Cyclopropanation of unactivated alkenes with non-stabilized iron carbenes

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Summary

Cyclopropanes are ubiquitous in medicines, yet robust synthetic access to a wide range of sterically and electronically diverse analogs remains a challenge. To address the synthetic limitations of the most direct strategy, (2+1) cycloaddition, we sought to develop a variant that employs non-stabilized carbenes. We present herein an $FeCl_2$-catalyzed cyclopropanation that uniquely employs aliphatic (enolizable) aldehydes as carbene precursors. A remarkably broad range of alkenes may be coupled with these non-stabilized, alkyl carbenes. This extensive scope enables the synthesis of novel classes of cyclopropanes bearing alkyl, benzyl, allyl, halide, and heteroatom substituents, as well as spirocyclic and fused bicycles. Over 40 examples illustrate the broad generality, efficiency, selectivity, functional group tolerance, and practical utility of this approach. Mechanistic insights, gathered from stereochemical probes and competition experiments, are included to reveal the applicability of this non-stabilized carbene route for novel cyclopropane synthesis.

Introduction

Cyclopropanes are the sixth most common ring found in medicines – second only to cyclohexanes among alicycles.[1] These small carbocycles are rigid structures, which can enhance biological target binding by decreasing flexibility while increasing three-dimensional vector space versus other alkyl or aryl motifs (**Figure 1A**).[2,3] Moreover, their inherent ring strain yields strong core C-C and peripheral C-H bonds that preclude oxidative metabolism of a drug molecule – and allow

their use as bioisosteres for various alkyl, aryl, and vinyl substitution patterns. Despite such benefits of this common medicinal motif, there are limited natural sources of cyclopropanes and few synthetic approaches to access their diverse analogs.[4,5] The most direct and general method for cyclopropane synthesis consists of a (2+1) cyclization of an alkene and a carbene. Yet, access to this high energy, divalent intermediate is often limited by the use of reactive precursors, such as diazoalkanes, whose release of N_2 provides the entropic and enthalpic driving forces needed for carbene generation (**Figure 1B**). However, given the tendency for unanticipated release of N_2 from these precursors, as well as runaway reactions or explosions, strong safety concerns necessitate the use of carbonyl or aryl stabilizing groups[6–9] – including among the most modern examples of carbene reactivity.[10–14] Alternatively, the only viable methods of employing non-stabilized diazo reagents entail in situ generation,[15] especially by flow chemistry techniques.[16–18] Still, even transient generation of such reagents, which decompose violently (>100 kcal/mol),[6] preclude their widespread use in the pharmaceutical industry. Herein, we present a safe, robust, and scalable alternative for the synthesis of alkyl cyclopropanes via non-stabilized carbenes derived from alkyl aldehydes and unactivated alkenes.

In designing our strategy, we were inspired by the Simmons-Smith cyclopropanation, which provides a parallel approach to introduce CH_2 via *gem*-diiodides as carbenoid precursors.[19,20] Unlike diazo precursors, stabilizing groups are not required for such Zn-bound carbenoids. Yet, since these alkyl halides are prone to elimination of HX, such applications rarely entail alkyl groups with α-hydrogens. A key recent advance in this area includes the development by Uyeda and coworkers of cobalt complexes to allow use of *gem*-dialkyl halides as carbenoid precursors without 1,2-H migration.[21–23] In parallel, Wilkerson-Hill and coworkers developed an elegant strategy that entails deprotonation of dialkyl sulfones as carbene equivalents.[24]

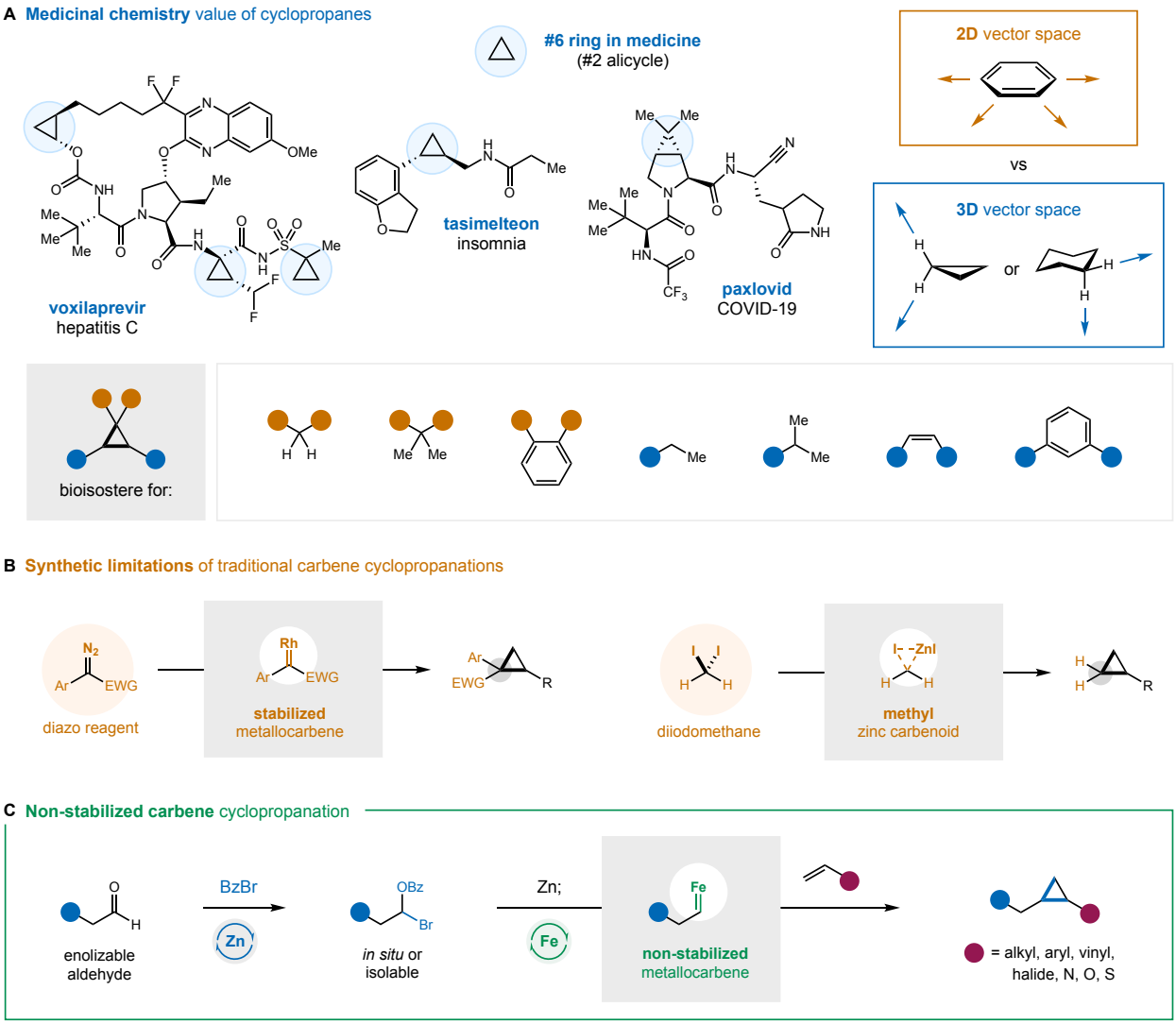


Figure 1. Strategies to access cyclopropanes, a privileged motif in medicine.
(A) Value, (B) Synthetic limitations, and (C) Our approach to access novel substitution patterns.

In our own efforts to harness non-stabilized carbenes from abundant and highly accessible carbonyls, we were inspired by the pioneering contributions of Motherwell.[25] To mimic and elucidate the Clemmenson reduction mechanism, which employs Brønsted acid activation (HCl) of a carbonyl alongside a Zn(Hg) reductant, Motherwell instead used a Lewis acid (Me_3SiCl) to access simple carbene reactivity, including deoxygenation and dimerization.[26,27] When a bespoke disilyl dichloride was employed, cyclopropanation was realized with benzaldehyde or α,β-unsaturated carbonyls as carbene precursors.[28] Yet, enolizable carbonyls were not tolerated

under these driving conditions needed for deoxygenation – due to carbene α-elimination. Building on this fundamental mechanistic understanding, we hypothesized that non-stabilized, alkyl carbenes could also be accessed by (1) milder deoxygenation conditions, and (2) use of transition metal catalysts to capture the Zn carbenoid and preclude α-elimination.

Strategy

Towards a solution to this key synthetic challenge, we sought to build on our observation that BzBr addition to carbonyls afford α-OBz bromides as stable carbene precursors (**Figure 1C**).[29] Upon reduction by Zn, transient generation of an α-OBz organozinc permits transmetallation by Earth-abundant metal catalyst, $FeCl_2$, and α-elimination yields non-stabilized metallocarbenes. In our preliminary study, we focused on exploring the reactivity of benzaldehyde-derived carbenes across several reaction types.[29] These **aryl carbenes** were particularly robust, enabling six classes of small-ring formation and five σ-bond insertions. However, *non-stabilized,* **alkyl carbenes** are highly prone to other types of undesired reactivity, including deoxygenative elimination, dimerization, rearrangement, and ring-expansion. Thus, we only observed the cyclopropanation of alkyl carbenes with highly reactive styrene (40-60% yield) – while other classes of alkenes afford no cyclization (**Figure 2**). To develop this important mode of reactivity and access novel classes of cyclopropanes, we targeted a mechanistically guided development of a general cyclopropanation of *unactivated* alkyl alkenes with *non-stabilized,* alkyl carbenes. In this study, we describe the development of a second-generation protocol that significantly expands the synthetic utility of the **alkyl carbene** cyclopropanation to afford several important, yet challenging-to-access motifs, such as all-alkyl, spirocyclic, fused bicyclic, and 1,2,3-tri-substitituted cyclopropanes, including amino acid-bound and heteroatom-rich analogs, which are highly desired motifs in medicine.

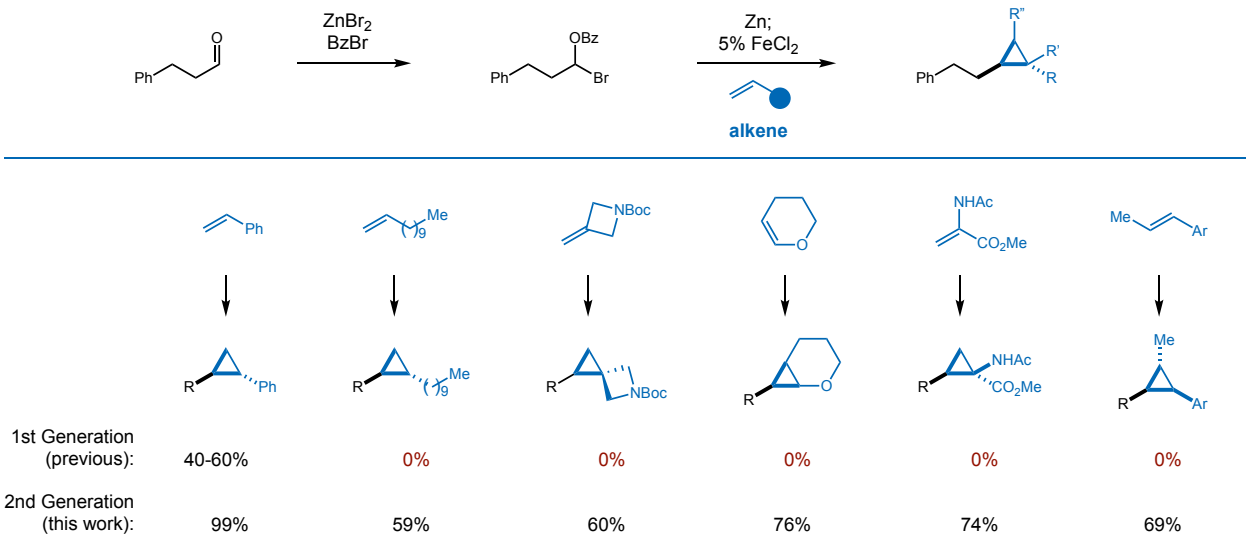


Figure 2. Limitations and expansion of scope of non-stabilized carbene cyclopropanation.

In our proposed mechanism for a *non-stabilized,* alkyl carbene cyclopropanation (**Figure 3**), we sought to access α-OBz bromide **A** quickly and efficiently by a $ZnBr_2$-catalyzed addition of BzBr to aldehydes (now at >20g scale with recrystallization, rather than chromatography).[30,31] We then proposed one-pot, sequential combination of reductant (Zn), activator (LiCl), and precatalyst ($FeCl_2$) may readily convert α-OBz bromide **A** to organozinc **B** then to organoiron **C**, in a more streamlined fashion – compared to our multi-step, first-generation protocol.[29] Without exogenous ligands, we expected transmetallation of the transient organozinc **B** to iron catalyst (FeX_2) could generate α-OBz organoiron **C**. Lastly, α-elimination of the benzoate anion would yield non-stabilized iron carbene **D** in a milder fashion than non-metal-catalyzed deoxygenation strategies mediated by either HCl or Me_3SiCl. Importantly, by influence of the metal catalyst, we proposed this electrophilic metallocarbene **D** could convert a wider range of *unbiased* alkenes to cyclopropanes, upon each catalyst turnover. Thus, the key aspects of this proposed mechanism entail use of an Fe catalyst to (1) mildly generate and stabilize the carbenoid intermediate, and (2) enable control of its reactivity, including imparting chemo- and stereo- selectivity.

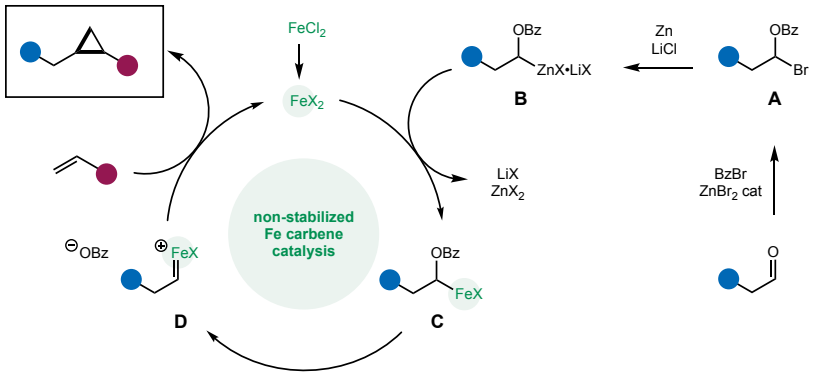


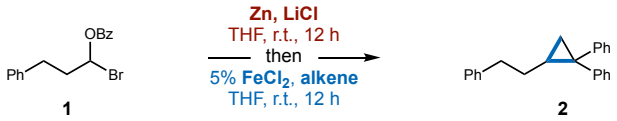
Figure 3. Proposed mechanism for Fe-catalyzed cyclopropanation via non-stabilized carbenes.

Results and discussion

Reaction Discovery.

To test our proposed catalytic strategy, we subjected α-benzoyloxy bromide **1** (1 equiv) to Zn and LiCl (2 equiv each) in THF for 12 hours, before adding to 5% $FeCl_2$ catalyst and α-phenyl-styrene (1 equiv) and stirring for 12 hours (**Table 1**). To our delight, this new protocol yields alkyl cyclopropane **2** in 50% yield (entry 1). Moreover, increasing the alkene trap to 3 or 5 equiv improves the reaction (65% or 90%, respectively; entries 2-3). Expecting the alkene to be more precious in many applications, we then reversed stoichiometry so the carbene precursor is in excess (3 equiv) to the alkene (1 equiv). This modification results in optimal efficiency with >99% yield (entry 4). If the duration of the first phase of the reaction is shortened to 6 hours, or if the Zn and LiCl additives are halved (x vs 2x equiv), then a modest decrease in reactivity is observed (85% or 87%, respectively; entries 5-6).

Table 1. Development of an Fe-catalyzed cyclopropanation.[a]



Entry	equiv **1**	**alkene** equiv	change to standard conditions	Yield **2**
1	1	1	-	50%
2	1	3	-	65%
3	1	5	-	90%
4	3	1	-	**>99%**
5	3	1	6 h (vs 12 h) for **Part A**	85%
6	3	1	Zn, LiCl (equal to **1**; not 2x)	87%
7	3	1	1:1 THF:DCM for **Part B**	63%
8	3	1	no rigorous Zn removal after **Part A**	>99%
9	3	1	all reagents added at once	75%
10	3	1	one-pot (10% $FeCl_2$, alkene added at 3 h)	**>99%**

[a] Conditions: **1** (X equiv), Zn and LiCl (2·X equiv each), THF (0.3 mL), 23 °C, 12 h, then add to 5% $FeCl_2$, alkene (0.1 mmol), THF (0.5 mL), 23 °C, 12 h. Yield determined by ^1H NMR.

Interestingly, two of our previous observations that (1) DCM is a critical co-solvent in the carbene reaction, and (2) rigorous removal of excess Zn reductant is required to prevent catalyst degradation, are no longer relevant to this new protocol.[29] Now, inclusion of DCM *reduces* efficiency to 63% yield (entry 7), and merely decanting the alkylzinc solution away from the Zn particles (rather than our previous procedure that entails settling for 30 minutes) still yields >99% yield (entry 8). This latter observation led us to question if the two stages could now be combined into a single, practical operation. Indeed, if all reagents are simply added together from the start (at t=0), this new, simplified protocol now results in 75% yield after 24 hours (entry 9). Alternatively, a one-pot protocol was also developed, wherein 10% catalyst and alkene may be added at t=3 hrs (by opening the reaction vial in a glovebox) to afford >99% yield (entry 10). Thus, we have developed three new procedures that each yield efficient reactivity based on whichever is most practical for the user – entailing catalyst addition at either t = 0, 3 hrs (in a glovebox; entries 9, 10), or 12 hrs (on the benchtop; entry 4) – enabling flexible applications in either high-throughput screening (HTS), structure-activity relationship (SAR) diversification, or scale-up settings.

Synthetic evaluation

To evaluate the synthetic generality of this Fe-catalyzed cyclopropanation by non-stabilized carbenes, we combined a diverse set of alkenes (styrenes, dienes, enynes, vinyl halides, enols, enamines, and unactivated alkenes) with alkyl aldehyde-derived **1** (**Figure 4**). Notably, an unexpectedly broad range of cyclopropanes could be prepared in this manner, including many that had been synthetically inaccessible previously. In the **benzylic** cyclopropane series (**2**-**15**), a variety of styrenes were tolerated with highly varied sterics and electronics, including extreme examples of electron-rich (OMe, **4**), -poor (CF_3, **5**), and sterically hindered (Mes, **6**) substitution. All cases reacted as efficiently as α-phenylstyrene (**2,** 99% yield) and with similar diastereoselectivity to the unsubstituted styrene (**3**, 2:1 d.r.). To probe future applications, we also cyclopropanated styrenes of the fragrance, piperonal (**7**), and medicine, ibuprofen (**8**). Since 1,1-disubstituted styrenes are tolerated, we then confirmed the viability of cyclopropane (**9**), CF_3 (**10**), and vinyl halide (F, Cl, Br, I; **11**-**14**) substituents in accessing novel *gem*-disubstituted cyclopropanes. In addition to these terminal α-styrenes, we were pleased to find internal β-styrenes may afford 1,2,3-tri-substituted cyclopropanes (**15**). In the next series, **allylic** cyclopropanes were also found to be accessible from either enynes (**16**) or dienes (**17**). While the terminal alkene may be either mono- or di-substituted, it is interesting to note that the terminal alkene in these examples reacts preferentially with the non-stabilized carbene over the alkyne or internal alkene.

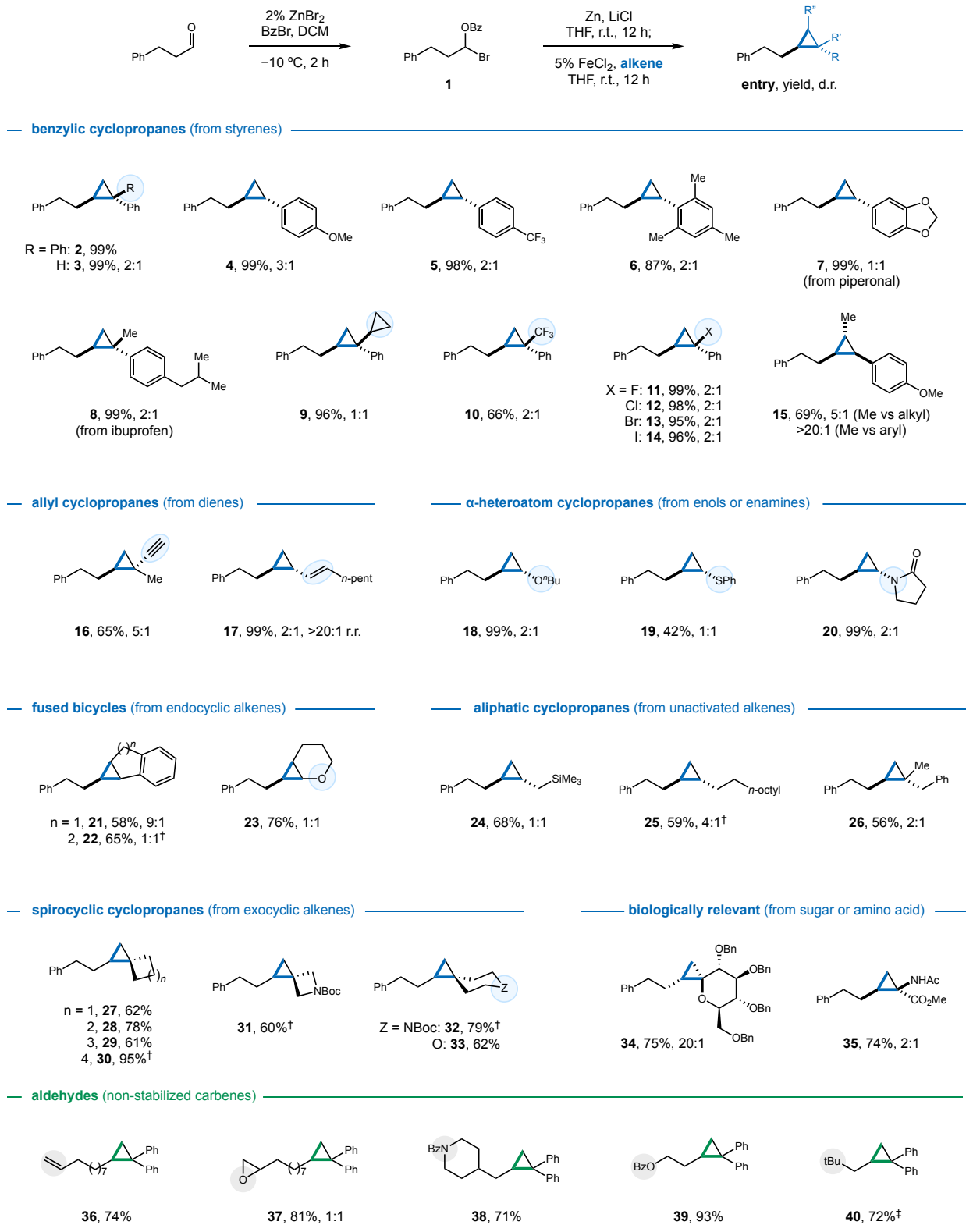


Figure 4. Synthetic evaluation of Fe-catalyzed cyclopropanation via non-stabilized carbenes.

[a] Conditions: **1** (3 equiv), Zn and LiCl (6 equiv each), THF (1.5 mL), 23 °C, 12 h, then add to 5% $FeCl_2$, alkene (1 equiv, 0.1 mmol), THF (2.5 mL), 23 °C, 12 h. Isolated yields. Diastereomeric ratio (dr) determined by ^1H NMR. [†] Conditions: Table 1, Entry 10. [‡] 60 °C

We next turned to the synthesis of **heteroatom**-substituted cyclopropanes (**18**-**20**), which are commonly found in medicines and natural products.[1] To this end, enol ethers (**18**), vinyl sulfides (**19**), and enamides (**20**) were each shown to react efficiently with the non-stabilized carbene. Notably, this cyclopropane synthesis provides a mild alternative to the classic approach for accessing α-heteroatom substitution via the Kulinkovich reaction, which requires a less mild combination of Grignard reagents and titanium(IV) alkoxides.[32] For the synthesis of fused **bicyclic** cyclopropanes (**21**-**23**), we subjected a series of endocyclic alkenes from both substrate classes, including styrenes (indene **21** and dialin **22**) and an enol ether (3,4-dihydropyran **23**).

Notably, **all-aliphatic** cyclopropanes (**24**-**26**) were also prepared from simple aliphatic alkenes – showcasing the valuable combination of non-stabilized carbenes with unactivated alkenes by this strategy. In this α-olefin series, an allyl silane (**24**), terminal alkene (**25**), and 1,1-disubstituted alkene (**26**) were each successfully cyclopropanated with the simple aliphatic aldehyde-derived carbene. Furthermore, if these unactivated alkenes are included on a ring (i.e. exocyclic alkenes), then **spirocyclic** cyclopropanes (**27**-**34**) are easily generated. Given the small, dense, and three-dimensionally rich nature of such motifs, we anticipate these diverse spirocyclic structures will find applications as key building blocks in medicinal chemistry.[1–3] Thus, we prepared spirocyclic cyclopropanes of cyclobutane (**27**), cyclopentane (**28**), cyclohexane (**29**), and cycloheptane (**30**), as well as the heterocycles: azetidine (**31**), piperidine (**32**), and tetrahydropyran (**33**). Lastly, we subjected the olefins of glucose (**34**) and dehydroalanine (**35**) to access cyclopropanes of **saccharides** and **α-amino acids**, providing further illustration of the likely applicability of this non-stabilized carbene route for medicinally relevant cyclopropane synthesis.

To systematically probe functional group tolerance, we next conducted the parent transformation (**1** to **3**) in the presence of a wide range of reactive additives (**Figure 5**).[33] By comparing the yield of **3** in these experiments with the additive-free transformations (99% yield), we determined how tolerant the carbene-based transformation is to these functional groups. Additionally, we also quantified the recovered additive to probe undesired consumption – and thereby provide a simple guide to whether each functional group may be tolerated in more complex substrates. As shown in the green box on the left (>60% product **3** and >60% recovered additive), several functional groups are well-tolerated in this strategy (often providing >95% **3**), including alkyl halides (I, Br, Cl), amines, internal alkenes, alkynes, ketones, esters, epoxides, aryl nitriles, and anisoles.

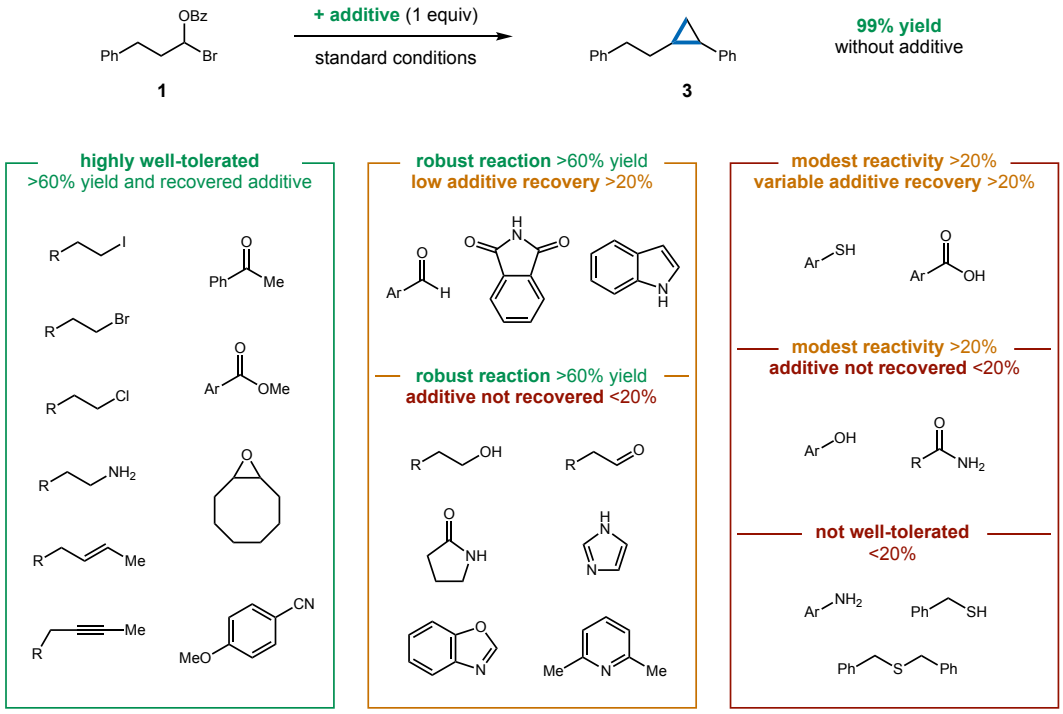


Figure 5. Evaluation of reaction robustness to functional group additives.

Interestingly, the middle box (orange) depicts several functional groups that did not inhibit the cyclopropanation (>60% **3**), but which were recovered in low yields, indicating they may have

reacted with excess carbene in solution. These examples of functional groups that resulted in low additive recovery are aryl aldehydes, phthalimide, and indole. Meanwhile, complete additive consumption occurred in the cases of alcohols, aldehydes, amides, pyridines, and nucleophilic bases. In this middle box, we recognized a possible solution, wherein the stoichiometry could be reversed (or made equal; i.e. 1:1 carbene:alkene) so that there is no excess carbene to react with these functional groups. Preliminary studies of such an approach yielded improved additive recovery. Lastly, the box on the right highlights additives that are poorly tolerated, as they inhibit reactivity either modestly (thiophenol, acid, phenol, amide) or significantly (aniline, thiol, disulfide). The latter cases are least surprising, as we have shown σ-bond insertions may occur with these groups, and that carbenes rapidly transfer to disulfides to make ylides.[29]

Mechanistic investigations

Having observed robust synthetic generality for this $FeCl_2$-catalyzed cyclopropanation across a diverse set of alkenes, we next sought to probe the mechanism of the (2+1) addition of these non-stabilized carbenes (**Figure 6**). Thus, we subjected a pair of 1,2-disubstituted alkenes with complementary geometries to the cyclopropanation. In the case of a *trans* alkene, the resulting cyclopropane perfectly retains the *anti* relationship among the alkene substituents in the product ring (**41**, >20:1 anti:syn). As an aside, the stereochemistry with respect to the alkyl carbene substituent resembles those observed in our previous synthetic evaluations (see **Fig 4**; e.g. **15**, 5:1 d.r.). Remarkably, when a *cis* alkene is employed instead, the resulting cyclopropane again perfectly retains the alkene geometry, albeit now resulting in a *syn* relationship (**42**, >20:1 syn:anti). Together, these results indicate this cyclization of non-stabilized carbenes likely occurs through a concerted (2+1) mechanism – affording diastereoselective retention akin to those observed with stabilized diazo reagents and Simmons-Smith variants.[34]

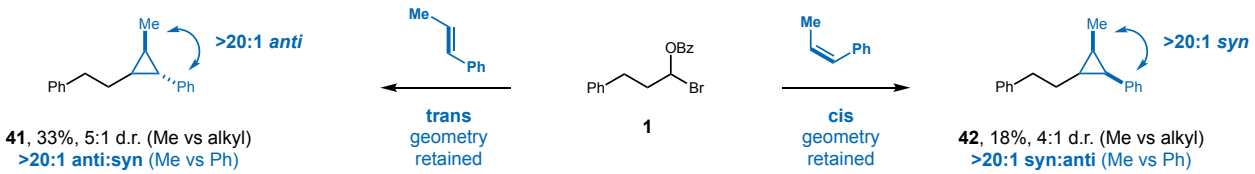


Figure 6. Stereochemical probes indicate retention of alkene geometry (via a concerted carbene addition).

We next designed a series of competition experiments to elucidate the relative rates of reactivity among different carbene traps. As indicated in the summary box atop **Figure 7**, terminal alkenes are most reactive, as illustrated by 1,1-disubstituted alkenes (k_{rel} 20) and mono-substituted alkenes (k_{rel} 10). In comparison, internal alkenes show a significant drop in reactivity, such as *trans*-1,2-disubstituted alkenes (k_{rel} 1) and *cis*-1,2-disubstituted alkenes (k_{rel} 0.5). The specific values for each competition experiment are indicated below, wherein two alkenes (**A** and **B**) were combined in a 1:1 ratio (1 equiv each) and allowed to react with excess carbene (2 equiv **1**). Equation 1 shows α-methyl styrene is far more reactive than β-methyl styrene (k_{rel} 20:1 terminal: internal), while Equation 2 confirms simple styrene is also more reactive than β-methyl styrene (k_{rel} 10:1 mono:terminal). Interestingly, among internal alkenes, the *trans* isomer of β-methyl styrene is more reactive than the *cis* isomer (k_{rel} 2:1 trans:cis), as shown in Equation 3, suggesting a likely steric clash between the alkene and metallocarbene. Lastly, in a non-styrenyl pair of terminal alkyl olefins (equation 4), the 1,1-disubstituted alkene was again twice as reactive as a mono-substituted alkene (k_{rel} 2:1 di:mono) – confirming the relationship implied by comparing equations 1 and 2. Together, these results indicate there is a strong steric influence on the rate of reactivity of the non-stabilized carbenes with alkenes, even overcoming expected cis vs trans effects. This observed reactivity trend better resembles the π-nucleophilicity scale measured by Mayr,[35] which although not universally predictive of reactivity (e.g. yields in **Fig 4**), accurately predicts the trends observed in these competition experiments.

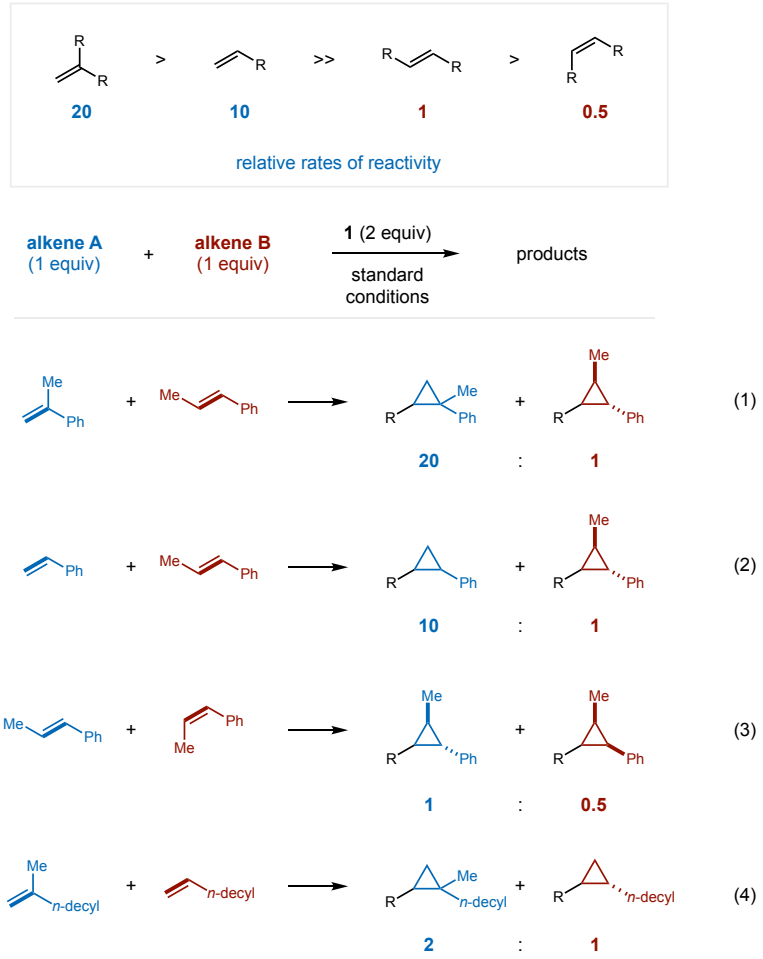


Figure 7. Competition experiments show relative rates of reactivity among alkenes.

To determine the effect of olefin coordination on these competition experiments, we designed another contest between a mono- and di- alkene (**Figure 8**). Since reactivity is diminished for *cis*-1,2-alkenes (the lowest in Figure 7), cyclooctene was not expected to have high reactivity, and indeed, this was observed (< 10% yield). However, if better alkene coordination assists reactivity (yielding increased rates of terminal/mono- vs internal/di- substitution), then 1,5-cyclooctadiene (1,5-COD), a diene known to chelate several metals, would be expected to exhibit increased reactivity. Instead, a similarly low rate of reactivity was observed, and no rate difference was detected for consumption of either the alkene or diene.

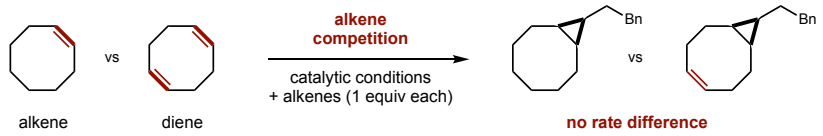
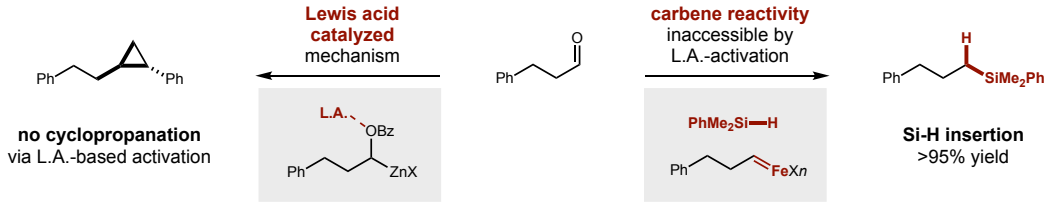


Figure 8. Olefin coordination does not increase rate of reactivity.

Lastly, we sought to determine if the $FeCl_2$ catalyst (a) truly generates a non-stabilized, iron metallocarbene intermediate, or (b) merely serves as a Lewis acid (L.A.) to assist benzoate removal and alkylzinc activation – as in some pioneering Simmons-Smith cyclopropanations with *gem*-dihalides.[34] To this end, we surveyed several Lewis acids that have been employed in these alkylzinc reactions, as well as many other hard and soft acids, and found such additives *do not* promote the reaction (**Figure 9,** left). In fact, *nearly all* investigated Lewis acids *are ineffective* (i.e. 0% yield) including: BF_3, AgOTf, $Sc(OTf)_3$, $In(OTf)_3$, $AuCl_3$, $(Ph_3P)AuCl$, and *in situ* formed $(Ph_3P)AuOTf$. Interestingly, only iron-based Lewis acids were *viable*, such as the less-effective Fe(II) salt, $Fe(OTf)_2$ (39% vs 99% with $FeCl_2$). Additionally, since the Fe(III) salt, $FeCl_3$, is a better L.A. than $FeCl_2$, but it is an inferior catalyst (25% vs 99%) since it likely needs to be reduced to $FeCl_2$ first, we concluded that Lewis acid reactivity is likely not operative.



Lewis acids (L.A.) investigated: $BF_3{\cdot}Et_2O$, AgOTf, $Sc(OTf)_3$, $In(OTf)_3$, $AuCl_3$, $(PPh_3)AuX$
Ligands are not tolerated: $FeCl_2$ (99%) vs $FeCl_3$ (25%) vs $FeCl_3$ + ligands (<25%)

Figure 9. Lewis acid activation versus metallocarbene reactivity. Typical Lewis acids used in Simmons-Smith cyclopropanations by alkylzinc intermediates do not work in this system (left); this iron-catalysis uniquely affords carbene reactivity that is not accessible by Lewis acids (right).

Moreover, we were pleased to find that this new protocol also quantitatively enables Si-H insertion in efficiency that now rivals more expensive Rh catalysts (**Figure 9,** right). Notably, since Simmons-Smith protocols do not afford such carbene reactivity, this provides further compelling evidence for a metallocarbene mechanism.[19,20] Finally, we have confirmed exogenous ligands are not tolerated in this strategy, as inclusion of various chelating ligands (e.g. diamines, tetraamines) reduced efficiency of the $FeCl_3$ catalyst (25%), which is itself less effective than the $FeCl_2$ catalyst (99%).

Conclusions

In summary, an $FeCl_2$-catalyzed cyclopropanation has been developed, which employs a broad range of alkenes in a (2+1) cycloaddition with non-stabilized carbenes. This new, robust harnessing of aliphatic (enolizable) aldehydes in couplings with unactivated alkenes now allows access to a wide range of novel cyclopropanes, including many which have been synthetically inaccessible previously. A thorough scope evaluation includes the synthesis of new classes of cyclopropanes bearing alkyl, benzyl, allyl, halide, and heteroatom substituents, as well as bicyclic fused and spirocyclic variants. Additionally, a systematic robustness analysis provides insights on the wide functional group tolerance of this new reaction. Finally, stereochemical probes and competition experiments illustrate the concerted nature of the cyclopropanation and the expected order of reactivity for different alkene classes. We anticipate this mechanistically novel approach for converting non-biased aliphatic aldehydes – and a wide range of alkenes – to diverse families of cyclopropanes will greatly expand access to these biologically important motifs.

EXPERIMENTAL PROCEDURES

Resource availability

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, David A. Nagib (nagib.1@osu.edu).

Materials availability

All reagents in this study are commercially available or can be easily prepared as indicated.

Data and code availability

There is no dataset or code associated with the paper.

METHODS (or Supplemental Experimental Procedures)

Full experimental procedures are provided in the supplemental information. For more details, see Tables S1-S4 for reaction optimization, and Figures S1–S4 for mechanistic experiments and characterization of new compounds.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at ...

ACKNOWLEDGMENTS

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AUTHOR CONTRIBUTIONS

B.M.D. discovered and developed the transformation, as well as designed, performed, and analyzed all experiments probing reaction scope, selectivity, and mechanism. L.Z. provided preliminary experimental contributions, and E.K.R. further evaluated synthetic utility and robustness. All authors contributed to writing the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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TOC Graphic: