Boron-Enabled Geometric Isomerization of Small Alkene Fragments via Selective Energy Transfer Catalysis

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The mammalian visual cycle epitomizes the importance of complex polyenes in biology. However, isomerization-based strategies to enable the sterodivergent construction of these important biomolecules from geometrically defined alkene linchpins remain conspicuously underdeveloped. Mitigating the thermodynamic constraints inherent to isomerization is further frustrated by the considerations of atom efficiency in idealized low molecular precursors. Herein, we report a general ambiphilic C3 scaffold that can be isomerized and bi-directionally extended. Predicated on highly efficient triplet energy transfer, the selective isomerization of β-borylacrylates is contingent on the participation of the boron *p*-orbital in the substrate chromophore. Rotation of the C(sp^2)-B bond by 90° in the product renders re-excitation inefficient and endows directionality. This subtle stereoelectronic gating mechanism enables the stereocontrolled syntheses of well-defined retinoic acid derivatives.

Complex polyenes provide an expansive structural framework for biological processes that occur in two-dimensional chemical space (*1*). Information is stored in one of two stereoisomeric forms, such that the spatio-temporal control of constituent alkene units encodes for a specific biological function (*2-4*). In cross-conjugated alkenes such as retinal (vitamin A), this interplay facilitates the regulatory gating mechanism that underpins the mammalian visual cycle (*5*). Despite powerful manifestations of this structure-function interplay in human medicine and materials research, isomerization platforms that enable the stereodivergent construction of complex polyenes from common linchpins remain conspicuously underdeveloped. Synthesis algorithms reported by Burke and co-workers have greatly facilitated the modular assembly of polyenes from common building blocks in a manner reminiscent of biopolymer assembly (*6, 7*). Despite these advances, the intractable challenges associated with inverting the geometry of small alkene fragments to enable stereodivergence from common precursors offer the opportunity for creative endeavor (*8*). In a broader sense, this strategic deficiency in alkene isomerization technology has been prominently highlighted by Baran and co-workers in the context of accessing dienophiles for cycloaddition chemistry (*9*). Terpene biosynthesis predicated on the sequential elongation of small (C5) alkene-containing linchpins such as DMAPP and IPP are conceptually attractive blueprints in reconciling this disparity (Figure 1A) (*10-12*). Under the auspices of enzyme catalysis, these fragments are unified with incredible fidelity thereby enabling the synthesis of well-defined polyenes by either stereodivergent biosynthesis (e.g. farnesyl diphosphate) or post-product isomerization routes (e.g. 9-*cis*-β-carotene) (*13*). Although challenging to implement in a synthetic context, these precedents highlight the need for an isomerization platform to enable stereodivergent access to both alkene geometries as being a pre-requisite for efficiency (*14*).

Consideration of step and atom economy (*15*) necessitates a common ambiphilic building block that contains the minimum number of carbon atoms for sequential manipulation to allow stereospecific downstream processing. The non-degeneracy of alkene stereoisomers and associated *contra*-thermodynamic challenges render Dexter-type energy transfer activation (*16-21*) ideally suited to mitigate microscopic reversibility intrinsic to ground state reactivity (*22-24*). Furthermore, the bio-compatibility of this activation strategy has recently been validated by MacMillan and co-workers (*25*). Photosensitized alkene isomerization has a venerable history, but efficiency often restricts the scope to styrenyl chromophores *(3)*. Seminal studies by Hammond and Arai are synonymous with stilbenes and styrene isomerization through the use of a photosensitizer (*26-29*), and triplet energy transfer-enabled selective isomerization of retinal in the visual cycle has been simulated by Walker and Radda (*30*). More recently, the Weaver group (*31*), and our own research group (*32-35*) has disclosed operationally simple isomerization protocols harnessing functionally diverse styrenes with various structural motifs in the β-position (Figure 1B). However, the presence of an aryl alkene fragment is a pre-condition to act as a suitable chromophore. The identification of a traceless chromophore would represent a major advance towards achieving operational parity with positional isomerization (*36*).

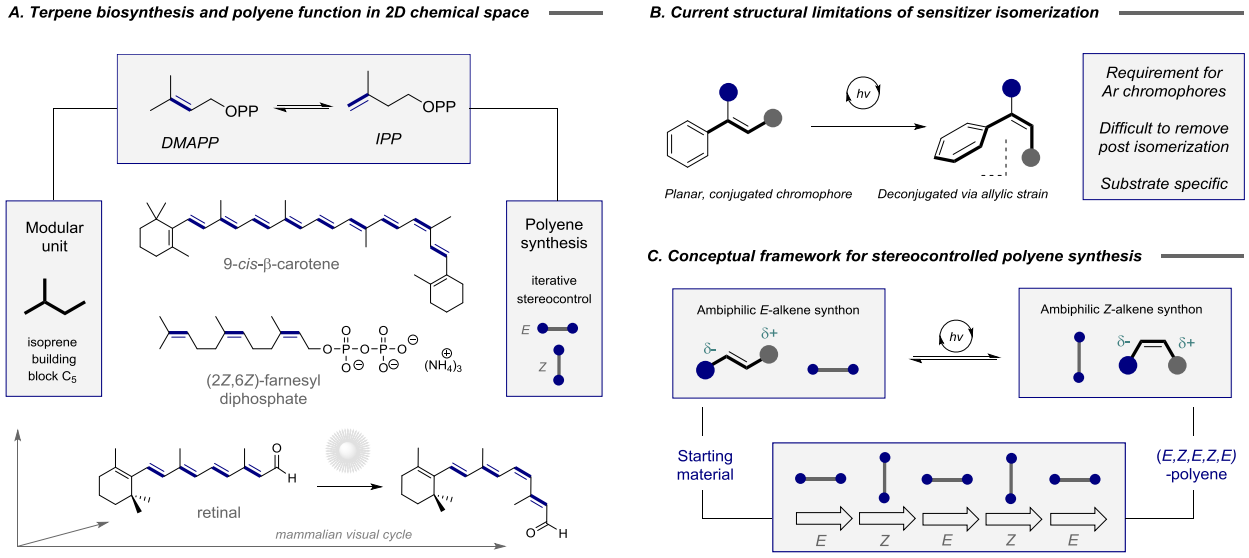

Fig. 1. Inspiration for the development of a photocatalytic isomerization. (**A**) The biosynthesis of complex terpenes via well-defined building blocks and the importance of alkene geometry in the visual cycle. (**B**) Photosensitized isomerization of alkenes and the pre-condition that the alkene be embedded in a larger chromophore (e.g. styrene). (**C**) Generic framework for a bio-inspired, stereodivergent polyene synthesis platform based on ambiphilic alkene synthons.

To circumvent this limitation and enable a modular assembly of polyenes (*6-8*, *37*) with spatiotemporal regulation (Figure 1C), the importance of acetyl derivatives in biosynthesis and the need for an ambiphilic fragment were consolidated in the β-borylacrylate scaffold (Figure 2, upper). Specifically, the β-BPin group was identified to enable both alkene isomers to be generated and provide a handle for traceless, stereospecific coupling. The conceptual framework of the alkene isomerization was predicated on rotation of the C(sp^2)-B bond as a stereoelectronic gating mechanism to enable selective energy transfer. The *p*-orbital of trigonal planar boron

systems plays a pivotal role in regulating the reactivity of organoboron compounds (*38*, *39*). It was envisaged that incorporation of a traceless boronic ester motif as an aryl surrogate would extend the acrylate chromophore and permit subsequent excitation of the planar *E*-isomer. Following excitation and subsequent isomerization, the C(sp^2)-B bond in the product *Z*-isomer would be twisted by 90° to mitigate non-bonding interactions and potentially engage in a dative interaction with the carbonyl group ($n_O \rightarrow p$) (*40*). This subtle bond rotation would shorten the chromophore and provide a structural foundation to bias the photostationary composition.

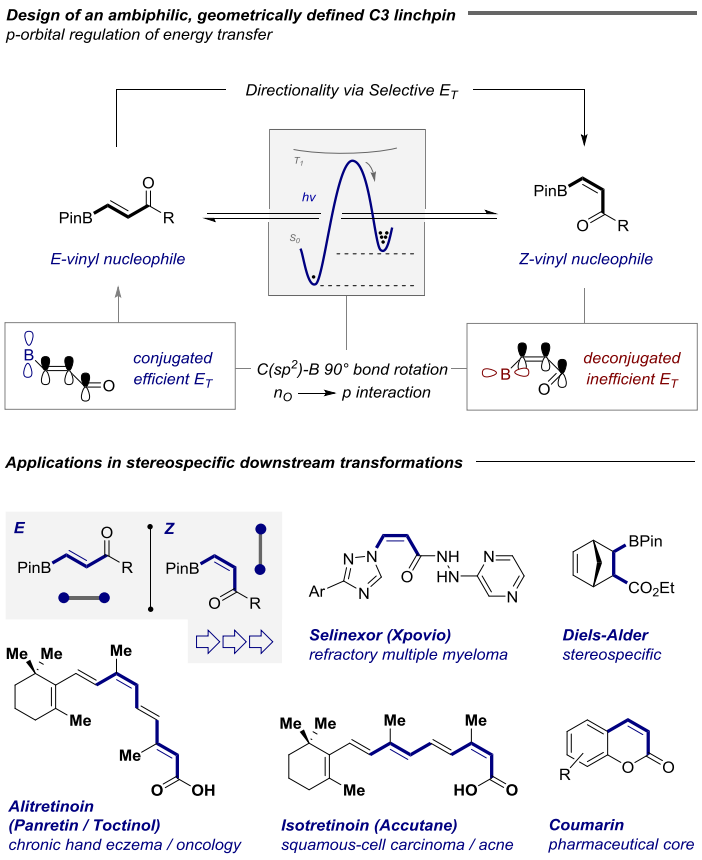

Fig. 2. Design of an ambiphilic C3 linchpin. Top: Selective Dexter energy transfer platform based on the β-boryl-acrylate scaffold. Bottom: Stereospecific applications of the geometrically define linchpins for the preparation of complex polyenes and pharmaceuticals.

Herein we report a photocatalytic isomerization of β-borylacrylate derivatives that facilitates access to both geometric isomers of ambiphilic C_3 linchpins. Stereodivergence is contingent on Dexter-type selective energy transfer using an inexpensive small molecule photosensitizer (402 nm). Directionality (*E* → *Z*) is a consequence of a subtle 90° C(sp^2)-B bond rotation thereby contracting the π-system of the *Z*-isomer. This strategy circumvents the reliance of alkene isomerization on styrenyl chromophores by replacing inert aryl rings with a traceless BPin handle. Both isomers of the vinyl boron species are compatible with stereospecific cross coupling thereby providing the basis of an iterative, stereodivergent entry to complex polyenes. Mechanistic validation and the total syntheses of the therapeutics isotretinoin and aletretinoin are disclosed. Moreover, the synthetic utility of these small, densely functionalized units in

stereospecific transformations is showcased (Figure 2, lower). Initially the geometric isomerization of the ambiphilic Weinreb amide ***E*-1** to ***Z*-1** was investigated (Fig. 3A. See SI for full details). Reactions performed in acetonitrile under visible light irradiation (402 nm) using thioxanthone as a photocatalyst (5 mol %) proved to be operationally simple and highly efficient (99% NMR yield, *Z:E* 94:6, Figures 2A and B). With optimized conditions in hand, the substrate scope and limitations of the method were explored (Fig. 3C). Relocating the methyl substituent to the *β*-position of the Michael acceptor ***E*-2** and ***E*-3** led to remarkable selectivity (>99:1). Modification of the alkyl substituent was extremely well tolerated furnishing the isomerized products in >99:1 selectivity and with high isolated yields (***E*-4, *E*-5** and ***E*-6**).

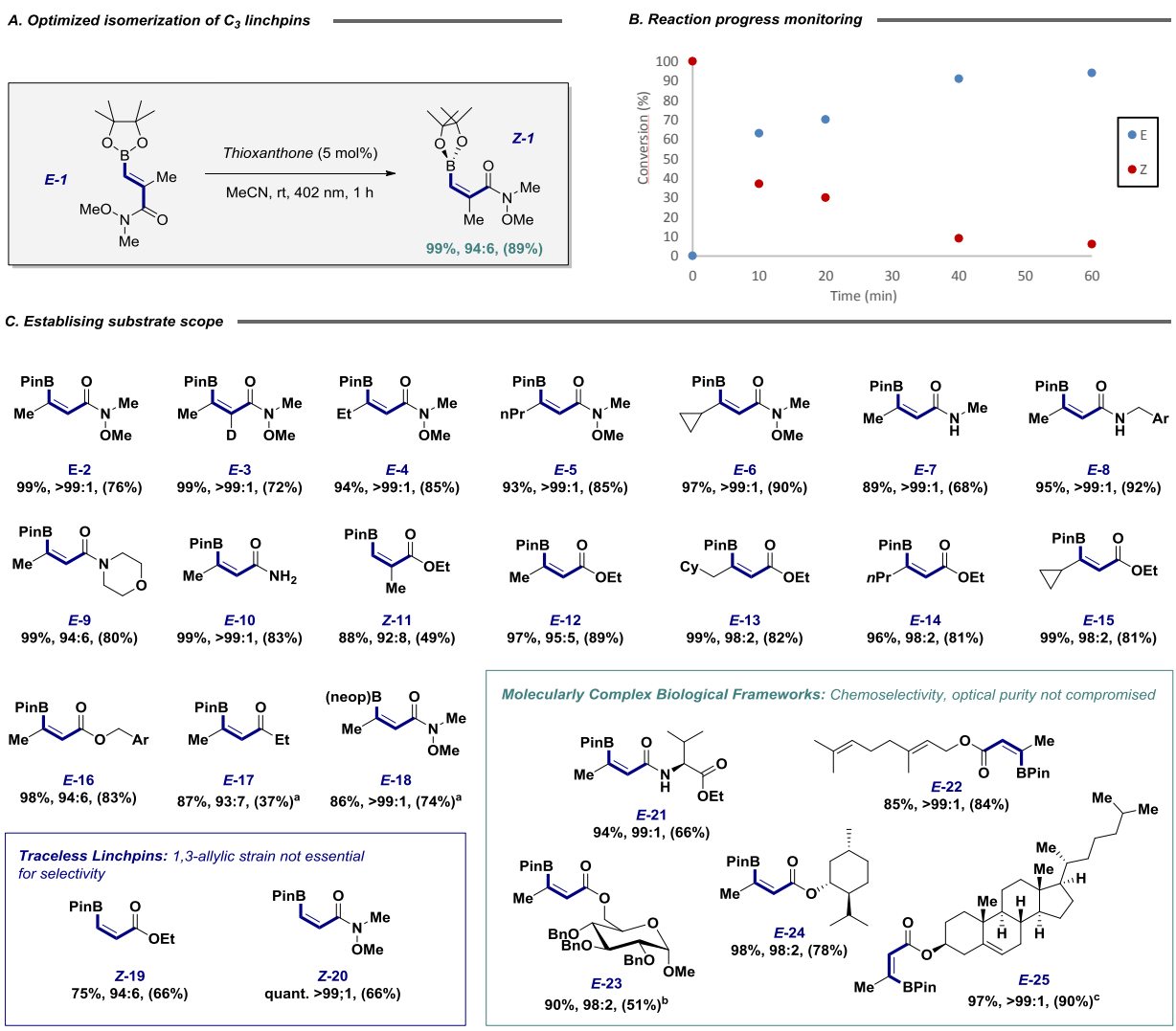

Fig. 3. The photocatalytic isomerization of small molecule ambiphilic C3 linchpins. (**A**) Optimized reaction conditions: substrate (0.3 mmol), thioxanthone (5 mol %), MeCN (9 mL), 402 nm, 1 h. (**B**) Reaction progress monitoring of ***E*-1 → *Z*-1**. (**C**) Establishing substrate scope and demonstrating efficiency in simple 1,2-disubstituted systems, chemoselectivity and compatibility with biomolecules. [a] Yield over 2 steps following cross coupling. [b] 0.1 mmol scale. [c] 16 hours. Yields and *E/Z* ratios determined by ^{1}H NMR (1,3,5-trimethoxybenzene as internal standard). Numbers in parentheses refer to isolated yields of the product isomer after column chromatography.

Replacement of the Weinreb amide by secondary amides (***E*-7** and ***E*-8**), tertiary amides (***E*-9**) and primary carboxamides (***E*-10**) had no impact on the efficiency of the transformation (up to >99:1). Ester groups were also found to be compatible with the general isomerization conditions, but the α-substituted Michael acceptor (***E*-11**) proved to be unstable towards silica gel chromatography. High levels of stereoselectivity and isolated yield were again observed with β-substituted analogs (***E*-12** to ***E*-16**, up to 98:2). Efficient isomerization was observed with ketones and neopentyl boronic esters (***E*-17** and ***E*-18**, 93:7 and >99:1, respectively), but the intrinsic instability of the products required a post-isomerization cross-coupling protocol to determine stereoselectivity. To explore the limitations of the method in simple 1,2-disubstituted frameworks, acrylates **19** and **20** were investigated. Photochemical alkene isomerization typically requires a substituent to generate 1,3-allylic strain in the product thereby causing deconjugation, reducing the efficiency of energy transfer and enabling directionality. In contrast to styrenyl systems, the isomerization of the basic β-borylacrylate also occurs with high levels of stereoselectivity (***E*-19** and ***E*-20**, 94:6 and >99:1, respectively) providing entry to simple 1,2-disubstituted ambiphilic linchpins. To ensure that the method does not compromise optical purity and is compatible with pre-existing alkenes thereby demonstrating chemoselectivity, **21** and **22** were prepared, respectively. Finally, extension of the scope to include common, biologically relevant frameworks included D-glucose derivative **23**, the (–)-menthol derivative **24** and modified cholesterol **25** (up to >99:1).

The efficiency of isomerization utilizing simple 1,2-disubstituted building blocks such as **19** and **20** indicate that the origin of stereoselectivity is not developing allylic strain such as is observed with styrenyl systems. To place selectivity on a structural basis, the effects of single point editing to the core substrate were investigated (Fig. 4A). These studies revealed that both the boron *p*-orbital and the carbonyl substituent are critical to achieve efficient directionality, as is clear from ***E*-26**, **27** and **28**. Determination of the quantum yield excludes the possibility of a radical chain process and control experiments demonstrate the need for both light and photocatalyst (Fig. 4B,C). In establishing the structural basis of directionality, inspection of the ^{11}B NMR spectra of the products proved instructive. Accumulation of electron density in the boron *p*-orbital is conspicuous in the Z-isomer of the amide derivatives [17.19 ppm for ***E*-8**]. This is indicative of a stabilizing dative ($n_O \rightarrow p$) interaction that is only geometrically viable when the C(sp^2)-B bond rotates out of the plane of the π-system (See SI for details). This deconjugative contraction of the chromophore does not manifest itself in the ^{11}B NMR spectra of the ester substrates [30.76 ppm for ***E*-16**] prompting further investigation.

Gratifyingly, it was possible to analyze the substrate / product antipodes of **8** and **16** by X-ray crystallography (Fig. 4C). Comparison of the starting isomers ***Z*-8** and ***Z*-16** confirmed the expected planar chromophore in which the boron group is conjugated (Fig. 3D top). Consistent with the ^{11}B NMR studies, a clear dative interaction is evident in the amide product ***E*-8** resulting from a 90° rotation of the C(sp^2)-B bond (Fig. 4D middle). This subtle contraction of the π-system would likely raise the triplet energy and render re-excitation inefficient. The ester derivative ***E*-16** shows no dative interaction but, consistent with the amide scenario, the boron *p*-orbital is perpendicular to the alkene π-system and no longer in conjugation. To further demonstrate the importance of conjugation for efficient sensitization, the *tetra*-substituted precursor ***Z*-29** was investigated. X-ray analysis (see ESI) reveals that the carbonyl group is out of plane thereby rendering excitation inefficient. Although *tetra*-substituted alkenes are seldom found in polyenes, this substrate is a useful control.

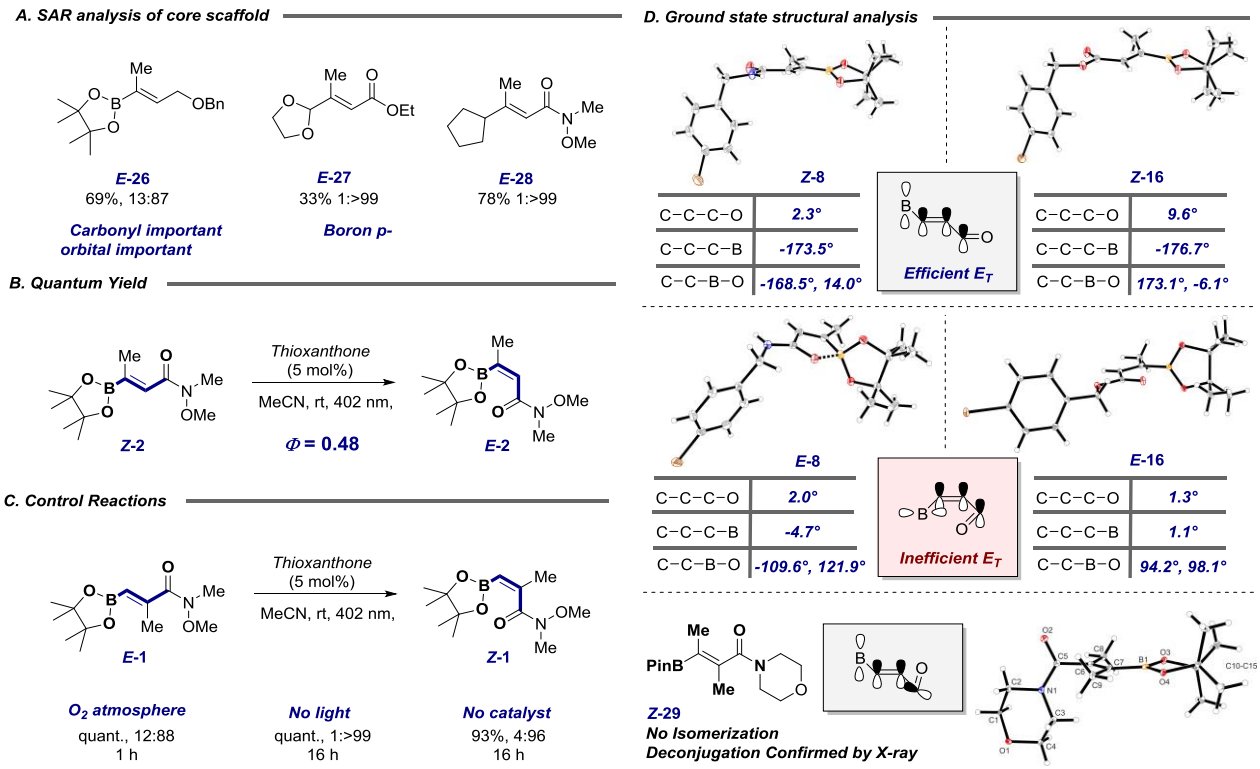

Fig. 4. Investigating the origin of stereoselectivity. (**A**) Structure activity relationship of core scaffold. (**B**) Quantum yield studies. (**C**) Control reactions (**D**) Ground state X-ray structural analysis of ***Z/E*-8**, ***Z/E*-16** and ***Z*-29**.

Finally, to validate this isomerization platform in stereocontrolled polyene synthesis, the synthetic utility of simple ambiphilic linchpins in target synthesis and a series of downstream manipulations were investigated (Fig. 5). Boronic ester protection to generate the corresponding trifluoroborate was facile (**30**, Fig. 5A). Similarly, stereospecific cross-coupling to form diene **31** with alternating geometrical isomers proceeded in high yields, whilst the use of 2-bromo phenol allowed the rapid generation of the coumarin scaffold **32**. A known covalent binder in medicinal chemistry, the oxaborole scaffold (**33**) could be accessed by standard reduction conditions. Isomerisation enabled stereodivergent Diels-Alder reactions to generate the *anti*-adduct **34** and the *syn*-adduct **35** proved facile (Fig. 5B). Our ultimate goal was to enable the programmed, stereocontrolled synthesis of polyenes by using simple geometrically defined alkenes (Fig. 5C). Employing easily accessible vinyl bromide **36**, stereospecific cross-coupling utilizing (*Z*)- and (*E*)-**2** allowed expedient access to geometrical isomers (*E*, *E*)- and (*E*, *Z*)-**37** in high yield and selectivity. Subsequent reduction to the aldehyde, boron-Wittig as developed by Morken and co-workers (*41*), followed by bromodeboronation furnished stereodefined vinyl bromide intermediate (*E*, *E*, *E*)- and (*E*, *Z*, *E*)-**38** (See SI for full details). Suzuki-Miyaura cross-coupling (*42-44*) with ***Z*-12** proceeded smoothly to furnish 13-*cis*-retinoic acid (Isotretinoin) after subsequent hydrolysis. The analogous sequence with ***E*-12** enabled a synthesis of 9-*cis*-retinoic acid (Alitretinoin) (*45*).

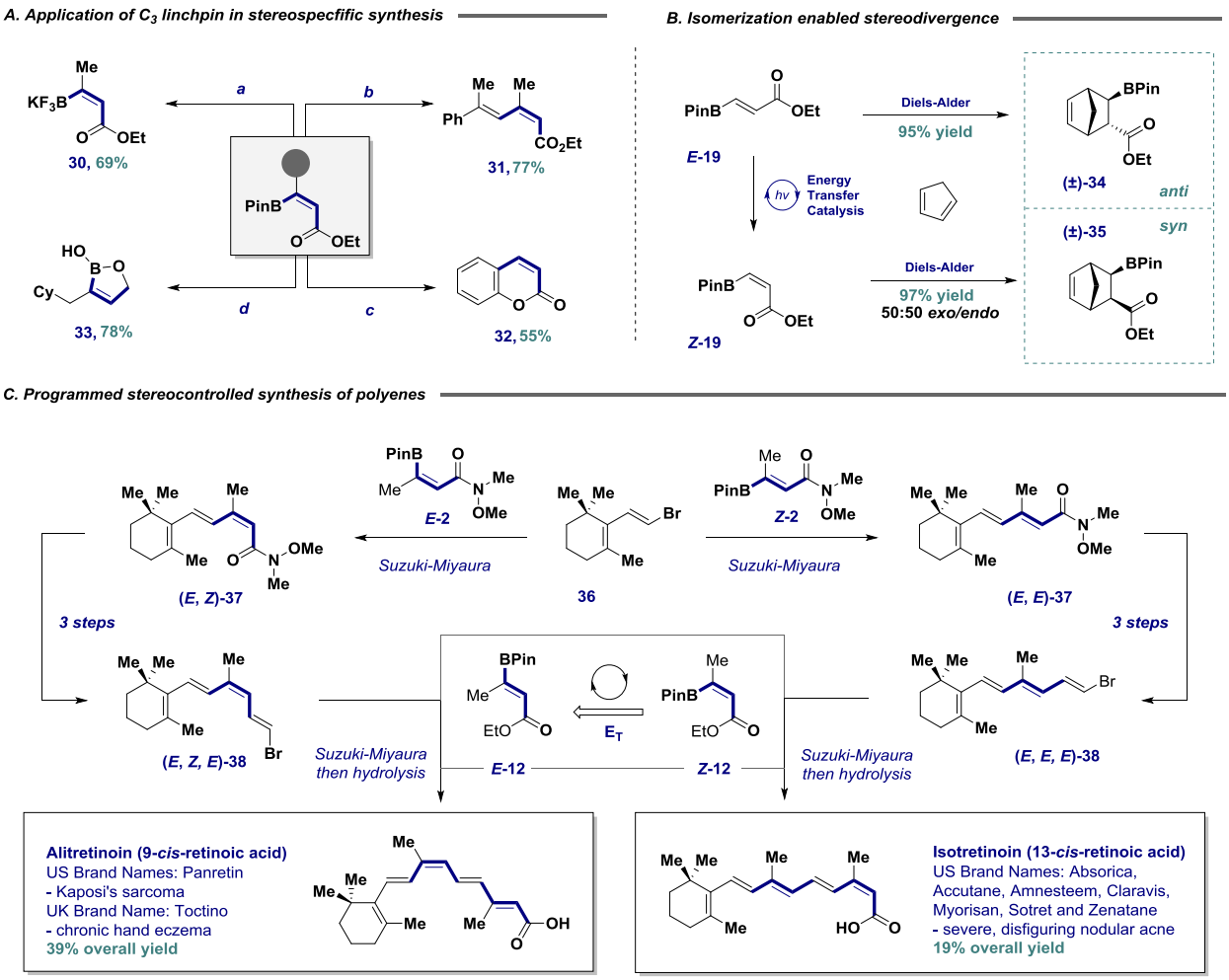

Fig. 5. Stereospecific and stereodivergent application of small molecule C_3 linchpins. (**A**) Application of product isomer in synthesis: a) ***E*-12** (1 equiv), aq. KHF_2 (4.5 M, 5 equiv), MeOH, rt; b) ***E*-12** (1 equiv), $Pd(OAc)_2$ (5 mol%), SPhos (10 mol%), K_3PO_4 (3 equiv), vinyl halide (1.2 equiv), H_2O (5 equiv), 1,4-dioxane, 80 °C; c) ***E*-12** (1 equiv), $Pd(OAc)_2$ (5 mol%), SPhos (10 mol%), K_3PO_4 (3 equiv), 2-bromophenol (1.2 equiv), H_2O (5 equiv), 1,4-dioxane, 80 °C; d) ***E*-13** (1 equiv), $NaBH_4$ (2 equiv), rt. (**B**) Stereodivergent Diels-Alder reaction: toluene, 16 h (**C**) Stereocontrolled synthesis of the polyene pharmaceuticals Alitretinoin (9-*cis*-retinoic acid) and Isotretinoin (13-*cis*-retinoic acid). Full details are provided in the ESI.

In conclusion, an operationally simple isomerization of ambiphilic C_3 linchpins is disclosed. The reaction is characterized by broad scope and high efficiency. Predicated on selective energy transfer from excited state thioxanthone to the conjugated substrate isomer, directionality results from subtle rotation of the $C(sp^2)$-B bond by 90° in the product. Deconjugation renders re-excitation inefficient by contracting the π-system, thereby providing an unprecedented gating mechanism for alkene isomerization. Harnessing the boron substituent for stereospecific transformations renders this component of the chromophore a traceless surrogate of the aryl groups that are synonymous with alkene photo-isomerizations. Application in the synthesis of drug scaffolds such as coumarins and oxoboroles is demonstrated, together with a stereospecific Diels-Alder reaction. Finally, the syntheses of therapeutic complex polyene isomers Aletretinoin

(9-*cis*-retinoic acid) and Isotretinoin (13-*cis*-retinoic acid) are disclosed. It is envisaged that this platform for the stereocontrolled generation of complex polyenes will prove to be expansive and facilitate the exploration of these fascinating bioactive materials in drug discovery.

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