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Catalytic, *contra*-Thermodynamic Positional Alkene Isomerization

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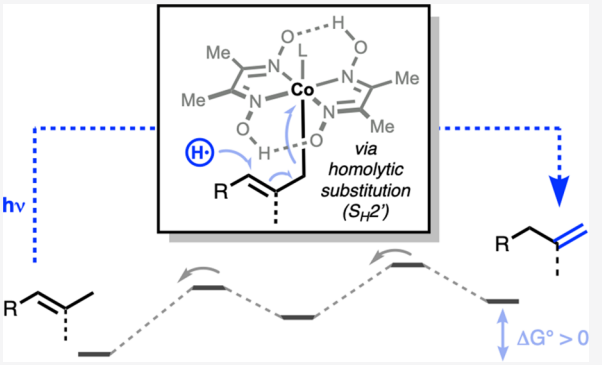
ABSTRACT: The positional isomerization of C=C double bonds is a powerful strategy for the interconversion of alkene regioisomers. However, existing methods provide access to thermodynamically more stable isomers from less stable starting materials. Here, we report the discovery of a dual catalyst system that promotes *contra*-thermodynamic positional alkene isomerization under photochemical irradiation, providing access to terminal alkene isomers directly from conjugated, internal alkene starting materials. The utility of the method is demonstrated in the deconjugation of diverse electron-rich/electron-poor alkenes and through strategic application to natural product synthesis. Mechanistic studies are consistent with a regiospecific bimolecular homolytic substitution (S_H2') mechanism proceeding through an allyl-cobaloxime intermediate.



INTRODUCTION

Alkenes are versatile chemical building blocks which can be readily transformed into diversely functionalized products. The positional isomerization of C=C double bonds enables the interconversion of alkene regioisomers, providing spatial control over downstream functionalization steps.[1] Positional alkene isomerization reactions can be promoted by diverse transition metal catalysts through metal hydride or π-allyl pathways involving radical or polar intermediates (Figure 1A).[2,3] Product selectivities can be governed by either thermodynamic or kinetic factors (Figure 1B), and conditions enabling long-range chain-walking,[4,5] monopositional isomerization,[6−8] and/or selective access to (*E*)-configured[9] or (*Z*)-configured[10] products have been developed.

Despite these achievements, general catalytic methods to promote the *contra*-thermodynamic positional isomerization of alkenes are underdeveloped. Thermal isomerization methods form more stable products (e.g., internal or conjugated alkenes) starting from less stable starting isomers (e.g., terminal or unconjugated alkenes). This limitation arises due to the significant thermochemical bias favoring the formation of (hyper)conjugated internal isomers from terminal or unconjugated starting materials, in conjunction with thermal catalytic mechanisms that proceed through microscopically reversible elementary steps. Alternative strategies to access terminal or deconjugated isomers from internal or conjugated starting materials involve multistep oxidation−reduction or deprotonation−protonation sequences coupled to the consumption of stoichiometric reagents; harsh and/or unselective reaction conditions limit the application of such tools in complex settings. Remote functionalization strategies can also deliver products arising from *contra*-thermodynamic isomerization by coupling reversible chain-walking isomerization with an irreversible terminal-selective functionalization step.[11−13] However, this approach has not yet been broadly integrated with diverse functionalization reactions, and subsequent defunctionalization steps are needed to restore the terminal alkene product, when desired.[14,15] Most often, terminal and unconjugated alkenes are prepared *de novo* through the olefination of carbonyl equivalents, commonly driven by the formation of transition metal/main group oxides.[16]

Photochemistry offers opportunities to promote *contra*-thermodynamic isomerization reactions by providing access to irreversible elementary steps via excited electronic states and/or by introducing thermochemical biases that enable endergonic product formation.[17−19] An extensive exploration of photostationary effects has led to the development of robust tools that promote *contra*-thermodynamic geometrical (*E*)/(*Z*)-alkene isomerizations,[20−22] yet only isolated examples of related deconjugation-driven positional alkene isomerization have been disclosed. For example, the isomerization of certain α,β-unsaturated carbonyl compounds to β,γ-isomers has been achieved under 254 nm irradiation via a vinylogous Norrish type II pathway.[23−26] Conversely, selected styrenyl substrates can deconjugate under strongly oxidizing, electron-transfer-initiated conditions.[27−29] While these precedents establish a conceptual framework through which alkene deconjugation

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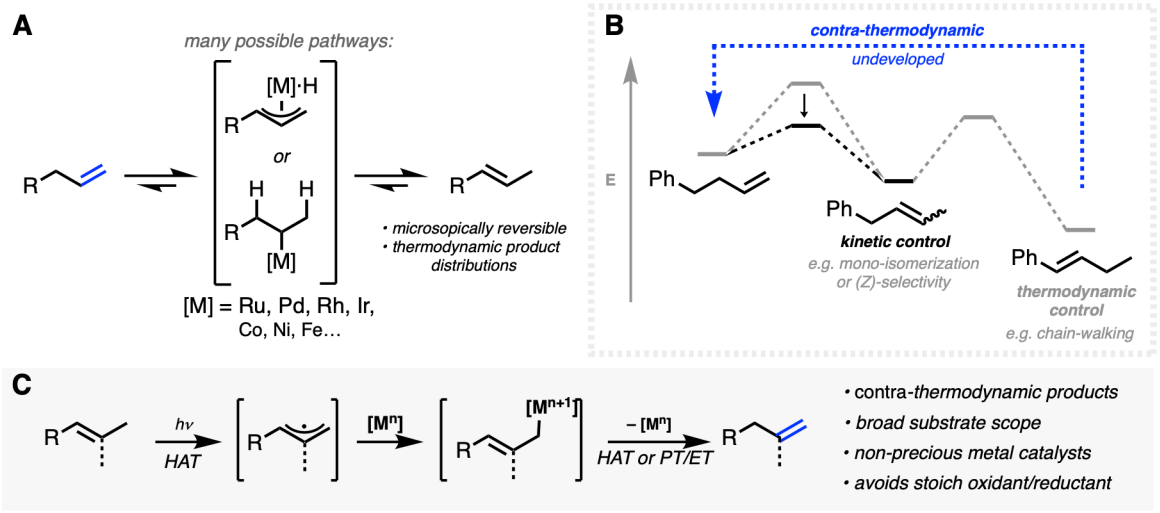


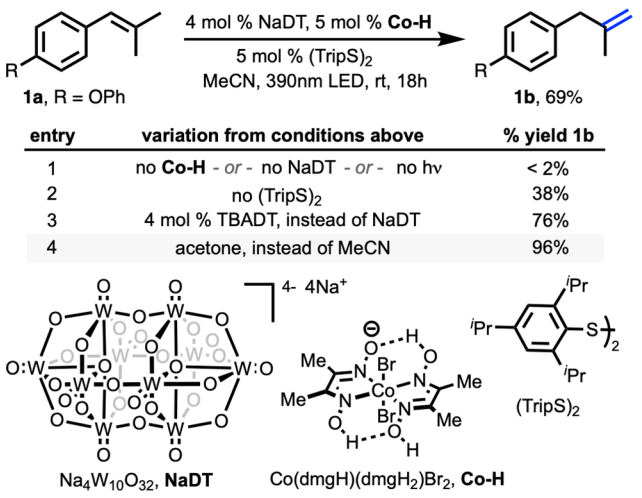
Figure 1. Previous and current approaches to alkene isomerization. (A) Common mechanistic pathways for thermal alkene isomerization proceed through microscopically reversible elementary steps and provide thermodynamically aligned product distributions. (B) Strategies to control selective positional alkene isomerization. (C) Proposed mechanistic framework to access *contra*-thermodynamic product distributions in alkene isomerization reactions.

can be achieved, energy-transfer- and electron-transfer-based deconjugation mechanisms intrinsically limit reaction scope to highly electron-deficient and electron-rich substrates, respectively, hindering the widespread application of these approaches.[30]

Here, we report catalytic conditions that promote *contra*-thermodynamic internal-to-terminal olefin isomerization, which proceeds through a fundamentally distinct mechanistic framework and exhibits an exceptionally broad substrate scope (Figure 1C). We sought to devise a photochemical π-allyl isomerization pathway featuring microscopically irreversible oxidative addition and reductive elimination steps. We envisioned that C–H bond "oxidative addition" might be achieved through neutral H atom abstraction followed by inner sphere allyl radical reduction by a transition metal cocatalyst. The resulting organometallic π-allyl intermediate might then undergo "reductive elimination" through M–C bond proton and electron transfer or homolytic substitution to furnish the desired product isomer. Under such a scheme, steric—rather than purely electronic—factors in the H atom abstraction and/or metal-allyl formation steps could be leveraged to promote terminal-selective product formation across an electronically diverse scope of substrates.

RESULTS AND DISCUSSION

We selected 1-(2-methyl-1-propenyl)-4-phenoxybenzene **1a** as a model substrate to test this hypothesis, as this conjugated, trisubstituted olefin is significantly more thermodynamically stable than its corresponding terminal isomer **1b** (ΔG°_{calc} = +2.5 kcal/mol, see the Supporting Information). The formation of terminal isomer **1b** was observed in 69% yield under reaction conditions employing catalytic quantities of $Na_4W_{10}O_{32}$ (NaDT, 4 mol %), Co(dmgH)(dmgH$_2$)Br$_2$ (**Co–H**, 5 mol %), and 2,4,6-triisopropylbenzene disulfide (TripS$_2$, 5 mol %) in MeCN at room temperature under near-UV (390 nm) LED irradiation (Figure 2).[31,32] Only trace isomerization was observed in the absence of NaDT, **Co–H**, or light. The reaction yield was diminished in the absence of disulfide (38% yield, entry 2); however, $(Bu_4N)_4W_{10}O_{32}$ (TBADT) was found to be an equally effective cocatalyst. Quantitative conversion of



entry	variation from conditions above	% yield 1b
1	no **Co-H** - *or* - no NaDT - *or* - no hν	< 2%
2	no (TripS)$_2$	38%
3	4 mol % TBADT, instead of NaDT	76%
4	acetone, instead of MeCN	96%

Figure 2. Reaction condition optimization. See the Supporting Information for full experimental details.

1a to **1b** was observed when the reaction solvent was switched from MeCN to acetone (96% yield; Figure 2, entry 4; see the Supporting Information for full reaction optimization details).

A range of conjugated internal olefins was evaluated as substrates under these conditions (Figure 3). Depending on the substrate, either NaDT or TBADT was employed in acetone or MeCN as a solvent. For many substrates, the addition of (TripS)$_2$ was found to be unnecessary, in which case this additive could be omitted without negative impact on the reaction outcome. Substrates featuring electron-donating or electron-withdrawing aromatic substituents react quantitatively (95–99% NMR yield; 88–94% isolated yield) to afford the corresponding terminal alkene isomer (**2b**–**7b**), and the isomerization of **5a** was carried out on a 10 mmol (2.0 g) scale with no impact on outcome (90% isolated yield of **5b**). The reaction of 2-methylindene **8a** proceeds to form exocyclic isomer **8b** in 67% isolated yield, and substrates possessing strongly electron-withdrawing heteroaromatic (**9a**, **10a**) or α-trifluoromethyl (**11a**) groups also react to form terminal isomers (33–66% yields). A competition Hammett experiment

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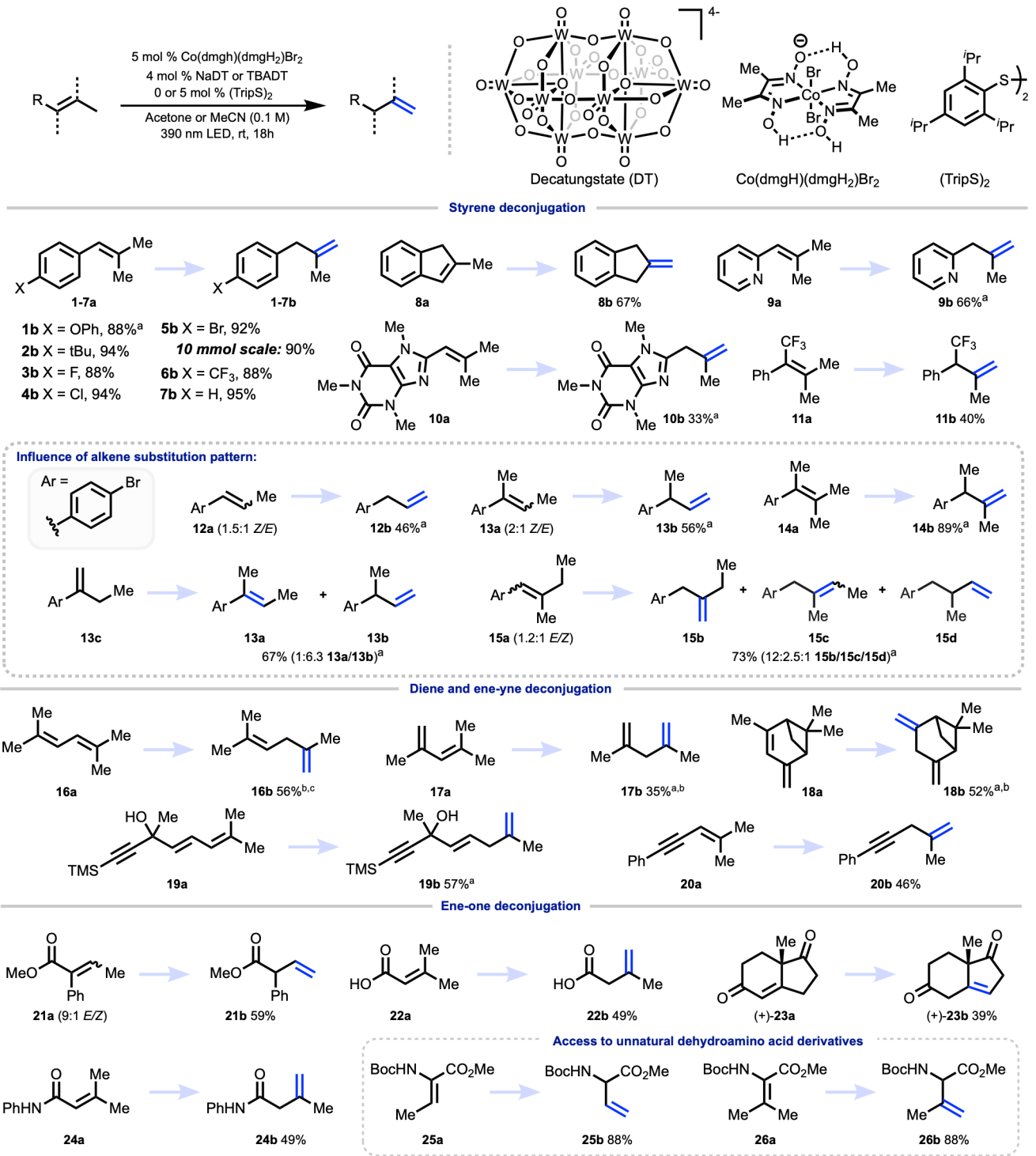

Figure 3. Substrate scope with conjugated alkenes. Reactions were conducted on a 0.5 mmol scale with 5 mol % Co(dmgH)(dmgH$_2$)Br$_2$ and 4 mol % TBADT or NaDT under 390 nm LED irradiation at room temperature in acetonitrile or acetone (0.1 M) for 18 h. Isolated yields are reported (average of two runs). See the Supporting Information for full experimental details. (a) Reaction was carried out with 5 mol % (TripS)$_2$ cocatalyst added. (b) Reaction yield was determined by ^{1}H NMR spectroscopy using nitrobenzene as an internal standard due to product volatility. (c) 19% yield of doubly isomerized product **16c** was also formed; see the Supporting Information.

between **1a** and **6a** revealed no difference in isomerization rate arising from electronic substitution on the aromatic ring (see the Supporting Information).

To explore the impact of the alkene substitution pattern on reactivity and selectivity, we prepared a range of disubstituted (**12a**, **13c**), trisubstituted (**13a**, **15a**), and tetrasubstituted (**14a**) styrenes bearing a common (4-bromophenyl) aryl group. Each of these substitution patterns is amenable to isomerization (46−89% yields), and the highest reaction yields were obtained for *β*,*β*-disubstituted alkene substrates.

The reaction conditions were readily extended to other classes of conjugated alkenes. Despite significant thermodynamic bias favoring the conjugated starting isomer (ΔG°_{calc} = +3.1 kcal/mol), 2,5-dimethylhexadiene **16a** reacts to form

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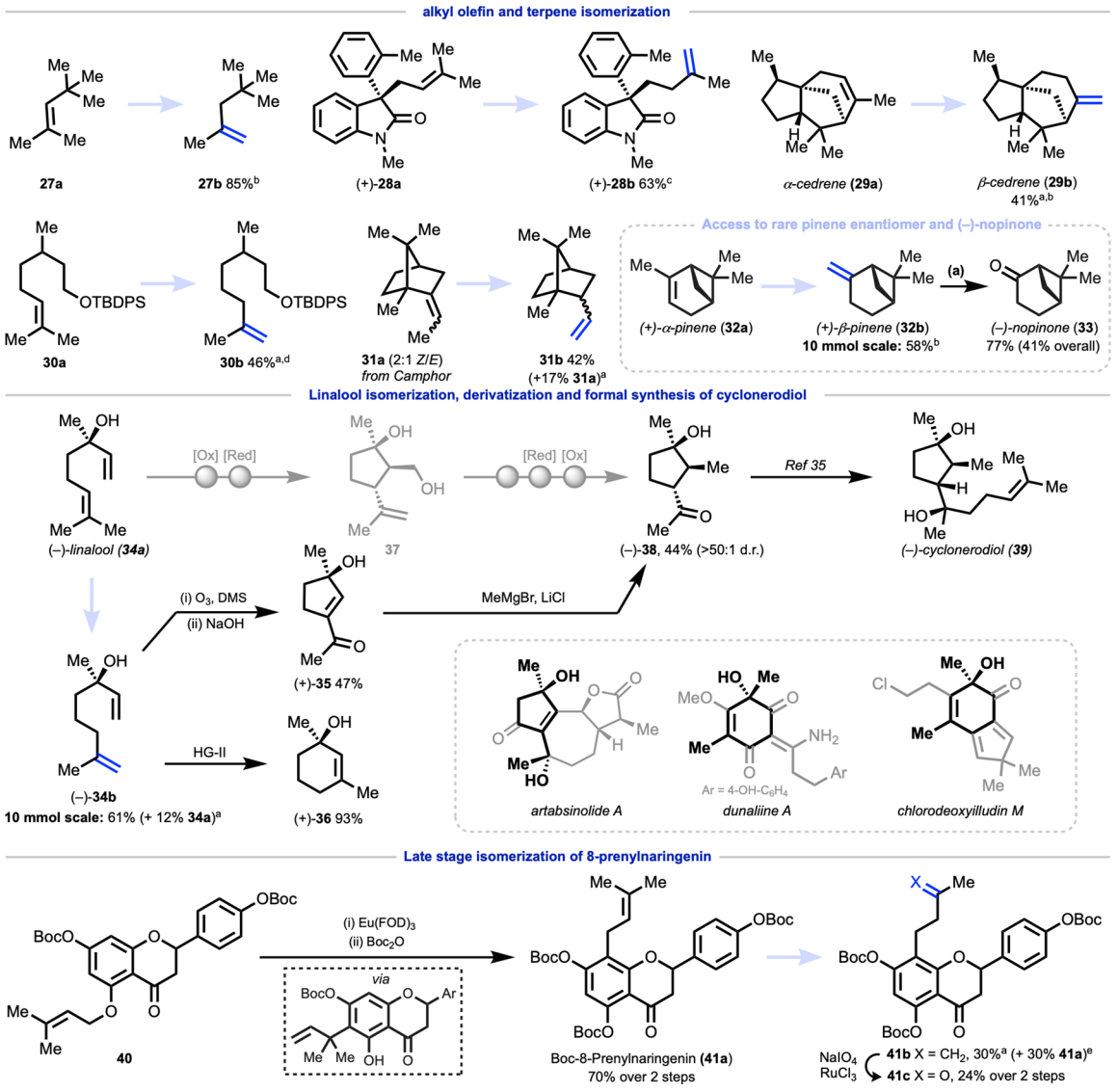

Figure 4. Substrate scope and applications in natural product synthesis and late stage diversification. Reactions were conducted on a 0.5 mmol scale with 5 mol % Co(dmgH)(dmgH$_2$)Br$_2$, and 4 mol % TBADT or NaDT under 390 nm LED irradiation at room temperature in acetonitrile or acetone (0.1 M) for 18 h. Isolated yields are reported (average of two runs). See the Supporting Information for full experimental details. (a) Reaction was carried out with 5 mol % (TripS)$_2$ cocatalyst added. (b) Reaction yield was determined by ^{1}H NMR spectroscopy using an internal standard. (c) Isolated as an 8:1 mixture of **28b**:**28a**. (d) Isolated as a 6:1 mixture of **30b**:**30a**. (e) Reaction mixture subjected directly to oxidative cleavage conditions. Conditions: (a) 3.0 equiv $NaIO_4$, 3 mol % TBAI, 3 mol % $RuCl_3$, EtOAc/H_2O, rt, 4 h.

deconjugated diene product **16b** in 56% yield. In addition to electron-rich conjugated diene and ene-yne substrates (**17a**–**20a**), highly electron-deficient α,β-unsaturated carbonyls also react under the optimized conditions. For example, ester **21a** reacts to form the significantly destabilized deconjugated isomer **21b** (ΔG°_{calc} = +4.9 kcal/mol) in 59% isolated yield, and the Hajos–Parish ketone (+)-**23a** reacts to form previously unknown chiral analogue (+)-**23b** in 39% isolated yield. α,β-Dehydroamino acids **25a** and **26a** each isomerize quantitatively to the corresponding β,γ-isomers in 88% yield.

While alkyl-substituted olefin isomers possess the least significant energetic bias (ΔG°_{calc} = +1.0–1.5 kcal/mol), selective isomerization of this substrate class presents the most significant synthetic challenge due to (a) the absence of a redox auxiliary required for electron-/energy-transfer-based deconjugation methods, and (b) additional selectivity challenges arising from unselective oxidation/reduction. Alternative synthetic routes for selective access to this class of terminal alkene products are also comparatively limited. Despite these potential obstacles, unactivated alkene substrates were also observed to undergo terminal-selective isomerization under standard conditions (Figure 4). For example, indanone (+)-**28a**, obtained in >99% ee using a Pd-catalyzed asymmetric prenylation,[33] reacted to form homoallyl isomer (+)-**28a** in 63% isolated yield.

The robust reactivity of prenyl groups led us to explore common chiral pool terpene feedstocks and their analogues as potential substrates. For example, α-cedrene (**29a**) reacts to form β-cedrene (**29b**) in 41% yield, and citronellol and camphor-derived substrates **30a** and **31a** afforded the analogous terminal isomers in 46% and 42% yields, respectively. The reaction of (+)-α-pinene (**32a**) affords (+)-β-pinene (**32b**) in 58% yield on a 10 mmol scale. The crude reaction was carried forward without purification to

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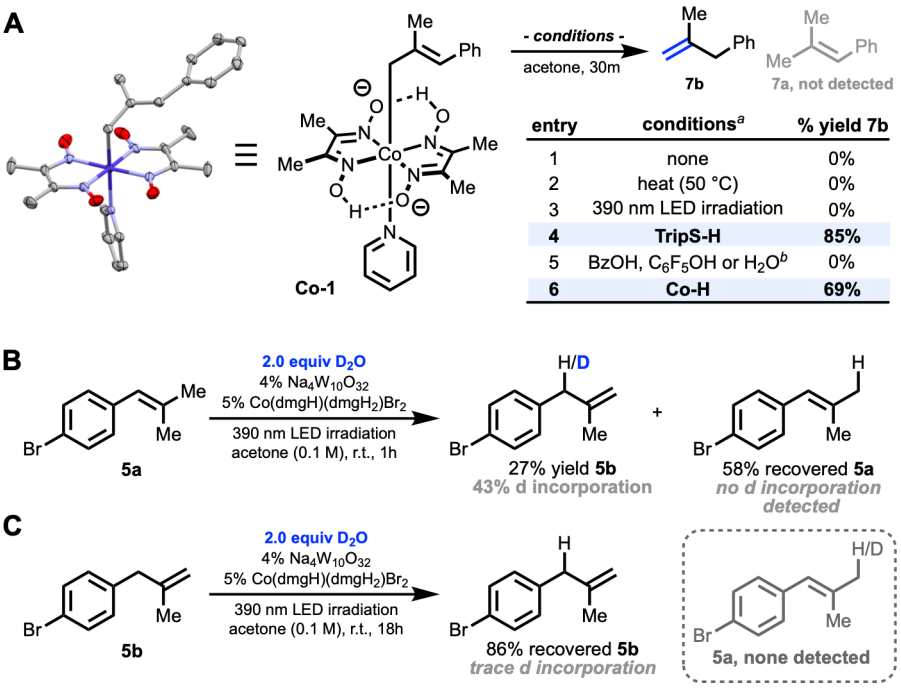

Figure 5. Mechanistic Studies. (A) X-ray crystal structure and stoichiometric studies of allylcobaloxime(III) **Co-1**. (B, C) Deuterium incorporation studies. (a) 2.0 equiv of additive was used. (b) 5.0 equiv of H_2O was added.

access >0.5 g of the rare (−)-nopinone isomer (**33**) in 41% yield overall.[34]

We further sought to showcase the synthetic versatility of *contra*-thermodynamic alkene isomerization in the context of complex molecule synthesis. We selected (−)-linalool (**34a**) as a model substrate, which reacts to form terminal isomer (−)-**34b** in 61% yield (along with 12% recovered **34a**) on a 10 mmol (1.5 g) scale. Ring-closing metathesis of the crude product mixture afforded enantiopure tertiary alcohol (+)-**36** in 93% yield, while the analogous 5-membered ring derivative (+)-**35** could be obtained in 47% yield after ozonolysis and condensation. Both chiral building blocks map onto natural product core structures (Figure 4, inset), and we completed a formal total synthesis of (−)-cyclonerodiol (**39**)[35] by methylation of (+)-**35** using MeMgBr conditions (modified by the addition of LiCl) to afford (−)-**38** in 44% yield as a single diastereomer (see the Supporting Information). The previous route to (−)-cyclonerodiol from (−)-linalool requires multiple oxidation/reduction sequences, including the installation and removal of structurally unnecessary C−O bonds (cf. intermediate **37**). In contrast, our isomerization-based approach to **39** reduces step-count and obviates unnecessary stoichiometric redox interconversions.

Finally, we sought to challenge this method by exploring isomerization applications in a late stage setting (Figure 4, bottom). The prenylflavanoid 8-prenylnaringenin (8-PN) displays striking estrogen receptor agonist activity[36] and has been investigated for therapeutic potential in diverse contexts.[37−40] Synthetic 8-prenylnaringenin (8-NG) can be efficiently prepared through a Eu(III)-catalyzed domino Claisen−Cope sequence, which enables exquisitely selective installation of the prenyl group at C8 but mechanistically limits the ability to prepare derivatives lacking the allyl motif.[41,42] The treatment of protected 8-NG analogue **41a** to standard isomerization conditions afforded terminal isomer **41b** in 31% yield (along with 30% recovered **41a**) and could be subjected directly to oxidative cleavage conditions to provide previously unknown ketone analogue **41c** (24% yield over 2 steps). Collectively, these examples demonstrate the utility of this isomerization method in both the initial and late stages of complex molecule synthesis.

Overall, the catalyst system described here provides a general strategy for the transformation of internal and conjugated alkenes to terminal, unconjugated isomers. In light of the insensitivity of the reaction to substrate electronic variation and the well-established precedent for hydrogen atom abstraction promoted by decatungstate photocatalysis,[43] we hypothesized that the reaction mechanism proceeds through initial H atom abstraction, followed by an addition of the resulting allyl radical to Co^{II}, furnishing an allylcobaloxime(III) intermediate. To assess the feasibility of such an intermediate and to investigate the mechanism of subsequent product formation, we independently prepared related allylcobaloxime(III) **Co-1** and subjected this well-defined species to a series of stoichiometric studies (Figure 5A; see the Supporting Information for full details).

A solution of **Co-1** in degassed acetone was stable at room temperature for 18 h, while elevated temperature (50 °C) or irradiation with 390 nm LED promoted the decomposition of **Co-1**, with no detectable formation of product **7b** (Figure 5A, entries 1−3).[44,45] However, the addition of TripSH to a solution of **Co-1** resulted in rapid and nearly quantitative formation of **7b** (85% yield after 30 min; Figure 5A, entry 4). Weakly acidic proton sources, such as BzOH, C_6F_5OH, or water, failed to promote the formation of product **7b**, implicating a role for thiol as a H atom donor, rather than proton donor (Figure 5A, entry 5). Consistent with this hypothesis, the formation of **7b** was also observed when **Co-1** was treated with **Co−H** (69% yield **7b** after 30 min; Figure 5A, entry 6), another plausible H atom donor.[46,47] No trace of conjugated isomer **7a** was detected in any of these stoichiometric experiments.

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These results provide strong evidence that product formation occurs via regiospecific bimolecular homolytic substitution (S_H2') of the allylcobaloxime(III) intermediate by a H atom donor, such as thiol, **Co−H**, or potentially by a reduced state of the decatungstate cocatalyst. Similar homolytic substitution pathways have been invoked in stoichiometric studies involving allylcobaloxime(III) derivatives.[48−50] The regiospecific formation of terminal isomer **7b** from **Co-1** implicates the formation of allylcobaloxime as a plausible selectivity-determining step in the catalytic reaction.

To test this hypothesis in the context of the catalytic reaction, we carried out the isomerization of **5a** in the presence of 2.0 equiv of D_2O (Figure 5B). An analysis of the reaction mixture after 1 h (27% yield **5b**) revealed 43% deuterium incorporation into the benzylic methylene of product **5b** and no deuterium incorporation observed in recovered starting material, **5a**. These data are consistent with the stoichiometric studies presented in Figure 5A, involving terminal-selective allylcobaloxime(III) formation followed by regiospecific H atom transfer by **Co−H** or reduced decatungstate cocatalysts that have undergone H/D exchange with added D_2O. However, this experiment does not rule out a dynamic kinetic process in which H atom delivery to the terminal allylcobaloxime isomer is product-selective.

To investigate whether the H atom abstraction step may also contribute to terminal product selectivity, we carried out a corresponding isotope exchange reaction employing **5b** as the substrate under standard conditions in the presence of 2.0 equiv of D_2O (Figure 5C). After 18 h, we observe only trace deuterium incorporation into recovered **5b**, suggesting that product isomer **5b** does not undergo H atom abstraction (see the Supporting Information for full experimental details). Collectively, these studies suggest that both H atom abstraction and allylcobaloxime formation steps contribute to the overall selectivity of the reaction, consistent with well-established steric preferences in decatungstate-mediated HAT steps[43] and organocobaloxime-mediated processes,[51] respectively.

CONCLUSION

In summary, we present a dual catalyst system that promotes *contra*-thermodynamic positional isomerization of diverse internal alkenes to terminal congeners. Our findings support a mechanistic picture involving allylic H atom abstraction and radical addition to form an allylcobaloxime intermediate, followed by regiospecific H atom substitution to form the terminal alkene product isomer. The compatibility of the present method with diverse electron-rich and electron-deficient conjugated alkenes, and unactivated substrates, is consistent with a selectivity model largely governed by steric factors.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c12043.

General methods, synthetic procedures, product isolation and characterization, and NMR spectra (PDF)

Accession Codes

CCDC 2122159 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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