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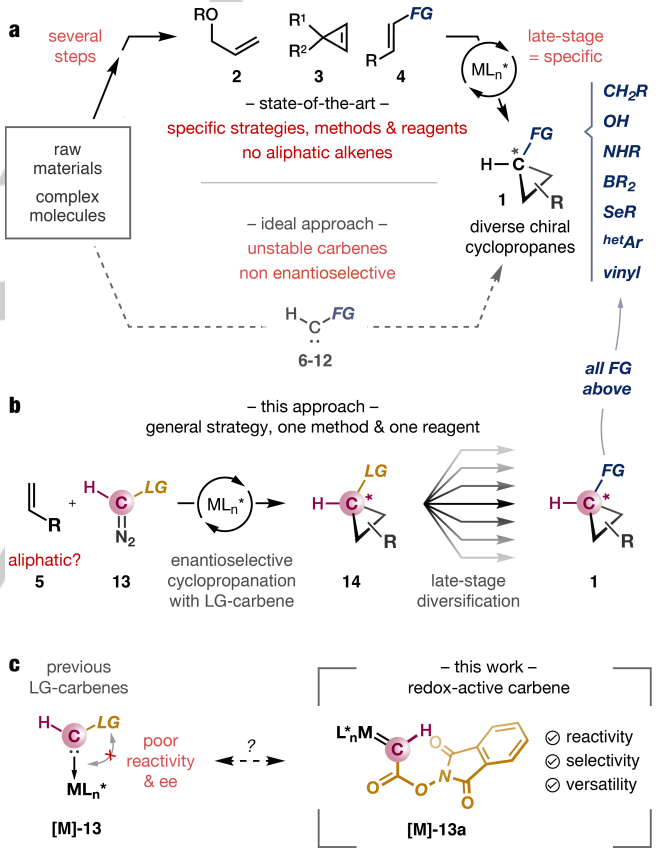
General Cyclopropane Assembly via Enantioselective Transfer of a Redox-Active Carbene to Aliphatic Olefins

Marc Montesinos-Magraner,[a]‡ Matteo Costantini,[a]‡ Rodrigo Ramírez-Contreras,[a] Michael E. Muratore,[b] Magnus J. Johansson[b] and Abraham Mendoza*[a]

Abstract: Asymmetric cyclopropane synthesis currently requires bespoke strategies, methods, substrates and reagents, even when targeting similar compounds. This slows down discovery and limits its available chemical space. 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 allowed for the asymmetric cyclopropanation of various olefins including unfunctionalized aliphatic alkenes, that enables 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,[1a] asymmetric catalysis[1b] and medicinal chemistry.[1c] Cyclopropanes are common in advanced total syntheses both as structural elements in challenging natural products,[1d] and as enabling instruments to drive creative disconnections.[1e] Different asymmetric syntheses of functionalized cyclopropanes **1** have thus been developed (Scheme 1a).[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 **2**,[4] 1,1-disubstituted cyclopropenes **3**,[5] or electron-deficient alkenes **4**.[6] The asymmetric cyclopropanation of unfunctionalized olefins (**5**; *i.e.* electron-rich and styrenes) with diazoesters, has been extensively developed with metal-,[7] and bio-catalysts.[8] However, common aliphatic alkenes[9] are, despite elegant approaches,[7b, 7c, 8c, 8d] still problematic due to their low nucleophilicity, and the flexibility and weak dispersive interactions of their alkyl substituent.[7b-i, 10] Importantly, many interesting functionalized carbenes **6-12** (FG-C̈-H), such as alkyl-,[11a, 11b] hydroxy-,[11c] amino-,[11d] boryl-,[11e] selenyl-,[11f] heteroaryl-,[11g] or alkenyl-methylidenes[11h] are too unstable to engage in cyclopropanation reactions. As a result, the derived cyclopropanes still require long and specific syntheses.[5, 6d, 6e, 11e, 12]



Scheme 1. State-of-the-art, concept and challenges towards the unified assembly of diverse chiral cyclopropanes. ^{het}Ar = heteroaryl, FG = functional group.

We conceived a unified strategy[13] to comprehensively address the formal asymmetric transfer of carbenes **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] late-stage diversification of the resulting intermediates **14.** This approach would produce chiral products with identical enantioselectivity regardless of their specific functionality, while simplifying the optimization of the enantioselective cyclopropanation by using a single carbene

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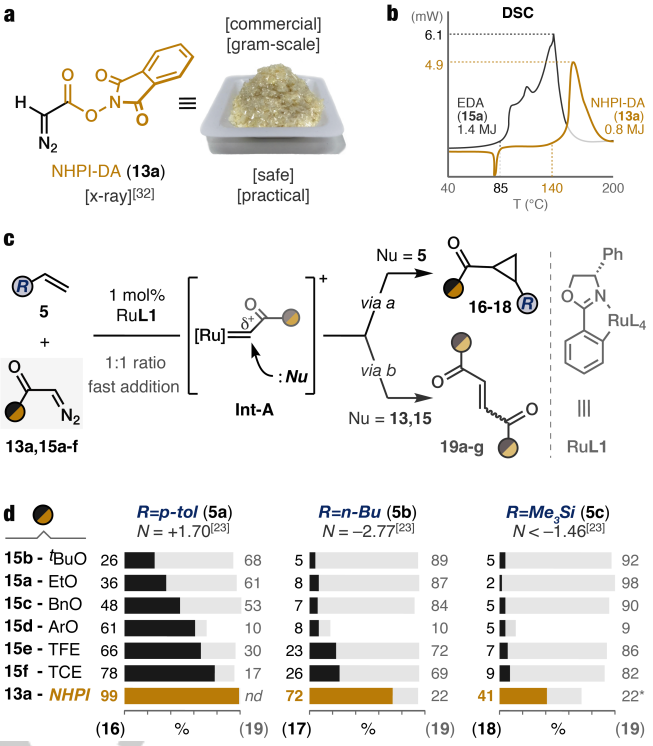
precursor. However, leaving group-functionalized carbenes **[M]-13** (Scheme 1c) are known to be poorly reactive, non-enantioselective, and their precursors tend to undergo substitution prior to the carbene transfer.[14] We envisioned that redox-active carbenes **[M]-13a** (Scheme 1c) – containing an *N*-hydroxyphthalimide (NHPI) ester leaving group – 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 radical precursors. Their vividly expanding C-C,[16] C-N,[17] C-O[18] or C-B[19] bond forming reactions, are well beyond the reach of current divergent strategies towards chiral cyclopropanes.[20, 21a] Despite their versatility, the orthogonality of NHPI esters 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]

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 Ru**L1**[21] (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, fast addition of **13a,15a-f**, and model olefins **5a-c** with distinct nucleophilicities (*N*;[23] Scheme 2d), to minimize substrate-specific bias. It was found that NHPI-DA (**13a**) outperforms diazocompounds **15a-f** using styrene (**5a**, *N*= +1.70), and this trend is importantly accentuated with more challenging olefins, such as 1-hexene (**5b**, *N*= –2.77) and vinyltrimethylsilane (**5c**, *N* < –1.46). 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).



Scheme 2. Properties and performance of NHPI-DA (**13a**). Conditions: **5** (0.1 mmol), Ru**L1** (1 mol%), **13,15** (0.1 mmol; 1 s addition time), CH_2Cl_2, 0 °C; DSC = differential scanning calorimetry, EDA = ethyl diazoacetate, Bn = benzyl, ArO = 2,6-di-(*tert*-butyl)-4-methylphenoxy, TFE = 2,2,2-trifluoroethoxy, TCE = 2,2,2-trichloroethoxy.

Although Ru**L1** 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. Importantly, weakly nucleophilic aliphatic olefins with flexible alkyl substituents,[7, 10] furnish cyclopropanes **17**,**35** with high diastereo- and enantioselectivity under standard conditions. We explored the functional group tolerance of this method in these series using substrates 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. Likewise, methylenecycloalkanes produce the interesting spiro-cyclopropane building blocks **42**,**43**, and protected amines (**44**) were also tolerated. As far as we are aware, the NHPI-DA / Ru**L1** combination is the simplest homogeneous system to achieve highly enantioselective cyclopropanation on a wide range of aliphatic alkenes.[7, 8, 10] Natural aliphatic 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)

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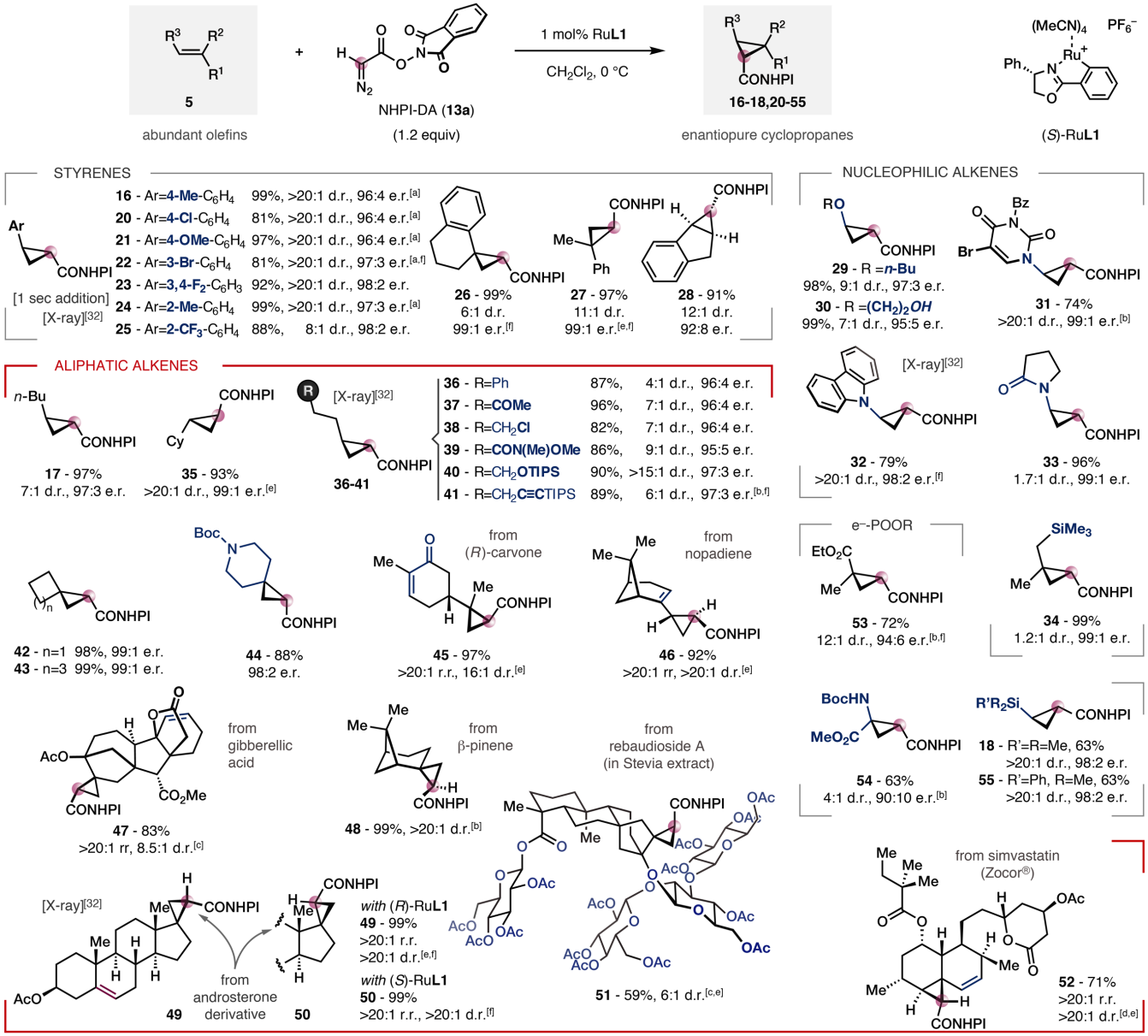
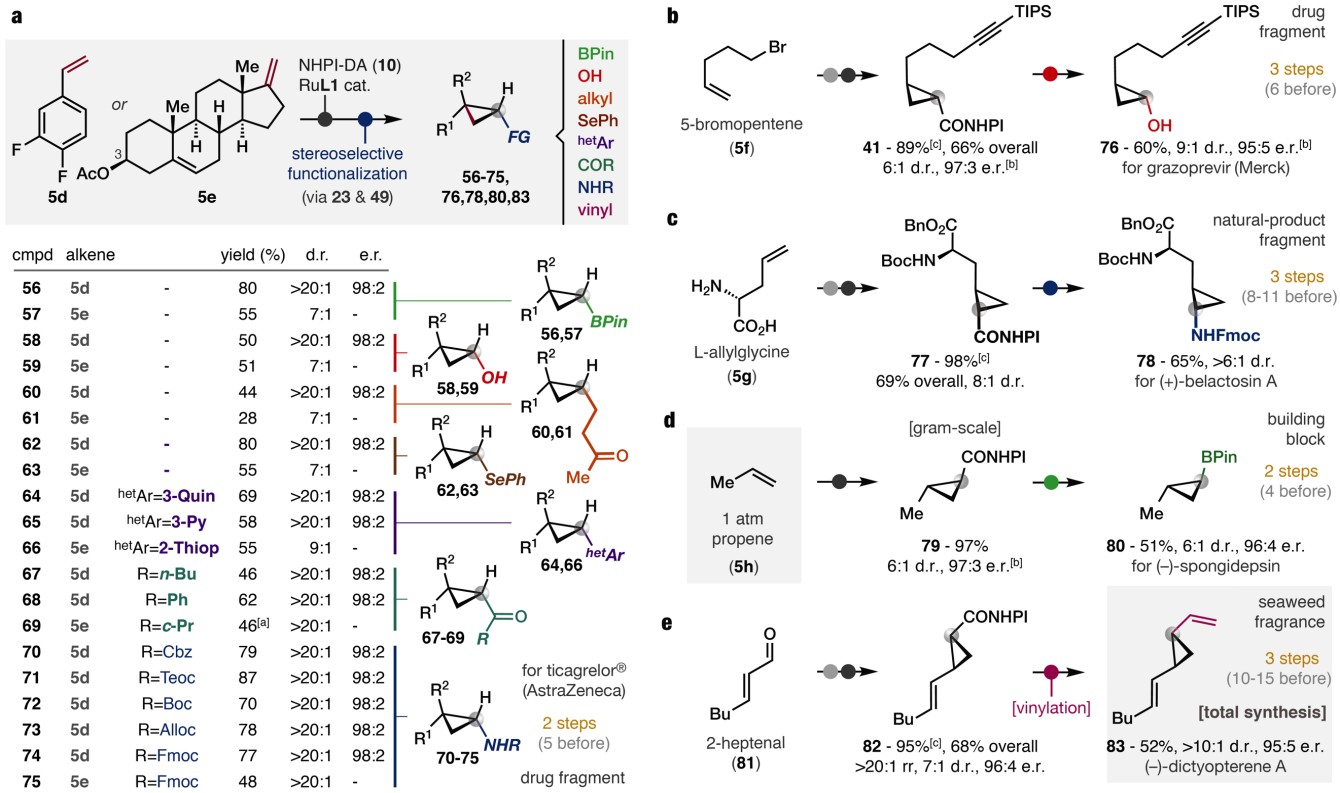


Scheme 3. Scope of the enantioselective cyclopropanation with NHPI-DA (**13a**). Conditions: **5** (1.0 equiv), **13a** (1.2 equiv, 40 min addition time), (*S*)-Ru**L1** (1 mol%), CH_2Cl_2, 0 °C. [a] **13a** (1 s addition time). [b] **13a** (6 h addition time), cat. (2 mol%). [c] **13a** (3 equiv, 16 h addition time), cat. (3 mol%), rt. [d] **13a** (3 equiv, 24 h addition time), cat. (5 mol%), rt. [e] Cat. (*R*)-Ru**L1**. [f] Absolute configuration confirmed. See SI for experimental details.[32] Bz = benzoyl, TIPS = triisopropylsilyl, Boc = *tert*-butyloxycarbonyl, Ac = acetyl.

enables the selective modification of carvone, nopadiene, and gibberellic acid (**45-47**). Hindered olefins in the pinane (**48**) and steroid (**49-50**) frameworks also undergo smooth cyclopropanations. In the latter, either enantiomer of the catalyst Ru**L1** 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.

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



Scheme 4. Synthesis of unrelated enantioenriched functionalized cyclopropanes *via* redox-active intermediates. See SI for experimental details.[32] [a]C-3 acetate cleaved. [b] Absolute configuration confirmed. [c] Yield of the cyclopropanation step. Yields are calculated on the isolated product. Bpin = boronic acid pinacol ester, 3-Quin = quinolin-3-yl; 3-Py = pyridin-3-yl, 2-Thiop = thiophen-2-yl, Cbz = benzyloxycarbonyl, Teoc = (2-(trimethylsilyl)ethoxycarbonyl), Alloc = allyloxycarbonyl, Fmoc = 9-fluorenylmethyloxycarbonyl.

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 accesible in one-step from feedstock alkenes using NHPI-DA (**13a**).

With these results in hand, we explored the valorization of simple feedstocks in the synthesis of relevant chiral cyclopropanes (Scheme 4b-d). As such, 5-bromopentene (**5f**) can be transformed in a three-step process into the enantioenriched cyclopropanol fragment **76** of the drug grazoprevir®.[27] *L*-allylglycine (**5g**) can be utilized to produce (*via* **77**) the cyclopropylamine fragment **78** of the bioactive natural product (+)-belactosin A (Scheme 4c).[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).[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[25b, 30] into the divinylcyclopropane natural product (–)-dictyopterene A (**83**).[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 (Ru**L1**). 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. The 2-step enantioselective formal transfer of carbenes **6-12** 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.

Keywords: Cyclopropane • Enantioselective catalysis • Redox-active • Diazocompound • Aliphatic Alkene

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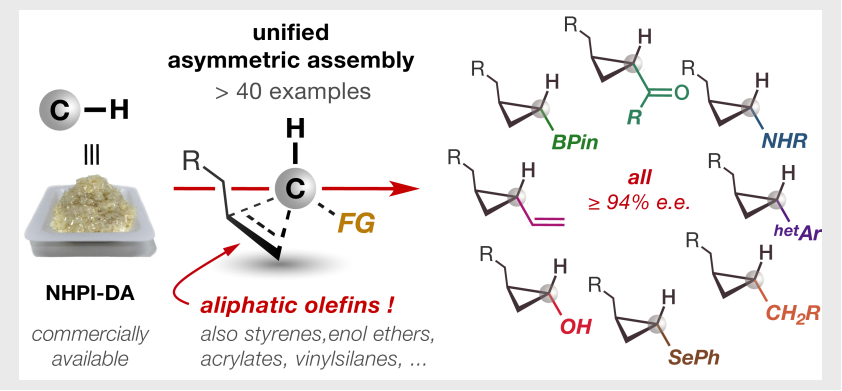

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General Cyclopropane Assembly via Enantioselective Transfer of a Redox-Active Carbene to Aliphatic Olefins

The asymmetric synthesis of cyclopropanes is currently designed using specific strategies that depend on the materials available and the final functionality of each target. In this communication, we present a comprehensive approach that engages simple feedstocks, including aliphatic olefins, with a single redox-active carbene precursor (NHPI-DA) that acts as a universal source of a chiral C–H unit.