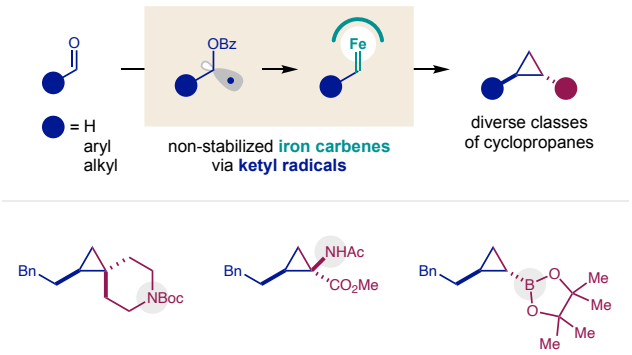
Cyclopropanation with Non-stabilized Carbenes via Ketyl Radicals

Duong T. Ngo,[†] Jacob J. A. Garwood,[†] and David A. Nagib*

Department of Chemistry and Biochemistry, The Ohio State University, Columbus, OH 43210, United States.

Supporting Information Placeholder

ABSTRACT: A radical mechanism enables simple and robust access to non-stabilized, *alkyl* iron carbenes for novel (2+1) cycloadditions. This Fe-catalyzed strategy employs simple, aliphatic aldehydes as carbene precursors in a practical, efficient, and stereoselective cyclopropanation. This air- and water- tolerant method permits convenient generation of iron carbenes and coupling to an exceptionally wide range of sterically and electronically diverse alkenes (nucleophilic, electrophilic, and neutral). A transient ketyl radical intermediate is key to accessing and harnessing this rare, *alkyl* iron carbene reactivity. Mechanistic experiments confirm the (a) intermediacy of ketyl radicals, (b) iron carbene formation by radical capture, and (c) non-concerted nature of the (2+1) cycloaddition.



Introduction

Cyclopropanes are ubiquitous among molecules that improve human health and happiness.[1,2] The most efficient synthesis of these novel, triangular scaffolds entails the (2+1) cycloaddition of alkenes and carbenes (Figure 1).[3–5] Yet, since carbene precursors often require stabilizing groups to prevent spontaneous decomposition,[6] lengthy synthetic sequences are frequently needed to remove these vestiges. Recent advances by the labs of Uyeda (*gem*-dihalides),[7–11] Wilkerson-Hill (sulfones),[12] and Koenigs/Xuan (hydrazones)[13] now allow *gem*-dimethyl incorporation into cyclopropanes. However, a general solution to harness other diverse classes of non-stabilized alkyl carbenes – and avoid typical β-elimination byproducts[14,15] – remains desirable. To this end, we recently introduced a method to access metallocarbenes via *organozinc* reagents (Figure 2a).[16] In that strategy, we showed the utility of α-acyloxy halides (readily accessed by BzBr addition to aldehydes) as iron carbene precursors. In a multi-step procedure entailing: (1) Zn insertion,[17,18] (2) transmetallation to $FeCl_2$,[19] and (3) α-oxy elimination,[20] we accessed several classes of non-stabilized carbene reactivity, including cyclopropanation. However, due to the tendency for protodemetallation of the key organozinc intermediate, many acidic motifs are not tolerated (e.g. alcohols, amines, amides) and strictly anhydrous conditions are necessary for robust reactivity.[21] Given our prior experience generating ketyl radicals from α-acyloxy halides,[22,23] and our knowledge that radicals are highly functional group tolerant[24] and even compatible with aqueous environments,[25] we proposed an alternate strategy to access non-stabilized carbenes via a *ketyl radical* mechanism.

Results and Discussion

Strategy. In this new radical-based design (Figure 2b), an aldehyde is instead converted to a highly bench-stable α-acyloxy chloride (by BzCl addition). Rather than direct insertion of Zn into this stronger C-Cl bond, we proposed *in situ* formation of a weaker C-I bond could enable mild, catalytic access to a ketyl radical. Upon capture with a suitable metal complex and subsequent elimination, we anticipated this ligated metal could impart improved chemo- and stereo- control on the reactive iron carbene intermediate. In contrast, our previous *organozinc*-mediated cyclopropanation affords low diastereoselectivity (1:1 d.r.) that could not be improved because ligands were not tolerated in that system. Yet, we expected this new approach could enable use of a stabilizing ligand on the iron complex – and perhaps impart significantly improved (a) functional group tolerance and (b) stereocontrol.

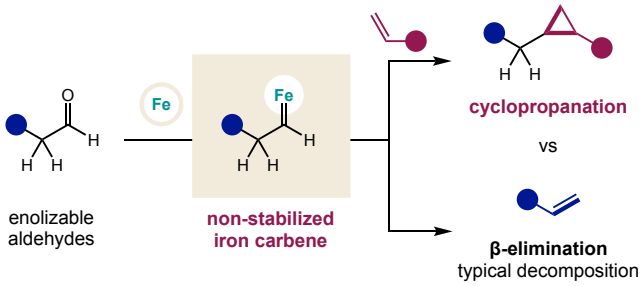


Figure 1. Non-stabilized iron carbene cyclopropanation.

Discovery. To test our hypothesis (Figure 3), several α-acyloxy halides (X = Cl, Br, or I; **I-III**) were prepared by ZnX_2-catalyzed addition of benzoyl halides (BzCl or BzBr ±NaI) to aliphatic, enolizable aldehydes. These carbene precursors were combined with styrene, reductant (Zn), and iron catalyst (10% FeTPPCl; TPP: tetraphenylporphyrin) in THF at 60 °C for 12 hours. Although the α-acyloxy chloride remained unreactive, likely because it is

difficult to reduce (**I**: –1.6 V vs SCE), we were pleased to find both the α-bromide (**II**: –1.3 V) and α-iodide (**III**: –1.1 V) were viable as non-stabilized carbene precursors, affording alkyl cyclopropane **1** in up to 12% yield. Intrigued that the most reactive candidate (α-iodide **III**) did not afford the highest yield, perhaps due to instability to reaction conditions (60 °C), we proposed the more stable α-chloride precursor (stable to water, base, air, and light) could instead be converted to the more reactive halides *in situ*. To this end, we included various LiX salts in the reaction with α-chloride **I**. Notably, this salt additive affords robust, clean, and complete reactivity – forming cyclopropane **1** in >99% yield with LiI.

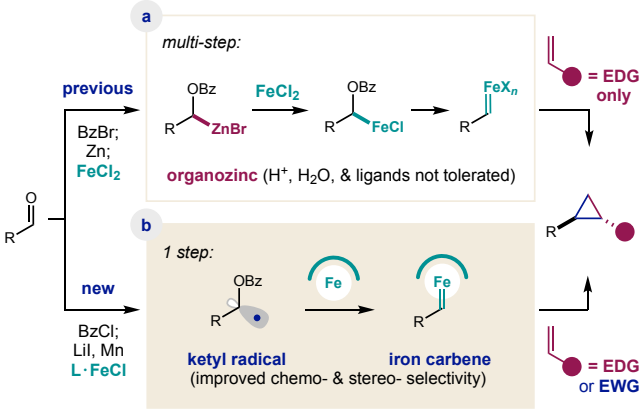
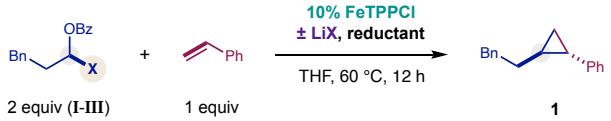


Figure 2. Novel strategies enabled by α-acyloxy halides: (a) *Organozinc*, and (b) *Ketyl radical* mechanisms.



Zn as reductant (−1.0 V)

reagent	X	E_{red}	yield (%)
I	Cl	−1.6 V	0
II	Br	−1.3 V	12
III	I	−1.1 V	<5

X	LiX	yield (%)
Cl	LiCl	5
Cl	LiBr	55
Cl	LiI	>99

Mn as reductant (−1.4 V)

standard conditions (I, LiI, Mn)	yield (%)
standard conditions	>99
LiOTf, LiOAc, Li_2CO_3, or $LiBF_4$ instead of LiI	0
no catalyst (FeTPPCl) or no reductant (Zn, Mn)	0
$FeCl_2$ or $FeCl_3$ instead of FeTPPCl	<10
10% $FeCl_3$, 15% $TPPH_2$ instead of FeTPPCl	>99
10% $CoCl_2$, 15% $TPPH_2$ instead of FeTPPCl	0
AcCl or PivCl instead of BzCl (aldehyde activation)	>99
2-MeTHF instead of THF	>99
1 equiv of **carbene precursor I**	85

Figure 3. Development of non-stabilized Fe carbene cyclopropanation.

Conditions: Styrene (1 equiv, 0.1 mmol), carbene precursor **I** (2 equiv), FeTPPCl (10 mol%), LiX (3 equiv), reductant (3 equiv), THF (1 mL), 60°C, 12 h. NMR yields.

Interestingly, we noted LiCl affords some reactivity (5%), likely due to activation of the Zn reductant.[19,26] We found Mn (–1.4 V)[27,28] also affords clean, efficient, and robust conversion of α-chloride **I** to cyclopropane **1** (>99% yield). As control experiments, we confirmed other Li salts that can activate the reductant or substrate by non-halide exchange mechanisms (e.g. LiOTf, LiOAc, Li_2CO_3, $LiBF_4$) were not viable substitutes for LiI. Moreover, both the Fe catalyst and reductant (either Zn or Mn) are essential for reactivity. Unlike our previous *organozinc* strategy, which does not tolerate the addition of ligands (0% yield),[16] this ketyl radical approach provides the opposite outcome. Instead, the use of $FeCl_2$ or $FeCl_3$ alone diminishes reactivity (<10% yield), while FeTPPCl is optimal. For practical convenience, we found *in situ* combination of $FeCl_3$ and $TPPH_2$ ligand provides similar efficiency to the preformed complex (>99% yield). Notably, a $CoCl_2$/$TPPH_2$ combination does not afford cyclopropanation – in contrast to other important Co-catalyzed strategies.[7,8,29,30]

We prefer the α-acyloxy chloride (**I**) obtained from BzCl addition (to an aldehyde) because it conveniently crystallizes to a white solid (long needles). However, we confirmed AcCl and PivCl each form α-acyloxy chlorides (as oils), which are also viable carbene precursors (>99% yield **1**). We found 2-Me-THF may also be used as a green or sustainable alternative to THF.[31] Lastly, a 1:1 stoichiometry may be employed between the carbene and alkene with only minimal loss in reactivity (85% yield).

Robustness. Given the high efficiency of this radical-to-carbene cyclopropanation, we next investigated reaction robustness under various parameters that might impact practical utility, including varying temperature, water, and atmosphere (Figure 4). For both reductants (Zn or Mn), room temperature conditions are viable (with more carbene; 3 equiv). However, we found the Mn reductant system (dark purple) was significantly more tolerant of H_2O than Zn (light purple) – with 100 equiv H_2O (15 vol%) still affording >70% yield for Mn (vs <40% for Zn). Conversely, the milder Zn reductant proved more tolerant of air – even retaining reactivity (>40%) in an entirely air atmosphere. Lastly, the Mn system proved more compatible with various LiX additives (LiI, LiBr, LiCl) and even soluble iodides (TBAI), but $LiBF_4$ remains a nonviable additive. Thus, while there may be practical advantages to using the Zn reductant (under air atmosphere), we opted to investigate the substrate scope with the more robust Mn reductant system.

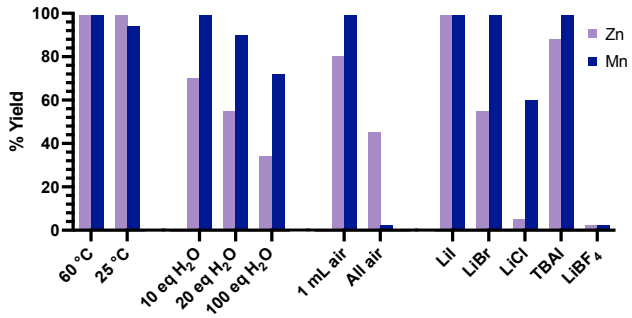


Figure 4. Robustness of newly developed reactions (Zn vs Mn).

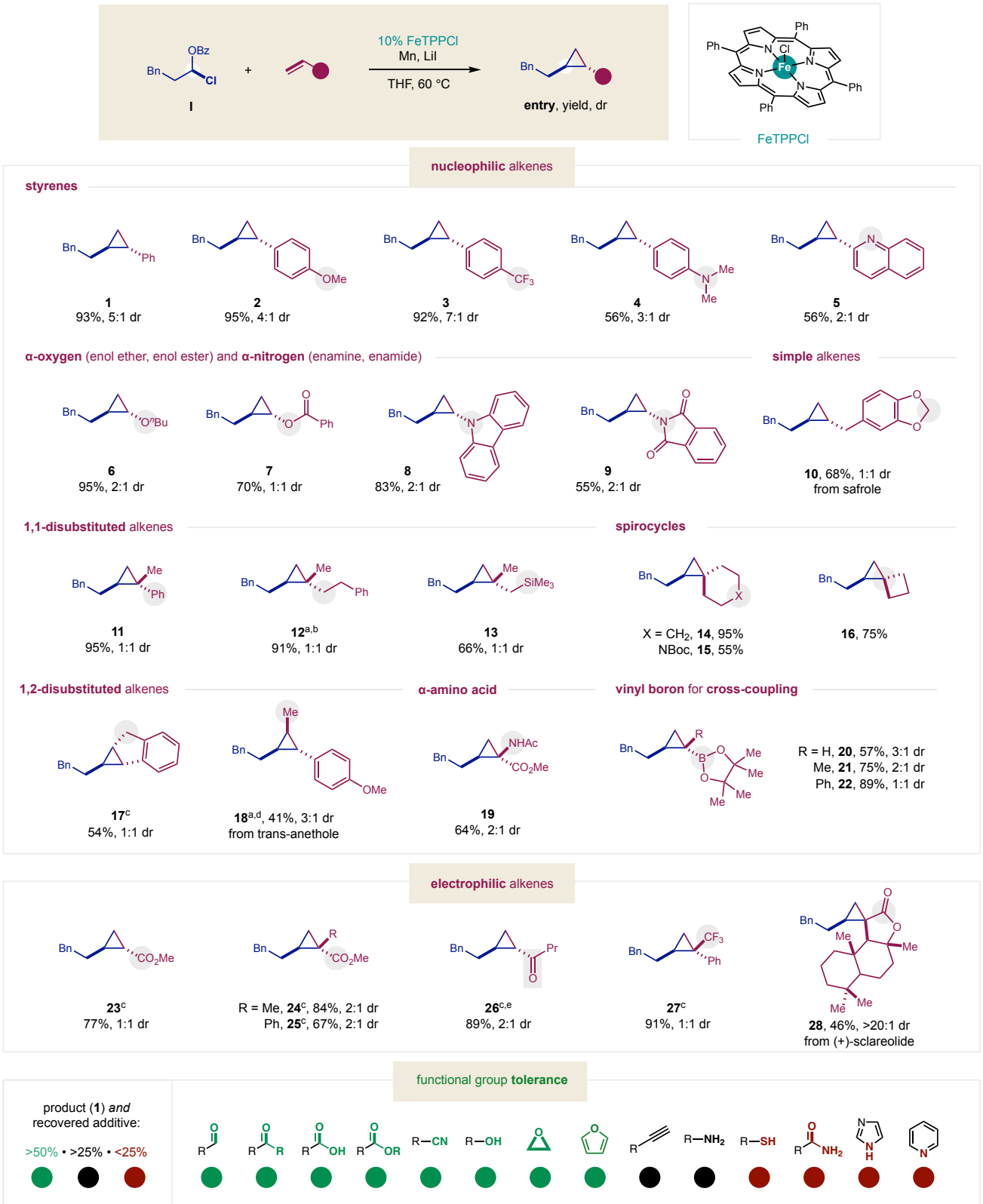


Figure 5. Scope, generality, and chemoselectivity of ketyl radical-mediated cyclopropanation.

Conditions: Alkene (0.2 mmol, 1 equiv), **I** (3 equiv), FeTPPCl (10%), Mn (3 equiv), LiI (3 equiv), THF (1 mL), 60°C, 12-18 h. [a]0.1 mmol scale. [b]**I**, Mn, LiI (6 equiv each). [c]NMR yield. [d]**I**, Mn, LiI (4 equiv each) [e]40°C. Isolated yields. Diastereomeric ratio (d.r.) by NMR. See SI for full details

Scope. The synthetic utility and generality of this non-stabilized Fe carbene cyclopropanation was then explored using a wide variety of aldehydes and alkenes (Figure 5). Notably, both *nucleophilic* and *electrophilic* alkenes are viable carbene traps in this mechanistically novel (2+1) reaction. For example, *nucleophilic* styrenes are highly efficient partners (**1**-**5**) for coupling with the carbene derived from α-acyloxy chloride **I**. Notably, both electron-rich (*p*-OMe; **2**) and electron-poor (*p*-CF_3; **3**) styrenes afford high reactivity – with the latter providing significantly higher diastereoselectivity (7:1 d.r.) than our previous organozinc system (1.6:1 d.r.) – as a result of the large porphyrin ligand that is now tolerated. We were pleased to find amino (*p*-NMe_2; **4**) and heteroaryl (quinoline; **5**) styrenes are also amenable. Interestingly, the electron-deficient alkenes afford higher diastereoselectivity – perhaps due to a lack of cation stabilization and a more concerted transition state.[5]

Given the tolerance of heteroatoms and electron-rich alkenes, we probed the system further with more *highly nucleophilic* alkenes, including enol ether (**6**), enol ester (**7**), enamine (**8**), and enamide (**9**). In all cases, we were pleased to see robust reactivity. To our great delight, a simple alkene, such as that found in safrole (**10**), was also efficiently cyclopropanated – illustrating the wide *electronic* scope of the alkene nucleophile. A *steric* focused investigation revealed disubstituted alkenes are also well-tolerated. For example, 1,1-disubstituted styrenes (**11**), simple alkenes (**12**), or allyl silanes (**13**), were all viable. Additionally, exocyclic methylenes provide rapid access to medicinally privileged spirocycles that fuse cyclopropanes with carbocycles (**14**), heterocycles (**15**), or small rings (**16**). Analogously, 1,2-disubstituted alkenes yield fused bicycles (**17**) and 1,2,3-trisubstituted cyclopropanes (**18**) that are otherwise challenging to synthesize. Lastly, α-amino acids (**19**) and vinyl boronic esters (**20**-**22**) are valuable motifs accessible by this method – with the latter providing easy access to other desirable heteroatoms (e.g. N, O, S) directly on the cyclopropane scaffold.

Surprisingly, we were pleased to discover *electrophilic* alkenes are also viable carbene traps in this (2+1) addition. In contrast to our organozinc-generated carbenes, which required a sulfide additive to generate a sulfonium ylide (for a Corey-Chaykovsky-type polarity reversal mechanism),[32,33] no sulfur additive is required in this case. Instead, direct, catalytic cyclopropanation is observed with acrylates – terminal (**23**), disubstituted (**24**), and styryl (**25**) – as well as enones (**26**), CF_3-alkenes (**27**), and natural products, such as sclareolide (**28**). We were intrigued by the Zhang group's recent study on the electronic nature of CF_3-bound iron carbenes, which they found to exhibit radical character at the α-CF_3 carbon.[34] This change in behavior by appending a porphyrin ligand – to stabilize a proposed Fe(IV) intermediate – may help explain the broader electronic reactivity observed in this system, which now precludes the need for sulfur ylide formation to react with such electrophiles.

Functional Group Tolerance. As a preliminary guide for suitability to more complex, drug-like molecules, we also included a series of functional group tolerance experiments (Figure 5, bottom). In this study, we found that many otherwise reactive groups were well-tolerated (>50% yield, >50% additive recovery). Notably, several synthetically useful carbonyl classes (aldehydes, ketones, acids, esters) were viable. This is a noteworthy departure from a synthetic limitation in the preparation of organozincs for our previous strategy. Other reactive functional groups (nitriles, alcohols, epoxides, and furans) were also well-tolerated – further showcasing the value of this ketyl radical-based strategy. Conversely, some functional groups exhibited low recovery (alkynes, amines), while not necessarily inhibiting reactivity (perhaps due to Zn adhesion). Lastly, strong nucleophiles were either also not recovered (thiols, amides) or hindered the cyclopropanation (pyridine).

Carbene Scope. We next sought to examine if further classes of aldehydes were suitable carbene precursors (Figure 6). Thus, we found other primary alkyl aldehydes were compatible, including with reducible aryl iodide (**29**) or imide (**30**) motifs. Secondary alkyl aldehydes were similarly tolerated – despite the increased steric requirements – including with ether (**31**) and alkene (**32**) probes of functional group tolerance. Lastly, benzaldehydes (**33**-**34**) and formaldehyde (**35**) are amenable as carbene precursors – showcasing the broad synthetic utility of this new mechanism.

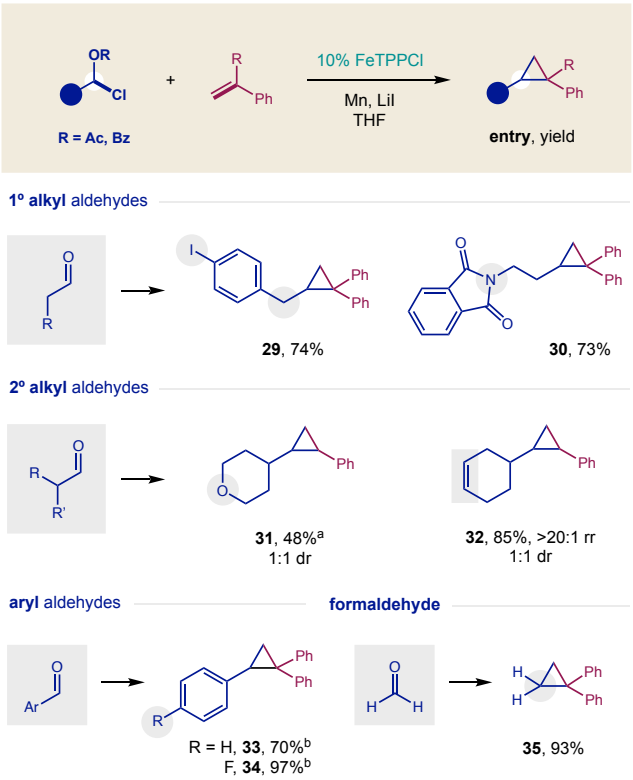


Figure 6. Additional aldehyde classes as ketyl/carbene precursors.

Conditions (same as Figure 4): Alkene (0.2 mmol, 1 equiv), carbene precursor (3 equiv), FeTPPCl (10%), Mn (3 equiv), LiI (3 equiv), THF (1 mL), 60°C, 12-18 h. [a]Carbene precursor (2 equiv). [b]25°C. Isolated yields.

One-pot from Aldehydes. Notably, the conditions for *in situ* activation of the aldehyde as an α-acyloxy chloride are compatible with the Fe-catalyzed cyclopropanation – enabling a one-pot transformation of the aldehyde to a cyclopropane (Figure 7). We were pleased to find this streamlined sequence is suitable for both alkyl (**36**) and aryl (**34**) classes of aldehydes. Moreover, these one-pot examples were performed at a 25x larger scale (2.5 mmol) for practical convenience and to showcase scalability.

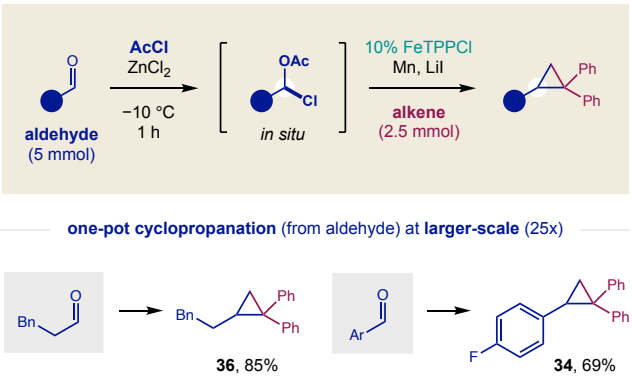


Figure 7. Cyclopropanation directly from aldehyde.

Conditions: Aldehyde (5 mmol, 2 equiv), AcCl (2.2 equiv), $ZnCl_2$ (4%), neat, −10°C, 1 h; Alkene (1 equiv), FeTPPCl (10%), Mn (3 equiv), LiI (3 equiv), THF (2.5 mL), 60°C (**36**) or 25°C (**34**), 12 h. Isolated yields.

Mechanism. Mechanistic studies were focused on elucidating the nature of the non-stabilized Fe carbene in this cyclopropanation (Figure 8). In our previous *organozinc* strategy,[21] an α-acyloxy zinc is pre-formed, decanted from excess Zn, and added to $FeCl_2$ and styrene. This organozinc-to-organoiron(II) strategy affords **1** (99%, 1.6:1 d.r.) (Figure 8a). Notably, however, the FeTPPCl complex provides *no* reactivity from the alkyl zinc (0%) – strongly suggesting different mechanisms are operative. We reasoned Fe(III)TPPCl must instead form an alkyl-Fe(III) upon transmetallation with alkyl zinc (vs alkyl-Fe(II) with $FeCl_2$). Thus, we proposed an additional reductant would be required to access alkyl-Fe(II)TPP – as proposed in our new, *radical* method. Indeed, addition of Mn renews reactivity – in a first example of a ligated, organozinc-derived complex – and provides a first experimental validation of the organoiron intermediate in our proposed mechanism.

Additional evidence for a radical intermediate is the termination of reactivity upon addition of TEMPO – accompanied by formation of a TEMPO-adduct of the proposed ketyl radical (Figure 8b). Moreover, when an acyclic, α-branched, ketyl radical precursor is employed (e.g. isopropyl aldehyde), then hydroalkylation (**37**) is observed instead of cyclopropanation (by radical addition to the alkene and subsequent reduction). We suspect this divergent reactivity is a result of the ketyl radical being too large to be efficiently captured by the Fe complex – and adding to the alkene instead.

If a *ketyl radical* mechanism is responsible for Fe-C bond formation, we then postulated a metal reductant is no longer necessary (Figure 8c). Indeed, the organic reductant, TDAE (tetrakis(dimethylamino)ethylene), which can promote SET (–0.8 V)[35] but not organometallation, generates the ketyl radical from α-iodide (–1.1 V) by overcoming a 0.3 V overpotential. Notably, this practical substitution of a homogenous reductant is not viable (0% yield) by our previous *organozinc* strategy.

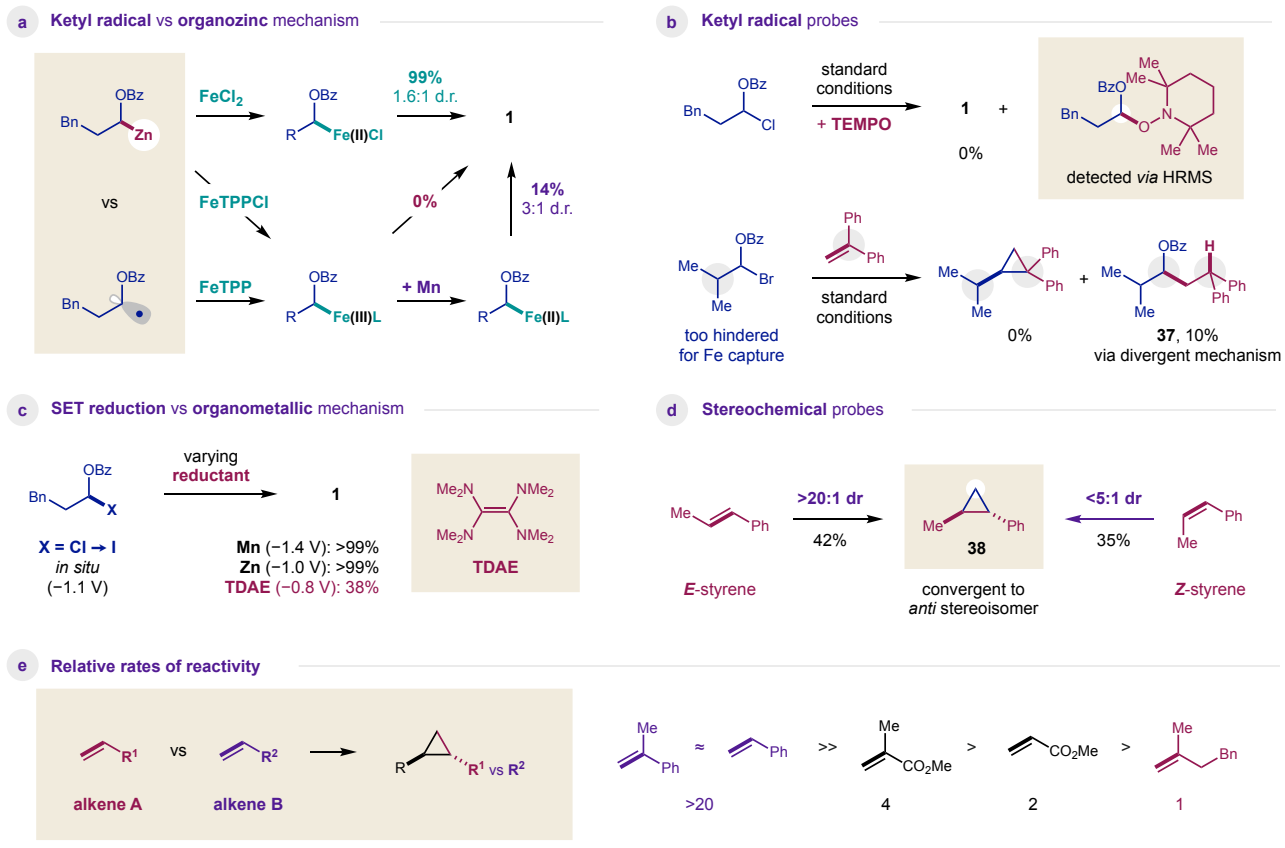


Figure 8. Mechanistic experiments probing non-stabilized Fe carbene cyclopropanation.

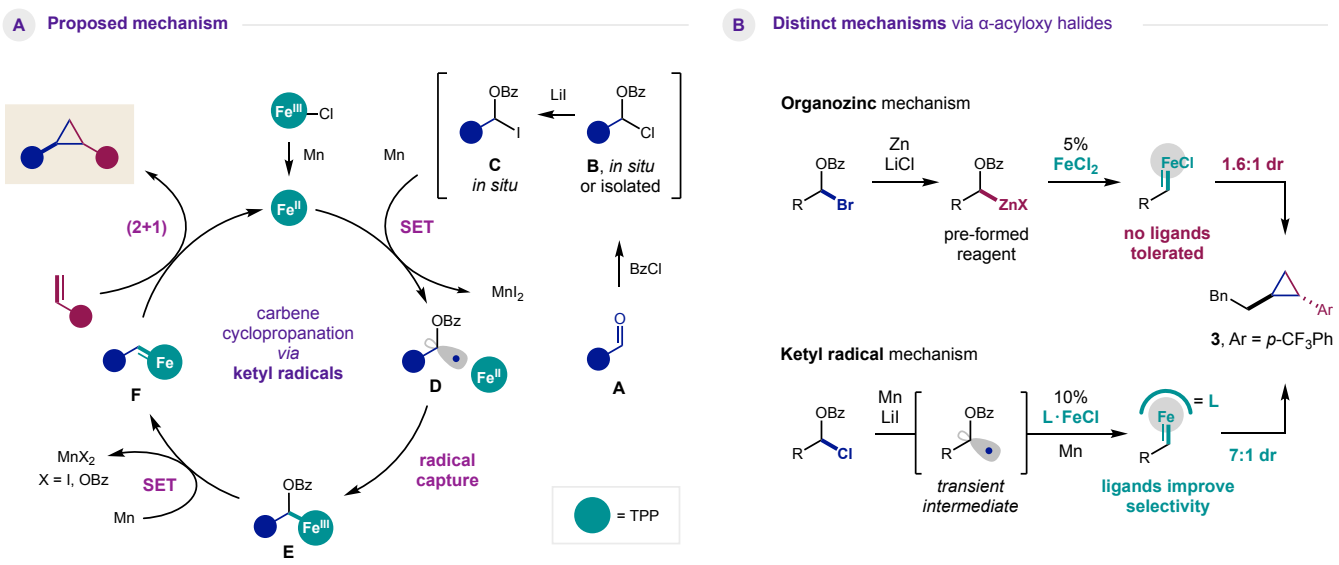


Figure 9. (a) Proposed *ketyl radical*-based mechanism, and (b) comparison of *organozinc* (previous) and *ketyl radical* (new) mechanisms.

Stereochemical probes indicate a non-concerted mechanism for the (2+1) cycloaddition (Figure 8d). For example, an *anti* product (**38**) is formed from both isomers, albeit in lower yields due to the larger steric requirement of 1,2-disubstiuted alkenes. This convergence to an *anti* isomer is observed with greater diastereoselectivity from an *E*-alkene (>20:1 d.r.) versus *Z*-alkene (<5:1 d.r.), as the latter requires epimerization within the cycloaddition. Lastly, the relative rates of reactivity of alkenes were examined by a series of competition experiments between sterically and electronically diverse reactants (Figure 8e). These experiments revealed that *nucleophilic* styrenes are 20x more reactive than a simple, aliphatic alkene (even if the alkene is 1,1-disubstituted, which is itself 10x more nucleophilic than a simple terminal alkene[36]). Intriguingly, the next most reactive class of carbene traps are *electrophilic* acrylates, which are 2-4x more reactive than the simple alkene. We expect this collective data will guide users in predicting chemoselectivity and reactivity order in more complex molecules (e.g. **32**; styrene > cyclohexene). Our net assessment is that *nucleophilicity* is the most important predictor of reactivity – followed by *steric* factors (i.e. smaller is better). For example, most 1,2-disubstituted alkenes are too hindered to react efficiently, but the highly nucleophilic β Me-styrenes still afford some reactivity (**38**).

Combining insights from these experiments, a proposed mechanism is illustrated in Figure 9a. Upon *in situ* (or prior) activation of aldehyde **A** by BzCl, the stable (or isolable) α-acyloxy chloride **B** (–1.6 V) is formed. Next, *in situ* halide exchange with LiI yields a more easily reduced α-acyloxy iodide **C** (–1.1 V). Since Mn (–1.4 V), Zn (–1.0 V), and TDAE (–0.8 V) are sufficiently reducing, a single-electron transfer (SET) mechanism by any of these mild reductants will promote formation of ketyl radical **D**. In parallel, the precatalyst FeTPPCl is also reduced from Fe(III) to Fe(II) by the same reductant to form a reservoir of FeTPP. This Fe(II) complex may readily capture radical **D** to form α-acyloxy organoiron **E**. We observed this alkyl-Fe(III) is inactive and does not yield cyclopropane on its own. Yet, SET reduction of **E** by the stoichiometric reductant, along with α-acyloxy elimination, will form reactive alkyl carbene **F**. Finally, (2+1) cycloaddition of this non-stabilized carbene and an *electronically rich*, *poor*, or *neutral* alkene affords the cyclopropane and regenerates the active TPPFe(II) catalyst.

In Figure 9b, we summarize our key observations of the difference between our (previous) *organozinc* mechanism and this (new) *ketyl radical* enabled strategy. Namely, whereas the *organozinc* approach necessitated a 12 h pre-stir to mediate Zn insertion to an α-acyloxy bromide (and subsequent decanting of excess Zn), this *ketyl radical* method allows convenient simultaneous addition of the catalyst, reductant, and substrate (a more stable α-chloride) – thanks to transient compatible intermediates. Moreover, whereas ligands were *not* tolerated in the former system – resulting in low stereocontrol (**3**, 1.6:1 d.r.), a porphyrin ligand is *now required* to stabilize the metal complex that captures the ketyl radical. The absence of this ligand precludes reactivity, and its presence enables high stereocontrol (**3**, 7:1 d.r.).

Conclusions

In summary, a new *ketyl radical*-mediated mechanism has been developed for the synthesis of sterically and electronically diverse cyclopropanes. This Fe-catalyzed approach that entails transient radical and metallocarbene intermediates enables harnessing of non-stabilized carbenes in this essential (2+1) cycloaddition. This novel mechanism allows rapid access to a wide range of cyclopropanes in a practical, efficient, and robust manner that even tolerates the inclusion of air and water. Mechanistic experiments confirm the (a) intermediacy of ketyl radicals, (b) metallocarbene formation by SET rather than organozinc, and (c) non-concerted nature of the

(2+1) cycloaddition. We envision many useful applications of this easy synthetic access to medicinally valuable motifs – enabled by a novel radical-to-carbene mechanism.[37]

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Experimental procedures and characterization for all new compounds (PDF)

^{1}H and ^{13}C NMR spectral data (PDF)

AUTHOR INFORMATION

Corresponding Author

nagib.1@osu.edu

ORCID

Jacob J. A. Garwood: 0009-0000-2848-0868
Duong T. Ngo: 0000-0003-0063-177X
David A. Nagib: 0000-0002-2275-6381

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We thank the National Science Foundation (CHE-2400304), National Institutes of Health (R35 GM119812), and Brown Institute for Basic Sciences for financial support. Long P. Dinh (Sevov Lab) assisted with collecting CV data for **I**, **II**, **III**.

REFERENCES

(1) Shearer, J.; Castro, J. L.; Lawson, A. D. G.; MacCoss, M.; Taylor, R. D. Rings in Clinical Trials and Drugs: Present and Future. *J. Med. Chem.* **2022**, *65* (13), 8699–8712. https://doi.org/10.1021/acs.jmedchem.2c00473.

(2) Talele, T. T. The "Cyclopropyl Fragment" Is a Versatile Player That Frequently Appears in Preclinical/Clinical Drug Molecules. *J. Med. Chem.* **2016**, *59* (19), 8712–8756. https://doi.org/10.1021/acs.jmedchem.6b00472.

(3) Ebner, C.; Carreira, E. M. Cyclopropanation Strategies in Recent Total Syntheses. *Chem. Rev.* **2017**, *117* (18), 11651–11679. https://doi.org/10.1021/acs.chemrev.6b00798.

(4) Charette, A. B.; Beauchemin, A. Simmons-Smith Cyclopropanation Reaction. In *Organic Reactions*; John Wiley & Sons, Inc.: Hoboken, NJ, USA, 2001; pp 1–415. https://doi.org/10.1002/0471264180.or058.01.

(5) Lebel, H.; Marcoux, J. F.; Molinaro, C.; Charette, A. B. Stereoselective Cyclopropanation Reactions. *Chem. Rev.* **2003**, *103* (4), 977–1050. https://doi.org/10.1021/cr010007e.

(6) Green, S. P.; Wheelhouse, K. M.; Payne, A. D.; Hallett, J. P.; Miller, P. W.; Bull, J. A. Thermal Stability and Explosive Hazard Assessment of Diazo Compounds and Diazo Transfer Reagents. *Org. Process Res. Dev.* **2020**, *24* (1), 67–84. https://doi.org/10.1021/acs.oprd.9b00422.

(7) Berger, K. E.; Martinez, R. J.; Zhou, J.; Uyeda, C. Catalytic Asymmetric Cyclopropanations with Nonstabilized Carbenes. *J. Am. Chem. Soc.* **2023**, *145* (17), 9441–9447. https://doi.org/10.1021/jacs.3c01949.

(8) Uyeda, C.; Kalb, A. E. Catalytic Reductive Carbene Transfer Reactions. *Chem Catal.* **2022**, *2* (4), 667–678. https://doi.org/10.1016/j.checat.2022.01.002.

(9) Werth, J.; Berger, K.; Uyeda, C. Cobalt Catalyzed Reductive Spirocyclopropanation Reactions. *Adv. Synth. Catal.* **2020**, *362* (2), 348–352. https://doi.org/10.1002/adsc.201901293.

(10) Werth, J.; Uyeda, C. Cobalt-Catalyzed Reductive Dimethylcyclopropanation of 1,3-Dienes. *Angew. Chem. Int. Ed.* **2018**, *57* (42), 13902–13906. https://doi.org/10.1002/anie.201807542.

(11) Werth, J.; Uyeda, C. Regioselective Simmons-Smith-Type Cyclopropanations of Polyalkenes Enabled by Transition Metal Catalysis. *Chem. Sci.* **2018**, *9* (6), 1604–1609. https://doi.org/10.1039/c7sc04861k.

(12) Johnson, J. D.; Teeples, C. R.; Akkawi, N. R.; Wilkerson-Hill, S. M. Efficient Synthesis of Orphaned Cyclopropanes Using Sulfones as Carbene Equivalents. *J. Am. Chem. Soc.* **2022**, *144* (32), 14471–14476. https://doi.org/10.1021/jacs.2c07063.

(13) Cai, B. G.; Empel, C.; Jana, S.; Xuan, J.; Koenigs, R. M. Catalytic Olefin Cyclopropanation with In Situ-Generated Dialkyl Diazomethanes via Co(II)-Based Metalloradical Catalysis. *ACS Catal.* **2023**, *13* (17), 11851–11856. https://doi.org/10.1021/acscatal.3c02468.

(14) Simmons, H. E.; Blanchard, E. P.; Smith, R. D. Cyclopropane Synthesis from Methylene Iodide, Zinc-Copper Couple, and Olefins. III. The Methylene-Transfer Reaction. *J. Am. Chem. Soc.* **1964**, *86* (7), 1347–1356. https://doi.org/10.1021/ja01061a017.

(15) Bull, J. A.; Charette, A. B. Intramolecular Simmons-Smith Cyclopropanation. Studies into the Reactivity of Alkyl-Substituted Zinc Carbenoids, Effect of Directing Groups and Synthesis of Bicyclo[n.1.0]Alkanes. *J. Am. Chem. Soc.* **2010**, *132* (6), 1895–1902. https://doi.org/10.1021/ja907504w.

(16) Zhang, L.; DeMuynck, B. M.; Paneque, A. N.; Rutherford, J. E.; Nagib, D. A. Carbene Reactivity from Alkyl and Aryl Aldehydes. *Science* **2022**, *377* (6606), 649–654. https://doi.org/10.1126/science.abo6443.

(17) Charette, A. B.; Beauchemin, A.; Francoeur, S. Acyloxymethylzinc Reagents: Preparation, Reactivity, and Solid-State Structure of This Novel Class of Cyclopropanating Reagents [12]. *J. Am. Chem. Soc.* **2001**, *123* (33), 8139–8140. https://doi.org/10.1021/ja0109287.

(18) Motherwell, W. B. On the Evolution of Organozinc Carbenoid Chemistry from Carbonyl Compounds - A Personal Account. *J. Organomet. Chem.* **2001**, *624* (1–2), 41–46. https://doi.org/10.1016/S0022-328X(00)00933-5.

(19) Knochel, P.; Singer, R. D. Preparation and Reactions of Polyfunctional Organozinc Reagents in Organic Synthesis. *Chem. Rev.* **1993**, *93* (6), 2117–2188. https://doi.org/10.1021/cr00022a008.

(20) Vargas, R. M.; Ronald, R. D.; Hossain, M. M. A New

Reaction for the Synthesis of Carbene Precursors from Aldehydes and Cp(CO)2Fe -M+ (M = Na, K). *J. Am. Chem. Soc.* **1992**, *114* (2), 777–778. https://doi.org/10.1021/ja00028a064.

(21) DeMuynck, B. M.; Zhang, L.; Ralph, E. K.; Nagib, D. A. Cyclopropanation of Unactivated Alkenes with Non-Stabilized Iron Carbenes. *Chem* **2024**, *10* (3), 1015–1027. https://doi.org/10.1016/j.chempr.2024.01.006.

(22) Wang, L.; Lear, J. M.; Rafferty, S. M.; Fosu, S. C.; Nagib, D. A. Ketyl Radical Reactivity via Atom Transfer Catalysis. *Science* **2018**, *362* (6411), 225–229. https://doi.org/10.1126/science.aau1777.

(23) Rafferty, S. M.; Rutherford, J. E.; Zhang, L.; Wang, L.; Nagib, D. A. Cross-Selective Aza-Pinacol Coupling via Atom Transfer Catalysis. *J. Am. Chem. Soc.* **2021**, *143* (15), 5622–5628. https://doi.org/10.1021/jacs.1c00886.

(24) Yan, M.; Lo, J. C.; Edwards, J. T.; Baran, P. S. Radicals: Reactive Intermediates with Translational Potential. *J. Am. Chem. Soc.* **2016**, *138* (39), 12692–12714. https://doi.org/10.1021/jacs.6b08856.

(25) Chatgilialoglu, C.; Barata-Vallejo, S.; Gimisis, T. Radical Reactions in Organic Synthesis: Exploring in-, on-, and with-Water Methods. *Molecules* **2024**, *29* (3), 569. https://doi.org/10.3390/molecules29030569.

(26) Feng, C.; Cunningham, D. W.; Easter, Q. T.; Blum, S. A. Role of LiCl in Generating Soluble Organozinc Reagents. *J. Am. Chem. Soc.* **2016**, *138* (35), 11156–11159. https://doi.org/10.1021/jacs.6b08465.

(27) Vanysek, P. "Electrochemical Series", in Handbook of Chemistry and Physics. In *Hand book*; 2000; pp 1–13.

(28) Charboneau, D. J.; Hazari, N.; Huang, H.; Uehling, M. R.; Zultanski, S. L. Homogeneous Organic Electron Donors in Nickel-Catalyzed Reductive Transformations. *J. Org. Chem.* **2022**, *87* (12), 7589–7609. https://doi.org/10.1021/acs.joc.2c00462.

(29) Chen, Y.; Ruppel, J. V.; Zhang, X. P. Cobalt-Catalyzed Asymmetric Cyclopropanation of Electron-Deficient Olefins. *J. Am. Chem. Soc.* **2007**, *129* (40), 12074–12075. https://doi.org/10.1021/ja074613o.

(30) Wang, X.; Peter Zhang, X. Catalytic Radical Approach for Selective Carbene Transfers via Cobalt(II)-Based Metalloradical Catalysis. In *Transition Metal-Catalyzed Carbene Transformations*; 2021; pp 25–66. https://doi.org/10.1002/9783527829170.ch2.

(31) Clarke, C. J.; Tu, W. C.; Levers, O.; Bröhl, A.; Hallett, J. P. Green and Sustainable Solvents in Chemical Processes. *Chem. Rev.* **2018**, *118* (2), 747–800. https://doi.org/10.1021/acs.chemrev.7b00571.

(32) Corey, E. J.; Chaykovsky, M. Dimethyloxosulfonium Methylide ((CH3)2SOCH2) and Dimethylsulfonium Methylide ((CH3)2SCH2). Formation and Application to Organic Synthesis. *J. Am. Chem. Soc.* **1965**, *87* (6), 1353–1364. https://doi.org/10.1021/ja01084a034.

(33) Aggarwal, V. K.; Winn, C. L. Catalytic, Asymmetric Sulfur Ylide-Mediated Epoxidation of Carbonyl Compounds: Scope, Selectivity, and Applications in Synthesis. *Acc. Chem. Res.* **2004**, *37* (8), 611–620. https://doi.org/10.1021/ar030045f.

(34) Lee, W. C. C.; Wang, D. S.; Zhu, Y.; Zhang, X. P. Iron(III)-Based Metalloradical Catalysis for Asymmetric Cyclopropanation via a Stepwise Radical Mechanism. *Nat. Chem.* **2023**, *15* (11), 1569–1580. https://doi.org/10.1038/s41557-023-01317-8.

(35) Burkholder, C.; Dolbier, W. R.; Médebielle, M.; Ndedi, A. Tetrakis(Dimethylamino)Ethylene (TDAE) as a Useful Reductant of Some Chlorodifluoromethylated Ketones. A New Approach for the Synthesis of α,α- Difluoroketone Derivatives. *Tetrahedron Lett.* **1998**, *39* (48), 8853–8856. https://doi.org/10.1016/S0040-4039(98)02028-0.

(36) Mayr, H.; Kempf, B.; Ofial, A. R. Π-Nucleophilicity in Carbon-Carbon Bond-Forming Reactions. *Acc. Chem. Res.* **2003**, *36* (1), 66–77. https://doi.org/10.1021/ar020094c.

(37) During peer review, a complementary photocatalytic strategy was reported: Boyle, B. T.; Dow, N. W.; Kelly, C. B.; Bryan, M. C.; MacMillan, D. W. C. Unlocking Carbene Reactivity by Metallaphotoredox α-Elimination. *Nature* **2024**, Accelerated Article Preview: https://doi.org/10.1038/s41586-024-07628-1.

Table of Contents Graphic