Modular Enantioselective Synthesis of *cis*-Cyclopropanes through Redox-Active Carbene Transfer and Stereoselective Photo-Decarboxylation

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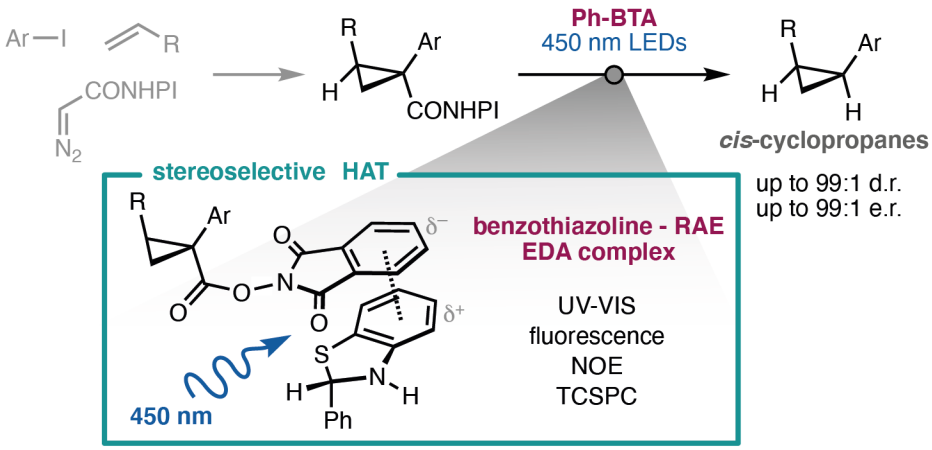


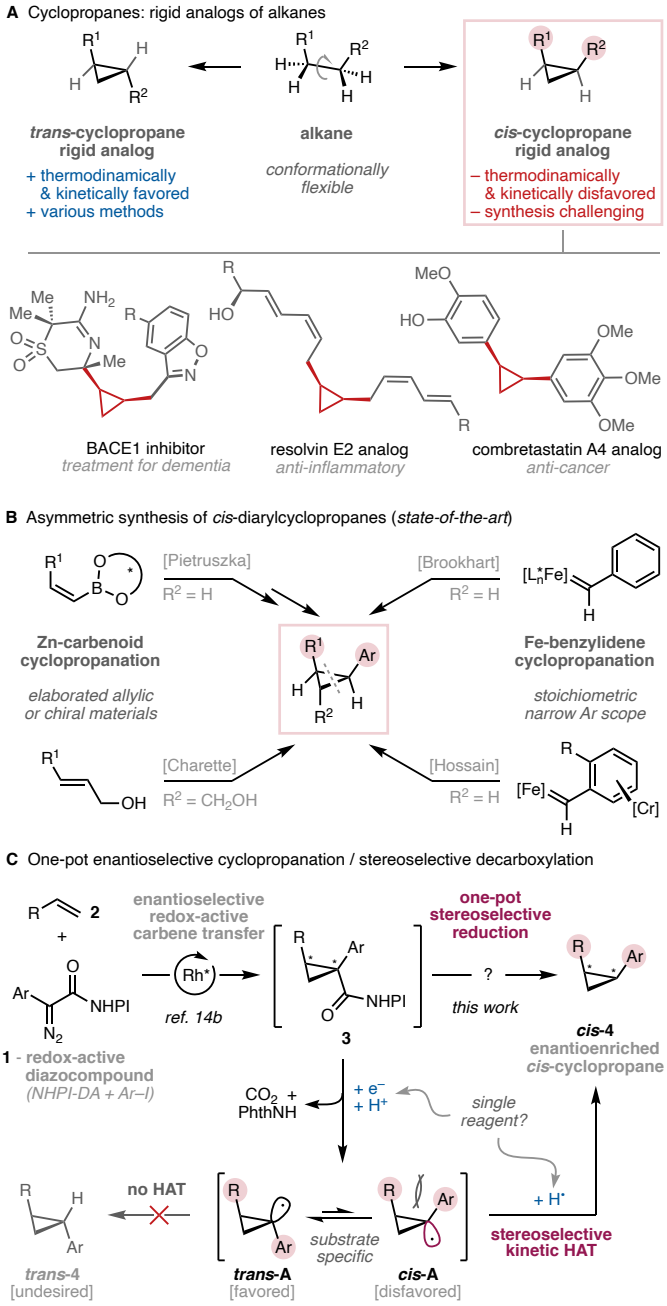
Abstract:

Chiral *cis*-cyclopropanes are strained rigid analogs of alkyl chains, whose study and application is still limited by their difficult synthesis. A modular approach for the synthesis of this challenging structures from abundant olefins is enabled by the discovery of the electron donor-acceptor (EDA) interaction between 2-substituted benzothiazolines and *N*-hydroxyphtalimide esters. These complexes are activated by visible light without photocatalysts. In this system, the benzothiazoline reagent plays a triple role as photoreductant, stereoselective hydrogen atom donor and Brønsted acid. Beyond the enantioselective synthesis of *cis*-cyclopropanes, these results introduce benzothiazolines as accessible and easily tunable self-sensitized photoreductants.

Main text:

Cyclopropanes are central motifs in organic synthesis.[1] They have been widely used in the field of medicinal chemistry to improve the properties of potential drug candidates due to their resistance towards metabolic degradation and their structural rigidity (**Scheme 1A**).[1c,2] As such, several enantioselective protocols have been developed over the years, mainly targeting the more thermodynamically and kinetically favored *trans*-cyclopropanes.[3] In contrast, the synthesis of *cis*-cyclopropanes, an important class of stable and conformationally restricted alkyl chain analogs,[1c,2a,4] remains a synthetic challenge with only a limited number of protocols reported.[5]

The asymmetric syntheses of these products require the preparation and derivatization of enantiopure *Z*-vinylboronates (**Scheme 1B**, top-left),[6] or complex catalytic systems employing transition metals[7] or engineered proteins.[8] The more desirable catalytic approaches only offer limited scope[9] or low diastereo- and enantioselectivity.[10] In particular, the *cis*-cyclopropanation of alkenes employing benzylidenes is still problematic, due to the instability of the phenyldiazomethane precursors and the difficult taming of the resulting reactive intermediates. Thus, current methodologies are mostly non-enantioselective,[11] and the only asymmetric catalytic methods require specific allylic alcohol materials (**Scheme 1B**, bottom-left).[12] Seminal studies with chiral iron benzylidene complexes have also been reported, but require stoichiometric chiral complexes and are limited in scope (**Scheme 1B**, right).[13] Also, a diastereoselective approach from the chiral pool has been demonstrated in a single example[5f] using the decarboxylation of a Barton ester with a large excess of tris(trimethylsilyl)silane to trap the *cis*-isomer of a cyclopropyl radical intermediate.

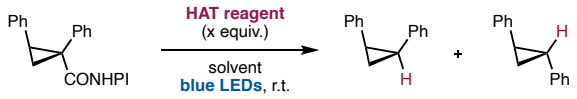


Scheme 1: Current methodologies towards chiral *cis*-cyclopropanes and our modular approach using redox-active carbenes and stereoselective decarboxylation.

Recently, our group reported the use of redox-active diazoacetate reagents for the general enantioselective synthesis of cyclopropane building blocks from feedstock olefins.[14] We envisioned that aryl-substituted redox-active diazoacetates **1** could be used to convert olefins **2** into *cis*-arylcyclopropanes **4**, by means of sequential asymmetric cyclopropanation and stereoselective decarboxylative reduction of the intermediate cyclopropyl redox-active ester (RAE) **3** (**Scheme 1C**). Given the higher stability of the *trans*-pyramidalized radical ***trans*-A**, the feasibility of this methodology was contingent upon the design of a suitable hydrogen atom donor that is able to kinetically favor the reduction of the less populated *cis*-conformer of the cyclopropyl radical ***cis*-A**. Ideally, the key HAT reagent should be easily tunable, accessible and autonomous at activating and controlling the stereoselective reduction to deliver a practical and general method.

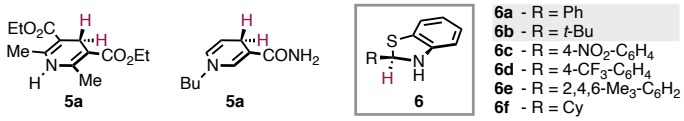
Initially, we evaluated known HAT reagents for the reduction of model substrate **3a** (**Table 1**). It was found that the known nickel-catalyzed protocol,[15] although highly diastereoselective, could only provide the desired cyclopropane ***cis*-4a** in low yields (entry 1). In contrast, chloroform[16] could not afford high stereoselectivity (entry 2). Exploration of the recently discovered photoreduction using *N*-substituted nicotinamides,[17] and Hantzsch esters,[18] was promising (entries 3,4), but further attempts to increase the yield or diastereoselectivity by tuning the structure of the dihydropyridines proved unsuccessful (see SI for details). On account of these results, we explored the possibility of employing a reductant with a more sterically hindered hydrogen atom. 2-Substituted benzothiazolines (BTA, **6**), have been used as an alternative hydride source to Hantzsch esters in transfer hydrogenation reactions.[19] More recently, these compounds have been used as hydrogen atom donors in photocatalytic reactions[20] requiring auxiliary thiyl radical carriers[20b] or metal photocatalysts.[20a] However, benzothiazolines have never been employed as self-sensitized photoreductants or in reductive decarboxylative reactions as far as we know. A screening of several benzothiazolines (entries 5-10) revealed their unforeseen potential for the desired transformation. In particular, phenyl- and *tert*-butyl-benzothiazolines **6a**,**b** (entries 5,6) provide optimal performance, whereas other substituents provide either lower yields or diastereomeric ratios (entries 7-10). Control experiments with the optimal reagents **6a,b** confirmed the need for blue light irradiation for efficient reduction (entries 11,12). These results introduce the benzothiazoline platform for the design of cheap, easy to handle, readily available and fine-tunable HAT reagents in reductive decarboxylative reactions without any auxiliary light harvesting or chain carrier systems.

Table 1: Optimization of the stereoselective decarboxylative reduction of redox-active ester **3a**.



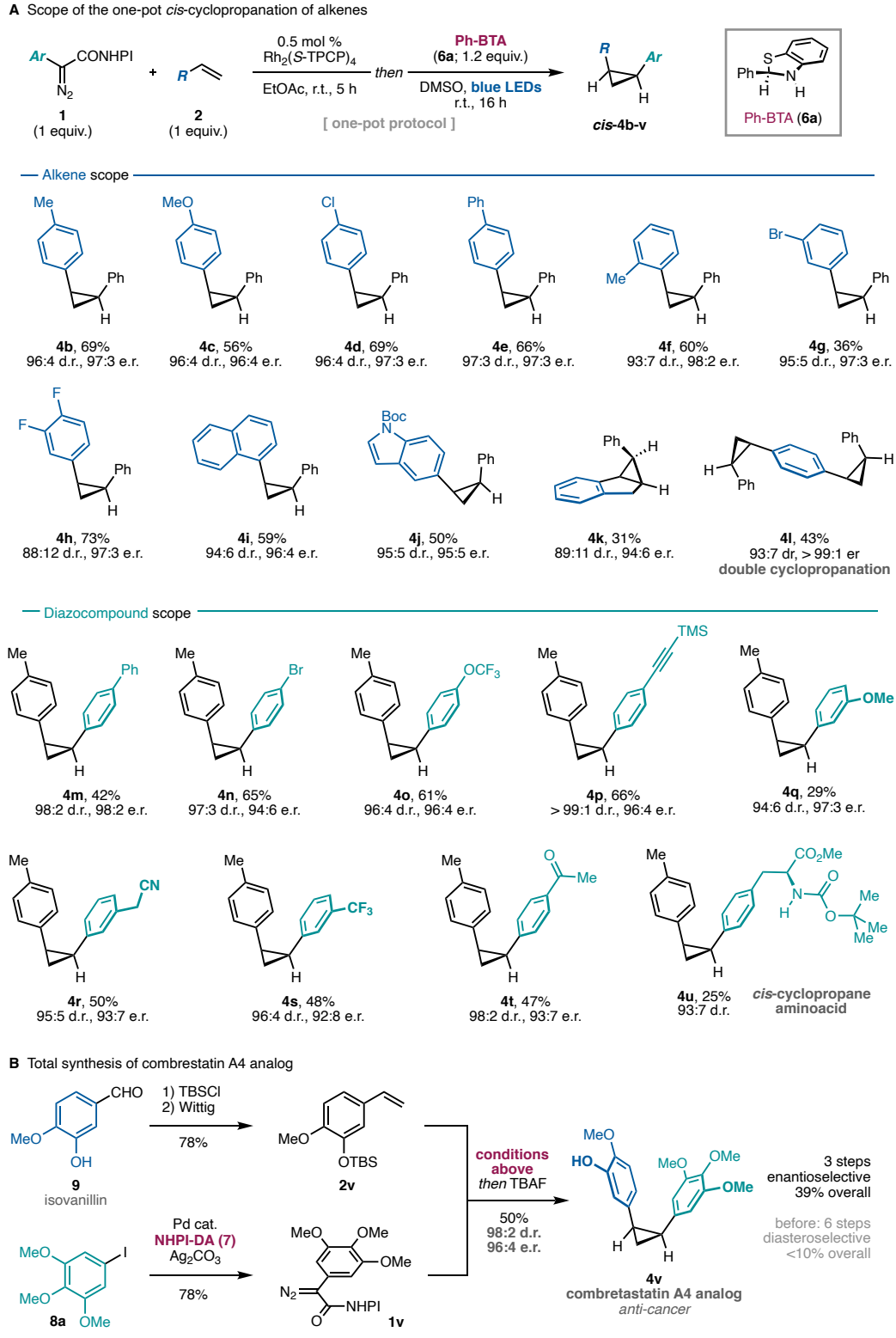
3a ***cis*-4a** **t*rans*-4a**

entry	HAT reagent	x (equiv.)	solvent	**4a** (%)[a]	d.r. (*cis*:*trans*)[b]
1[c,d]	$PhSiH_3$	1.5	THF:DMF:^{i}PrOH	30	90:10
2[e]	$CHCl_3$	> 100	$CHCl_3$	43	77:23
3	**5a**	1.2	DMSO	76	90:10
4	**5b**	1.2	DMSO	60	94:6
5	**6a**	1.2	DMSO	88	95:5
6	**6b**	1.2	DMSO	81	95:5
7	**6c**	1.2	DMSO	n.d.	-
8	**6d**	1.2	DMSO	92	89:11
9	**6e**	1.2	DMSO	54	88:12
10	**6f**	1.2	DMSO	44	90:10
11[c]	**6a**	1.2	DMSO	< 10	97:3
12[c]	**6b**	1.2	DMSO	n.d.	-



See SI for experimental details. [a]Yields measured by ^{1}H-NMR using 1,1,2,2-tetrachloroethane as an internal standard. [b]Diastereomeric ratio determined by GC-MS. [c]No light irradiation. [d]Reaction conditions: $PhSiH_3$ (1.5 equiv.), Zn (0.5 equiv.), $NiCl_2(H_2O)_6$ (10 mol%), 4,4'-di-*t*-Bu-2,2'-bipyridyl (20 mol%), THF:DMF:^{i}PrOH 10:2:1, 40 °C. [e]Reaction conditions: Et_3N (2 equiv.), 4CzIPN (2 mol%), $CHCl_3$.

The simplicity of the new photoreduction system allowed to telescope the cyclopropanation and stereoselective reduction in a one-pot method that deliver *cis*-cyclopropanes ***cis*-4** from olefins **2** and redox-active diazocompounds **1**. The latter are modularly synthesized from unsubstituted NHPI-DA (**7**) and aryl iodides **8** through a method previously developed in our group.[14b] The scope of the one-pot synthesis of *cis*-cyclopropanes was explored using the optimal benzothiazoline **6a**, which was easily prepared and stored in multi-gram amounts. For the initial cyclopropanation step, we adapted the recently reported conditions by our group[14b] using strictly stoichiometric amount of the olefin (1.0 equiv.) and shorter reaction time (5 h). As shown in **Scheme 2A**, electron-rich and electron-poor styrenes were tolerated in this transformation, furnishing *cis*-diarylcyclopropanes **4b-l** in good yields and high enantio- and diastereoselectivities. Substitution 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 stereoselectivity observed in the tricyclic indene derivative **4k**, may be explained by a slower stereo-inversion equilibrium or the particular instability of the corresponding trisubstituted *cis*-cyclopropyl radical intermediate. Divinyl benzene undergoes double *cis*-cyclopropanation 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 notice that negligible erosion of stereoselectivity was observed for all products relative to the intermediate cyclopropanes,[14b] indicating that the stereochemical information is conserved throughout the photochemical reduction step. 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 in a number of *cis*-cyclopropane products decorated with different functionalities (**4m-u**), that include pendant alkyne (**4p**), nitrile (**4r**), and ketone (**4t**) moieties. To further explore the synthetic potential of this system, we obtained a *cis*-cyclopropane-modified phenylalanine amino acid (**4u**) in two steps from commercially available 4-iodophenylalanine. Moreover, the asymmetric total synthesis of the combretastatin A4 analog **4v**[6a] was achieved in three steps starting from isovanillin in 39% overall yield (**Scheme 2B**). To put this results in perspective, twice as many steps (including a resolution) were previously required to obtain this product in < 10% overall yield from comparable materials.[6a]



Scheme 2: Scope studies and synthetic applications. Reactions conditions: **1** (1 equiv.), **2** (1 equiv.), Rh_2(*S*-TPCP)$_4$ (0.5 mol %), dry EtOAc (0.05 M), r.t., 5 h; then **6a** (1.2 equiv.), dry DMSO (0.1 M), blue LEDs (450 nm), r.t., 16 h. Isolated yields. Diasteromeric ratios determined by HPLC.

The autonomous photoactivation of benzothiazoline **6a** was unexpected based on the previously known reactivity of these systems based on HAT-transfer followed by pro-aromatic radical reduction with auxiliary photosensitization or chain carriers.[20] 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 maximum when **3a** and **6a** are mixed in a 1:1 stoichiometry, consistent with a bimolecular EDA complex[21] absorbing at the LED irradiation wavelength. Clearly defined excitation and emission features (λ_{max} = 435 nm; λ_{em} = 490 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 allow to identify different fluorescence lifetimes for the benzothiazoline **6a** (τ_0 = 1.7 ns) and the EDA complex (τ = 1.4 ns). Stern-Volmer quenching studies performed by increasing the concentration of redox-active ester **3a** revealed an unconventional raise in steady-state fluorescence intensity (see SI), while the corresponding fluorescence lifetime remains 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 of the observed fluorescence lifetime.

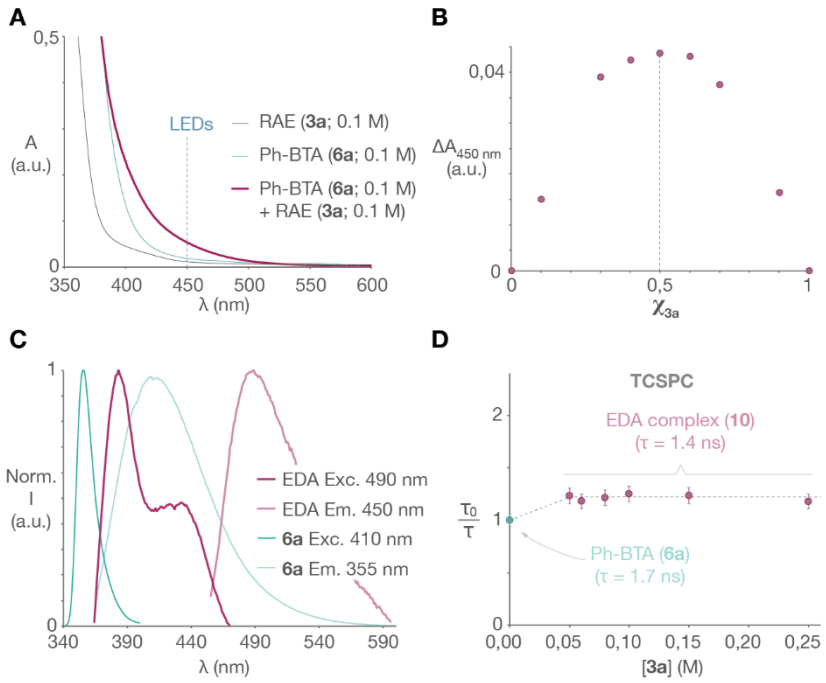
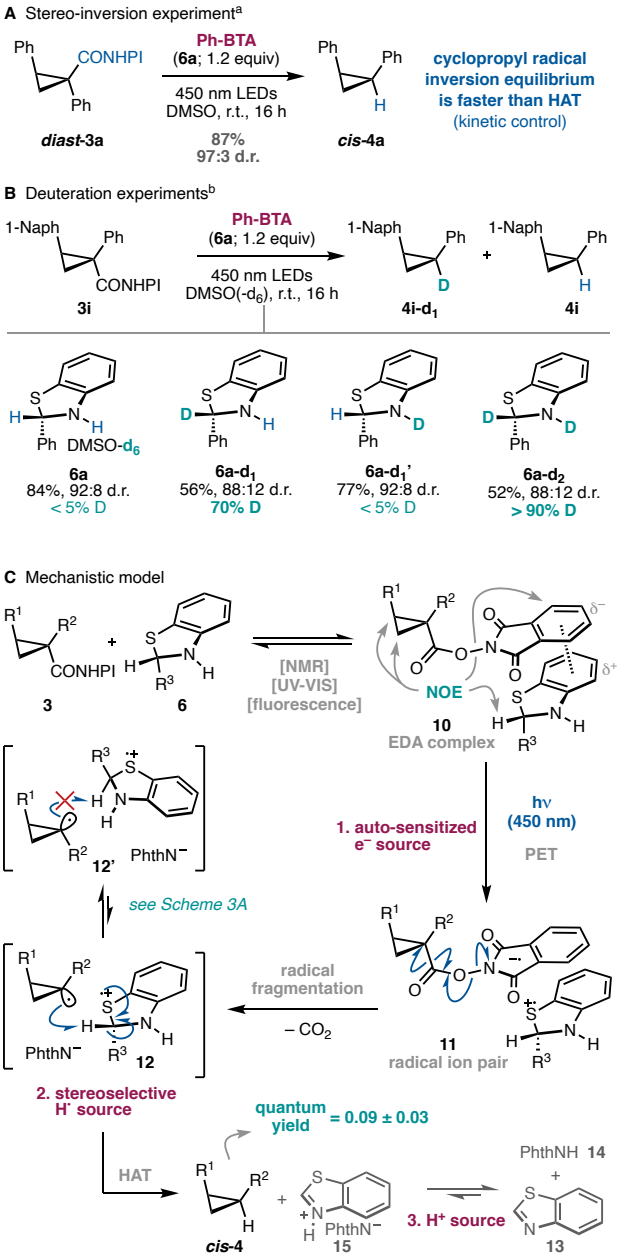


Figure 1: Photophysical characterization of the stereoselective photo-decarboxylation. (A) UV-visible spectrum of NHPI-ester **3a**, Ph-BTA (**6a**) and their 1:1 mixture. (B) Job plot of the mixture between **3a** and **6a** measured at 450 nm (c_{tot} = 0.1 M). (C) Normalized excitation and emission spectra of Ph-BTA (**6a**; 0.02 M) and its EDA complex (0.1 M) with NHPI-ester **3a**. (D) Lifetime Stern-Volmer plot of Ph-BTA **6a** (c = 0.1 M) with NHPI-ester **3a** (λ_{ex} = 450 nm).

Although we initially hypothesized that the diastereoselectivity would be kinetically controlled by the hydrogen atom transfer (HAT) process, our results could also be explained by a fast stereo-retentive HAT before stereo-inversion. To distinguish between these possibilities, the diastereoisomer of the redox-active cyclopropane ***diast*-3a** was independently synthesized and subjected to the reaction conditions (**Scheme 3A**). Similar yield and stereoselectivity for the product ***cis*-4a** is

observed, demonstrating that the stereo-inversion equilibrium is faster than the HAT process, and the latter is kinetically controlled. In principle, benzothiazoline radical cations have two hydrogen atoms susceptible of undergoing the key HAT transfer. To assess their relative contribution, several deuterium incorporation experiments were carried out (**Scheme 3B**). A first control experiment with DMSO-d_6 ruled out any relevant contribution from the solvent. The monodeuterated benzothiazoline at the benzylic carbon **6-d_1** resulted in 70% deuterium incorporation (56% yield), while the analogue deuterated in the N–H moiety led to < 5% isotopic labelling and higher efficiency (77% yield). These observations indicate that the benzylic C–H bond is the main hydrogen atom donor, but HAT from either the N–H moiety or the imine tautomer[22] of **6a** may have a secondary role. Indeed, the use of benzothiazoline **6-d_2** increased the degree of deuteration to >90%, thus accounting for the most relevant HAT processes. These results are consistent with the variable diastereoselectivities observed in the benzothiazoline screening (**Table 1**) with aliphatic (entries 6,10) and aromatic substituents (entries 5,8,9) of different size in the benzylic position, which affect the relative barriers of the HAT. Furthermore, the quantum yield of the reaction was determined to be 0.09 ± 0.03 (**Scheme 3C**), disfavoring the possibility of a radical-chain mechanism. This behavior contrasts with that of related dihydropyridine systems **5a,b**, operating through radical chain reactions.[17c,18e] The formation of the EDA complex was also directly observed by ^{1}H-NMR NOE experiments (see SI),[23] that clearly evidence the spatial proximity of **3a** and **6a** in their equimolar mixture in DMSO (**Scheme 3C**).



Scheme 3: Mechanistic experiments and model. See SI for details. [a]Diasteromeric ratios determined by GC-MS. [b]Diasteromeric ratios determined by ^{1}H 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 photo-induced electron transfer (PET) in the excited state to form the radical ion pair **11**. After fragmentation of the NHPI moiety with loss of CO_2, 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 than the alternative *trans*-conformer (intermediate **12'**). The HAT produces benzothiazole (**13**) and phtalimide (**14**) after acid-base reaction of the phthalimidate 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 based on the quantum yield measurements. Remarkably, the benzothiazoline **6a** has a triple role in this system as self-sensitized single-electron photo-reductant

to promote the fragmentation of the redox-active ester, sterically tuned hydrogen atom source to enhance stereoselectivity, and proton source to neutralize the phthalimidate anion by-product.

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- 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 photo-decarboxylation 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 photo-reductants.

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