

Title:

Carbene reactivity from alkyl and aryl aldehydes

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Abstract: Carbenes are highly enabling reactive intermediates that facilitate a diverse range of otherwise inaccessible chemistry, including small ring formation and insertion into strong σ -bonds. To access such valuable reactivity, reagents with high entropic or enthalpic driving forces to product are often employed, including explosive (diazo) or unstable (*gem*-dihalo) compounds. Here, we report that common aldehydes are readily converted (via stable α -acyloxy halide intermediates) to electronically diverse, donor or neutral carbenes to facilitate >10 reaction classes. This strategy enables safe reactivity of non-stabilized carbenes from alkyl, aryl, and formyl aldehydes via zinc carbenoids. Earth-abundant metal salts (FeCl₂, CoCl₂, CuCl) are effective catalysts for these chemoselective carbene additions to σ - and π -bonds.

One Sentence Summary: A new strategy for generating electronically diverse carbenes from carbonyls enables novel, broader, safer, and more sustainable reactivity.

Main Text:

In organic synthesis, several important classes of chemical reactivity are uniquely mediated by carbenes and carbenoids (Fig. 1A) (1–5). However, access to these versatile intermediates is often limited by the need for highly energetic diazoalkane precursors. Given the strong entropic and enthalpic driving forces inherent in the release of N₂ from these reagents, strict precautions are necessary to prevent explosive, uncontrolled chain reactions (6). Strategies to address this underlying safety issue include flow chemistry and *in situ* diazotization (7–9). Carbonyl and arene stabilizing groups are also frequently employed (10) – influencing carbene polarity and selectivity (11, 12). Yet, non-stabilized, alkyl carbenes (with eliminable α -protons) remain largely unharnessed for the diazo strategy (13).

In a complementary approach, Simmons-Smith cyclopropanations by Zn carbenoids (from *gem*-dihalides) enable incorporation of the smallest divalent carbon, CH₂ (14, 15). However, α -protons are rarely tolerated due to 1,2-H-migration of the Zn carbenoid (16). Despite elegant solutions for Matteson rearrangement by Li/boronate carbenoids (17–20), Mo-mediated ketone deoxygenation (21, 22), and Au-catalyzed alkyne cyclizations (23, 24), there remains no general approach to access non-stabilized alkyl carbenes, nor for their use in the wide range of carbene reactivity available to stabilized diazo reagents (25).

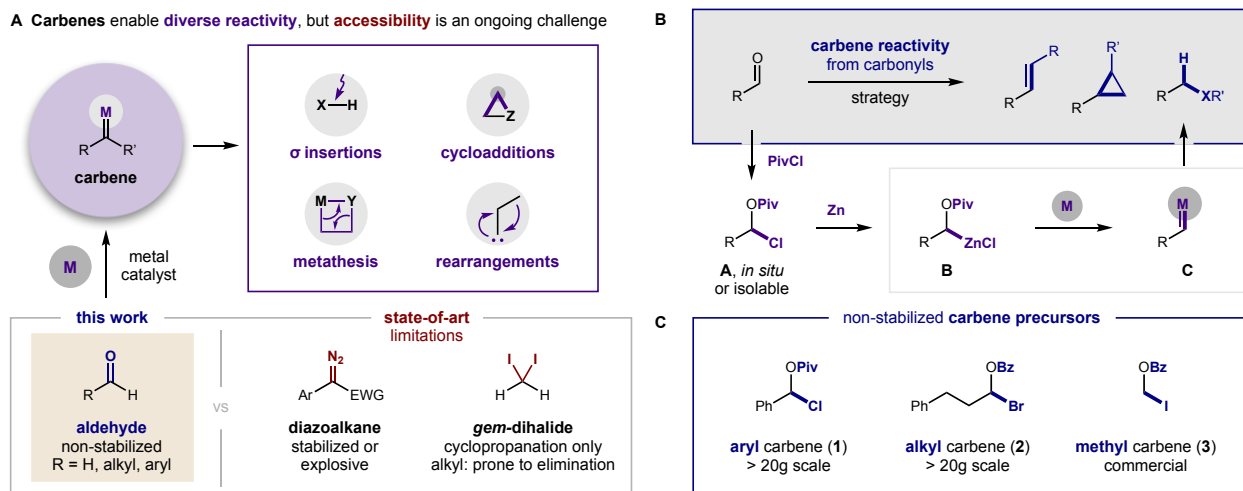


Figure 1. Strategies to harness carbene reactivity. (A) Synthetic approaches to carbenes either rely on loss of N_2 from diazoalkanes or reduction of *gem*-dihalides. Both reagent classes exhibit limited scope, stability, and reactivity in absence of aryl or α -carbonyl stabilization. (B) Our design converts carbonyls to non-stabilized carbenes via Zn insertion into α -acyloxy halides and activation by Earth-abundant metal catalysts. (C) Three classes of carbene precursors are readily prepared and exhibit significantly improved safety profiles versus diazo reagents.

The carbonyl is an ideal carbene precursor, as it is highly accessible – both commercially and synthetically. Towards this goal, we were inspired by the classic Clemmensen reduction of carbonyls with $Zn(Hg)$ and HCl (26, 27). Motherwell also harnessed this Zn carbenoid reactivity to deoxygenate ketones by 1,2-H-migration of siloxy analogs (28). However, this tendency toward α -elimination precludes access to the broad range of diazo-based carbene reactivity (29).

In designing a general, catalytic strategy to convert carbonyls to electronically diverse carbenes (Fig. 1B), we sought to develop a safe, stable carbenoid precursor that does not rely on activation by highly eliminable diazo, dihalo, or siloxy groups. Instead, we were cognizant acyl chloride, $AcCl$, readily adds to carbonyls, yielding stable α -acyloxy halides – even with enolizable aldehydes (30). We previously showed acyl iodide, AcI , adducts of carbonyls enable distinct ketyl radical reactivity by atom- or electron- transfer reduction mechanisms (31, 32). In contrast, we hypothesized a more stable pivaloyl chloride, $PivCl$, adducts of carbonyls may prevent the radical pathway and permit chemoselective formation of α -acyloxy Zn carbenoid **B** (33). Importantly, by accessing this key intermediate in the absence of strong acids, we proposed the controlled α -acyloxy elimination by base metal catalysts could form reactive, metal carbene **C**. We anticipated catalyst influence could also impart distinct reactivity compared to simple Zn carbenoids. Ideally, the resulting (i) carbene dimerization, (ii) σ -bond insertion, or (iii) small ring formation, would be chemoselectively dictated by these catalysts – and override innate 1,2-rearrangements of alkyl Zn carbenoids.

Another key design element is that several classes of these carbene precursors are easily prepared, stable for months in cold storage, and handled safely at large scale. As shown in Fig. 1C, we found less electrophilic carbonyls are best paired with more electrophilic acyl halides ($Cl < Br < I$) to afford increasingly reactive carbene precursors ($\alpha-Cl < \alpha-Br < \alpha-I$). For example, $PivCl$ readily adds to benzaldehyde to generate bench-stable aryl carbene precursor **1**. Yet, less electrophilic,

aliphatic aldehydes are best combined with benzoyl bromide, BzBr, to form non-stabilized alkyl analog **2**, which is nonetheless stable to chromatography. Both reactions can be performed at >20 g scale without safety concerns inherent to analogous diazo analogs, which violently decompose upon loss of N₂ near 100°C (with a decomposition enthalpy, ΔH_D , > 200 kJ/mol, as measured by differential scanning calorimetry; DSC)(6). Conversely, these α -acyloxy halides are considerably more stable – with drastically less decomposition enthalpies observed (ΔH_D < 30 kJ/mol in all cases) and only at much higher temperatures than typical reaction conditions (T_{init} : **1**, 155°C; **2**, >300°C; **3**, 235°C). Lastly, benzoyl iodide, BzI, readily combines with the least reactive aldehyde, formaldehyde, to access methyl carbene precursor **3**, which is a common protecting-group that is commercially available in kilogram quantities and provides a safe alternative to diazomethane.

To investigate our design, carbene dimerization was examined by subjecting benzaldehyde to the proposed strategy, a three-stage sequence entailing (i) PivCl addition, (ii) Zn insertion, (iii) and metal catalysis. This procedure can either be completed successively in one-pot or by pre-isolation of PivCl adduct **1**. As shown in Fig. 2, several base metal salts (e.g. CuCl, CoCl₂) enable efficient dimerization to stilbene **4** – with notably high catalyst stereocontrol observed via CoCl₂ (90%, 18:1 *E:Z*, via **1**), surprising, given the absence of bulky ligands that have been shown to be integral for selectivity in other carbenoid reactions (16). As further evidence of catalyst control, no reaction was observed with NiCl₂ or without catalyst. In addition to serving as proof of concept of carbene reactivity, these mechanistic probes also demonstrate electronically diverse substituents (**6-8**) are well-tolerated in the aryl carbene component.

We next tested our hypothesis that alkyl carbene reactivity may be harnessed by this catalytic approach in a safer and more selective manner than by diazoalkanes or dihalides. The uniquely broad scope of aliphatic aldehydes (even with eliminable α -protons) that could be converted to carbenes was the highlight of this initial study. To this end, we found CoCl₂ effectively catalyzes carbene dimerization from hydrocinnamaldehyde (to alkene **5** via **2**: 99%, 2:1 *E:Z*). Notably, no α -elimination is observed – in contrast to the uncatalyzed siloxy variant, which is limited to α,β -unsaturated carbonyls to prevent such a pathway (28, 34). For further comparison, the diazo strategy was examined by subjecting a hydrazone to various catalysts and bases to access its carbene. In all cases, only α -elimination is observed (up to 61% **5'**), likely due to the high temperatures (100°C) required for reactivity.

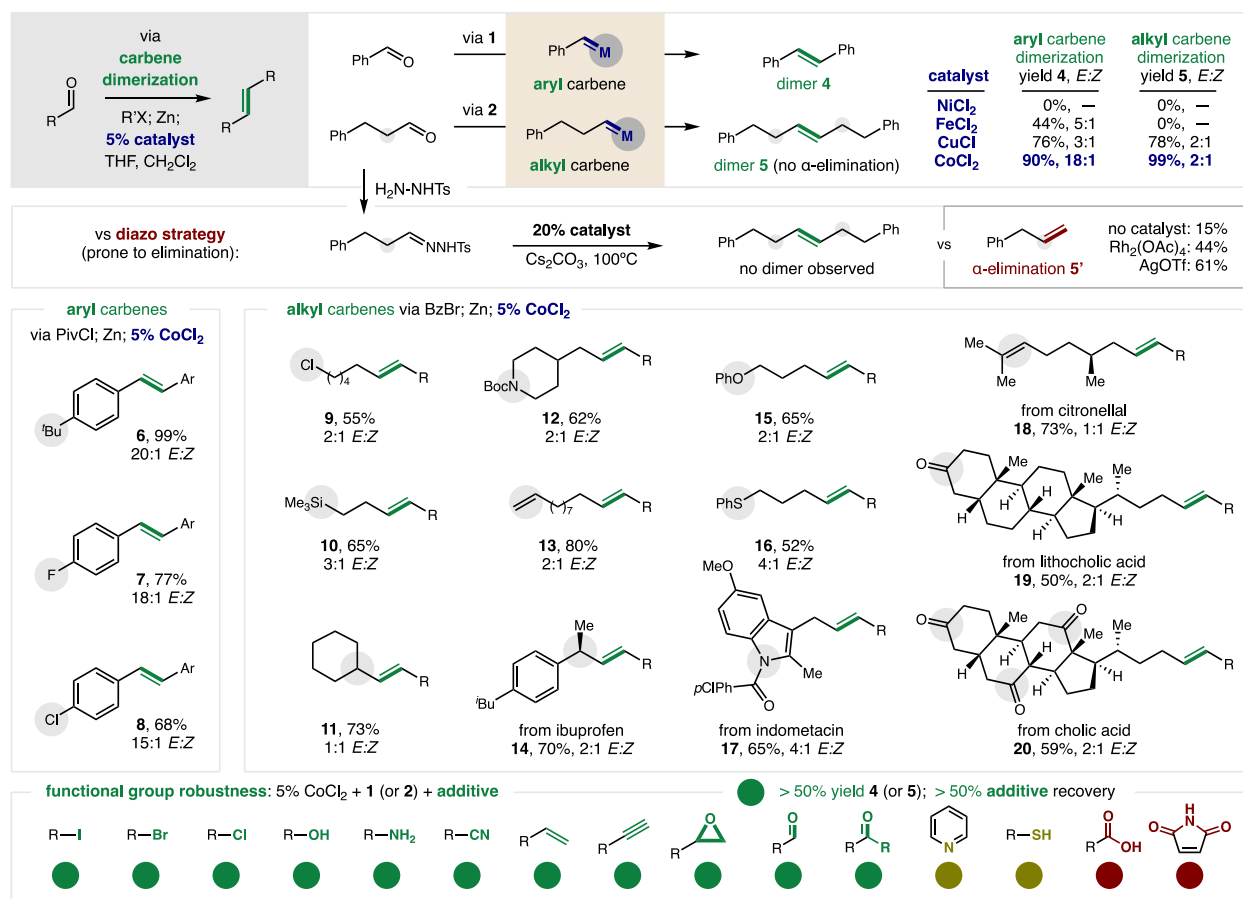


Figure 2. Carbene dimerization. Catalytic dimerization of aldehyde-derived aryl and alkyl carbenes enabled by several base metal salts. The synthetic generality and broad functional group tolerance of this carbene dimerization is shown. **Aryl carbene:** Aldehyde (1 equiv), PivCl (2 equiv), 2% ZnCl₂, CHCl₃, 2 h; Zn (2 equiv), LiCl (2 equiv), THF, 12 h; 5% CoCl₂, CH₂Cl₂: THF, 2 h. **Alkyl carbene:** Aldehyde (1 equiv), BzBr (1.2 equiv), 2% ZnBr₂, CH₂Cl₂, 2 h; Zn (2 equiv), LiCl (2 equiv), THF, 12 h; 5% CoCl₂, CH₂Cl₂: THF, 2 h. **Robustness:** Experiments performed with additive and either **1** or **2** (1 equiv each). See *Supplementary Materials* for full experimental details. Isolated yield and alkene stereochemistry (*E/Z*) indicated. Abbreviations: Piv, pivaloyl; Bz, benzoyl.

In contrast, the valuable alkyl carbene reactivity enabled by this approach includes dimerization of aldehydes containing synthetically tractable halides, alkenes, silanes, carbamates, ethers, sulfides, amides, ketones, and α -substituents, including within natural product and drug scaffolds (**9-20**). In all cases, rapid dimerization preferentially occurs over other types of carbene reactivity, such as intramolecular cyclopropanation (**18**). Moreover, a robustness study (35) was conducted to further assess the broad functional group tolerance of this strategy, wherein chemically diverse additives were combined with catalyst and carbene precursors **1** (or **2**) to explore their viability in the dimerization step.

We then subjected these aldehyde-derived carbene precursors to several distinct classes of reactivity, including signature carbene reactions: cyclopropanation and X-H insertion (36, 37) (Fig. 3A). While probing reactivity with several common carbene traps, we observed the catalysts that promoted rapid dimerization (*vide supra*; CoCl₂, CuCl) are less efficient at chemoselective cross-coupling. On the other hand, metallocarbenes generated from FeCl₂ or Rh₂(OAc)₄ enable alternate modes of carbene reactivity aside from dimerization. For example, cyclopropanation of

styrenes with aryl carbenes is efficiently catalyzed by FeCl₂ (**21-22**, up to 95%), but not CoCl₂. In contrast with typical Simmons-Smith selectivity (38, 39), this Fe-catalyzed strategy is uniquely selective for more-substituted, electron-rich alkenes (e.g. monoterpene **23**). Conversely, cyclopropanation of electron-deficient alkenes does not occur, as expected. However, if Me₂S is added as a co-catalyst to access the polarity-reversed sulfonium ylide (*c.f.* Fig 4c) as has been demonstrated with diazoalkanes (40), then electrophilic acrylates and enones can now be selectively benzylated (**24-25**), including in selective competition over other alkenes, as in the case of carvone (**26**). This sulfonium-mediated strategy also affords epoxides and aziridines by combination of these aldehyde-derived carbenes with electronically diverse aldehydes and imines (**27-30**) – without the need for diazoalkanes, and in a more modular fashion that relies on aldehyde rather than typical sulfonium ylide precursors.

Besides cyclopropanation, the most commonly employed reactivity of metal carbenes is catalytic X-H insertion (36, 37). Although Zn-carbenoids have not been useful in enabling such reactivity, we sought to examine if our metal-catalyzed activation could mirror the robust reactivity of diazo reagents. We found that a range of alkyl and aryl amines efficiently underwent N-H insertion to generate benzyl amines (**31-33**). Insertion into a less polarized P-H bond also occurred with three classes of organophosphorus compounds, to access phosphates, phosphine oxides, and phosphine sulfides (**34-36**). Given the electrophilic nature of this carbene, other nucleophilic X-H donors were also examined. Si-H insertion into silanes occurred smoothly with either FeCl₂ (56% **37**) or more typical carbene catalyst, Rh₂(OAc)₄ (83%). Insertion into Si-D yielded complete α -deuteration (>95% D, **38**) in THF, confirming the carbene nature of this catalytic mechanism, which is amenable to several classes of alkyl silanes (**37-39**). Insertion also occurred into σ -bonds of varying polarity, including B-H and S-H bonds (**40-41**). Overall, we observed more nucleophilic H-donors (e.g. phosphine, silane, borane) are highly suited to this carbene reactivity, which has now been applied to 10 reaction classes (dimerization, four (2+1) cyclizations, five X-H insertions).

Since none of these alkyl carbene reactions has been previously accessible by Zn carbenoid activation of carbonyls, we sought to test the limits of this reactivity with non-stabilized, alkyl aldehydes (Fig. 3B). First, we noted typical 1,2-H-migration (28, 34) did not occur in this mild system at room temperature. Instead, heating (60°C) was needed to promote catalytic deoxygenation (**42**). This lack of background H-migration enables successful realization of several classes of alkyl carbene reactivity, including cyclopropanation (**43-44**), epoxidation and aziridination (**45-46**), and σ -bond insertion (**47-49**) – all with similar efficiency to aryl carbenes. Notably, alkyl carbene reactivity is typically challenging to access by other methods since diazoalkane and dihalide precursors are highly prone to H-migration. Having harnessed this new substrate class, we also investigated C-C insertion, wherein ring-expansion of α -cyclobutanes and rearrangement of α -cyclopentanes were each observed (**50-53**). Lastly, we confirmed viability of the simplest carbene (CH₂) for both reaction classes (Fig. 3C): π -bond cycloaddition (**54-56**) and σ -bond insertion (**57-58**). We expect this formaldehyde-based approach to provide a safer alternative to conventional diazomethane reactivity and to complement modern methods entailing *in situ* generation (7–9).

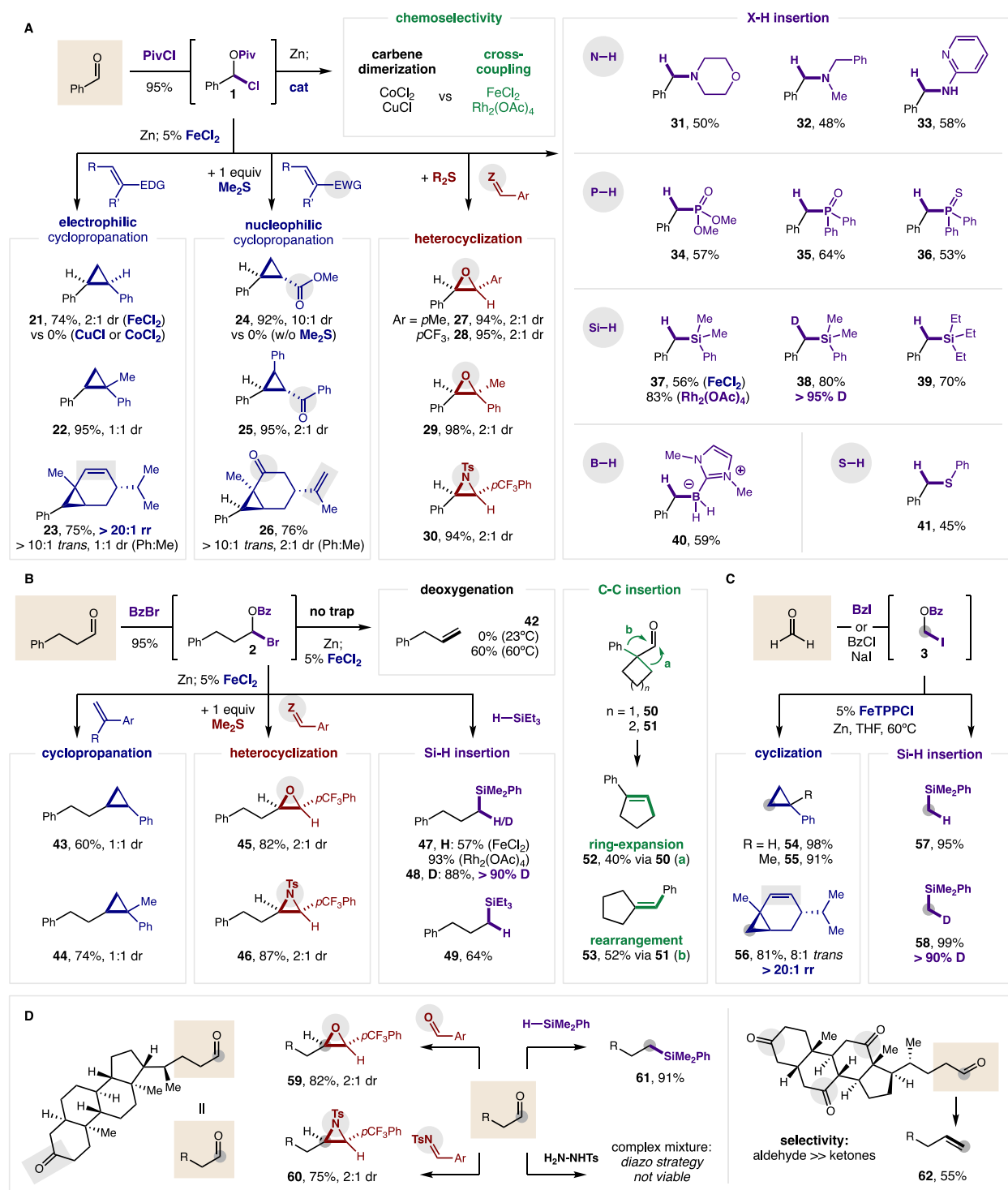


Figure 3. Catalytic carbene reactivity. (A) **Aryl carbene.** Aldehyde (2 equiv), PivCl (4 equiv), 4% ZnCl_2 , CHCl_3 , 2 h; Zn (2 equiv), LiCl (2 equiv), THF, 6 h; 5% FeCl_2 or 2.5% $\text{Rh}_2(\text{OAc})_4$, carbene trap (1 equiv), CH_2Cl_2 : THF, 12 h. (B) **Alkyl carbene.** Aldehyde (3 equiv), BzBr (3.6 equiv), 4% ZnBr_2 , CH_2Cl_2 , 2 h; Zn (3 equiv), LiCl (3 equiv), THF, 6 h; 5% FeCl_2 , carbene trap (1 equiv), CH_2Cl_2 : THF, 12 h. (C) **Methyl carbene.** Iodide (3 equiv), Zn (3 equiv), 5% FeTPPCL , carbene trap (1 equiv), CH_2Cl_2 : THF, 4 h. (D) **Complex molecule applications.** See *Supplementary Materials* for full experimental details. Isolated yield and diastereomeric ratio (dr) indicated. Abbreviations: Piv, pivaloyl; Bz, benzoyl; Ts, toluenesulfonyl.

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Our mechanistic understanding of this catalytic carbene reactivity from aldehydes is based on a collection of experiments, including intermediate characterization, reactivity comparisons, and kinetic data (Fig. 4). An investigation of various bases (NaH, Cs₂CO₃), temperatures (0–100°C), and catalysts (Fig. 4A) verify the carbene dimerization is not accessible via diazoalkanes. The

proposed Zn carbenoid, generated in absence of catalyst, was characterized by protodechlorination with HCl (**63**) (Fig. 4B). Conversely, a stronger Mn reductant affords pinacol coupling via ketyl radicals (**64**). This product remains unchanged and does not afford stilbene (**4**) when resubjected to reaction conditions. In probing the electronic nature of the catalytic carbene intermediate, we noted its electrophilicity, as evidenced by higher efficiency of reactivity with nucleophilic alkenes (α -Me-styrene) versus electrophilic traps (acrylate) (Fig. 4C). However, upon introduction of a sulfide co-catalyst, a transient sulfonium ylide (observed by GC-MS) enables inverted reactivity with such electrophiles (*cf.* **24**) – without the need for diazo intermediates (**40**). Furthermore, in a 1:1 competition of an alkene and aldehyde as potential carbene traps, exclusive selectivity is observed for epoxidation with Me₂S – versus only cyclopropanation without Me₂S (Fig. 4D). Notably, the metal catalyst also dictates reaction chemoselectivity. For example, in a competition experiment among three classes of carbene traps, dimerization is exclusively observed with CuCl (73%) and CoCl₂ (80%), yet FeCl₂ predominantly affords cyclopropanation (77%) and Rh₂(OAc)₄ yields Si-H insertion (94%). Lastly, *in situ* IR experiments of the carbene dimerization reaction and variable time normalization analysis (VTNA) (**41**) indicate the dimerization reaction is second order in catalyst (see *Supp Mat*).

Since this carbene generation mechanism does not rely on evolution of N₂ gas, a significant improvement in thermal stability was observed for these carbene precursors (ΔH_D : 0 kJ/mol **2**, 6 kJ/mol **3**) relative to diazoalkanes ($\Delta H_D > 200$ kJ/mol) (Fig. 4E). To harness this superior safety profile, large-scale, batch reactions were performed with quantities that would be prohibitively unsafe with diazoalkanes (e.g. CH₂N₂). In these cases, cyclopropanations succeeded at up to 1000 times larger scale without event.

In summary, we have introduced a catalytic strategy for harnessing carbene reactivity from carbonyls. We expect the approach will have a threefold impact on the expanded development of carbene reactions, including via the use of base metal catalysts, safe and scalable reagents, and improved synthetic access to non-stabilized carbenes.

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Competing interests: Authors declare no competing interests.

Data and materials availability: All data is available in the main text or the supplementary materials.

SUPPLEMENTARY MATERIALS

Materials and Methods

Figures S1 to S14

Tables S1 to S17

NMR Spectra