General Cyclopropane Assembly via Enantioselective Redox-Active Carbene Transfer to Aliphatic Olefins

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Abstract: Asymmetric cyclopropane synthesis currently requires bespoke strategies, methods, substrates and reagents, even when targeting similar compounds. This limits the speed and chemical space available for discovery campaigns. Here we introduce a practical and versatile diazocompound, and we demonstrate its performance in the first unified asymmetric synthesis of functionalized cyclopropanes. We found that the redox-active leaving group in this reagent enhances the reactivity and selectivity of geminal carbene transfer. This effect enabled the asymmetric cyclopropanation of a wide range of olefins including unactivated aliphatic alkenes, enabling the 3-step total synthesis of (−)-dictyopterene A. This unified synthetic approach delivers high enantioselectivities that are independent of the stereoelectronic properties of the functional groups transferred. Our results demonstrate that orthogonally-differentiated diazocompounds are viable and advantageous equivalents of single-carbon chirons.
Cyclopropanes have attracted the attention of chemists for decades. The high strain and unique bonding of these carbocycles display enhanced conformational control and oxidative resistance that have been exploited in organic synthesis,\textsuperscript{[1a]} asymmetric catalysis\textsuperscript{[1b]} and medicinal chemistry.\textsuperscript{[1c]} Cyclopropanes are common in advanced total syntheses both as structural elements in challenging natural products,\textsuperscript{[1d]} and as enabling instruments to drive creative disconnections.\textsuperscript{[1e]} Different asymmetric syntheses of functionalized cyclopropanes 1 have thus been developed (Scheme 1a).\textsuperscript{[2],[3]} However, similar targets with different peripheral functionality still require discrete strategies based on specific reagents, catalysts, and substrates that are elaborated over several steps from raw sources. The key enantioselective step on these routes are often based on allylic alcohols \textsuperscript{[2],[4]} 1,1-disubstituted cyclopropanes \textsuperscript{3,}\textsuperscript{[5]} or electron-deficient alkenes \textsuperscript{4,}\textsuperscript{[6]} Simple unfunctionalized olefins (5) are abundant feedstocks and frequent in complex intermediates but only some classes can engage in asymmetric cyclopropanation using advanced metal catalysts,\textsuperscript{[7]} or engineered enzymes.\textsuperscript{[8]} While electron-rich alkenes and styrenes are efficient in these reactions, the most common aliphatic alkenes\textsuperscript{[9]} are poorly reactive, and problematic in asymmetric catalysis because of their structural flexibility and weak dispersive interactions.\textsuperscript{[10]} Although elegant approaches have been documented,\textsuperscript{[7b, 7c, 8c, 8d]} the asymmetric cyclopropanation of aliphatic olefins is yet to be achieved with a general and simple catalytic system.\textsuperscript{[7b-i, 10]} Importantly, many interesting functionalized carbenes \textsuperscript{6-12} (FG-\textsuperscript{C}-\textsuperscript{H}; Scheme 1a, bottom) are still unsuitable for cyclopropanation reactions: alkyl-,\textsuperscript{[11a, 11b]} hydroxy-,\textsuperscript{[11c]} amino-,\textsuperscript{[11d]} boryl-,\textsuperscript{[11e]} selenyl-,\textsuperscript{[11f]} heteroaryl-,\textsuperscript{[11g]} or alkenyl-methylenes \textsuperscript{[11h]} are either unstable or prone to oligomerization. As a result, the syntheses of the cyclopropanes bearing these functions are lengthy and specific, typically requiring overmanipulation of other cyclopropane intermediates.\textsuperscript{[5, 6d, 6e, 11e, 12]}

We conceived a unified strategy\textsuperscript{[13]} to comprehensively address the enantioselective formal transfer of carbenes \textsuperscript{6-12} to alkene feedstocks 5 through a two-stage process (Scheme 1b): (1) enantioselective cyclopropanation of 5 with a diazocompound featuring a leaving group (13); and (2) diversification of the resulting intermediates 14. This late-stage functionalization is critical to access chiral products with identical enantioselectivity regardless of their specific functionality. Unlike current tailored syntheses, this approach simplifies the optimization of the enantioselective step using a single carbene precursor. However, leaving group-
functionalized carbenes [M]-13 (Scheme 1c) are known to be poorly reactive, and non-enantioselective. Their precursors tend to undergo substitution prior to the carbene transfer, and require additional stabilizing groups.\[^{14}\] We envisioned that redox-active carbenes bearing an N-hydroxyphthalimide ester leaving group [M]-13a (LG = CONHPI; Scheme 1c) could become equivalent to all the distinct carbenes 6-12, due to the dual capacity of NHPI esters to act as acyl electrophile\[^{15}\] and carbon-centered radical precursors. The latter manifold is vividly expanding into new C-C,\[^{16}\] C-N,\[^{17}\] C-O\[^{18}\] or C-B\[^{19}\] bond forming reactions. This diversity is beyond the reach of current divergent strategies towards chiral cyclopropanes.\[^{20}\][\(^{21a}\)] Despite the versatility of NHPI esters, their orthogonality to metal-carbenes was unknown, and a logical concern when considering their facile irreversible fragmentation upon activation with various transition metals and/or visible light.\[^{16-19}\]

**Scheme 1.** State-of-the-art, concept and challenges towards the unified assembly of diverse chiral cyclopropanes.

After extensive experimentation, we found that the designed N-hydroxyphthalimidoyl diazoacetate reagent (NHPI-DA, 13a; Scheme 2a)\[^{22}\] can be isolated in gram-amounts as a
crystalline solid that is bench-stable for months. NHPI-DA (13a) does not require solution storage, and thus allows for easier handling. It also displays higher stability than the benchmark ethyl diazoacetate, as evidenced by DSC (EDA, 15a; Scheme 2b). Initial evaluation of NHPI-DA (13a) in cyclopropanation reactions using common rhodium, copper and palladium catalysts\(^2\) displayed low efficiency and selectivity (Table S3), as anticipated for this challenging transformation (vide supra). Fortunately, we discovered that NHPI-DA (13a) is effective in combination with the electron-rich metallacyclic ruthenium catalyst RuL1\(^{[22]}\) (Scheme 2c), displaying a remarkable cyclopropanation selectivity over the competing dimerization pathway (16-18/19). We compared this intrinsic selectivity against various conventional diazo reagents with different steric and electronic properties (15a-f). For this study, we used equimolar conditions without slow addition of the carbene precursors to minimize any substrate-specific bias. Model olefins 5a-c with distinct nucleophilicities (\(N_j\);\(^{[23]}\) Scheme 2d), were used as representative substrates. Using styrene (5a, \(N = +1.70\)), it was found that NHPI-DA (13a) outperforms diazocompounds 15a-f. More importantly, this trend is accentuated when exploring more challenging olefins, such as 1-hexene (5b, \(N = −2.77\)) and vinyltrimethylsilane (5c, \(N < −1.46\)), which are cyclopropanated with NHPI-DA in 72% and 41% yield, respectively (<26% and <9% yield using 15a-f). This effect can be rationalized by the stronger electron-withdrawing effect of the ester moiety in 13a, which allows less reactive olefins to effectively compete for the electrophilic carbene Int-A (Scheme 2c).
Although RuL1 is a competent catalyst in asymmetric cyclopropanation,[21] we have found that NHPI-DA (13a) expands its scope into an unprecedentedly wide selection of alkenes with surprisingly high enantioselectivities (Scheme 3).[2] Functionalized styrenes with various substitution patterns lead, without slow addition, to redox-active cyclopropanes 16,20-28 in excellent yields, and with high diastereo- and enantioselectivities. Different nucleophilic enol ethers smoothly produce push-pull products 29,30, even in the presence of a primary alcohol (no O–H insertion observed). Various types of enamines (31-33) or an allylic silane (34), are also efficiently cyclopropanated. Aliphatic olefins are challenging substrates in enantioselective cyclopropanation,[7, 10] but to our delight, non-coordinating and structurally flexible alkenes furnished cyclopropanes 17,35 with high diastereo- and enantioselectivity under standard conditions. We explored the functional group tolerance of this method in these series using unactivated olefins equipped with a pendant arene (36), ketone (37), chloride (38), Weinreb amide (39), alcohol derivative (40) and alkyne (41), observing high enantioselectivity in all cases. Methylene cycloalkanes produce the interesting spiro-cyclopropane building blocks 42,43. Additionally, protected amines (44) were also tolerated. As far as we are aware, the NHPI-DA / RuL1 combination is the simplest homogeneous system to achieve highly enantioselective cyclopropanation on a wide range of aliphatic alkenes.[7, 8, 10] Natural unactivated olefin feedstocks offer an opportunity to explore its performance in complex settings. Complete discrimination between olefins of different nucleophilicity (including enones and 1,3-dienes) enables the selective modification of carvone, nopadiene, and gibberellic acid (45-47). Olefins at hindered positions in the pinane (48) and steroid (49-50) frameworks are also suitable in smooth cyclopropanations. In the latter, either enantiomer of the catalyst RuL1 can be used to access alternative diastereomers 49 and 50 with complete facial discrimination. This system is also primed for late-stage functionalization of macromolecular natural glycosides and pharmaceuticals that would be problematic with existing biocatalysts,[8] like rebaudioside A obtained from a Stevia extract (51) and the cholesterol-regulating drug simvastatin (Zocor®) (52). Electron-poor olefins produce the
differentiated bis-carboxylate 53 and the cyclopropyl amino acid derivative 54. Silylcyclopropanes 18,55 are also obtained with high diastereo- and enantioselectivity from vinylsilanes, despite their high steric bulk.

Scheme 3. Scope of the enantioselective cyclopropanation with NHPI-DA (13a). Conditions: 5 (1.0 equiv.), 13a (1.2 equiv., 40 min addition time), catalyst (S)-RuL1 (1 mol%), CH2Cl2, 0 °C. † 13a (1 s addition time). ‡ 13a (6 h addition time), catalyst (2 mol%). ‡ 13a (3 equiv., 16 h addition time), catalyst (3 mol%), rt. § 13a (3 equiv., 24 h addition time), catalyst (5 mol%), rt. ¶ catalyst (R)-RuL1. ∗ Absolute stereochemistry confirmed. See Supporting Information for experimental details. Supplementary crystallographic data: CCDC 1851521 (22), 1851524 (32), 1851525 (41), 1851522 (50).

We explored the synthetic potential of enantioenriched redox-active cyclopropane scaffolds derived from the representative olefins 5d,e (Scheme 4a). Upon decarboxylation, these are versatile precursors of catecholboronates[19b] that can be readily converted into pinacolboronates 56-57 or oxidized to cyclopropanols 58-59. Radical decarboxylative...
alkylation (60,61) and selenation (62,63)\[24\] yield enantioenriched alkyl- and selenylcyclopropane products. To the best of our knowledge, this represents the first enantioselective synthesis of selenyl cyclopropanes. Basic and electron-rich heteroaromatics can be installed through telescoped cross-coupling with the corresponding bromides or lithiated heterocycles\[25\] (see 64-66). Taking advantage of the capacity of NHPI esters as acyl donors,\[15\] we added Grignard nucleophiles to produce the corresponding alkyl- and arylketones 67-69. We also developed a direct Curtius amination protocol towards cyclopropylamines 70-75, including the ticagrelor® fragments 70-74.\[26\] It is important to highlight that the synthesis of products 56-75 did not require neither an individual synthesis of suitable carbene precursors, nor custom catalysts to accommodate their diverse functionalities. These results illustrate the unique versatility of enantioenriched redox-active cyclopropane carboxylates, now accessible in one-step from feedstock alkenes using NHPI-DA (13a).

Scheme 4. Synthesis of unrelated enantioenriched functionalized cyclopropanes via redox-active intermediates. See Supporting Information for experimental details. 'C-3 acetate cleaved. ' Absolute stereochemistry confirmed. \[\dagger\] Yield of the cyclopropanation step. Yields are calculated on the isolated product. Bpin, boronic acid pinacol ester; \textsuperscript{[67]}Ar, heteroaryl; FG, functional group; 3-Quin, quinoline-3-yl; 3-Py, pyridine-3-yl; 2-Thiop, thiophene-2-yl; Cbz, benzoyloxycarbonyl; Teoc, (2-(trimethylsilyl)ethoxycarbonyl); Alloc, allyloxycarbonyl; Fmoc, fluorenlymethyloxycarbonyl; Bn, benzyl.
With these results in hand, we explored the valorization of simple feedstocks in the synthesis of relevant chiral cyclopropanes (Scheme 4b-d). As such, 4-bromobutene (5f) can be transformed in a three-step process into the enantioenriched cyclopropanol fragment 76 of the drug grazoprevir.\textsuperscript{[27]} L-allylglycine (5g) can be utilized to produce 77, which can be transformed into the cyclopropylamine fragment 78 of the bioactive natural product (+)-belactosin A (Scheme 4c).\textsuperscript{[28]} Moreover, propene gas (5h), the simplest pro-chiral aliphatic olefin, leads efficiently on a gram-scale to 79 en-route to the enantiopure cyclopropylboronate building block 80, used in the total synthesis of (−)-spongidepsin (Scheme 4d).\textsuperscript{[29]} After olefination of the inexpensive 2-heptenal (81; Scheme 4e), the resulting 1,3-diene, is cyclopropanated to yield 82 and further vinylated using a telescoped Zweifel process\textsuperscript{[25b, 30]} into the divinylcyclopropane natural product dictyopterene A (83).\textsuperscript{[31]} To put these results in perspective, it is important to highlight that the synthesis of the diverse cyclopropane fragments in commercial drugs (70-74,76), natural products (78,80), and the shortest total synthesis of 83 invariably required 2-3 steps from feedstock materials, utilizing a single strategy, carbene precursor (13a) and catalyst (RuL1). If step count is used to illustrate the tactical value of this new scheme, previous strategies for the asymmetric synthesis of products 70-74,76,78,80,83 required at least twice as many, and up to 15 steps (see Scheme 4) using custom methods, materials, and reagents. This has been realized through the 2-step enantioselective formal transfer of carbenes 6-12, which is unprecedented to the best of our knowledge. The current momentum of redox-active ester chemistry and the rich reactivity of carbene transfer suggest future synthetic upgrades of this technology, some of which are underway in our laboratories.

In summary, NHPI-DA (13a) is a practical, safe, and crystalline methine precursor that provides a comprehensive solution to the enantioselective formal transfer of various functionalized methylidenes. This reagent (i) renders the synthesis of custom and unstable carbene reagents unnecessary, (ii) simplifies the optimization of the asymmetric carbene transfer step, and (iii) enables the synthesis of targets with distinct functionalities with the same enantioselectivity and conceptual approach. The unexpected synergistic effect between the geminal redox-active ester and carbene functions enables the general asymmetric cyclopropanation of challenging aliphatic alkenes. Moreover, the NHPI ester function has the unique capacity to promote both acyl-transfer and radical derivatization reactions that
enhance the synthetic utility of the resulting enantioenriched cyclopropane intermediates. NHPI-DA (13a) provides the foundation for further asymmetric assembly of ubiquitous carbon stereocenters from single carbon units: their simplest retrosynthetic chirons.

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Conflict of interest

A priority patent application has been filed (1850940-6), where A.M., M.M-M., M.C. and E.M.-C. are listed as inventors.

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