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Strain-Inducing Positional Alkene Isomerization

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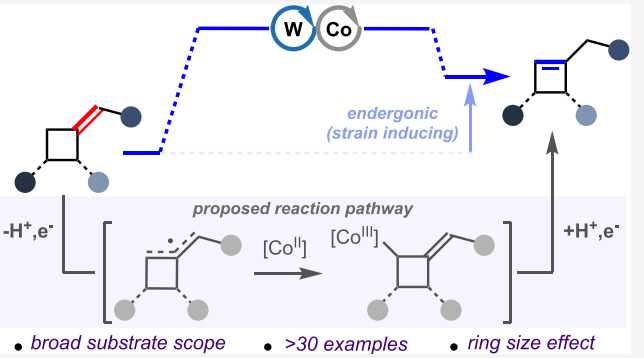
ABSTRACT: Small, strained ring systems are important pharmacophores in medicinal chemistry and versatile intermediates in organic synthesis. However, the kinetic and thermodynamic instability of many strained organic molecules renders them challenging to prepare. Here, we report a strain-inducing positional alkene isomerization reaction that provides mild and selective access to cyclobutene building blocks from readily obtained cyclobutylidene precursors. This endergonic isomerization relies on the sequential and synergistic action of a decatungstate polyanion photocatalyst and cobaloxime co-catalyst to store potential energy in the form of ring strain. The versatility of the cyclobutene products is demonstrated through diverse subsequent strain-releasing transformations. Mechanistic studies reveal a steric basis for strain-selective product formation.



INTRODUCTION

Strained ring systems possess unique chemical and physical properties arising from their distorted bond angles and the presence of destabilizing nonbonded interactions (e.g., eclipsing torsional angles and diaxial interactions).[1,2] In smaller ring systems, bond angle distortion is the principal contributor to strain energy, whereas nonbonded interactions dominate strain within larger, more flexible rings that can adopt conformations to minimize angular distortion. (Figure 1A). The thermodynamic instability of strained molecules is frequently correlated with kinetic instability, conferring enhanced reactivity in downstream "strain-releasing" reactions. The spring-loaded nature of strained rings compared with unstrained counterparts has been exploited in highly significant synthetic settings, including biorthogonal conjugation reactions,[3] ring-opening polymerizations,[4,5] and organic synthesis.[6−8] Medicinal chemists have further recognized the versatility of strained rings in molecular optimization campaigns, in which their rigidity, lipophilicity, metabolic stability, and distinct exit vectors are leveraged to fine-tune target structures.[9−11]

The synthesis of strained molecules poses significant thermodynamic and kinetic challenges,[12] as a large energetic input is required, and high-energy reactive intermediates (e.g., carbenes, nitrenes, and diradicals) are often necessary to forge strained bonds.[13,14] Strain-inducing steps are typically exergonic reactions driven by the irreversible formation of (co)products possessing strong bonds (e.g., N_2, CO_2, Si−F) or consumption of stoichiometric reagents (Figure 1B).[15,16] Lengthy synthetic sequences to preinstall latent reactive groups limit the overall efficiency of such approaches to strained rings.

An ideal synthesis of strained molecules would proceed through a catalytic, endergonic strain-inducing process starting from stable, readily accessible precursors and under mild reaction conditions. Such a transformation would avoid lengthy substrate preactivation but require an external energetic input and a catalytic strategy to harness and store potential energy in the form of ring strain. Photons are an ideal selective energy source, and photochemistry has been extensively employed to facilitate kinetic access to strained rings along exergonic reaction coordinates. However, photochemical strategies to form stained rings through otherwise endergonic processes are exceedingly rare.[17]

To assess the feasibility of this general strategy for strained ring synthesis, we targeted the synthesis of cyclobutene building blocks. Cyclobutenes comprise a core structural motif in many natural products and bioactive compounds,[18,19] and can be engaged in diverse strain-releasing transformations.[20−25] The synthesis of cyclobutenes most commonly involves [2 + 2] cycloaddition between an alkyne and a suitable alkenyl derivative.[26] Although exceptionally powerful in principle, this exergonic reaction suffers practical limitations, such as regioisomeric product formation, the requirement for specific preactivated coupling partners, and the formation of overly functionalized products (Figure 1C). General access to

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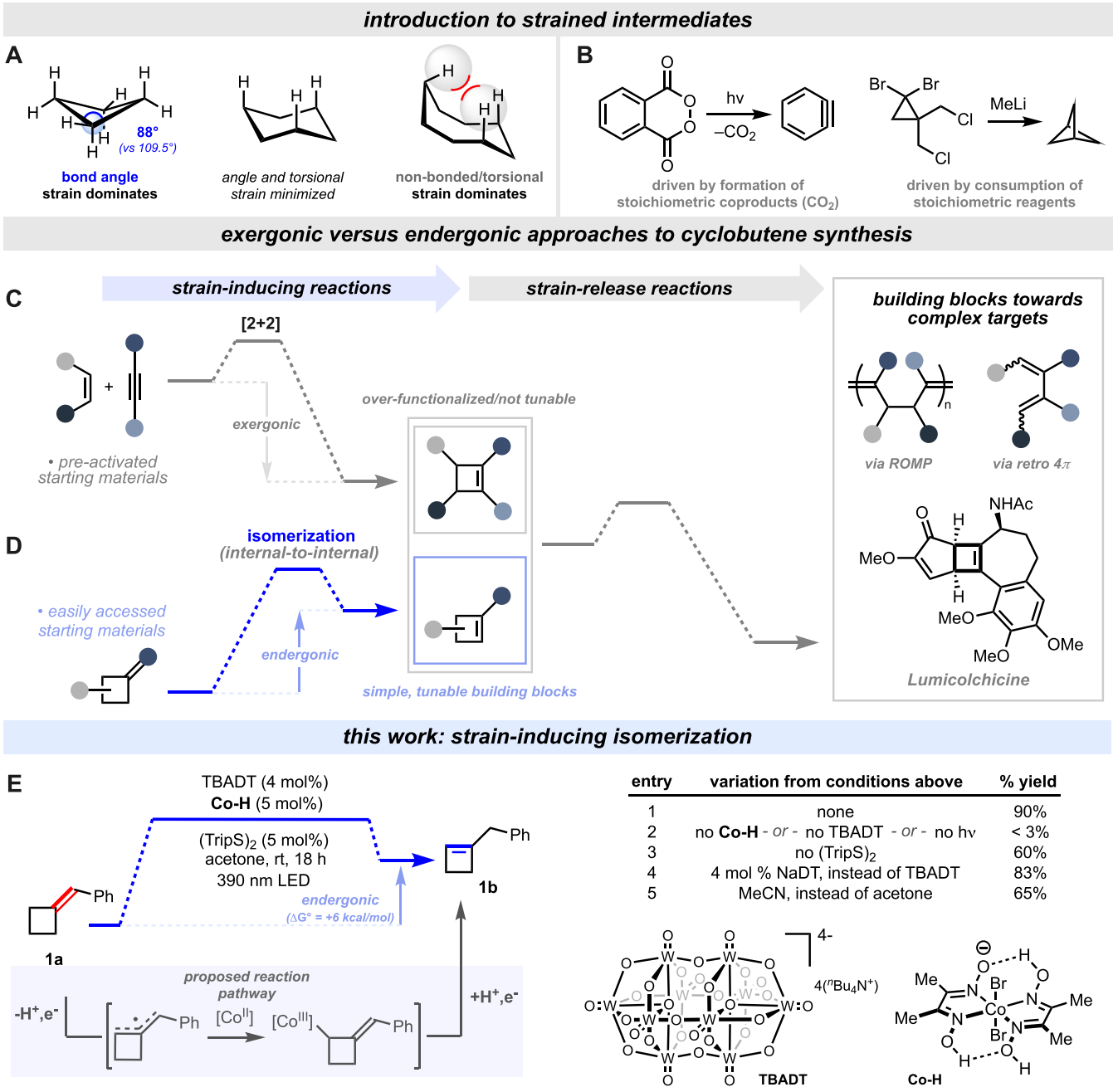

entry	variation from conditions above	% yield
1	none	90%
2	no **Co-H** - *or* - no TBADT - *or* - no hν	< 3%
3	no $(TripS)_2$	60%
4	4 mol % NaDT, instead of TBADT	83%
5	MeCN, instead of acetone	65%

Figure 1. Overview of strain-inducing reactions. (A) Different manifestations of strain in cyclic systems. (B) Representative examples of exergonic strain-inducing reactions. (C) Alkene/alkyne [2 + 2] approach to cyclobutene synthesis. (D) Proposed strain-inducing isomerization approach to cyclobutene synthesis. (E) Reaction optimization.

simple, minimally substituted cyclobutene building blocks remains an unsolved synthetic challenge.

We thus envisioned a complementary retrosynthetic logic for accessing cyclobutenes from the corresponding cyclobutylidene isomer via a strain-inducing positional alkene isomerization reaction (Figure 1D). In contrast to cyclobutenes, the lower energy exocyclic cyclobutylidene isomers can be readily obtained through olefination from a corresponding carbonyl precursor. Important precedents have established the feasibility of harnessing energy from photons for catalytic *contra*-thermodynamic positional olefin isomerization reactions that drive alkenes from internal-to-terminal positions,[27,28] and/or out of conjugation[29−31] in selected settings. *contra*-Thermodynamic product distributions can also be obtained in isomerizations powered by energy from stoichiometric reagents.[32−34] Despite these advances and the substantial development of acid- and transition metal-mediated thermal alkene isomerization reactions,[35−38] strain-inducing positional alkene isomerizations are exceedingly rare. More importantly, it remains unclear what factors could be leveraged to govern selectivity within *contra*-thermodynamic internal-to-internal isomerizations.

RESULTS AND DISCUSSION

We selected cyclobutylidene **1a** as a model substrate with which to test this proposal, envisioning a mechanism proceeding through allyl radical and allylcobaloxime intermediates (Figure 1E). The combination of cobaloxime[39] with

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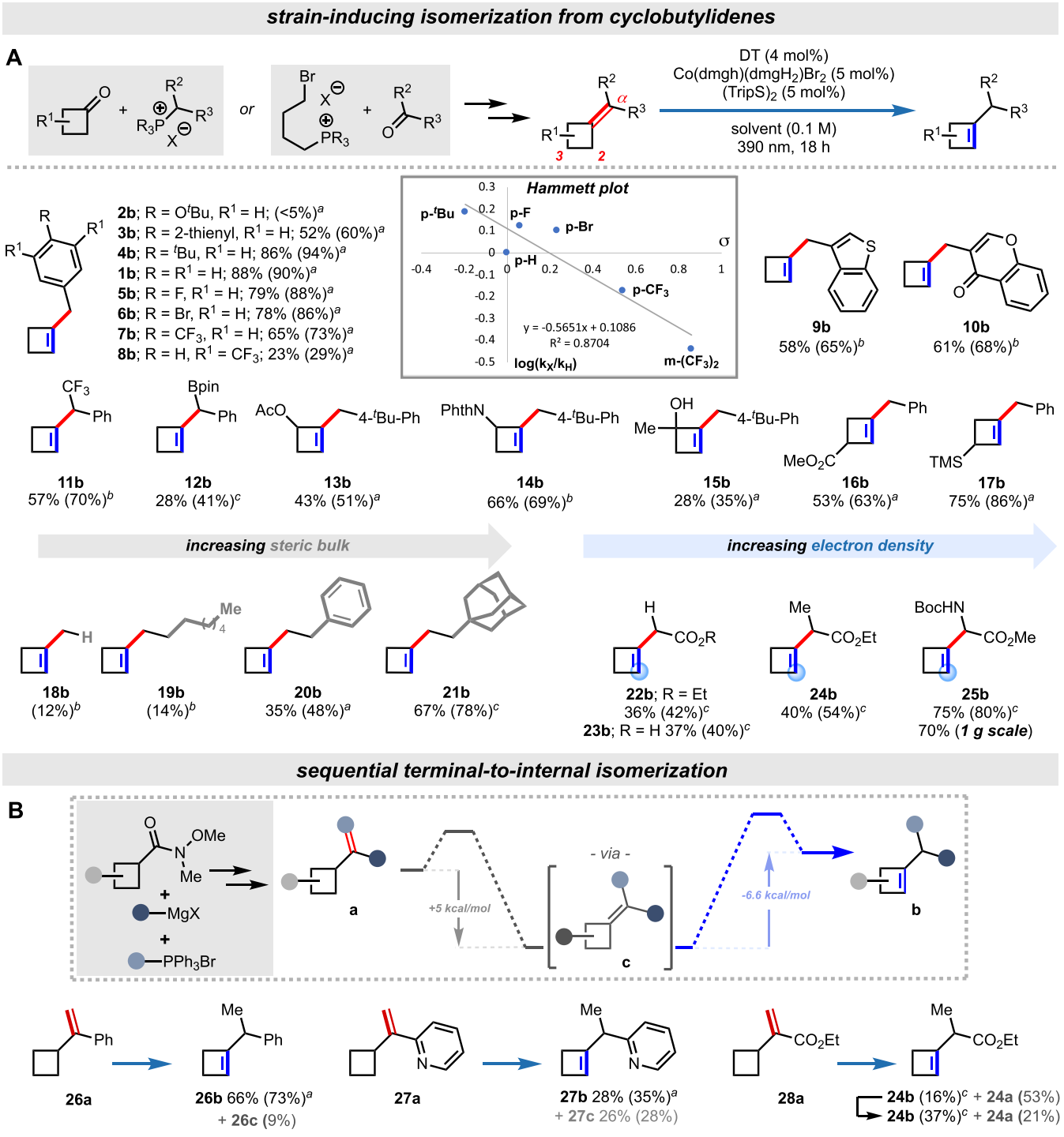

Figure 2. Substrate scope. (A) Strain-inducing isomerization to furnish cyclobutenes from cyclobutylidenes. (B) Sequential isomerization to access cyclobutenes from terminal methylenes. Reactions were performed on 0.1 to 0.5 mmol scale with 4 mol % DT with either $(^nBu_4)N^+$ counterions (TBADT) or Na^+ counterions (NaDT), 5 mol % $Co(dmgh)(dmgH_2)Br_2$ and 5 mol % $(TripS)_2$ under 390 nm LED irradiation at 23 °C in acetone (0.1 M) or MeCN (0.1 M) for 18 h. Isolated yields are the average of two runs. Yields in parentheses represent proton nuclear magnetic resonance (^1H NMR) yield determined with nitrobenzene as an external standard, before isolation. [a]Reaction was performed with TBADT in acetone as solvent. [b]Reaction was performed with NaDT in acetone as solvent. [c]Reaction was performed with TBADT in MeCN as solvent.

DT photocatalysts[40−43] has been found to operate synergistically in internal-to-terminal olefin isomerizations,[28] as well as in other transformations.[44,45] We observed the formation of higher energy isomer cyclobutene **1b** (ΔG_{calc} = +6 kcal/mol) in 90% yield under reaction conditions employing catalytic quantities of $(Bu_4N)_4W_{10}O_{32}$ (TBADT, 4 mol %), $Co(dmgh)(dmgH_2)Br_2$ (Co−H, 5 mol %), and 2,4,6-triisopropylbenzene disulfide ($(TripS)_2$, 5 mol %) in acetone at room temperature under near-UV (390 nm) light-emitting diode (LED) irradiation for 18 h (Figure 1E, entry 1). In the absence of TBADT, Co−H, or light, only trace isomerization was detected (Figure 1E, entry 2). Substitution of NaDT for TBADT, removal of $(TripS)_2$, or performing the reaction in

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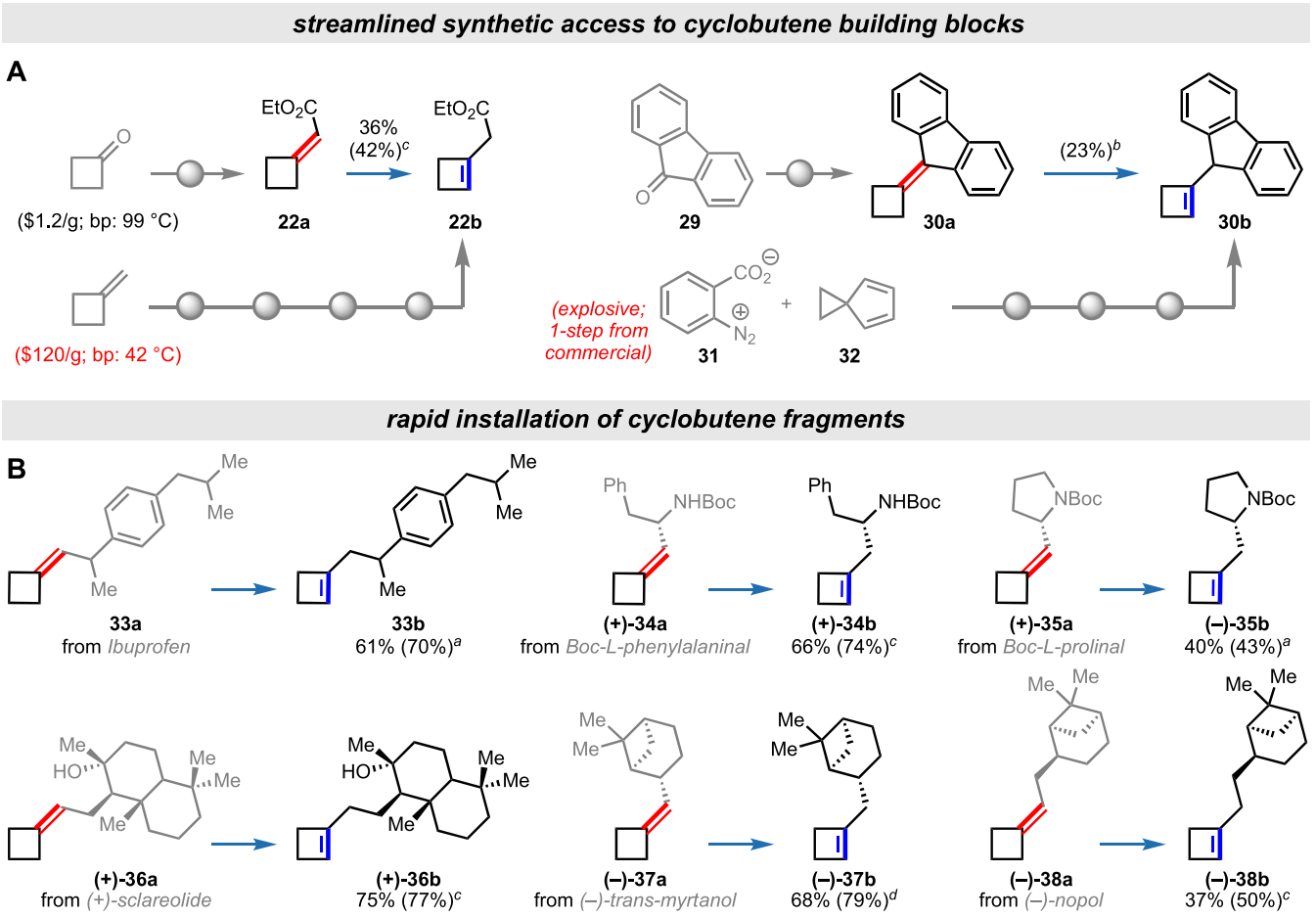

Figure 3. Substrate scope. (A) Streamlined synthesis of cyclobutene building blocks. (B) Rapid, late-stage installation of cyclobutene fragments into complex substrates. Reactions were performed on 0.1 to 0.5 mmol scale with 4 mol % DT with either $(^nBu_4)N^+$ counterions (TBADT) or Na^+ counterions (NaDT), 5 mol % Co(dmgh)(dmgH$_2$)Br$_2$ and 5 mol % (TripS)$_2$ under 390 nm LED irradiation at 23 °C in acetone (0.1 M) or MeCN (0.1 M) for 18 h. Isolated yields are the average of two runs. Yields in parentheses represent proton nuclear magnetic resonance (^{1}H NMR) yield determined with nitrobenzene as an external standard, before isolation. [a]Reaction was performed with TBADT in acetone as solvent. [b]Reaction was performed with NaDT in acetone as solvent. [c]Reaction was performed with TBADT in MeCN as solvent. [d]Reaction was performed with NaDT in MeCN as solvent. Prices were obtained from Combi-Blocks and Sigma-Aldrich (Aug 2023).

acetonitrile resulted in decreased reaction yields (Figure 1E, entries 3−5).

A range of cyclobutylidene substrates were evaluated under these conditions to assess the scope and limitations of the strain-inducing alkene isomerization (Figure 2A). The synthetic practicality of this method derives from the simplicity of accessing the substrates via Wittig olefination from cyclobutanones or corresponding ketones. Aryl cyclobutylidene substrates featuring both electron-donating and electron-withdrawing substituents reacted to form 1-substituted cyclobutenes **3b**−**8b** in moderate-to-good yields. A linear correlation with a small negative slope (ρ = −0.6, R^2 = 0.87) between Hammett σ constants and log(k_X/k_H) was observed (where k_X and k_H are the rates of the substituted and unsubstituted substrates obtained from a series of competitive experiments) with these substrates. Although these data reveal the preferential reactivity of substrates bearing electron-donating substituents, diminished reaction yields were observed for some electron-rich substrates, such as **2a**, **3a**, and **9a**. Substrates bearing substitution at the α-, 2-, and 3-positions were found to undergo isomerization in moderate-to-good yields (**11b** to **17b**). The presence of acetate or phthalimide in the 2-position led to perfectly regioselective isomerization to form **13b** and **14b**, respectively. However, regioisomeric mixtures were obtained when cyclobutylidenes bearing alkyl or aryl substituents in the 2-position were employed as substrates (See the Supporting Information). Alkyl- and carboxyester-substituted cyclobutylidene substrates were also evaluated. Improved reaction yields were obtained when (a) the steric profile of α-alkyl substituents was increased (**18b**−**21b**), and (b) electron-donating substituents were introduced into carboxyester-cyclobutenes (**22b**−**25b**). The reaction to form cyclobutene **25b**, a potentially intriguing unnatural amino acid derivative, was carried out on a 1 g scale, with no impact on the outcome (70% isolated yield of **25b**).

We next assessed the feasibility of sequential isomerization events to furnish 1-cyclobutene products from cyclobutane starting materials possessing a terminal methylene motif (Figure 2B). Synthetically, such substrates are conveniently prepared from a cyclobutyl Weinreb amide and a suitable Grignard reagent. Under standard reaction conditions, cyclobutane **26a** reacted to form cyclobutene **26b** in 73% yield along with intermediate **26c** in 9% yield. The yield of desired 1-cyclobutene isomer was significantly decreased by the presence of electron-withdrawing groups, resulting in stagnation at the cyclobutylidene intermediate (c.f. **27a** to **27b**/**c** and

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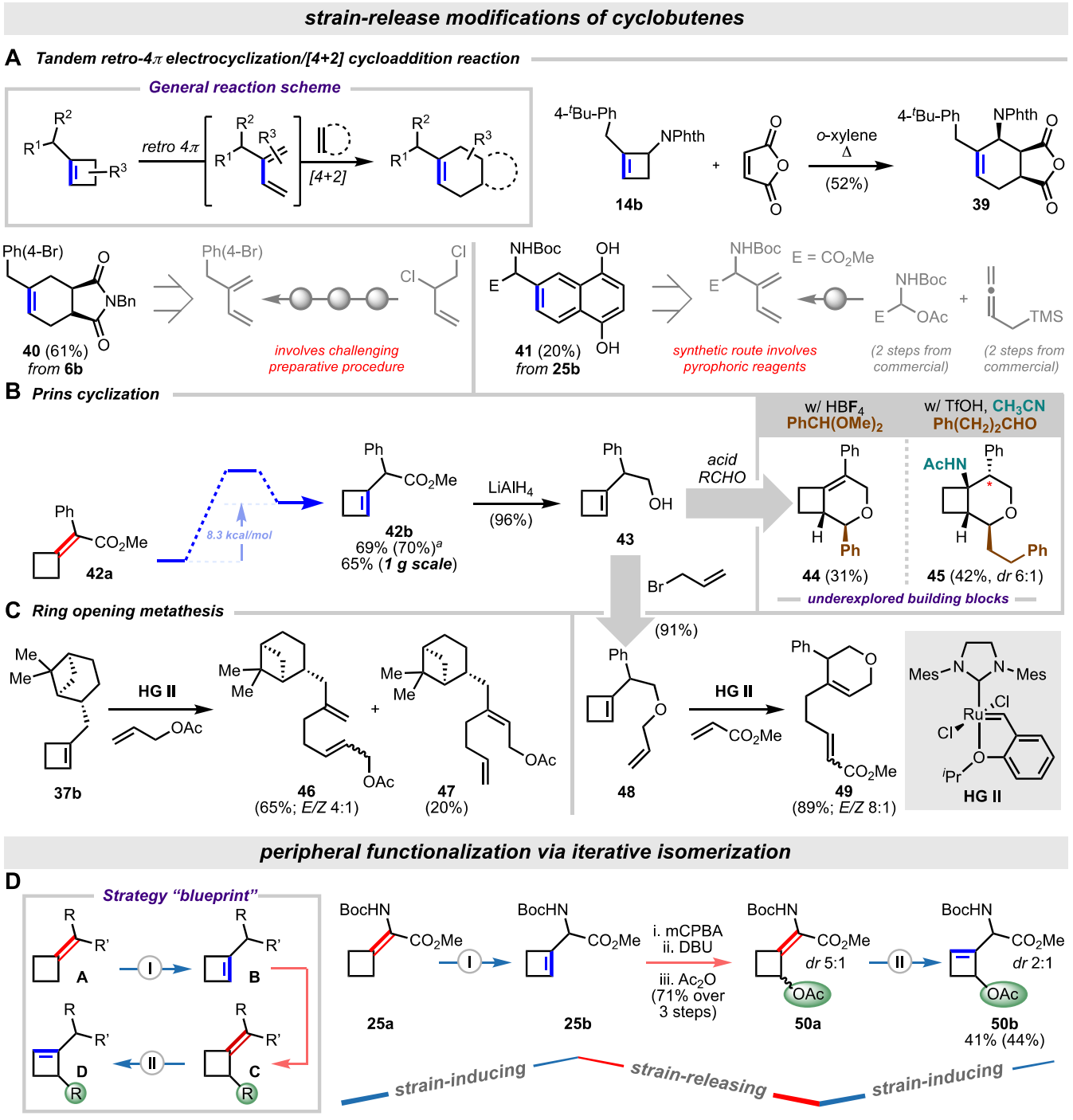

Figure 4. Strain-release-driven transformations of cyclobutenes. (A) Tandem retro-4π/[4 + 2] sequence. (B) Prins cyclization. (C) Ring-Opening Metathesis. (D) Iterative isomerization approach to peripheral functionalization. [a]The reaction was performed with NaDT in acetone as solvent under otherwise standard conditions. Proton nuclear magnetic resonance (^{1}H NMR) yield was determined to be 70% using nitrobenzene as an external standard, before isolation.

28b to **24b**/**24a**). However, improved yields of the cyclobutene isomer could be obtained following resubjection of the product mixture to the standard reaction conditions.

The structural simplicity of the minimally substituted cyclobutene building blocks accessed using this method belies their synthetic complexity. For example, a previous synthesis of cyclobutene carboxyester **22b** was accomplished in 4 steps from methylenecyclobutane, which is challenging to prepare due to its volatility and high cost to source from commercial suppliers (Figure 3A).[46] Likewise, cyclobutene **30b** was previously obtained through a four-step sequence commencing from explosive and expensive starting materials.[47] By employing a strain-inducing isomerization step, both **22b** and **30b** can be accessed in only two steps from inexpensive commercial starting materials, cyclobutanone and fluorenone, respectively, and with substantial improvements to the overall atom economy of the synthetic sequence (Figure 3A).

We prepared a series of cyclobutylidene substrates from aldehydes derived from (±)-ibuprofen (**33a**), amino acid derivatives (**34a** and **35a**), and common chiral pool terpene

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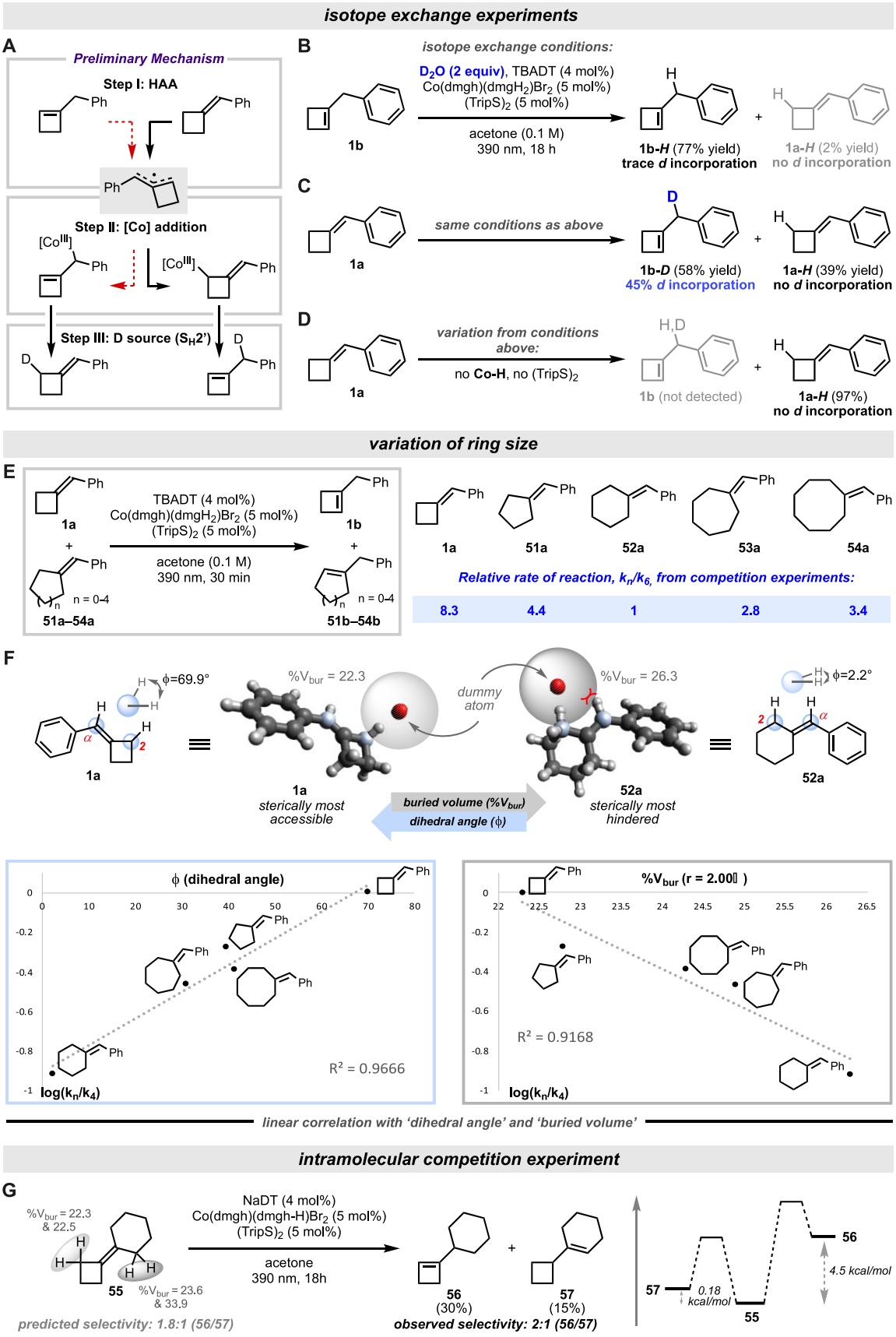

Figure 5. Mechanistic studies. (A) Simplified mechanistic pathway involving allyl radical and allylcobaloxime(III) intermediates. (B–D) Isotope exchange experiments. (E) Intermolecular competition experiments employing substrates with varying ring sizes. (F) Free energy relationships relating steric descriptors to relative reaction rates. (G) Intramolecular competition experiment.

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building blocks (**36a**−**38a**) in order to illustrate the simplicity with which cyclobutenyl groups can be installed into more complex substrates (Figure 3B). Corresponding 1-cyclobutene products **33b**−**38b** were obtained in good yields, with no detectable epimerization or racemization of existing stereocenters (See the Supporting Information).

We next sought to showcase the versatility of the 1-cyclobutene products in diverse strain-releasing transformations (Figure 4A). Bicyclic compounds **39**−**41** were obtained directly from the parent cyclobutene through a retro-4π electrocyclization/[4 + 2] cycloaddition domino reaction sequence carried out in xylenes at 160 °C. In these examples, cyclobutenes are convenient precursors to substituted 1,3-dienes, which are otherwise challenging to prepare and involve undesirable synthetic sequences. For comparison, a previous synthetic route to access the diene precursor to **40** proceeds through chloroprene, which is both toxic and challenging to handle;[48] similarly, the diene precursor to **41** is generated through a less step-economical sequence requiring pyrophoric reagents in multiple steps.[49] We next envisioned that Prins-type cyclizations could be employed to enable rapid construction of structurally complex and underexplored bicyclic scaffolds (Figure 4B). To explore this possibility, **42b** was obtained from **42a** in 69% isolated yield (65% yield on 1 g scale), despite significant destabilization of the product isomer relative to starting **42a** (ΔG°_{calc} = +8.3 kcal/mol). Reduction of **42b** led to the quantitative formation of cyclobutene alcohol **43**, which reacted with benzaldehyde dimethyl acetal and HBF_4 in dichloromethane to form **44** as a single diastereomer (31% yield). An analogous product, **45**, was obtained in 42% yield through a tandem three-component Prins−Ritter reaction with hydrocinnamaldehyde in acetonitrile.[50] We then examined the susceptibility of 1-substituted cyclobutenes for ring-opening metathesis (Figure 4C).[51] While exploratory work has previously revealed the feasibility of employing selected 1-cyclobutenes as ROMP monomers, poor synthetic accessibility has limited the exploration of this class of substrate in materials synthesis.[52] Using HG-II conditions, cyclobutene **37b** reacted to form a 3:1 regioisomeric ratio of dienes **46** and **47** in 85% overall yield; allylated cyclobutene **48** underwent a regioselective ring-opening/cross metathesis with methyl acrylate to provide dihydropyran **49** in 89% yield.

Lastly, we envisioned that an iterative isomerization/functionalization sequence could enable rapid peripheral derivatization of cyclobutene products (Figure 4D, "blueprint"). To assess the feasibility of this approach, we prepared cyclobutene **25b** from **25a** using standard isomerization conditions. Subsequent epoxidation, ring opening, and acetate protection resulted in the formation of cyclobutylidene **50a** in 71% yield overall. A second regioselective isomerization was then carried out to furnish the densely functionalized cyclobutene (**50b**) in 41% isolated yield. Energetically, this sequence alternates between strain-inducing and strain-releasing transformations to rapidly introduce functionality in a controlled manner at circumferential sites of the cyclobutane core.

A simplified mechanistic pathway for isomerization is outlined in Figure 5A, involving (i) generation of an allyl radical, (ii) formation of an allylcobaloxime(III) intermediate, and (iii) proton and electron transfer to form the cyclobutene product. The reaction of alkenes with decatungstate photocatalyst has been proposed to lead to the formation of allyl radical intermediates via a charge-transfer mechanism: single electron oxidation of the alkene by the DT relaxed excited state (**wO**) forms an alkene radical cation/$W_{10}O_{32}^{5-}$ ion pair, followed by deprotonation or proton/electron transfer to generate the allyl radical with formation of $(H^+)W_{10}O_{32}^{5-}$ or $W_{10}O_{32}^{4-}$, respectively.[53−55] Subsequent reduction of allyl radical by cobaloxime(II) could form allylcobaloxime (III) intermediate,[56] which can lead to the formation of an isomeric olefin product following proton and electron transfer.[28]

We performed a series of isotope exchange experiments to gather insight into the basis for selectivity. Product **1b** was resubjected to standard reaction conditions in the presence of 2.0 equiv of D_2O (Figure 5B). After 18 h, 77% of **1b** was recovered along with trace **1a** (2% yield), with no detectable deuterium atom incorporation into either species. A similar isotope exchange experiment was carried out using **1a** as the starting material (Figure 5C). After 1 h, 58% **1b** was observed with 45% *d*-incorporation product into the benzylic methylene; no *d*-incorporation was detected in the 39% recovered starting material **1a**. Collectively, these experiments suggest that both radical generation and formation of allylcobaloxime(III) are selective for the formation of the cyclobutene isomer. A final isotope exchange experiment was carried out using **1a** as a substrate but in the absence of cobaloxime co-catalyst (Figure 5D). After 18 h, 97% **1a** was recovered, with no detectable *d*-incorporation and with no formation of **1b**, suggesting that Co−H may play a synergistic role in the DT-mediated formation of allyl radical (See the Supporting Information).

To probe these steps further and to build a predictive model for reactivity and selectivity, we explored the impact of ring size on the selectivity and efficiency of isomerization (Figure 5E). Although parent cyclobutylidene **1a** reacted to form **1b** in 90% yield, larger cycloalkylidenes **51a**−**54a** were poor substrates under the standard reaction conditions: moderate yields (36−52%) of 5-, 7-, and 8-membered cycloalkenes **51b**, **53b**, and **54b** were obtained, and only 17% yield cyclohexene **52b** was formed from the reaction of cyclohexylidene **52a** (See the Supporting Information). Relative reaction rates for these substrates were determined from a series of intermolecular competition experiments conducted between **1a** and each other cycloalkylidene substrate (**51a**−**54a**), and followed a similar general trend as reaction yields. Cyclobutylidene **1a** was consumed 2−3× faster than the corresponding 5,7, and 8-membered cycloalkylidenes, and >8× faster than cyclohexylidene **52a** (Figure 5E).

A linear correlation (R^2 = 0.966) between the Cα-C2 dihedral angle ϕ and $\log(k_n/k_4)$ was observed (where k_n and k_4 are the rates of the larger ring and 4-membered ring substrates). Dihedral angle was obtained from energy-minimized structures of each cycloalkylidene, and correlates intuitively with minimization of the steric environment around the allylic C2−H bond (Figure 5F). To further simulate the steric environment around the allylic C−H bond, we calculated the percent buried volume (%V_{bur}) determined around a 'dummy atom' 2.58 Å from the C_2 atom.[57] Similar linear correlation (R^2 = 0.9168) was observed between $\log(k_n/k_4)$ and %V_{bur}. In contrast, poor linear correlation was observed between $\log(k_n/k_4)$ and the experimentally determined electrochemical potential of the substrate, or ΔG°_{calc} (See the Supporting Information).

To test the predictive model, we carried out an analogous intramolecular competition experiment using substrate probe **55** (Figure 5G). Under the standard reaction conditions, **55** reacts to form cyclobutene **56** and cyclohexene **57** in a 2:1

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ratio, which closely parallels the predicted 1.8:1 (**56**/**57**) relative rate of radical formation obtained from the difference in calculated $\%V_{bur}$ at the allylic positions (See the Supporting Information). Collectively, these free energy relationships support a steric model for product selectivity, aligned with well-established steric preferences in decatungstate-mediated[58] and organocobaloxime-mediated[59,60] steps, respectively. If this hypothesis is correct, the increased angular strain in the final cyclobutene isomer can be attributed to product-selective steps that leverage the inherently minimal nonbonded (steric) interactions in the starting cyclobutylidene isomer.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.3c06935.

Materials and methods; experimental procedures; product isolation and characterization information; UV−vis spectroscopic data of TBADT and NaDT; and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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