REPORT

ORGANIC CHEMISTRY

Carbene reactivity from alkyl and aryl aldehydes

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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 are often used, 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 nonstabilized carbenes from alkyl, aryl, and formyl aldehydes via zinc carbenoids. Earth-abundant metal salts [iron(II) chloride ($FeCl_2$), cobalt(II) chloride ($CoCl_2$), copper(I) chloride (CuCl)] are effective catalysts for these chemoselective carbene additions to σ and π bonds.

In organic synthesis, several important classes of chemical reactivity are exclusively 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 N_2 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 used (*10*), which influence carbene polarity and selectivity (*11*, *12*). Yet nonstabilized alkyl carbenes (with eliminable α protons) are rarely accessed by diazoalkanes (*13*).

In a complementary approach, Simmons-Smith cyclopropanations by Zn carbenoids (from *gem*-dihalides) enable incorporation of the smallest divalent carbon, CH_2 (*14*, *15*). However, α protons are rarely tolerated owing 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 nonstabilized alkyl carbenes or for their use in the wide range of carbene reactivity available to stabilized diazo reagents (*25*).

The carbonyl is an ideal carbene precursor, because it is highly accessible, both commercially and synthetically. Toward 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 that acyl chloride (AcCl) readily adds to carbonyls, yielding stable α-acyloxy halides, even with enolizable aldehydes (*30*). We previously showed that acyl iodide (AcI) adducts of carbonyls enable distinct ketyl radical reactivity by atom- or electron-transfer reduction mechanisms (*31*, *32*). By contrast, we hypothesized that the more stable pivaloyl chloride (PivCl) adduct **A** 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 that the controlled α-acyloxy elimination by base metal catalysts could form reactive, metal carbene **C**. We anticipated that catalyst influence could also impart distinct reactivity compared with 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

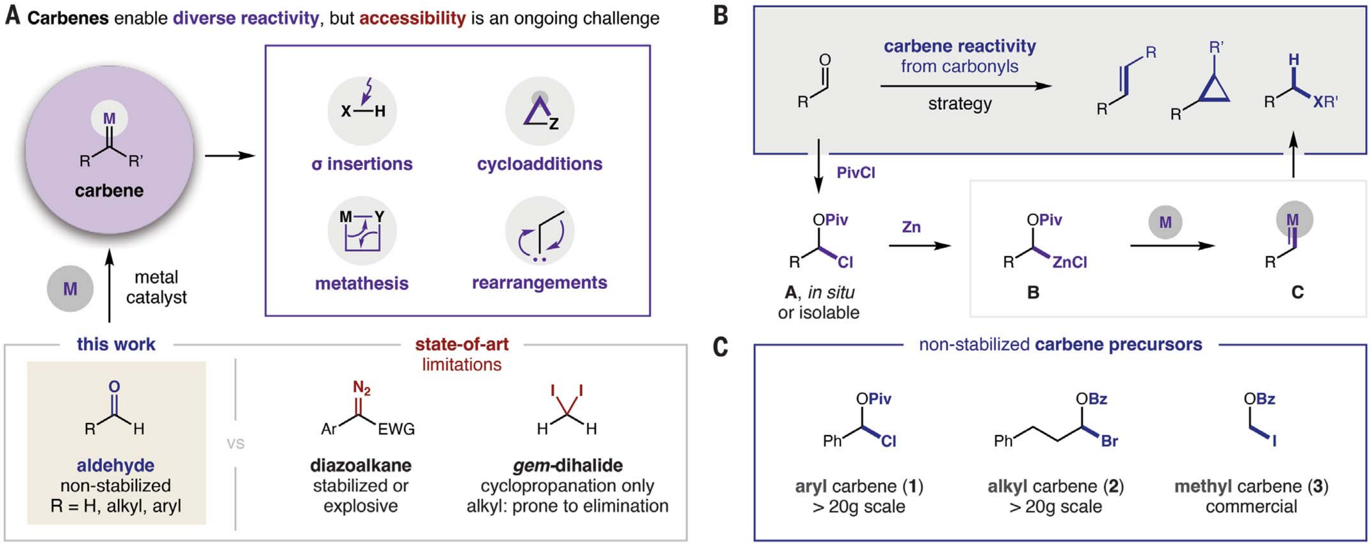

Fig. 1. Strategies to harness carbene reactivity. (**A**) Synthetic approaches to carbenes rely on either loss of N_2 from diazoalkanes or reduction of *gem*-dihalides. Both reagent classes exhibit limited scope, stability, and reactivity in the absence of aryl or α-carbonyl stabilization. (**B**) Our design converts carbonyls to nonstabilized 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 substantially improved safety profiles versus diazo reagents. Ar, aryl; Bz, benzoyl; EWG, electron-withdrawing group; M, metal catalyst; Ph, phenyl; Piv, pivaloyl; X, Y, and Z, generic atoms.

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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 that less-electrophilic carbonyls are best paired with more-electrophilic acyl halides (Cl < Br < I) to afford increasingly reactive carbene precursors (α-Cl < α-Br < α-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 nonstabilized alkyl analog **2**, which is nonetheless stable to chromatography. Both reactions can be performed at >20-g scale without the safety concerns that are inherent to analogous diazo analogs, which violently decompose upon loss of N_2 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 preisolation of PivCl adduct **1**. As shown in Fig. 2, several base metal salts (e.g., CuCl, $CoCl_2$) enable efficient dimerization to stilbene **4**, with notably high catalyst stereocontrol observed for $CoCl_2$ [90%, 18:1 *E:Z*, via **1**], which is 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 $NiCl_2$ or without catalyst. In addition to serving as a proof of concept of carbene reactivity, these mechanistic probes also demonstrate that electronically diverse substituents (**6** to **8**) are well tolerated in the aryl carbene component.

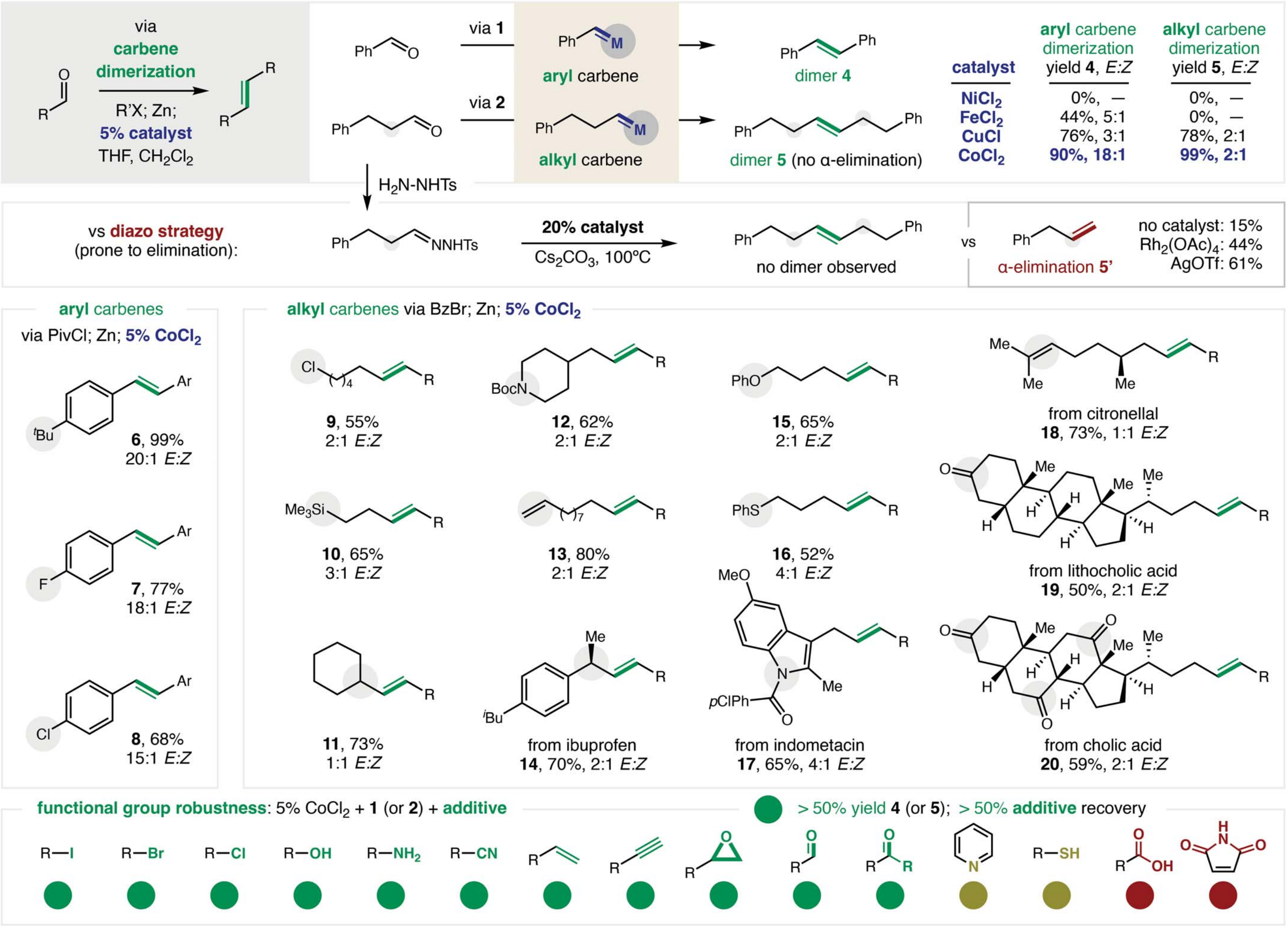

Fig. 2. Carbene dimerization. Catalytic dimerization of aldehyde-derived aryl and alkyl carbenes enabled by several base metal salts. The synthetic generality and broad functional group tolerance of this carbene dimerization are shown. Reaction conditions for the aryl carbene are as follows: aldehyde (1 equiv), PivCl (2 equiv), 2% $ZnCl_2$, $CHCl_3$, 2 hours; Zn (2 equiv), LiCl (2 equiv), THF, 12 hours; 5% $CoCl_2$, CH_2Cl_2:THF, 2 hours. Reaction conditions for the alkyl carbene are as follows: aldehyde (1 equiv), BzBr (1.2 equiv), 2% $ZnBr_2$, CH_2Cl_2, 2 hours; Zn (2 equiv), LiCl (2 equiv), THF, 12 hours; 5% $CoCl_2$, CH_2Cl_2:THF, 2 hours. To evaluate robustness, experiments were performed with additive and either **1** or **2** (1 equiv each). See the supplementary materials for full experimental details. Isolated yield and alkene stereochemistry (*E:Z*) are indicated. OTf, trifluoromethanesulfonate; *p*, *para*; ^{t}Bu, *tert*-butyl; Ts, toluenesulfonyl.

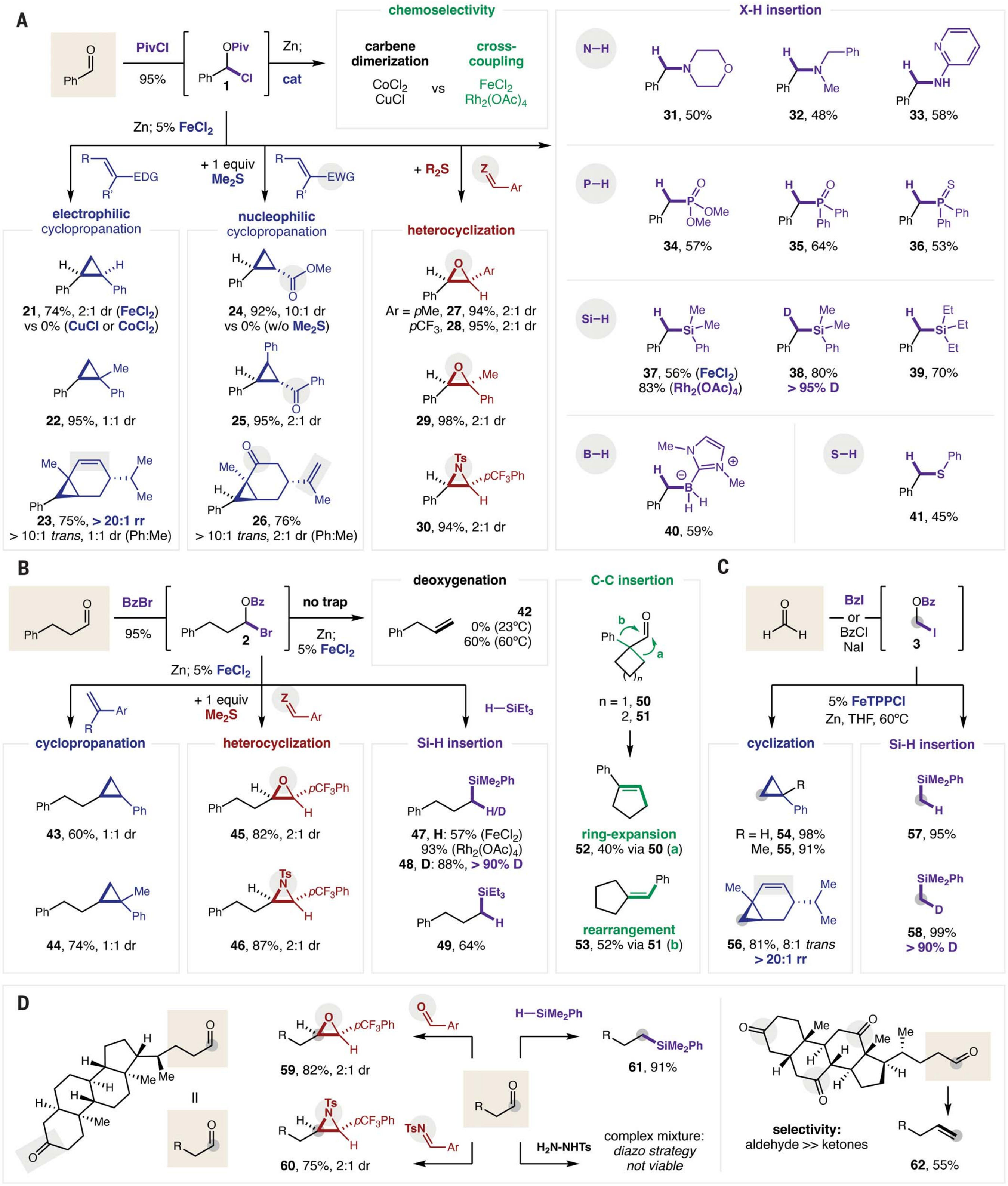

Fig. 3. Catalytic carbene reactivity. (**A**) Aryl carbene. Reaction conditions are as follows: aldehyde (2 equiv), PivCl (4 equiv), 4% $ZnCl_2$, $CHCl_3$, 2 hours; Zn (2 equiv), LiCl (2 equiv), THF, 6 hours; 5% $FeCl_2$ or 2.5% $Rh_2(OAc)_4$, carbene trap (1 equiv), CH_2Cl_2:THF, 12 hours. (**B**) Alkyl carbene. Reaction conditions are as follows: aldehyde (3 equiv), BzBr (3.6 equiv), 4% $ZnBr_2$, CH_2Cl_2, 2 hours; Zn (3 equiv), LiCl (3 equiv), THF, 6 hours; 5% $FeCl_2$, carbene trap (1 equiv), CH_2Cl_2:THF, 12 hours. (**C**) Methyl carbene. Reaction conditions are as follows: iodide (3 equiv), Zn (3 equiv), 5% FeTPPCl, carbene trap (1 equiv), CH_2Cl_2:THF, 4 hours. (**D**) Complex molecule applications. See the supplementary materials for full experimental details. Isolated yield, diastereomeric ratio (dr), and regioselectivity ratio (rr) are indicated. D, deuterium; EDG, electron-donating group; Et, ethyl; Me, methyl.

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 distinctively 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 that $CoCl_2$ 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 owing to the high temperatures (100°C) required for reactivity.

By contrast, the valuable alkyl carbene reactivity enabled by this approach includes dimerization of aldehydes that contain synthetically tractable halides, alkenes, silanes, carbamates, ethers, sulfides, amides, ketones, and α substituents, including within natural product and drug scaffolds (**9** to **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 that the catalysts that promoted rapid dimerization (vide supra; $CoCl_2$, CuCl) are less efficient at chemoselective cross-coupling. Conversely, metallocarbenes generated from $FeCl_2$ or rhodium(II) acetate [$Rh_2(OAc)_4$]

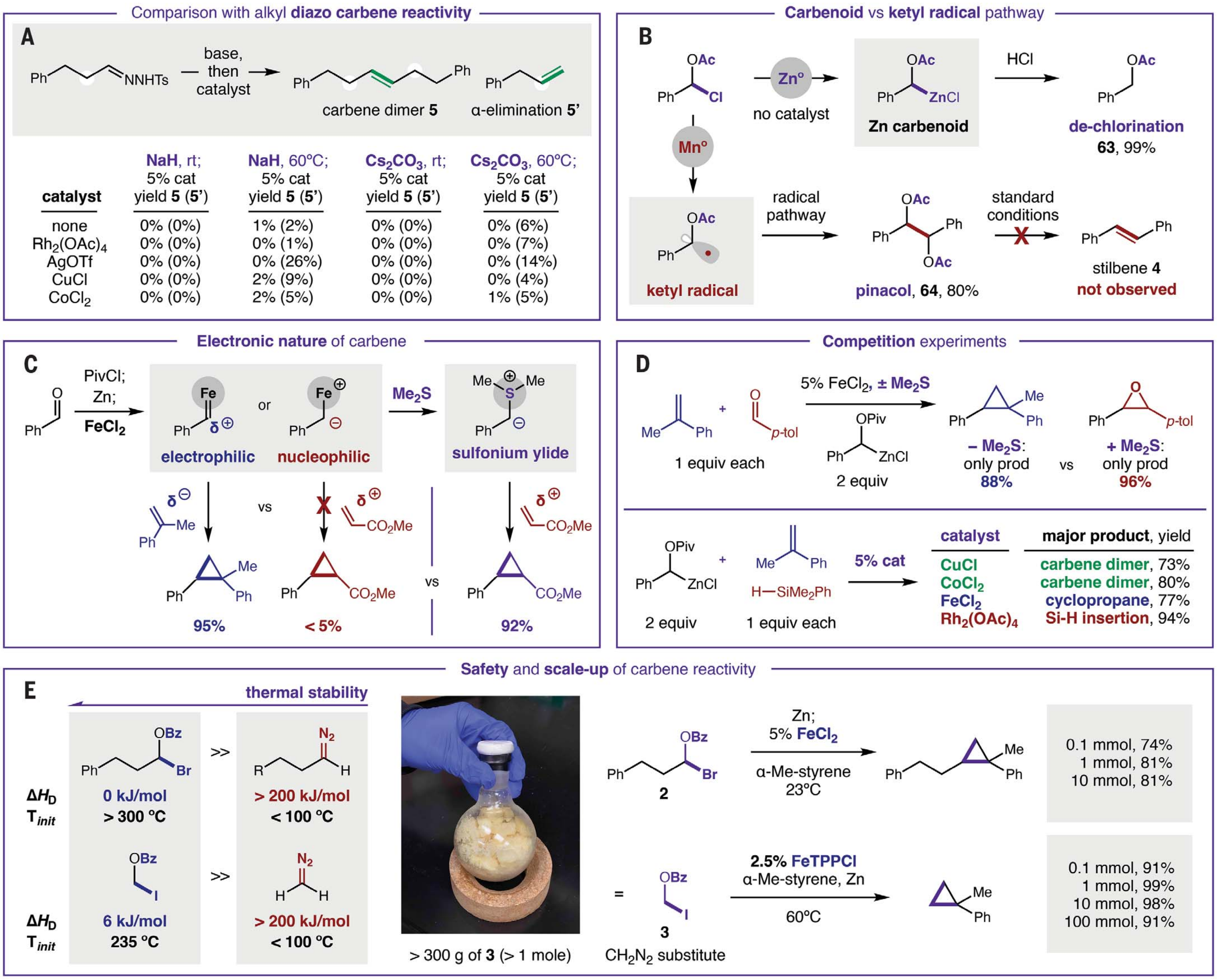

Fig. 4. Mechanistic experiments. (**A**) The carbene dimerization reactivity shown above is not accessible via diazoalkanes. (**B**) The proposed Zn carbenoid is validated by an acidic quench. Conversely, single-electron reduction by Mn affords ketyl radical reactivity but not carbene dimerization. (**C**) Electrophilic character of carbene is illustrated by selective reactivity with nucleophilic traps; sulfonium ylide affords polarity-reversed reactivity with electrophiles. (**D**) Competition experiments illustrate catalyst control of product selectivity. (**E**) The improved thermal stability of these carbene precursors relative to diazoalkanes allows a safer scale-up of batch chemistry. The photo shows the simple handling of a large quantity of **3**, which is a safer alternative to diazomethane. Ac, acetyl; cat, catalyst; rt, room temperature; tol, tolyl. [Photo credit: D.A.N.].

enable alternate modes of carbene reactivity aside from dimerization. For example, cyclopropanation of styrenes with aryl carbenes is efficiently catalyzed by $FeCl_2$ (**21** and **22**, up to 95%) but not $CoCl_2$. In contrast with typical Simmons-Smith selectivity (*38*, *39*), this Fe-catalyzed strategy is specifically selective for more-substituted, electron-rich alkenes (e.g., monoterpene **23**). Conversely, cyclopropanation of electron-deficient alkenes does not occur, as expected. However, if Me_2S is added as a cocatalyst to access the polarity-reversed sulfonium ylide (see Fig. 4C) as has been demonstrated with diazoalkanes (*40*), then electrophilic acrylates and enones can now be selectively benzylated (**24** and **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** to **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 used 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** to **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** to **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 $FeCl_2$ (56% **37**) or a more typical carbene catalyst, $Rh_2(OAc)_4$ (83%). Insertion into Si-D yielded complete α-deuteration (>95% D, **38**) in tetrahydrofuran (THF), confirming the carbene nature of this catalytic mechanism, which is amenable to several classes of alkyl silanes (**37** to **39**). Insertion also occurred into σ bonds of varying polarity, including B–H and S–H bonds (**40** and **41**). Overall, we observed that 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].

Because 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 nonstabilized alkyl aldehydes (Fig. 3B). First, we noted that 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** and **44**), epoxidation and aziridination (**45** and **46**), and σ bond insertion (**47** to **49**), all with similar efficiency to aryl carbenes. Notably, alkyl carbene reactivity is typically challenging to access by other methods because 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** to **53**). Lastly, we confirmed viability of the simplest carbene (CH_2) for both reaction classes (Fig. 3C): π bond cycloaddition (**54** to **56**) and σ bond insertion (**57** and **58**). We expect this formaldehyde-based approach to provide a safer alternative to conventional diazomethane reactivity and to complement modern methods that entail in situ generation (*7*–*9*).

To demonstrate viability in more complex settings, the aldehydes of two bile acids (among the most complex carbonyls dimerized in Fig. 2) were subjected to four distinct classes of carbene reactivity (Fig. 3D). First, the lithocholic acid containing both a ketone and aldehyde was selectively elongated at the aldehyde by epoxidation (**59**), aziridination (**60**), and Si-H insertion (**61**). A comparison with the diazo strategy was not possible because hydrazone formation was unselective between the two carbonyls within this molecule. Additionally, this approach distinctively enables deoxygenation of an aldehyde in the presence of three ketones (**62**).

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, Cs_2CO_3), temperatures (0° to 100°C), and catalysts (Fig. 4A) verifies that the carbene dimerization is not accessible via diazoalkanes. The proposed Zn carbenoid, generated in the 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; Me, methyl) versus electrophilic traps (acrylate) (Fig. 4C). However, upon introduction of a sulfide cocatalyst, a transient sulfonium ylide (observed by gas chromatography–mass spectrometry) enables inverted reactivity with such electrophiles (e.g., **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 Me_2S versus only cyclopropanation without Me_2S (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 $CoCl_2$ (80%), yet $FeCl_2$ predominantly affords cyclopropanation (77%) and $Rh_2(OAc)_4$ yields Si-H insertion (94%). Lastly, in situ infrared spectroscopy of the carbene dimerization reaction and variable time normalization analysis (VTNA) (*41*) indicate that the dimerization reaction is second order in catalyst (see supplementary materials).

Because this carbene generation mechanism does not rely on the evolution of N_2 gas, a substantial improvement in thermal stability was observed for these carbene precursors (ΔH_D = 0 kJ/mol for **2** and 6 kJ/mol for **3**) relative to diazoalkanes (ΔH_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., CH_2N_2). In these cases, cyclopropanations succeeded at up to a 1000-times-larger scale without event.

We have introduced a catalytic strategy for harnessing carbene reactivity from carbonyls. We expect that the approach will have a threefold impact on the expanded development of carbene reactions, including through the use of base metal catalysts, the use of safe and scalable reagents, and improved synthetic access to nonstabilized carbenes.

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ACKNOWLEDGMENTS

C. Acarturk and L. Burris assisted with DSC measurements. J. Herbort and T. V. RajanBabu assisted with VTNA experiments. **Funding:** This work was funded by the National Institutes of Health (NIH R35 GM119812), the National Science Foundation (NSF CAREER 1654656), and the Sloan Foundation. J.E.R. is supported by an NIH Fellowship (F31). **Author contributions:** L.Z. and D.A.N. designed this strategy, and L.Z. demonstrated its viability. All authors contributed to designing, performing, and analyzing experiments, as well as to writing this manuscript. B.M.D., A.N.P., and J.E.R. contributed equally and are listed alphabetically. **Competing interests:** The authors declare no competing interests. **Data and materials availability:** All data are available in the main text or the supplementary materials.

SUPPLEMENTARY MATERIALS

science.org/doi/10.1126/science.abo6443
Materials and Methods
Figs. S1 to S14
Tables S1 to S17
NMR Spectra

Submitted 16 February 2022; accepted 10 June 2022
10.1126/science.abo6443