Modular Enantioselective Synthesis of cis-Cyclopropanes through Self-Sensitized Stereoselective Photodecarboxylation with Benzothiazolines

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ABSTRACT: Chiral cis-cyclopropanes are strained rigid analogues of alkyl chains, whose study and application are limited by their difficult synthesis. A modular approach from olefin materials is enabled by the discovery of the electron donor−acceptor (EDA) interaction between 2-substituted benzothiazolines and N-hydroxyphthalimide esters. These complexes are activated by visible light without photocatalysts, and the benzothiazoline reagent plays a triple role as a photoreductant, a stereoselective hydrogen-atom donor, and a Brønsted acid. Beyond the enantioselective synthesis of cis-cyclopropanes, these results introduce benzothiazolines as accessible and easily tunable self-sensitized photoreductants.

KEYWORDS: redox-active carbene, EDA complex, photochemistry, cis-cyclopropanes, stereoselective decarboxylation, benzothiazoline

Cyclopropanes are central motifs in organic synthesis. They have been widely used in the field of medicinal chemistry to improve the properties of potential drug candidates due to their resistance toward metabolic degradation and their structural rigidity. As such, several enantioselective protocols have been developed over the years, mainly targeting the more thermodynamically and kinetically favored trans-cyclopropanes. In contrast, the synthesis of cis-cyclopropanes, an important class of stable and conformationally restricted alkyl chain analogues, remains a synthetic challenge with only a limited number of protocols being reported.

The asymmetric syntheses of these products require the preparation and derivatization of enantiopure (Z)-vinylboronates (Scheme 1B, top left) or complex catalytic systems employing transition metals or engineered proteins to obtain cyclopropyl esters. The complexity of these catalysts highlights the challenge to kinetically favor cis-cyclopropanes over their more stable trans diastereoisomers. Desirable catalytic approaches only offer limited scope or low diastereo- and enantioselectivity. In particular, the cis-cyclopropanation of alkenes employing benzylidenes is still problematic, due to the instability of the phenyldiazomethane precursors and the difficult tuning of the resulting reactive intermediates. Thus, current methodologies are mostly nonenantioselective, and the only asymmetric catalytic methods require specific allylic alcohol materials (Scheme 1B, bottom left). Seminal studies with chiral iron benzylidenes have also been reported but require stoichiometric chiral complexes and are limited in scope (Scheme 1B, right). Also, a diaastereoselective approach from the chiral pool has been demonstrated by a single example using the decarboxylation of a Barton ester. Nevertheless, this approach has not found further applications due to the long route to access chiral cyclopropyl Barton esters and the large excess of expensive tris(trimethylsilyl)silane required to trap the cis isomer of the cyclopropyl radical intermediate.

Recently, our group reported the use of redox-active diazoacetate reagents for the general enantioselective synthesis of cyclopropane building blocks from feedstock olefins. We envisioned that redox-active aryldiazoacetates could be used to convert olefins into cis-arylcylopropanes cis-4, by means of sequential asymmetric cyclopropanation and stereoselective decarboxylative reduction of the redox-active ester (RAE, 3; Scheme 1C). The cyclopropyl radical intermediates cis-A and trans-A are known to be σ-hybridized (pyramidal) and more electrophilic than conventional alkyl σ-radicals. Their stereoconversion is rapid even at extremely low temperatures (k_{\text{avg}} \approx 10^{8}−10^{9} \text{ s}^{-1}), and this results in thermodynamically controlled stereoselectivities. Thus, the feasibility of this

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methodology was contingent upon the design of a suitable hydrogen atom transfer (HAT) reagent that would kinetically control the reaction with the least populated (less stable) cis-cyclopropyl radical conformer (cis-Δ) in the equilibrium. In this respect, the high reactivity of cyclopropyl radicals15a further complicates the challenge to combine chemoselectivity (efficiency) and stereocontrol.

Initially, we evaluated known HAT reagents for the reduction of model substrate 3a (Table 1). It was found that the known nickel-catalyzed protocol,16 although highly diastereoselective, could only provide the desired cyclopropane cis-4a in low yields (entry 1). In contrast, chloroform17 could not afford high stereoselectivity (entry 2). The photoreductions using Hantzsch ester18 or N-butyl dihydropyridinamide (5b)19 recently developed by Shang et al.18a and our group19 were promising (entries 3 and 4), but further attempts to increase the yield or diastereoselectivity by tuning the diastereoisomer with a more sterically hindered hydrogen atom to impose a higher kinetic barrier in the HAT toward the undesired diastereoisomer trans-4a. 2-Substituted benzothiazolines (BTA, 6) have been used as alternative hydride sources to Hantzsch reductants or in reductive decarboxylative reactions, as far as we know. We explored several benzothiazolines in this context, finding promising results (entries 5–6) providing cis-4a in high stereoselectivity (entry 5) and yield (entry 6).

Table 1. Optimization of the Stereoselective Decarboxylative Reduction of Redox-Active Ester 3a*

| entry | HAT reagent (x equiv) | solvent | cis-4a (%) | d.r. (cis:trans) |
|-------|----------------------|---------|------------|-----------------|
| 1     | PhSiH3 (1.5 equiv)   | CHCl3 >100 | 90:10     |
| 2     | CHCl3 >100          | CHCl3   | 77:23     |
| 3     | 5a (1.2 equiv)      | DMSO    | 90:10     |
| 4     | 5b (1.2 equiv)      | DMSO    | 94:6      |
| 5     | 6a (1.2 equiv)      | DMSO    | 95:5      |
| 6     | 6b (1.2 equiv)      | DMSO    | 95:5      |
| 7     | 6c (1.2 equiv)      | DMSO    | nd        |
| 8     | 6d (1.2 equiv)      | DMSO    | 89:11     |
| 9     | 6e (1.2 equiv)      | DMSO    | 88:12     |
| 10    | 6f (1.2 equiv)      | DMSO    | 90:10     |
| 11    | 6a (1.2 equiv)      | DMSO <10 | 97:3      |
| 12    | 6b (1.2 equiv)      | DMSO    | nd        |

*See the Supporting Information for details. †Yields measured by 1H NMR using 1,1,2,2-tetrachloroethane as an internal standard. ‡Determined by GC-MS. §No light irradiation. (Reaction conditions: PhSiH3 (1.5 equiv), Zn (0.5 equiv), NiCl2(H2O)6 (10 mol %), 4,4′-di-t-Bu-2,2′-bipyridyl (20 mol %); Ti(OiPr)4/POH 10:2:1, 40 °C.) Also see Table S3 for details.
furnishing cis-diarylcyclopropanes 4b–1 in good yields and high enantio- and diastereoselectivities. Substitutions in various positions in the aromatic ring were tolerated. Interesting naphthyl (4i) and indolyl (4j) cyclopropanes could also be
generated with this protocol. The slightly lower stereo-selectivity observed in the tricyclic indene derivative \(4k\) may be explained by a slower stereoinversion equilibrium or the particular instability of the corresponding trisubstituted \(ciscyclopropyl\) radical intermediate. Divinylbenzene undergoes double \(ciscyclopropanation\) to afford the \(C_2\)-symmetric product \(4l\) as a single enantiomer in 43% yield over the four reactions performed in one pot. It is important to note that negligible erosion of stereoselectivity was observed for all reactions performed in one pot. It is important to note that negligible erosion of stereoselectivity was observed for all products relative to the intermediate cyclopropanes,\(^1^{14b}\) indicating that the stereochemical information is conserved throughout the photochemical reduction step. The photodecarboxylation can also proceed with aliphatic substrates, albeit with lower stereoselectivity (82:18)\(^2^{22}\) likely due to lower facial discrimination in the key HAT process. Further optimization of the benzothiazoline structure to address the limitation in this substrate class is ongoing in our laboratories. The modular nature of the NHPI-aryldiazoacetates allows for the asymmetric transfer of a variety of aromatic fragments. This way, olefin \(2a\) can be transformed into a number of \(ciscyclopropane\) products decorated with different functionalities (\(4m-u\)), which include pendant alkyne (\(4p\)), nitrile (\(4r\)), and ketone (\(4t\)) moieties. To further explore the synthetic potential of this system, we obtained a \(ciscyclopropane\)-modified phenylalanine amino acid (\(4u\)) in two steps from commercially available 4-iodophenylalanine. Moreover, the asymmetric total synthesis of the combretastatin A4 analogue \(4v\)\(^{30}\) was achieved in three steps starting from isovanillin (\(9\)) in 39% overall yield (Scheme 2B). To put these results in perspective, twice as many steps (including a resolution) were previously required to obtain this product in <10% overall yield from comparable materials.\(^3^{30}\)

The autonomous photoactivation of benzothiazoline \(6a\) was unexpected on the basis of the previously known reactivity of these systems based on HAT followed by proaromatic radical reduction with auxiliary photosensitization or chain carriers.\(^2^{21}\) Thus, photochemical studies were performed to investigate the mechanism of the photoreduction. UV–visible spectroscopy revealed that neither 2-phenylbenzothiazoline \(6a\) nor NHPI-ester \(3a\) absorb light effectively in the visible range (Figure 1A). Upon mixing, enhanced absorption in the visible range (450 nm) is observed, and a Job plot (Figure 1B) revealed that it is at a maximum when \(3a\) and \(6a\) are mixed in a 1:1 stoichiometry, suggesting that a bimolecular EDA complex\(^2^{23}\) absorbing at the LED irradiation wavelength is the dominant species in solution. Clearly defined excitation and emission features (\(\lambda_{\text{ex}} = 435 \text{ nm}; \lambda_{\text{em}} = 490 \text{ nm}\)) of the new EDA complex can also be detected by fluorescence (Figure 1C).

The formation of this species is further confirmed by time-correlated single photon counting (TCSPC), which allowed us to identify different fluorescence lifetimes for the benzothiazoline \(6a\) (\(\tau_0 = 1.7 \text{ ns}\)) and the EDA complex (\(\tau = 1.4 \text{ ns}\)). Stern–Volmer quenching studies performed by increasing the concentration of redox-active ester \(3a\) revealed an unconventional increase in the steady-state fluorescence intensity (see the Supporting Information), while the corresponding fluorescence lifetime remained constant (Figure 1D). This feature strongly supports a static quenching scenario through the formation of a more emissive bimolecular EDA complex, and it rules out dynamic processes involving the excited state of free benzothiazoline (\(6a\)) that would instead result in a concentration-dependent decrease in the observed fluorescence lifetime.

Despite our initial hypothesis, our results could also be explained by a fast stereoretentive hydrogen atom transfer (HAT). To explore this possibility, the diastereoisomer of the redox-active cyclopropane \(\textit{diast}-3a\) was independently synthesized and subjected to the reaction conditions (Scheme 3A). A
Scheme 3. Mechanistic Experiments and Model

A Stereoconversion experiment

B Deuteration experiments

C Mechanistic model

similar yield and stereoselectivity for the product cis-4a is observed, demonstrating that the stereoinversion equilibrium is faster than the HAT process and that the latter is kinetically controlled. This result opens the door for future stereoconvergent applications. In principle, benzothiazoline radical cations have two hydrogen atoms susceptible to undergo the convergent applications. In principle, benzothiazoline radical controlled. This result opens the door for future stereo-inversion equilibrium is faster than HAT (kinetic control).

405 nm LEDs, r.t., 16 h

87% 97:3 d.r.

Scheme 3 B. A deuterium incorporation experiments were carried out key HAT transfer. To assess their relative contribution, several cations have two hydrogen atoms susceptible to undergo the convergent applications. In principle, benzothiazoline radical controlled. This result opens the door for future stereo-inversion equilibrium is faster than HAT (kinetic control).

Diastereomeric ratios were determined by (a) GC-MS or (b) 1H NMR. See the Supporting Information for details. Diastereomeric ratios were determined by (a) GC-MS or (b) 1H NMR.

The data presented above supports the mechanism presented in Scheme 3C. Redox-active esters 3 and benzothiazoline 6 associate in solution to form the EDA complex 10, which undergoes photoinduced electron transfer (PET) in the excited state to form the radical ion pair 11. After fragmentation of the NHPI moiety with loss of CO2, the resulting cyclopropyl radical abstracts a hydrogen atom primarily from the benzylic C–H bond in the benzothiazoline radical cation (intermediate 12). The alternative HAT process through the N–H bond seems to have a secondary role. Either way, the cis-cyclopropane product 4 is kinetically preferred despite the higher energy of the cis-cyclopropyl radical in comparison to that of the alternative trans conformer (intermediate 12'). The HAT produces benzothiazole (13) and phthalimide (14) after an acid–base reaction of the phthalimide salt 15. The alternative possibility of the cyclopropyl radical undergoing HAT directly with the benzothiazoline 6 would result in radical chain reactions that can be ruled out on the basis of the quantum yield measurements. Remarkably, the benzothiazoline 6a has a triple role in this system as a self-sensitized single-electron photoreductant to promote the fragmentation of the redox-active ester, a sterically tuned hydrogen atom source to enhance stereoselectivity, and a proton source to neutralize the phthalimide anion byproduct.

In summary, a general and highly enantioselective method to obtain cis-diarylcyclopropanes from olefins and redox-active carbenes has been developed. This protocol allows for quick and modular access to ring-strained and conformationally strained compounds from available olefin materials, ultimately facilitating the synthesis of interesting bioactive molecules. These advances are bestowed by a new, efficient, and stereoselective photodecarboxylation driven by a novel EDA complex between redox-active esters and benzothiazoline reagents. The photophysical properties of the newly discovered system have been investigated, disclosing a new reactivity manifold of benzothiazolines as single-electron transfer reagents. Beyond enantiopure cis-cyclopropanes, these discoveries open the door for further progress in reductive decarboxylative reactions driven by benzothiazolines as a new platform to develop fine-tuned autonomous photoreductants.
**ASSOCIATED CONTENT**

**Supporting Information**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.1c03949.

Experimental procedures, characterization data, and mechanistic experiments (PDF)

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**Notes**

The authors declare no competing financial interest.

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