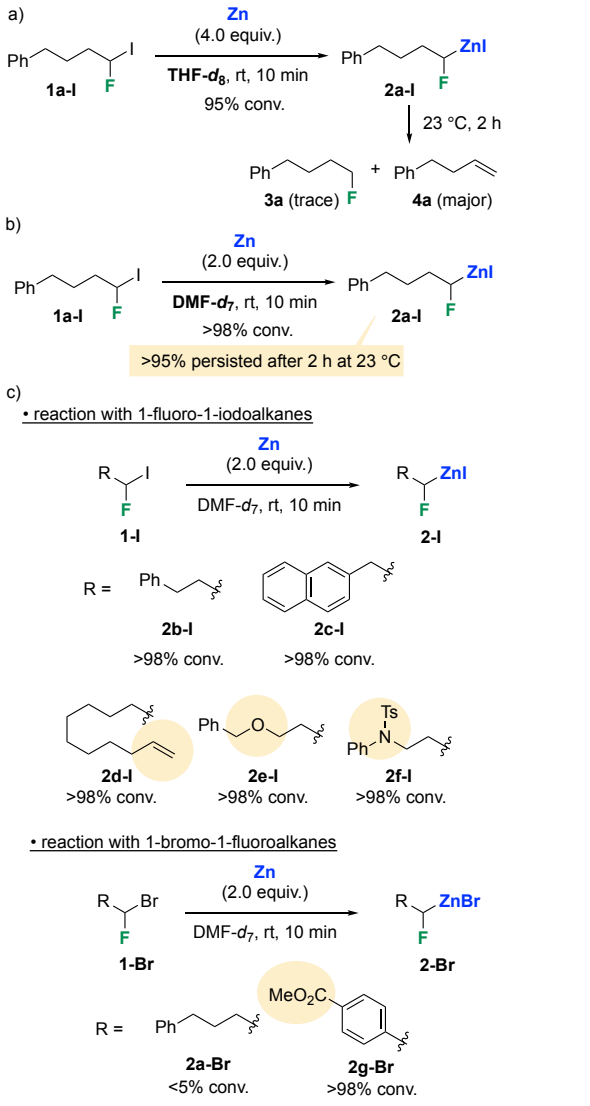
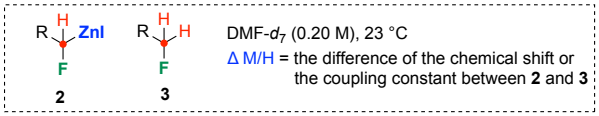


Figure 2. Generation of α-monofluoroalkylzinc **2**. a) Oxidative addition in THF-d_8. b) Oxidative addition in DMF-d_7. c) Scope of the generation of α-monofluoroalkylzinc **2**.

NMR analysis of Zn/F carbenoids.

Zn/F carbenoids **2** are stable at ambient temperature in DMF, allowing their detailed NMR spectroscopic analysis. NMR spectra of organometallic species often provide direct information about their structures, electronic natures, and equilibrium states.[17] The NMR chemical shifts and coupling constants of Zn/F carbenoid **2**, along

with a comparison to the corresponding fluoroalkanes **3**, are shown in Table 1. ^{1}H, ^{13}C and ^{19}F NMR spectra of **2a-I** are shown in Figures 3 as representative examples for Zn/F carbenoids.



R =		δ_{1H} [ppm]	δ_{13C} [ppm]	δ_{19F} [ppm]*	$^{1}J_{C-F}$ [Hz]	$^{2}J_{H-F}$ [Hz]
Ph	**2a-I**	4.88	105.0	–216.8	168	46.8
	Δ M/H	+0.39	+20.2	+1.8	+7.0	–0.9
Ph	**2b-I**	4.81	103.7	–218.4	169	46.6
	2c-I	4.94	103.5	–214.8	173	46.0
	2d-I	4.76	104.6	–216.3	168	45.1
Ph O	**2e-I**	4.92	100.6	–220.5	169	47.2
Ts Ph N	**2f-I**	4.81	100.8	–221.0	169	46.9
	Δ M/H	+0.30	+19.5	+0.5	+7.0	–0.3
MeO_2C	**2g-Br**	6.02	102.7	–224.4	183	47.2
	Δ M/H	+0.47	+28.8	–12.1	+20	0.0

* chemical shift of the major peak

Table 1. Summary of the results of NMR analysis of Zn/F carbenoids **2** and comparison with the corresponding fluoroalkanes **3**.

In ^{1}H NMR spectra, the peaks of the α-hydrogen of **2** arise around 4.9 ppm for alkyl-substituted α-monofluoroalkylzinc (**2a-I**–**2f-I**) and 6.02 ppm for aryl-substituted α-monofluoroalkylzinc **2g-Br** (Table 1). The observed down-field shift of the α-hydrogen of **2** in ^{1}H NMR indicates the deshielding of the α-hydrogen due to the increased polarization of the C—F bond. In ^{13}C{^{1}H} NMR spectra, the peak of α-carbon of **2** was observed around 100 ppm, with *a noticeable down-field shift* compared to the corresponding fluoroalkanes **3**. The chemical shift differences (Δδ(^{13}C) M/H) for the α-carbon between **2** and **3** are around 20 ppm for alkyl-substituted α-monofluoroalkylzinc (**2a-I**, **2f-I**) and 28.8 ppm for aryl-substituted α-monofluoroalkylzinc **2g-Br** (Table 1). The down-field shift is a *characteristic feature of carbenoids*.[1b,2a,2b] The coupling constants of the α-carbon of **2** ($^{1}J_{C-F}$) were around 170 Hz for alkyl-substituted α-monofluoroalkylzinc (**2a-I**–**2f-I**) and 183 Hz for aryl-substituted α-monofluoroalkylzinc **2g-Br**, which are larger than those of **3a**, **3f**, and **3g** (161–163 Hz). Increased coupling constants $^{1}J_{C-F}$ of **2** in comparison to those of fluoroalkanes **3** were observed.[18] The ^{19}F NMR spectra of **2a-I** is shown in (Figure 6, c. above). We observed three pairs of doublet/triplet peaks around −217 ppm in ^{19}F NMR spectra of **2a-I**, and the integral ratios of the major peaks and minor peaks was 60/1. We obtained similar results from analyses of other alkyl-substituted α-monofluoroalkylzinc (**2b-I**–**2f-I**). The addition of ZnI_2 causes disappearance of the minor peaks (Figure 6, c. bottom), indicating that the minor peaks belong to the diastereomeric pair of dialkylzinc **2a'** (Figure 6, d). K_{eq} of the equilibrium between **2a-I** and **2a'** was calculated to be 2.78 × 10^{-4} (ΔG ~ 4.9 kcal/mol), which is comparable to that of typical organozinc species.[19]

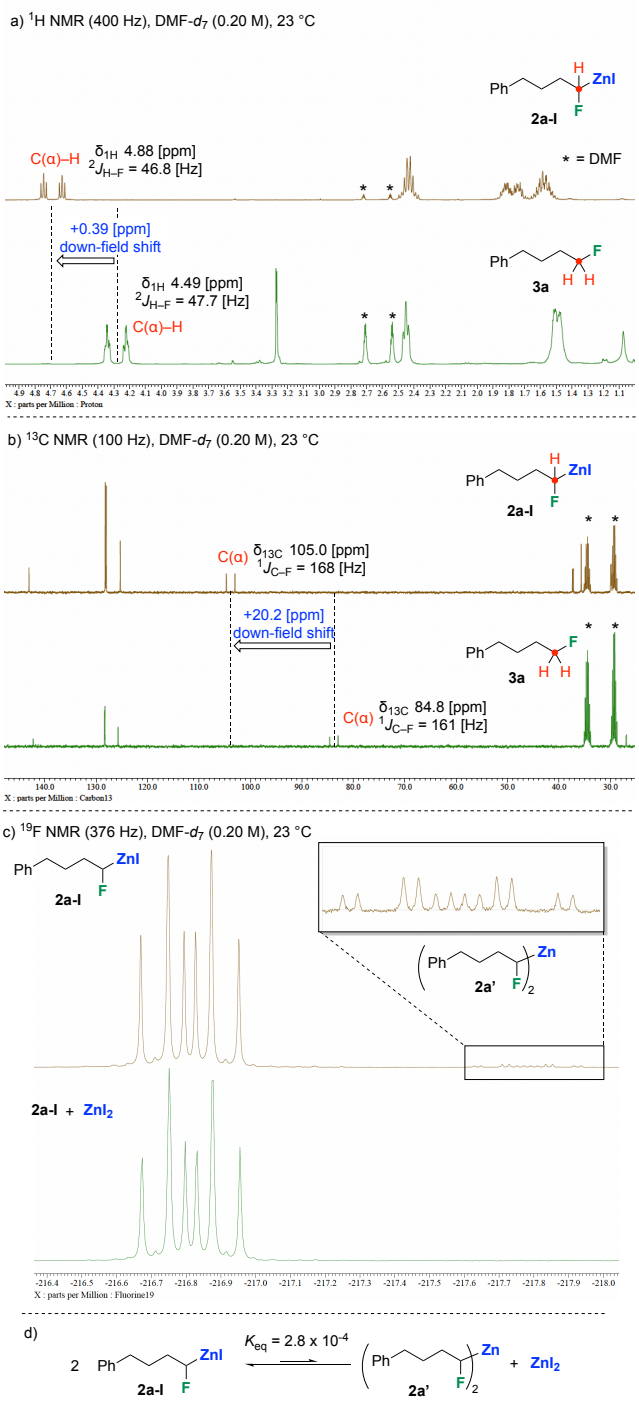


Figure 3. NMR spectroscopy of **2a-I** and the corresponding fluoroalkane **3a**. a) ^{1}H NMR spectra. b) ^{13}C NMR spectra. c) ^{19}F NMR spectra.

The most characteristic NMR property of carbenoids concerns the α-carbon atom. The down-field shift of the α-carbon atom in ^{13}C NMR spectra, relative to those of the corresponding

protonated congeners, serves as a metric for the carbenoid nature. Since carbon-13 (^{13}C) have paramagnetic term as the principal chemical shift effect, a down-field shift in ^{13}C NMR indicates a reduced energy gap between the filled and empty orbitals around the concerned atom, with the angle between the two orbitals approaching perpendicular. Therefore, the extent of the down-field shift of the α-carbon in carbenoids is qualitatively linked to the similarity of the carbenoid structure to that of the corresponding free carbenes. Compared to Δδ(^{13}C) M/H of known carbenoids, the down-field shift of the α-carbon of Zn/F carbenoid **2** (Δδ(^{13}C) M/H = 19.5~28.8 ppm) is less pronounced than that in the case of Li/X carbenoids (Δδ(^{13}C) M/H = 40~90 ppm)[2b] and Mg/X carbenoids (Δδ(^{13}C) M/H = 25~36 ppm)[20] but *more pronounced than that in the case of Zn/I carbenoids (Δδ(^{13}C) M/H = 4 ppm)*.[6a,7a] On the basis of the Δδ(^{13}C) M/H values, Zn/F carbenoids **2** have more sp^2-hybridized structures than Zn/I carbenoids.

DFT calculation of Zn/F carbenoid.

To gain more insight into the structural aspects of Zn/F carbenoid **2a-I**, we conducted DFT calculations (M06-2X/6-311+G(2d,2p) solvent=DMF // M06-2X/6-31G(d)). Gibbs free energies were calculated at 298 K. The DFT calculations showed that 2a-I•2DMF (iodoalkylzinc) is more stable than 2a'•2DMF (dialkylzinc) by 4.0 kcal/mol (Figure 4, a), aligning with the equilibrium constant observed experimentally through ^{19}F NMR analysis (Figure 3, c). Considering similar bond lengths and angles in optimized structures of other conformational isomers of 2a-I•2DMF and 2a'•2DMF (dialkylzinc), the structural information of the most stable conformer will be utilized in subsequent discussions.

In the optimized structure of 2a-I•2DMF (Figure 4, b), the C—F bond length is 1.44 Å, which is 0.06 Å longer than that of the corresponding fluoroalkane 3a (4% elongation). The Zn-C1-F angle, at 107.9 °, deviates from the ideal tetrahedral structure. The sum of bond angles C2-C1-Zn, Zn-C1-H1, and H1-C1-C2 is 337 °, which is larger than that of fluoroalkane 3a (331 °C; for details, see SI). The structural information indicates that the α-carbon of 2a-I has a more sp^2-hybridized character than that of the fluoroalkane 3a, with an increased p-character of the C—F bond (C($sp^{5.4}$)—F). This aligns with the experimentally observed down-field shift of the α-carbon atom in ^{13}C NMR spectroscopy analyses. The Zn–F distance in 2a-I•2DMF measures 2.81 Å as compared to 2.02 Å in ZnF_2 (139% elongation).

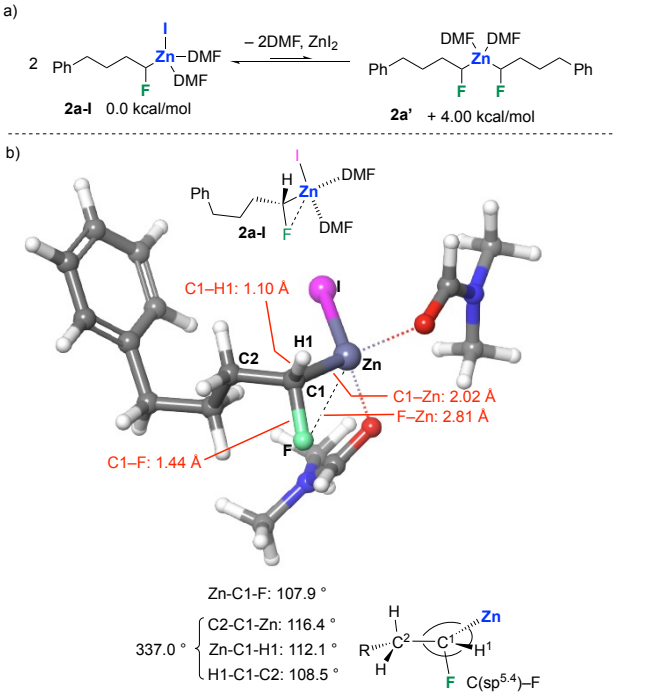
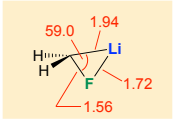
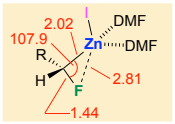
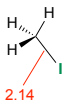
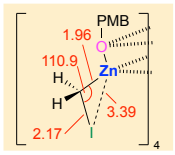


Figure 4. DFT calculations. a) Comparison of Gibbs free energies of **2a-I•2DMF** and **2a'•2DMF**. b) Optimized structure of **2a-I•2DMF**.

Structural comparisons among Li/F,[21] Zn/F, and Zn/I[6c] carbenoids are outlined in Table 2. The elongation of the C—F bond of 2a-I•2DMF (4%) is smaller than that of the calculated structure of the fluoromethyllithium monomer (Li/F carbenoid, 13.9% elongated C—F bond) but slightly larger than that of solid-state Zn/I carbenoid tetramer (1% elongated C—I bond). The M-C(α)-X bond angle in 2a-I•2DMF (107.9 °) is significantly larger than that of the Li/F carbenoid (59.0 °) but only marginally smaller than that of the Zn/I carbenoid (110.9 °). Considering the Zn–F distance in 2a-I•2DMF (2.81 Å, 139% length of ZnF_2), the metal-halogen interaction in Zn/F carbenoid 2a-I is much weaker than that in the Li/F carbenoid, of which the calculated Li–F distance is 1.72 Å (only 110% length of that in LiF). The diminished metal-halogen interaction, along with the less elongated C—F bond, can contribute to the increased stability of Zn/F carbenoids 2 compared with that of Li/F carbenoids.

M/X conbination	haloalkane	carbenoid	metal salt	C–X bond length[a]	M–X bond length[b]
Li/F[c]				114%	110%
Zn/F *this work*				104%	139%
Zn/I[d]				101%	142%

[a]Percentage compared to the carbon-halogen bond length in the corresponding haloalkenes. [b]Percentage compared to the metal-halogen bond length in the corresponding salts. [c]Calculated structure (MP4) described in reference 21b. [d]X-ray structure obtained in reference 6c (CCDC deposition No. 1213324).

Table 2. Structural comparisons of Li/F, Zn/F, and Zn/I carbenoids.

The time course of decay and the degradation pathway of Zn/F carbenoid 2.

We investigated the thermal stability and the decomposition pathway of Zn/F carbenoids **2**. As mentioned before, >95% of α-Zn/F carbenoid **2a-I** remained for 2 hours in DMF at 23 ℃, which enabled detailed NMR analysis of Zn/F carbenoids **2**. However, after an additional 22 hours, only trace amounts of **2a-I** were detected, and the generation of olefin **4a** was observed (Figure 5, a). These strange kinetic profiles of Zn/F carbenoids **2** prompted further investigation into the decomposition mechanism and the time course of the decay of **2-I**.

The conversion of **2-I** to olefin **4** suggests two possible decomposition scenarios (Figure 5, b). In the first scenario, Zn/F carbenoids **2-I** is decomposed through α-elimination to give carbene **5**, followed by a 1,2-hydride shift to form olefin **4**. In the second scenario, **2-I** is decomposed through intermolecular E2 elimination of **2-I** and/or intramolecular E2 elimination of **2'** to produce vinylzinc **6** and fluoroalkane **3**. Vinylzinc **6** further abstracts hydrogen of unreacted **2-I** through E2 elimination to generate olefin **4** and regenerate vinylzinc **6**. Fluoroalkane **3** is also converted to olefin **4** through E2 elimination.

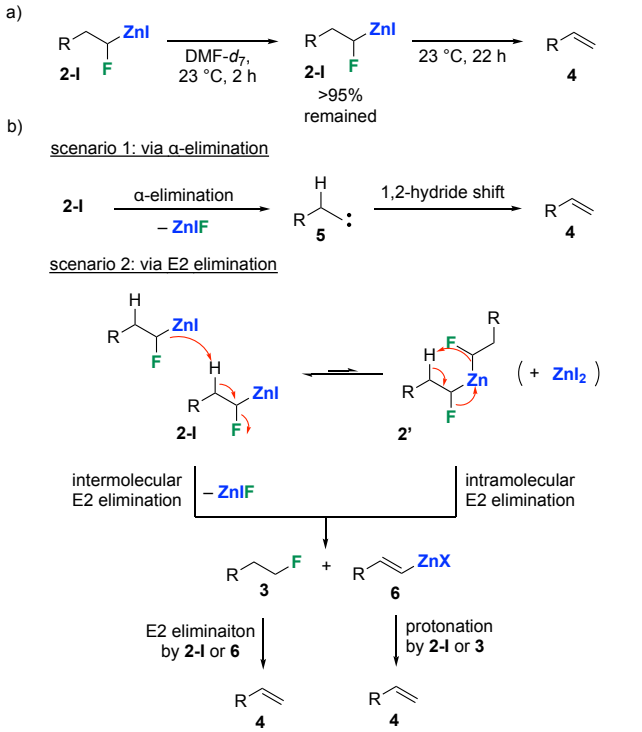


Figure 5. Decomposition of **2-I**. a) Decomposition of **2-I** to olefin **4**. b) Two possible scenarios of the decomposition pathway of **2-I**.

To assess the two possibilities, we monitored the time course of decay of Zn/F carbenoids **2** by NMR spectroscopy analysis (Figure 6). The time course of the decay of **2a-I** was tracked at two different concentrations (0.10 (denoted as ●) and 0.20 M (denoted as ○) in DMF-d_7) as shown in Figure 6, a. The plots of relative concentration versus time showed the *sigmoid curves*. The half-life times of **2a-I** were approximately 19.0 hours at 0.10 M and 8.5 hours at 0.20 M, representing a more than 10^6-fold increase compared to that of Li/F carbenoids **B**. Notably, the half-life time of **2a-I** was prolonged at a lower concentration. The concentration-dependent kinetic profiles indicate that the major decomposition pathway of **2a-I** is through intermolecular E2 elimination of **2a-I** or intramolecular E2 elimination of dialkylzinc **2a'** (scenario 2 in Figure 5), rather than unimolecular α-elimination (scenario 1). The addition of 0.2 equiv. of zinc salts (ZnI_2 or ZnF_2) did not change the decomposition rate (Figure 6, b). In contrast, the addition of vinylzinc **6c** to the solution of **2c-I** accelerated the decomposition rate of **2c-I** (Figure 6, c). These results suggest that the observed sigmoid curves can be rationalized by an autocatalytic decomposition process (Scheme 1); the intermediate vinylzinc **6** reacts with Zn/F carbenoid **2-I** through E2 elimination, producing olefin **4** and regenerating vinylzinc **6**, and the E2 elimination by **6** is faster than the initial E2 elimination between two **2-I**.

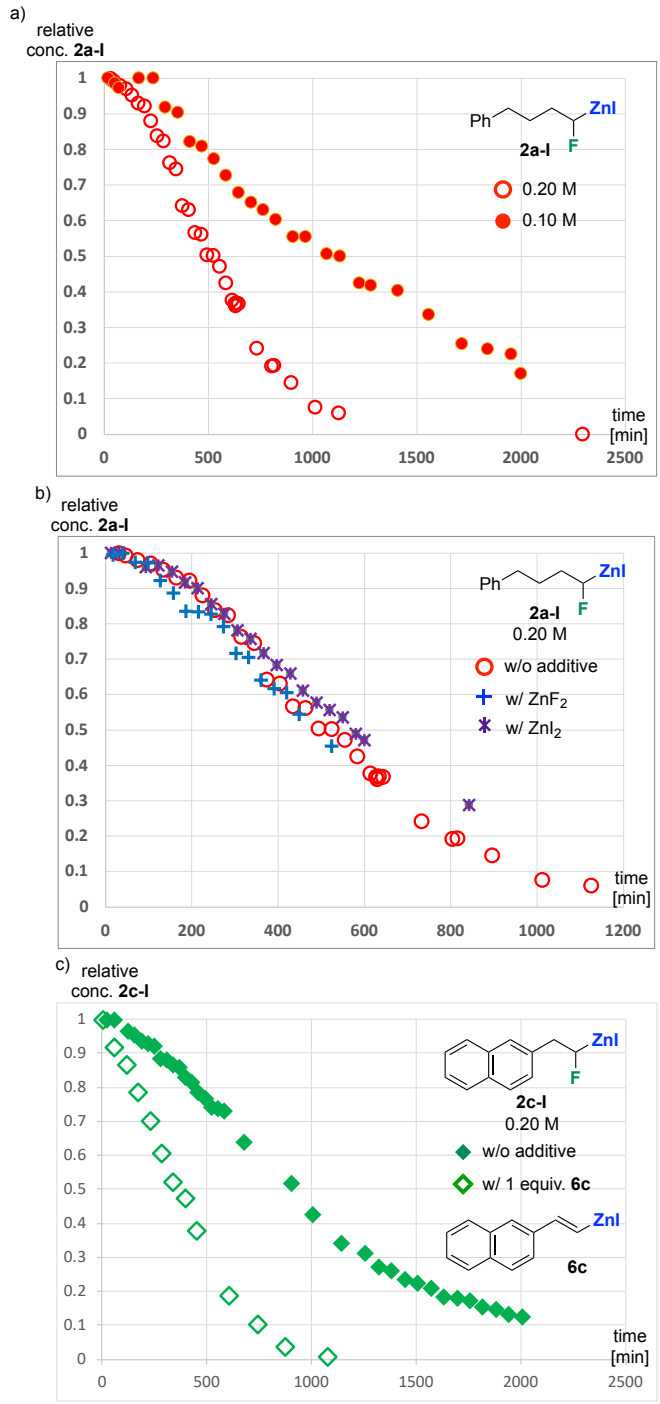
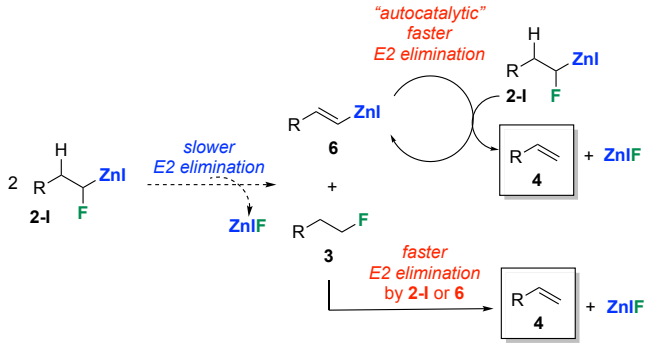


Figure 6. Time course of decay of **2a-I** a) at different concentrations b) in the presence of zinc salts. c) Time course of decay of **2c-I** in the presence of vinylzinc **6c**.



Scheme 1. Rationale for the observed time course of decay of **2-I** with sigmoid kinetics.

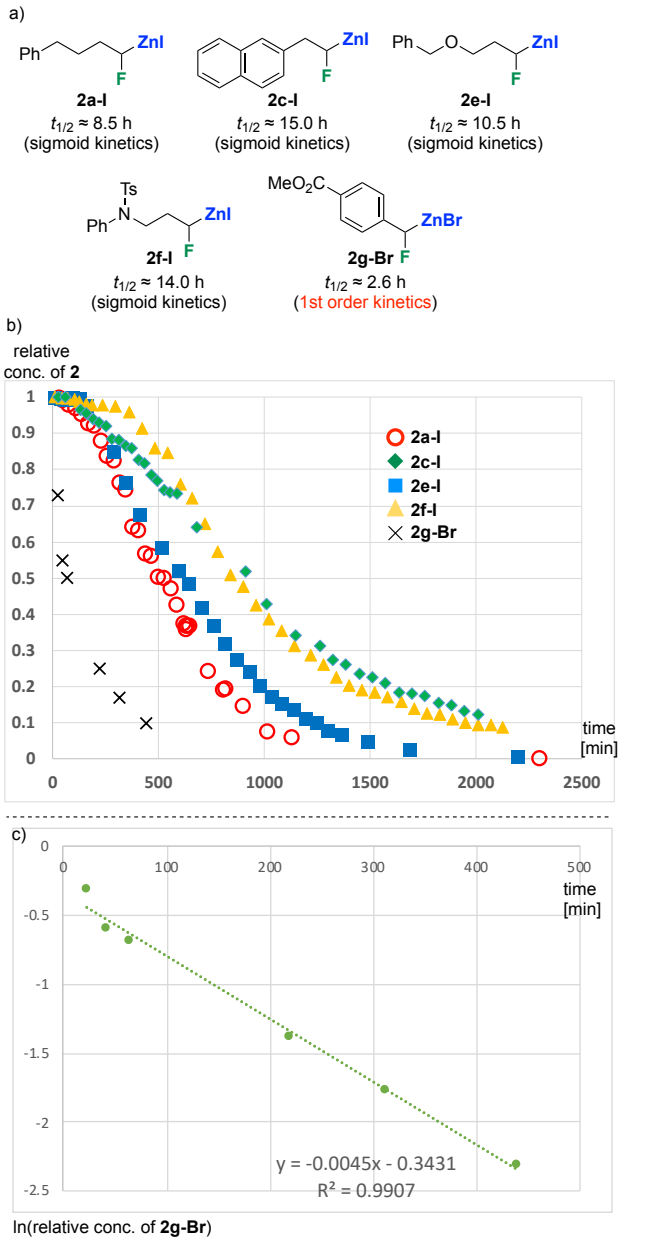


Figure 7. Stability of Zn/F carbenoids **2** at 0.20 M in DMF. a) Summary of half-life times of Zn/F carbenoids **2**. b) Time course of decay of Zn/F carbenoids **2**. c) Logarithmic plot of the time courses of decay of aryl-substituted Zn/F carbenoids **2g-Br**.

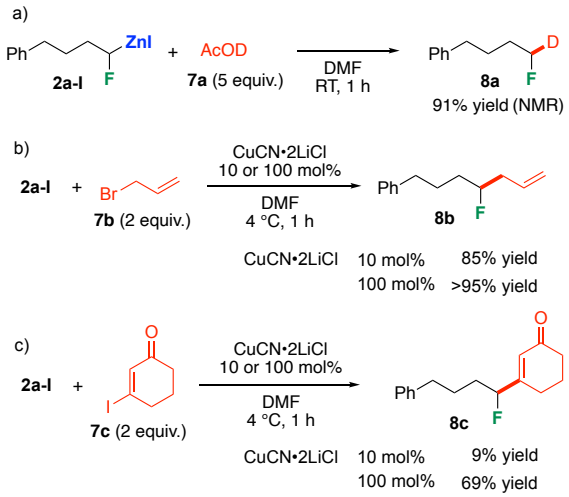
The time courses of decay of various Zn/F carbenoids **2a-l**, **2c-l**, **2e-l**, **2f-l**, and **2g-Br** are summarized in Figure 7. The half-life times of **2c-l**, **2e-l**, **2f-l**, and **2g-Br** are about 15.0 h, 10.5 h, 14.0 h, and 2.6 h, respectively. The carbenoids bearing β-hydrogen decomposed in sigmoid kinetic profiles, whereas **2g-Br**, which has no β-hydrogen, decays in first order kinetics to convert complex mixtures (Figure 7, c). These kinetic profiles are consistent with the assumed decomposition mechanism.

Nucleophilic monofluoroalkylation.

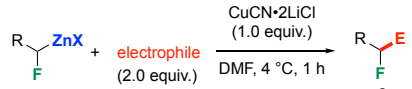
The enhanced thermal stability of Zn/F carbenoids **2** led us to use them in nucleophilic monofluoroalkylation reactions. Monofluoroalkanes have gained significant attention in pharmaceutical chemistry,[22] as substituting C—H bonds with C—F bonds often improves the properties of bioactive compounds[23,24] and change their stable conformations.[24–27] Given the need for rapid synthesis of a wide range of lead compounds in drug discovery, monofluoroalkylation (C—C bond formation)[28] stands as a favorable strategy compared with fluorination (C—F bond formation).[29] Transition-metal-catalyzed or -mediated monofluoroalkylation using α-fluoro-α-haloalkanes and organometallic reagents (electrophilic monofluoroalkylation) have become a robust methodology for synthesizing monofluoroalkanes.[30] However, nucleophilic monofluoroalkylation, a complementary approach, has been restricted to reactions involving α-fluorocarbonyl compounds[31–33] and α-fluorosulfones,[34] or employing unstable Li/F carbenoids in flow techniques under cryogenic conditions.[14a,14c–14e] The restricted application of nucleophilic monofluoroalkylation is primarily attributed to the instability of α-monofluorinated alkylmetal species (*i.e.*, M/F carbenoids).

We utilized Zn/F carbenoids **2** in nucleophilic monofluoroalkylation reactions. Initially, we assessed their nucleophilicity using acetic acid-d_1 allyl bromide, and 3-iodocyclopent-2-en-1-one as electrophiles (Scheme 2, a–c). The reaction of **2a-l** with acetic acid-d_1 (**7a**), proceeded smoothly at room temperature, yielding deuterated fluoroalkane **8a** quantitatively. However, the reaction with less electrophilic allyl bromide (**7b**) and 3-iodocyclopent-2-en-1-one (**7c**) resulted in lower yields of the corresponding adducts (**8b** and **8c**). To enhance the reaction efficiency, we considered using CuCN•2LiCl, a commonly used copper reagent for *in situ* generation of reactive alkylcopper species.[35] In the presence of 10 mol% or 100 mol% of CuCN•2LiCl, Zn/F carbenoid **2a-l** efficiently coupled with allyl bromide (**7b**) to give **8b** in 85% and >95% yield, respectively. The reaction with 3-iodocyclopent-2-en-1-one (**7c**) required 100 mol% of CuCN•2LiCl to yield the adduct (**8c**) in high yield.

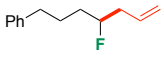
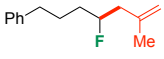
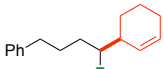
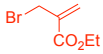
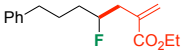
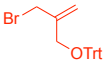
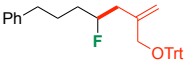
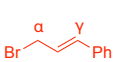
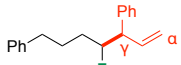
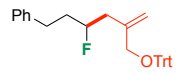
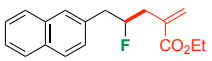
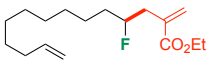
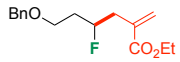
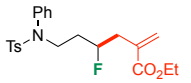
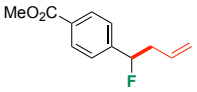
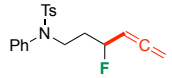
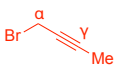
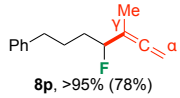
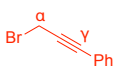
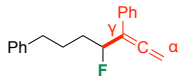
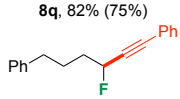
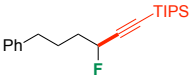
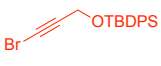
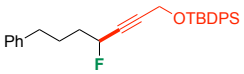
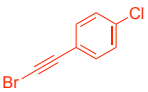
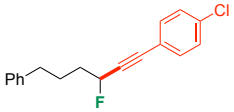
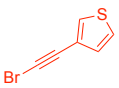
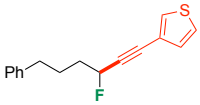
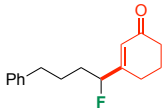
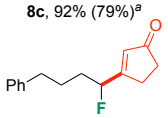
The scope of the nucleophilic monofluoroalkylation using α-monofluoroalkylzinc **2** was investigated in the presence of CuCN•2LiCl, and the results are summarized in Table 3. Various allyl bromides (**7d–7h**) reacted with **2a-l** to produce β-fluorinated alkenes (**8b–8g**) in high yields without deterioration of several ester group and trityl-protective group. In the case of cinnamyl bromide (**7h**), a mixture of α-adduct **8h'** and γ-adduct **8h** was obtained in a 1:3.3 ratio. Various Zn/F carbenoids (**2b-l–2g-Br**) coupled with allyl bromide derivatives to afford diverse of β-fluorinated alkenes (**8i–8n**). Propargyl bromides (**7h–7j**) reacted with **2** at the γ-position, producing monofluoroallenes (**8o–8q**) in high yields. Due to the high reactivity of the allene moiety, practical synthetic methods for monofluoroallenes, such as **8o–8q** have been quite limited. Aryl-, alkyl, and silyl-substituted alkynyl bromides (**7k–7o**) also underwent facile reactions with **2a-l** in the presence of CuCN•2LiCl, yielding propargyl fluorides (**8r–8v**). Alkenylation of **2a-l** with β-iodo-α,β-unsaturated cyclic ketone **7p** gave γ'-fluoro-α,β-unsaturated ketone **8w** in high yields, while the reaction with less reactive acyclic β-iodo-α,β-unsaturated ester **7q** was sluggish, producing **8x** in 25% yield. Acylation of **2a-l** was achieved using dibenzyl carbamothioic thioanhydride derivatives (**7r–7w**) as acylating reagents (for detailed optimizations, see SI), providing various α-monofluorinated alkyl-alkyl ketones (**8y**, **8aa**, **8ab**, and **8ad**) and alkyl-aryl ketones (**8z** and **8ac**) in good yields. Although there is room for yield improvement,[36] preparing such α-monofluorinated alkyl-alkyl ketones through electrophilic fluorination of the corresponding enolates would be challenging due to the site-selectivity issues. Thiocarbamoylation, aminomethylation, and deuteration are also possible, affording α-monofluorinated thioamide **8ae**, β-fluorinated amine **8af**, and α-deuterio-α-fluoroalkane **8ag**, respectively. Although the 1,2-addition of **2** to ketones (**7z–7ab**) proceeded, successive elimination of fluorine atoms occurred, resulting in non-fluorinated products. Isocyanate **7ac** and aziridine **7ad** were recovered almost quantitatively probably due to insufficient electrophilicity. Consequently, Zn/F carbenoids **2** demonstrates broad functional group tolerance, reacting with various electrophiles in the presence of CuCN•2LiCl to produce the corresponding functionalized fluoroalkanes, exhibiting significantly different synthetic applications compared to the Li/F carbenoids.



Scheme 2. Initial trials for nucleophilic addition of Zn/F carbenoid **2a-l** at 0.20 M and the effects of the copper reagent. a) Reaction with acetic acid-d_1. b) Reaction with allyl bromide (**7b**). c) Reaction with 3-iodocyclohex-2-en-1-one (**7c**).



NMR yield [%] (isolated yield [%])

2	7	8
2a-l	 **7b**	 **8b**, >95% (79%)
2a-l	 **7d**	 **8d**, >95% (76%)
2a-l	 **7e**	 **8e**, >95%, dr = 1:1 (97%)
2a-l	 **7f**	 **8f**, >95% (96%)
2a-l	 **7g**	 **8g**, >95% (99%)
2a-l	 **7h**	 **8h**, 69% dr = 1:1, (66%)
2b-l	**7g**	 **8i**, >95% (91%)
2c-l	**7f**	 **8j**, >95% (99%)
2d-l	**7f**	 **8k**, 94% (94%)
2e-l	**7f**	 **8l**, >95% (99%)
2f-l	**7f**	 **8m**, >95% (81%)
2g-Br	**7b**	 **8n**, 88% (79%)
2f-l	 **7h**	 **8o**, >95% (92%)
2a-l	 **7i**	 **8p**, >95% (78%)
2a-l	 **7j**	 **8q**, 82% (75%)
2a-l	 **7k**	 **8r**, 58% (51%)
2a-l	 **7l**	 **8s**, 73% (61%)
2a-l	 **7m**	 **8t**, 61% (46%)
2a-l	 **7n**	 **8u**, 57% (48%)
2a-l	 **7o**	 **8v**, 68% (59%)
2a-l	 **7c**	 **8c**, 92% (79%)[a]
2a-l	 **7p**	 **8w**, 84% (72%)
2a-l	 **7q**	**8x**, 25% (21%)
2a-l	**7r**	**8y**, 65% (40%)
2a-l	**7s**	**8z**, 46% (35%)
2a-l	**7t**	**8aa**, 50% (33%)
2a-l	**7u**	**8ab**, 79% (16%)
2a-l	**7v**	**8ac**, 57% (57%)
2a-l	**7w**	**8ad**, 45% (44%)
2a-l	**7x**	**8ae**, 48% (47%)
2f-l	**7y**	**8af**, 31% (26%)
2f-l	AcOD **7a**	**8ag**, >95%, 92% D (98%)[a,b]

unsuccessful electrophiles so far

Table 3. Scope of the copper-mediated nucleophilic monofluoroalkylation with Zn/F carbenoids **2**. The reaction was performed using 0.1 mmol of Zn/F carbenoids **2** and the concentration was 0.20 M. [a]5.0 equiv. of electrophile was used. [b]The reaction was performed without CuCN•2LiCl.

Conclusions

In this study, we conducted comprehensive investigations of Zn/F carbenoids **2**. Our findings revealed that Zn/F carbenoids **2** can be generated through oxidative addition of 1-fluoro-1-haloalkanes **1** to zinc at room temperature. The half-life of Zn/F carbenoids **2** is several hours at 23℃, which is more than 10^6-times greater than that of known Li/F carbenoids. NMR spectroscopy analyses, along with DFT calculations, indicated

that the Zn/F carbenoid has a more pronounced carbene-like structure than that of the Zn/I carbenoid but a much less pronounced carbene-like structure than that the structures of Li/X and Mg/X carbenoids. Kinetic analyses revealed the decomposition pathway of **2**: E2 elimination for alkyl-substituted Zn/F carbenoids **2**. In the presence of a copper reagent, Zn/F carbenoids **2** reacted with various electrophiles to gives diverse functionalized monofluoroalkanes. We hope our findings will be helpful for future studies on carbenoid chemistry and will lead to further developments of pharmaceutical chemistry and agricultural chemistry through organofluorides synthesis.

Author Contributions

Y. Sato and K. Morisaki conceived the work; K. Morisaki, K. Miyamoto, and E. Kawaguchi devised the experiments, carried out the experiments, and supported analyses of data; Y. Sato and K. Morisaki wrote the paper.

Conflicts of interest

The authors declare no competing financial interest.

Acknowledgements

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Notes and references

1 For reviews on carbenoids, see: (a) G. Boche and C. W. Lohrenz, The Electrophilic Nature of Carbenoids, Nitrenoids, and Oxenoids, *Chem. Rev.*, 2001, **101**, 697–756; (b) V. H. Gessner, Stability and reactivity control of carbenoids: recent advances and perspectives, *Chem. Commun*., 2016, **52**, 12011–12023.

2 For reviews on lithium-based carbenoids, see: (a) G. Körbich, A. Akhtar, F. Ansari, W. E. Breckoff, H. Büttner, WE Drischel, R. H. Fischer, K. Flory, H. Fröhlich, W. Goyert, H. Heinemann, I. Hornke, H. R. Merkle, H. Trapp and W. Zündorf, Chemistry of Stable α-Halogenoorganolithium Compounds and the Mechanism of Carbenoid Reactions, *Angew. Chem. Int. Ed.*, 1967, **6**, 41–52; (b) D. Seebach, R. Hässig and J. Gabriel, ^{13}C-NMR.-Spektroskopie von Organolithiumverbindungen bei tiefen Temperaturen. Strukturinformation aus der ^{13}C, ^{6}Li-Kopplung, *Helv. Chim. Acta.*, 1983, **66**, 308–337; (c) V. Capriati and S. Florio, Anatomy of Long-Lasting Love Affairs with Lithium Carbenoids: Past and Present Status and Future Prospects, *Chem. Eur. J.*, 2010, **16**, 4152–4162.

3 For reviews on magnesium-based carbenoids, see: (a) T. Satoh, Recent advances in the chemistry of magnesium carbenoids, *Chem. Soc. Rev.*, 2007, **36**, 1561–1572; (b) T. Kimura, Recent Advances in Magnesium Carbenoid Chemistry, *Synthesis*, 2017, **49**, 5105–5119.

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