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Pushing the Boundaries of Vinylogous Reactivity: Catalytic Enantioselective Mukaiyama Aldol Reactions of Highly Unsaturated 2-Silyloxyindoles

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Abstract: The first example of catalytic, enantioselective hypervinylogous Mukaiyama aldol reaction (HVMAR) involving multiply unsaturated 2-silyloxyindoles is reported. The reaction utilizes a chiral Lewis base-catalyzed Lewis acid-mediated technology to deliver homoallylic 3-polyenylidene 2-oxindoles with extraordinary levels of regio-, enantio-, and geometrical selectivity. This work highlights a subtle yet decisive influence of the indole *N*-substituents on the propagation of the vinylogous reactivity space of the donor substrates up to ten bonds away from the origin of the vinylogy effect. Analysis of the ^{13}C NMR chemical shifts of the C-ω remote site within homologous silyloxyindole donors enabled rationalization of the results and easy qualitative prediction of the HVMAR reactivity/inertia toward a given aldehyde acceptor.

Introduction

Chiral secondary homoallylic alcohols, featuring a carbon–carbon double bond and a hydroxy group in a 1,3-relationship, are widespread structural motifs in natural products and useful materials in organic synthesis, amenable to further elaboration toward a realm of products varied in shape and complexity.[1] Many biologically active molecules including polyenic amides (e.g. compounds **1** and **2**, Figure 1),[1c,2] polyene macrolide antibiotics (e.g. RK-397, **3**),[1a,3] and carotenoids,[1d,4] contain an extended, highly unsaturated homoallylic alcohol module, where geometrically defined conjugated olefins often terminate into an ester (lactone) or amide function. The distinctive topology and three-dimensional arrangement of these polyenic homoallylic frames strongly shape the overall conformational and stereochemical presentation of the molecules they are embedded in, thus affecting their biology which spans from antibiotic to antifungal and antineoplastic activities.[1c,5] In addition, the presence of conjugated polyene chains renders most of these scaffolds sensitive to light irradiation and photoinduced isomerization, properties that prompted their use as suitable matrices for molecular switching devices, light-harvesting materials, and solar energy transducers.[6]

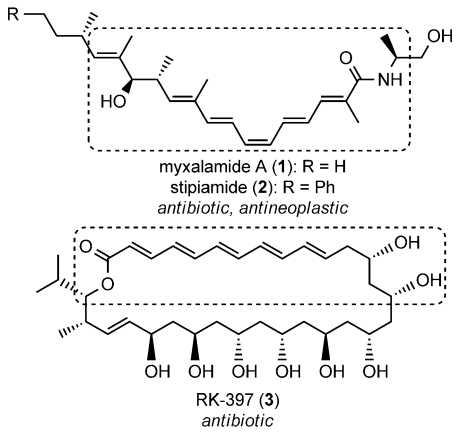

Figure 1. Representative bioactive natural products embedding a stereogenic polyenic homoallylic alcohol motif (circled).

The majority of synthetic studies toward these products have focused on stepwise approaches, in which the homoallylic alcohol moiety was built stereoselectively through vinylogous aldol or metal-mediated allylation reactions, whereas the elongation of the polyene chain was usually achieved through iterative Wittig-type reactions or transition metal-catalyzed

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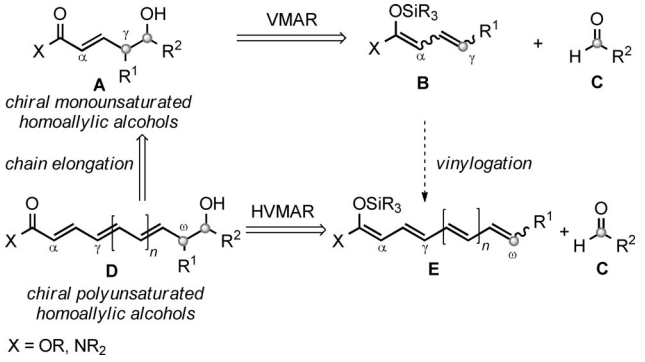
cross couplings.[1c,2c,3c] In particular, to access the homoallylic alcohol moiety, the vinylogous Mukaiyama aldol reaction (VMAR) emerged as one of the most versatile and efficient methodologies, and many catalytic asymmetric versions of this reaction have been developed toward this end.[7] Thus, an ester- or amide-derived silyl ketene acetal **B** may be added to an aldehyde **C** selectively at its vinylogous γ-position to deliver δ-hydroxy-α,β-monounsaturated carbonyl compounds of type **A**, in which up to two stereocenters and one double bond can be created simultaneously (Scheme 1, top).

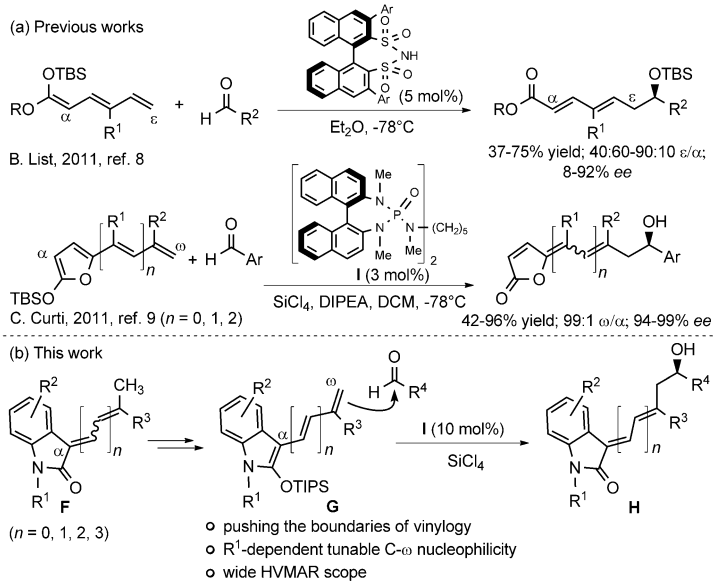


Scheme 1. Vinylogous vs. hypervinylogous Mukaiyama aldol reaction (VMAR vs. HVMAR) strategies toward chiral polyenic homoallylic alcohol functionalities.

Despite noteworthy advances in monovinylogous strategies, a crucial point remains elusive in this field; to simultaneously establish both the homoallylic carbinol center and the extended polyene backbone with fair geometrical and absolute stereocontrol. To this end, application of the higher vinylogy concept would be an attractive solution. Polyunsaturated silyl ketene acetals **E** could be easily accessed (Scheme 1, bottom), serving as extended polydentate carbon nucleophiles in hypervinylogous aldol addition reactions (HVMAR) with aldehydes **C**. Should it be possible to perfectly direct the coupling at the most distant ω position of the molecule (ω-regioselectivity), densely functionalized polyunsaturated homoallylic alcohols **D** would be at hand, where the issue of geometrical control of the newly formed carbon–carbon double bonds adds to the usual problems of diastereo- and enantiocontrol. In the context of asymmetric HVMAR, there are two precedents; List and co-workers[8] and, independently, our research group[9] have both recently described the asymmetric bisvinylogous and hypervinylogous Mukaiyama-type aldol reactions of polyunsaturated silyl ketene *O,O*-acetals catalyzed by either axially chiral disulfonamide or bisphosphoramide/$SiCl_4$ systems, two complementary protocols that enabled the production of linear silyloxy polyenoates and γ-alkylidene butenolide carbinols, respectively, with good to excellent margins of regio-, diastereo-, and enantioselectivity (Scheme 2, top).

Despite these successful developments, exploitation of asymmetric HVMAR to access amide(lactam)-derived polyunsaturated carbonyl compounds has, to our knowledge, never been reported. Moreover, some crucial points render polyunsaturated silyl ketene *N,O*-acetal donors particularly attractive. Transmission of the enolate reactivity along the conjugated polyene chain (vinylogous transmittal) may well be influenced, in synergy with structural and conformational factors, by the nature of the amide nitrogen atom, whose electronic behavior may be tuned by a suitable appendage attached to it.[10] In principle, a strong electron-donating group is expected to amplify the vinylogous transmittal of the enolate functionality along the polyene chain, allowing formation of highly extended homoallylic functionalities. In addition, the enhanced remote nucleophilicity could pave the way to couplings with less reactive aliphatic aldehydes, a maneuver that has not to date been achieved in the asymmetric HVMAR.

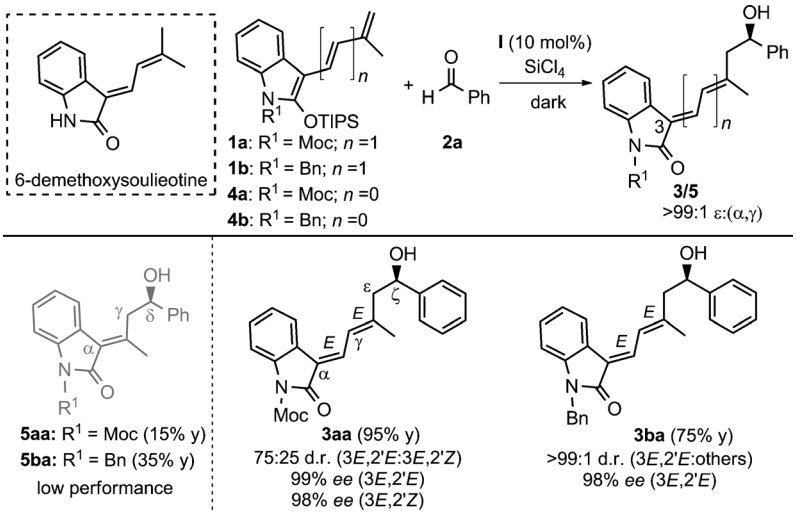
As a proof of concept, we focused our attention on 3-butadienyl-2-silyloxyindoles and higher homologues of type **G** (Scheme 2, bottom), which are readily obtainable from the corresponding highly conjugated 3-alkenylidene 2-oxindoles **F**, an intriguing yet overlooked progeny of natural compound-related indole pronucleophiles.[11] When remotely coupled to aldehyde acceptors in an asymmetric context, silyl nucleophiles **G** would hopefully generate chiral, multiply unsaturated 2-indolinones **H**, in which the carbinol stereocenter is created at the most distant point of the molecule, several atoms away from the original oxindole lactam function. Needless to say, there are inherent challenges behind this goal: 1) *Regiocontrol*, given the presence of multiple, competitive nucleophilic sites within component **G** (potential α, γ, ε, η, … ω-site attacks); 2) *polyene control*, given the presence of extended emerging alkene bonds within products **H** (alkene *E/Z*-geometry, positioning,



Scheme 2. Catalytic, asymmetric hypervinylogous Mukaiyama aldol reaction (HVMAR) in action. DIPEA = diisopropylethylamine; TBS = *tert*-butyldimethylsilyl; TIPS = triisopropylsilyl.

isomerization, migration); 3) *enantiocontrol*, given the facial discrimination potential of the electrophile by the chiral catalyst; 4) *syn/anti diastereocontrol*, arising when prochiral nucleophiles are involved. Thus, full mastery of these issues remains a crucial task.

Herein we describe the execution of this ideal and report perfect remote site-selectivity and superb geometrical, enantio-, and diastereoselectivities in the HVMAR addition of 3-butadienyl-, 3-hexatrienyl-, and 3-octatetraenyl-2-silyloxyindoles to both aromatic and aliphatic aldehydes, realized by use of the enabling combination of silicon tetrachloride and the chiral bisphosphoramide base **I** (Scheme 2), developed and exploited by Denmark and coworkers several years ago.[12] Also, reliable ^{13}C NMR-based empirical methods coupled with density functional theory (DFT) calculations on selected nucleophiles were provided, which could give a measure and prediction of the hypervinylogous aldol reactivity of homologous silyl ketene-*N*,*O*-acetal polyene donors as a function of both the oxindole lactam *N*-substituent and the overall conformation/coplanarity of the extended polyene chain. Finally, focused experiments aimed at the selective photoisomerization of representative polyene products were performed, a prelude to possible applications in photo-responsive material science.



Scheme 3. Catalytic, enantioselective ε-selective HVMAR. Reactions were carried out using donor **1** (or **4**) (0.2 mmol), aldehyde **2a** (2.0 equiv), catalyst **I** (10 mol%), $SiCl_4$ (1.5 equiv), DIPEA (10 mol%) in CH_2Cl_2 (0.1 M) at −45 °C for 16 h in dark. Yields (y) refer to combined isolated products; d.r. is determined by HPLC or ^1H NMR analysis; *ee* is determined by HPLC on chiral stationary phase. Moc = methoxycarbonyl; Bn = benzyl.

Results and Discussion

Synthesis

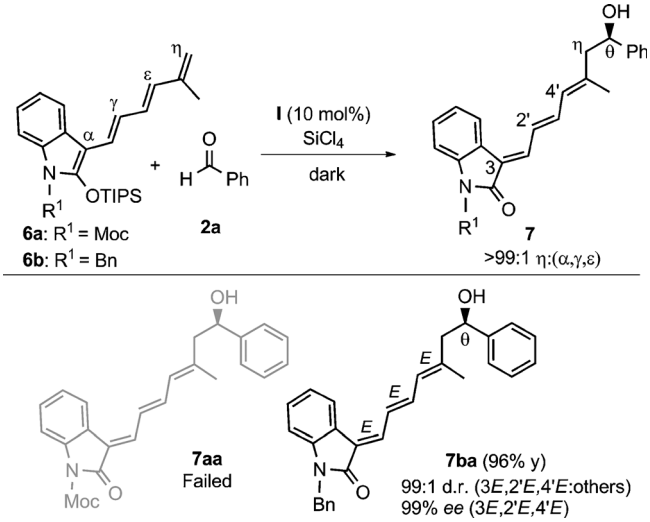
We commenced our studies by examining the bisvinylogous Mukaiyama aldol reaction involving variously protected 3-butadienyl-2-silyloxyindoles of type **1** (Scheme 3), which were obtained by *N*-protection and enolization/silylation of the common 3-alkylidene oxindole precursor 6-demethoxysoulieotine, a yellow pigment isolated from the rhizomes of several *Cimicifuga* and *Actaea* genera (*Ranunculaceae*).[13] From a synthetic point of view, it is noteworthy that compounds **1**, along with the set of olefinic 2-silyloxyindoles tested in this work, are relatively stable compounds, which are readily synthesized from the parent oxindoles or isatins in few conventional steps in good yields, and could be isolated and purified by standard silica-gel flash chromatographic techniques and stored for months (see the Supporting Information for more details).[14] For optimum reaction conditions, critical parameters as the nature of the indole *N*-protecting group and the silicon substitution, as well as catalyst loading, molar ratio between reagents, reaction time and temperature were surveyed in the addition to benzaldehyde (**2a**), as detailed in Table S1 in the Supporting Information. Although fairly similar results were obtained with diverse R^1 substituents in the indole nucleophiles, it was determined that the *N*-Moc/*O*-TIPS and the *N*-Bn/*O*-TIPS combinations gave the most promising results in terms of a balance between yield, geometric control, and enantioselectivity, as well as ease of substrate preparation and product stability.

Interestingly, during the optimization study we were soon challenged by poor data reproducibility under standard reaction conditions, resulting in highly variable *E*/*Z* diastereomeric ratios of products **3**. In particular, for diene product **3aa**, the prevailing all-*trans* isomer 3*E*,2′*E*-**3aa** was accompanied by minor amounts of the 3*E*,2′*Z* geometrical isomer, along with variable quantities of the 3*Z*,2′*E* counterpart. This problem was solved by running the reactions in the dark, away from direct sunlight irradiation, which resulted in reproducible data with almost complete suppression of the *Z*,*E* isomer's formation (see the Supporting Information, Figure S1).

Thus, under optimized reaction conditions, exposure of *N*-Moc-protected indole **1a** to benzaldehyde (**2a**) in the presence of a combination of $SiCl_4$, (*R*,*R*)-bisphosphoramide **I** (10 mol%), and DIPEA (10 mol%) in CH_2Cl_2 at −45 °C in the dark returned a 3:1 (*E*:*E*,*Z*) diastereomeric mixture of the desired ζ-hydroxylated alkenylidene product **3aa** isolated in a remarkable 95% combined yield, with superb regio- and stereocontrol (>99:1 ε vs. α,γ; 99% *ee* for the *R*-configured *E*,*E* isomer; 98% *ee* for the *R*-configured *E*,*Z*-isomer, Scheme 3). Switching from indole **1a** to the more electron rich *N*-benzyl silyloxindole **1b** proved also successful, affording adduct **3ba** in a 75% isolated yield as a sole (*E*,*E*)-isomer, with remarkable levels of regio- and enantioselectivity (Scheme 3). Notably, treating silyloxyindoles **4a** or **4b**—shorter homologues of **1**—with benzaldehyde in the optimized reaction conditions afforded the corresponding products **5** in low yield and poor stereocontrol, pointing to the

notion that under these experimental conditions the vinylogous transmittal is effective in the butadienyl donors, whereas it is somehow hampered in the lower ethenyl series (see below).[15]

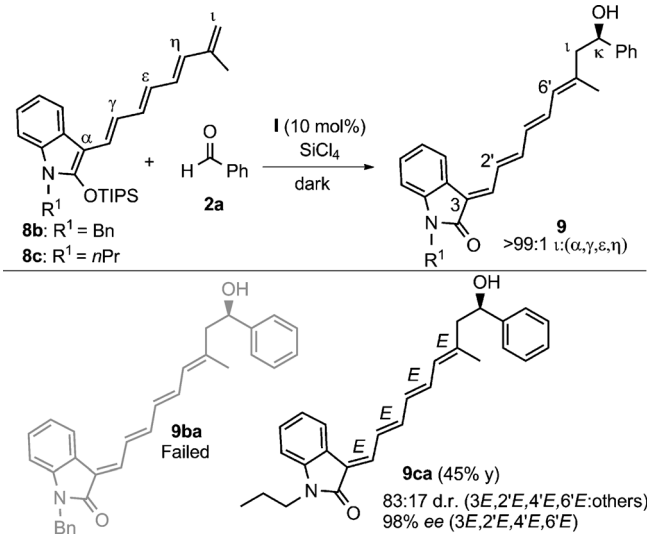
Next, we turned our attention to widening even more the vinylogous reactivity scope of this class of donor substrates as a route to triply unsaturated oxindole carbinols. Accordingly, we explored the challenging tris-vinylogous Mukaiyama aldol reaction using *N*-Moc silyloxytetraene **6a** (Scheme 4), which



Scheme 4. Catalytic, enantioselective η-selective HVMAR. For conditions, see legend of Scheme 3, using donors **6** instead of **1** or **4**.

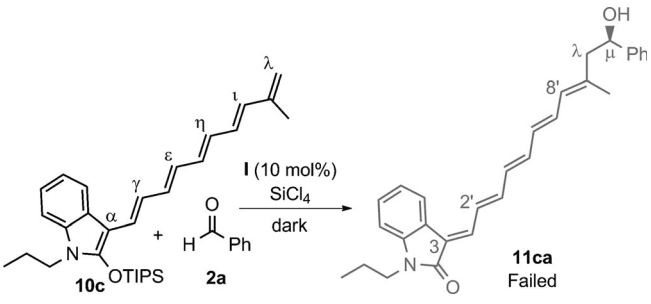
was quickly obtainable from the parent protected hexenylidene oxindole in one enolization–silylation step. Regrettably, the addition failed here to deliver any product, returning instead solely the all-*trans*-configured 3-alkenylidene precursor. Any attempts to promote the coupling by modifying the reaction conditions were equally frustrated. The inertia of this reaction is possibly due to the fact that the electron-withdrawing *N*-Moc substituent mitigates the nucleophilic character of the very remote η-olefinic carbon of the substrate, thus hampering the addition to the aldehyde carbonyl. We thus reasoned that the polyene η-nucleophilicity could be enhanced by switching the electron-withdrawing *N*-Moc function to an electron-donating group such as the benzyl, whose good performance in the previous bisvinylogous coupling has been corroborated. Our expectations turned out to be correct and we were pleased to see that *N*-Bn silyloxytetraene **6b** cleanly and efficiently underwent addition to **2a** under the previously optimized reaction conditions, delivering θ-hydroxytrienyl oxindole **7ba**, isolated in an outstanding 96% yield, with virtually complete all-*E* selectivity and excellent enantiomeric purity (99% *ee*, Scheme 4). Noticeably, the newly formed θ-carbon stereocenter stands *eight bonds away* from the origin of the vinylogous effect (the *N*,*O*-acetal C2 carbon).

With this result in hand, the next question was: How far could we push the limits of the vinylogous reactivity transmittal in such indolyl compounds? Facing this challenging task,

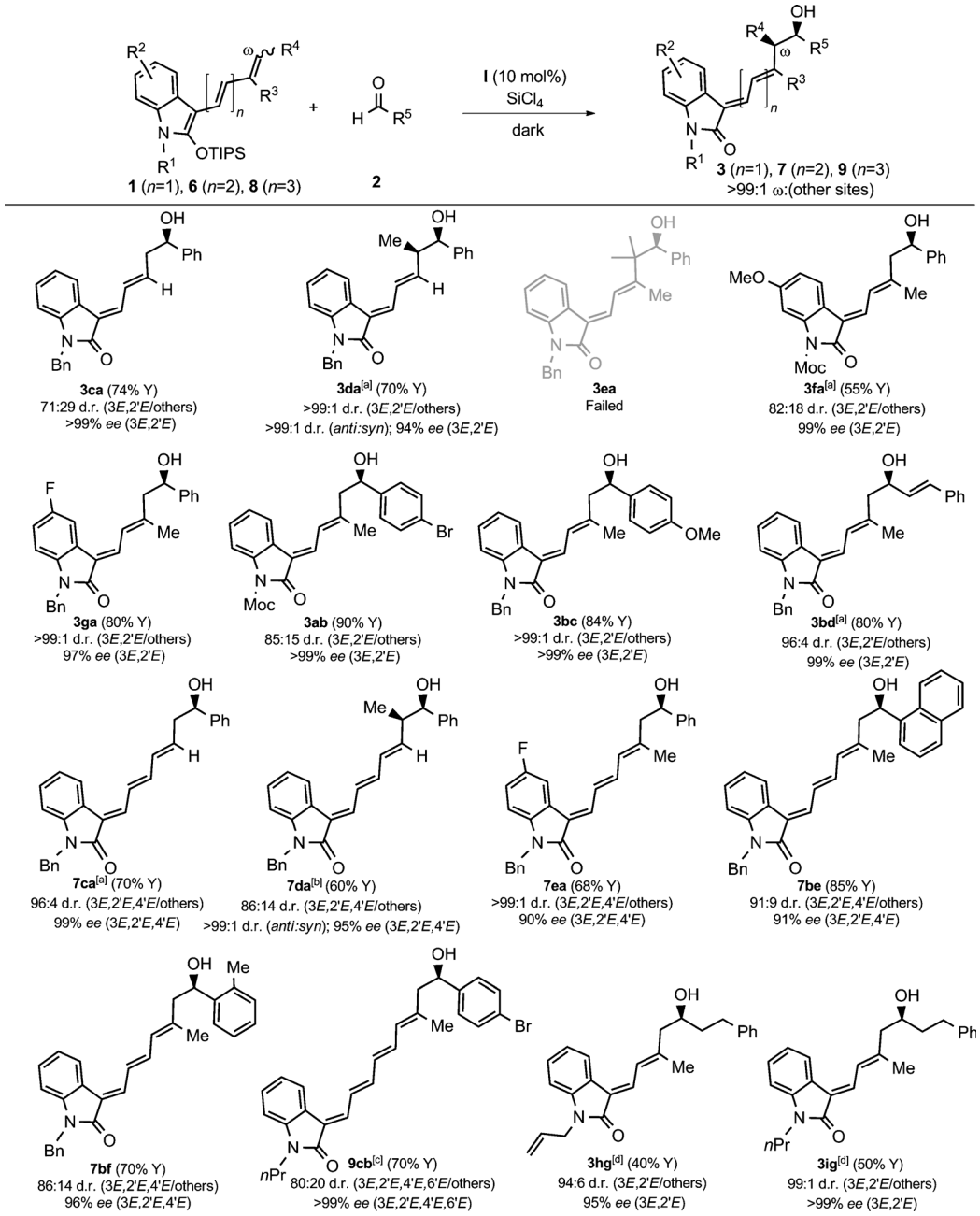


Scheme 5. Catalytic, enantioselective ι-selective HVMAR. For conditions, see legend of Scheme 3, using donors **8** instead of **1** or **4**.

we constructed chain-extended benzyl-protected silyloxyindole pentaene **8b** and explored its vinylogous reactivity space by coupling to benzaldehyde (**2a**) under the previously optimized catalytic conditions. As shown in Scheme 5, the reaction failed to afford the desired ι-selective adduct **9ba**, while 70% of the alkylidene oxindole precursor of **8b** could be recovered from the crude reaction mixture as a single all-*E* isomer after chromatographic purification. We thus opted to tune the nucleophilic character of the indole pentaene by searching for a suitable substituent at the indole nitrogen that could improve the electron density of the polyene terminus. After a brief survey, we chose to use *N*-*n*Pr derivative **8c**. When put to the test, **8c** proved to be a competent nucleophile in the asymmetric HVMAR to benzaldehyde (**2a**), and returned all-*trans* tetraene oxindole **9ca** in a reasonable 45% yield, with almost complete enantiocontrol (98% *ee*). Remarkably, the chiral hydroxy function was here installed at the κ-position in the chain, *ten bonds away* from the indole C2 carbonyl. Moving forward and eager to explore the limits of this vinylogous transmittal, we opted to synthesize a higher homologue of **8c**, namely, *N*-propyl silyloxyindole hexaene **10c**, and sought to explore its vinylogous behavior, again, by coupling to benzaldehyde **2a** (Scheme 6).



Scheme 6. Attempts toward catalytic, enantioselective λ-selective HVMAR. For conditions, see legend of Scheme 3, using donor **10c** instead of **1** or **4**.



Scheme 7. Substrate scope of the catalytic, enantioselective HVMAR. For conditions, see legend of Scheme 3, using donors **1**, **6** or **8** and acceptors **2**. [a] Due to partial peak overlapping in chiral HPLC profile, the reported *ee* value could be affected by an insignificant margin of error; [b] stereochemical structure ascertained by chemical correlation studies; [c] stereochemical structure ascertained by single-crystal X-ray diffraction analysis of its enantiomer *ent*-**9cb**;[17] [d] $T = -30\,^{\circ}C$; tetrabutylammonium triflate (TBAOTf; 10 mol%) added.

Unfortunately, under the standard reaction conditions, the reaction failed, returning 65% of the alkylidene oxindole precursor of **10c** as a single all-*E* geometrical isomer. We thus decided to stop our survey at this point, setting the limit of the vinylogous transmittal for these indole-based systems up to five conjugated double bonds, aware that a key for further success would possibly imply the search for a suitable electron-donating group at the indole nitrogen atom.

Reaction scope

By using the optimized reaction conditions, we then wished to explore the scope and limitation of this catalytic HVMAR with respect to both the donor and the acceptor reaction components, and the results of this study are collectively displayed in Scheme 7. As for the bisvinylogous products of type **3**, in addition to **3aa** and **3ba**, a varied repertoire of doubly unsaturated oxindole carbinols was efficiently assembled with precise regio- and stereocontrol. Different indole-based trienoxysilanes

of type **1**, bearing either the Moc- or benzyl group at the indole nitrogen atom, were tested in reactions with **2a**.

Variation of the R^3 and R^4 substituents within the C3 diene appendages as well as the R^2-benzo-ring substituent were well tolerated, returning the corresponding products **3ca**, **3da**, and **3ga** in good yields and stereoselectivities. The 6-methoxy derivative **1f**, reminiscent of the natural soulieotine precursor, instead furnished product **3fa** with a diminished yield (55% isolated), albeit with good *E*,*E*-diastereocontrol and excellent enantioselectivity. Among the above examples, particularly noteworthy is triene **1d**, which embodies a prochiral terminal alkene as an inseparable 2:1 *E*/*Z* mixture; it could react productively with benzaldehyde **2a** to form carbinol **3da** as a single 3*E*,2′*E*-, *anti*-configured isomer with high levels of enantioselectivity (94% *ee*). As an exception, siloxyindole **1e**, bearing a highly congested tetrasubstituted terminal olefin, failed to couple to benzaldehyde **2a**, and no traces of the expected product **3ea** were obtained. We also investigated reactions with diverse electron-rich and electron-poor aldehydes, namely 4-bromobenzaldehyde (**2b**), 4-methoxybenzaldehyde (**2c**), and *trans*-cinnamaldehyde (**2d**). We were pleased to find that all aldehydes were converted into the corresponding 3*E*,2′*E*-adducts (e.g., **3ab**, **3bc**, and **3bd**) in 80–90% yields and 99% enantioselectivities. The viability of the hypervinylogous protocol was further demonstrated by treating several *N*-benzyl silyloxytetraene indole substrates with a range of aromatic aldehydes. Precise control of the geometry, regiochemistry, and stereochemistry was attained in all cases, to deliver oxindole trienes **7ca**, **7da**, **7ea**, **7be**, and **7bf** isolated in acceptable 60–85% yields and rewarding selectivities. Once more, when a 2:1 (1′*E*,3′*E*,5′*Z*:1′*E*,3′*E*,5′*E*) mixture of prostereogenic derivative **6d** reacted with **2a**, the all-*E*-configured carbinol **7da** was formed in 60% yield, with excellent *anti*/*syn* diastereoselectivity and high enantiocontrol (95% *ee*). Switching to higher homologues, the reaction of *n*Pr-protected silyloxypentaene donor with 4-bromobenzaldehyde **2b** was carried out, affording crystalline tetraene carbinol **9cb**, isolated in a pleasing yield of 70%, with good diastereoselectivity and almost complete regio- and enantioselectivities (>99% *ee*). These reactions demonstrated perfect relaying of the *N*,*O*-silylketene acetal functionality along the limiting series of five conjugated double bonds.

As pointed out in the introduction, one of the challenging goals of this work was to demonstrate the feasibility of the HVMAR involving aliphatic aldehydes, whose behavior as sluggish or unreactive acceptors in Mukaiyama-type aldol reactions catalyzed by the Denmark's bisphosphoramide **I**/$SiCl_4$ system is renowned.[16] In our hands, when coupled to *N*-Moc or *N*-benzyl-protected 3-butadienyl-2-siloxyindoles **1a** or **1b**, aliphatic 3-phenylpropanal (**2g**) failed to deliver any addition product, testifying its poor reactivity vis-à-vis the aromatic counterparts. Aware of the previous results likely suggesting vinylogous reactivity amplification of polyene donors as a function of the electronic properties of the indole *N*-substituent, a brief survey of differently protected trienolates of type **1** was carried out. *N*-Allyl- and *N*-*n*-propyl silyloxyindoles **1h** and **1i** were identified and selected, as their ^{13}C NMR spectroscopic profiles rendered them promising candidates to be tested in the asymmetric HVMAR addition to **2g** (for ^{13}C NMR-based prediction of reactivity, see below). Pleasingly, under slightly modified reaction conditions (reaction temperature −30 °C and 10 mol% TBAOTf additive), both nucleophiles **1h** and **1i** reacted with **2g** to yield the bisvinylogous adducts **3hg** and **3ig**, respectively, with high regio-, diastereo- and enantiocontrol, albeit in rather modest yields of the isolated products (40 and 50%, respectively). To our knowledge, this is the first example of catalytic, enantioselective, bisvinylogous Mukaiyama aldol reactions on aliphatic aldehyde acceptors.

The overall alkene geometry and absolute configuration of homoallylic tetraeneoxindole **9cb** was unequivocally determined as 3*E*,2′*E*,4′*E*,6′*E*,9′*R*, based on the X-ray diffraction analysis of its enantiomer *ent*-**9cb** (obtained using catalyst (*S*,*S*)-**I**).[17]

To ascertain the configuration of triene oxindole **7da**, chemical correlation studies were performed, definitively assessing its relative and absolute configuration (see the Supporting Information). The absolute configurations of all other products in this work were assigned by analogy. Polyenic alcohol products in this study (coming from catalyst *(R,R)*-**I**) turned out to possess (*R*)-configuration at the carbinol center (*S* for compounds **3hg** and **3ig**, due to formal priority exchange according to CIP rules), resulting from an attack of the polyene donor on the *Re*-face of the aldehyde acceptor. This is in full accordance with previous experimentation where Mukaiyama aldol (and vinylogous aldol) reactions were carried out under the same bisphosphoramide/$SiCl_4$ activation modality.[12a]

HVMAR of 3-polyenyl 2-silyloxyindoles: Electronic and conformational clues

At this point, we reasoned that rationalization of the experimental evidences could be useful to better evaluate successful results and failures and, even more importantly, to find out a reliable method upon which prediction abilities could be established. The efficiency in channeling the nucleophilicity of the indole *N*,*O*-silyl ketene acetals through the π-conjugate system to the very remote ω-site is likely dependent upon a combination of electronic, steric, and conformational factors. As a first point, the nucleophilic ω-reactivity (HOMO activation) proved strongly influenced by the indole *N*-substituent, whose electron-withdrawing or electron-donating nature modulates the charge distribution along the polyene chain up to the reactive ω-site. In this study, as a rule, the "activating" action followed the progression: *n*Pr ≈ allyl > benzyl > methoxycarbonyl.[18]

In this context, analysis of diagnostic C-ω peaks in the ^{13}C NMR spectra of polyenolates **1**, **4**, **6**, **8**, and **10** was found to be helpful in deciphering the behavior of these donor species during the asymmetric catalytic HVMAR (Figure 2). ^{13}C NMR chemical shift is primarily controlled by the σ and π electron density located on each carbon atom, undergoing an upfield shift when the electron density increases.[19] In other words, the more the C-ω ^{13}C NMR peak shifts to the right side of the spectrum, the higher the nucleophilicity.[20]

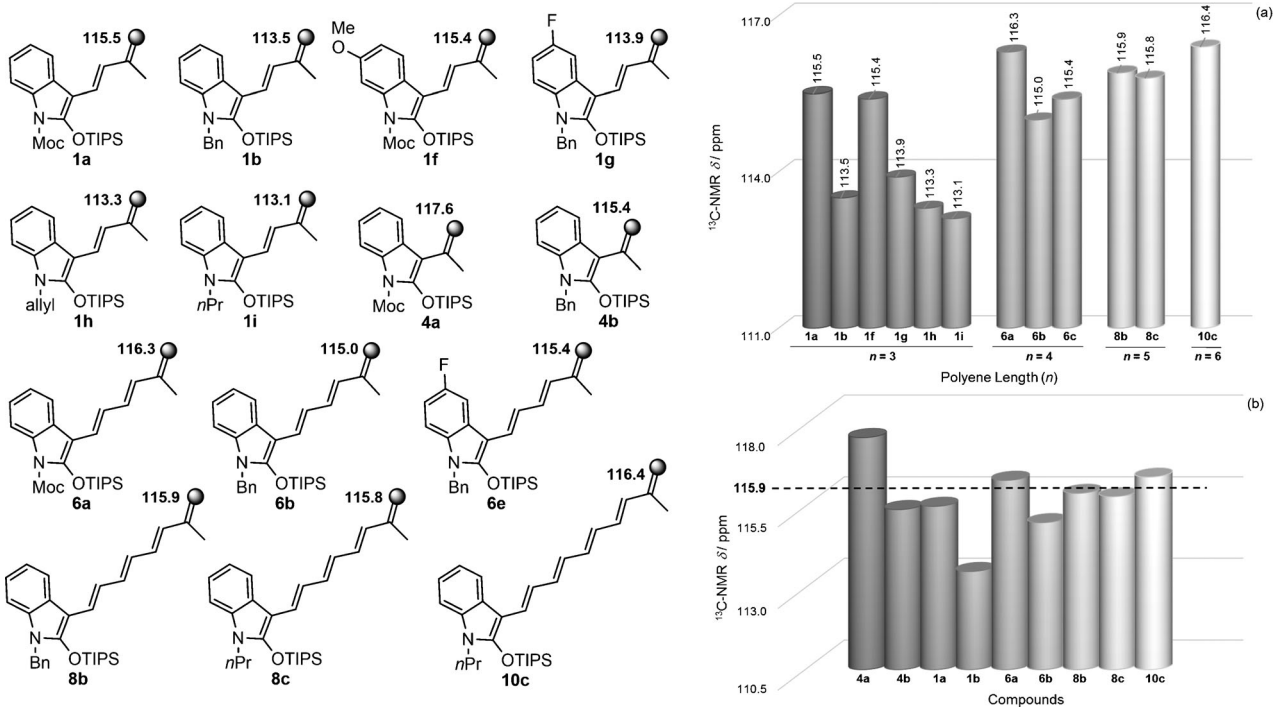


Figure 2. Left: Chemical structures of selected 3-polyenyl 2-silyloxyindoles in this study and ^{13}C NMR chemical shift of the C-ω methylene (ppm, 75 MHz, $CDCl_3$). Right: Graphical representation of C-ω ^{13}C NMR values (a), and cut-off line (dotted line) determining the boundary between successful and unsuccessful HVMAR coupling to benzaldehyde (b).

Along the series of methylene-ending donor homologues **1** (e.g., **1a**, **1b**, **1f**, and **1g**), bearing either the Moc or benzyl protecting groups, C-ε chemical shifts were in the range $\delta =$ 113.5–115.5 ppm, indicating a remote nucleophilicity "good" for coupling towards aromatic aldehydes but not "good enough" for couplings involving aliphatic aldehydes. Lowered C-ε peaks at $\delta = 113.1$–113.3 ppm as shown in the ^{13}C NMR spectra of allyl/propyl-protected siloxyindoles **1h** and **1i** translated into successful couplings also to aliphatic aldehydes. When passing to tetraenes of type **6**, a ^{13}C NMR chemical shift of $\delta = 116.3$ ppm for **6a** corresponded to a completely inhibited HVMAR coupling to benzaldehyde, whereas lower values for **6b** and **6e** ($\delta = 115.0$ and 115.4 ppm, respectively) corresponded to successful couplings to the same aldehyde. The boundary between reactivity and inertia was much less obvious considering pentaenes **8**, whose subtle chemical shift difference ($\delta = 115.9$ ppm for **8b** and 115.8 ppm for **8c**) was enough to decree HVMAR success or failure. Also, the chemical shift for hexaene **10c** ($\delta = 116.4$ ppm) was clearly "too high" for the coupling to benzaldehyde to occur.[21]

Steric effects may also play a role in the HVMAR coupling, as demonstrated in the reaction involving triene **1e**, which completely failed to producing adduct **3ea** due to the presence of a highly encumbered quaternary C-ε terminal.

Lastly, conformational concerns have to be considered, since π-conjugation and electronic transmission are really effective when coplanarity of the whole polyene chain is guaranteed. Conformational analysis of selected polyenes was performed, revealing low-energy planar all-*E* conformations for both trienes **1a** and **1b**, and higher polyenes **6a**, **6b**, **8c**, and **10c** (Figure 3 and Tables S3 and S4 in the Supporting Information). In contrast, shorter dienes **4a** and **4b** (C-γ: $\delta = 117.6$ and 115.4 ppm), which had very low reactivity profiles in VMAR couplings, displayed low-lying conformational arrangements in which the exocyclic alkenyl chain bends 43° away from the

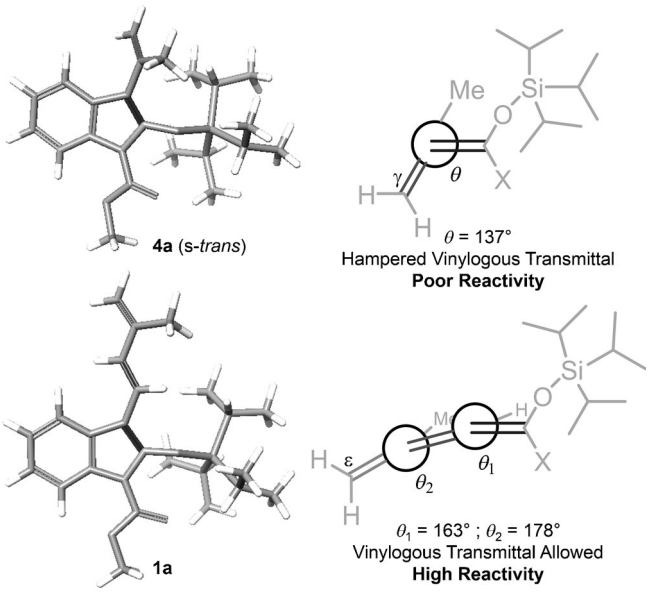


Figure 3. Low-energy conformations of 3-propenyl 2-silyloxyindole **4a** (top) and 3-butadienyl 2-silyloxyindole **1a** (bottom), as obtained from DFT calculations. Compound **4a** shows significant deviation of the exocyclic alkenyl chain from the indole ring plane, whereas longer homologue **1a** shows almost perfect coplanarity of the polyene system.

indole ring plane (Figure 3 and Table S2 in the Supporting Information); and this may be responsible for limited conjugation, and hence delayed vinylogous transmittal, between the *N*,*O*-silyl ketene acetal function and the remaining unsaturated chain.

From the above considerations, one could conclude that elongation of the exocyclic carbon chain within the 3-polyenyl-2-silyloxyindoles in this study, while being responsible for a certain mitigation (in absolute value) of nucleophilicity at the remote site, is beneficial for securing coplanarity, a prerequisite for fair electronic transmission in hypervinylogous systems.

Photoisomerization experiments

During the experimental optimization, a crucial point emerged concerning the use of dark conditions, which could preserve the geometrical integrity of HVMAR products while guaranteeing reaction reliability. The marked photosensitivity of HVMAR products upon sunlight stimulus—testifying to extensively conjugated molecular systems—required further investigation. The impact of photoisomerizable compounds as powerful tools in biomedical engineering, material science, and biology is hardly overestimated, and a plethora of studies have been reported pertaining to this wide and ever-emerging research field.[22] Thus, optically pure, all-*E*-configured tetraene carbinol **9 cb** was selected for representative photoisomerization experiments (Figure 4). Irradiation of an ethanol solution of *E*,*E*,*E*,*E*-**9 cb** (UV/Vis spectrum, $\lambda_{max} = 410$ nm, log $\varepsilon = 4.38$; see the Supporting Information for details) was performed by using a 23 W white light CFL bulb and monitored by HPLC analysis at different time intervals until the photostationary state (PSS) was reached (after 1 h). An almost equimolar isomeric mixture at PSS was obtained containing *E*,*E*,*E*,*E*-**9 cb** and *Z*,*E*,*E*,*E*-**9 cb**. After chromatographic separation of the isomers, pure *Z*,*E*,*E*,*E*-**9 cb** was isolated, which preserved its geometrical integrity on standing in dark conditions for weeks. By photoirradiation of *Z*,*E*,*E*,*E*-**9 cb** with the same light source, the PPS was reached over a 2 h period and a 55:45 ratio was obtained in favor of the 3*Z*-isomer.

Remarkably, the isomerization process proved strictly regioselective, since it involved geometry change of the alkenylidene at the oxindole C3 position solely, leaving the remaining exocyclic olefins untouched. Even in their preliminary status, these experiments highlight that chiral oxindole-based polyenic carbinols in this study are effective light-responsive molecules whose stereochemical arrangement could be modulated, depending upon the presence (or absence) of an external light stimulus.

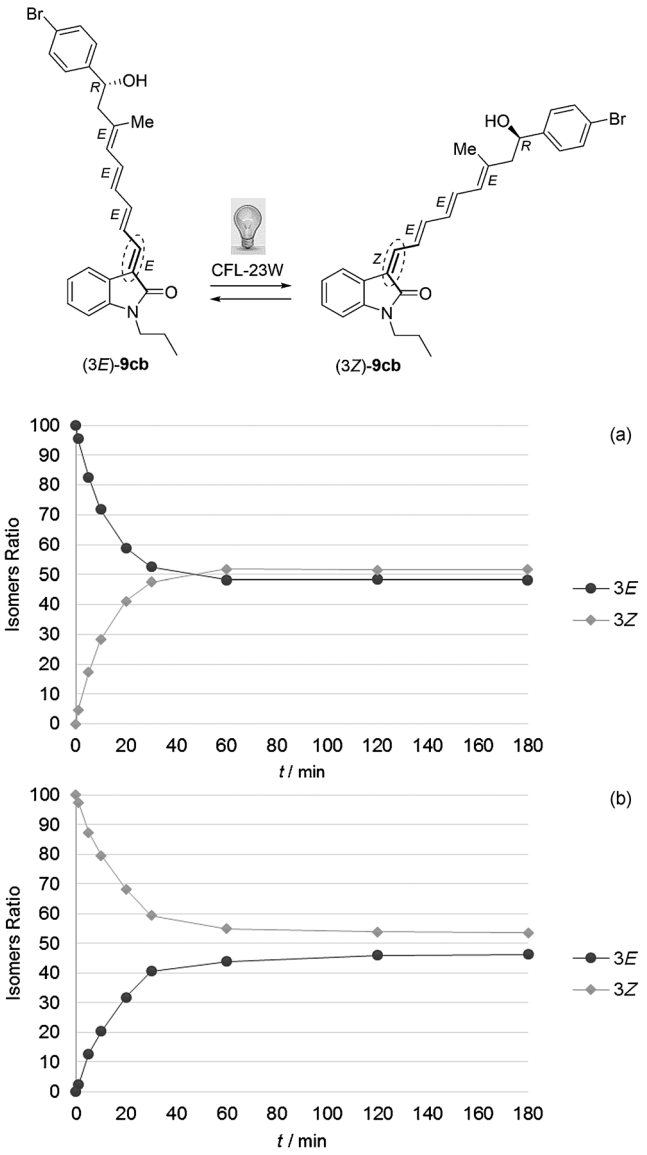


Figure 4. Isomeric ratio vs. irradiation time starting from *E*,*E*,*E*,*E*-**9 cb** (a) and *Z*,*E*,*E*,*E*-**9 cb** (b) respectively, using a 23 W white light CFL bulb.

Conclusion

We developed an asymmetric catalytic hypervinylogous Mukaiyama aldol reaction coupling variously extended 3-polyenyl-2-silyloxyindole donors with aromatic or aliphatic aldehyde acceptors. The products, featuring a 3-polyenylidene homoallylic carbinol motif conjugated to the 2-oxindole lactam, were obtained in good to excellent yields, with superb enantioselectivities, good to excellent *E*/*Z* and *anti*/*syn* diastereoselectivities, and complete ω-site selectivities. To our knowledge, it is the first time that the simultaneous, stereocontrolled installation of up to four olefinic bonds and one homoallylic alcohol has been reported in synthetic ventures. The judicious choice of the *N*-oxindole substituent proved crucial in pushing the boundaries of vinylogous reactivity at the most remote reactive carbon site, up to ten bonds away from the oxindole directing group. ^{13}C NMR analysis and DFT calculations carried out on the reacting donor species provided rational analysis of the results while giving certain degree of HVMAR prediction capabilities. We believe that this study is a proof of concept of furthering the limits of vinylogous transmission in Mukaiyama aldol reactions. The synthetic method reported herein offers the opportunity to access highly unsaturated, enantioenriched lactam carbinols, useful molecular motifs in the chemistry of both natural products and photoresponsive materials.

Experimental Section

Typical procedure for HVMAR reactions

In a suitable brown glass vessel, DIPEA (3.5 μL, 0.02 mmol, 0.1 equiv) was added via syringe to a solution of catalyst **I** (17 mg, 0.02 mmol, 0.1 equiv) in anhydrous CH_2Cl_2 (1.0 mL), under argon atmosphere. To this solution, benzaldehyde (41 μL, 0.4 mmol, 2.0 equiv) was added in one portion, and the reaction mixture was cooled to −45 °C. After 15 min, a solution of freshly distilled $SiCl_4$ (35 μL, 0.3 mmol, 1.5 equiv) in anhydrous CH_2Cl_2 (0.5 mL) was added dropwise to the reaction mixture, followed by the addition of the silyloxyindole (0.2 mmol, 1.0 equiv) dissolved in anhydrous CH_2Cl_2 (0.5 mL). The resulting mixture was stirred at −45 °C for 16 h, whereupon chilled CH_2Cl_2 (3.0 mL) was added and the cold reaction mixture was poured into a rapidly stirring solution of 1:1 saturated aqueous $NaHCO_3$/brine (25 mL) at 0 °C. This biphasic mixture was stirred vigorously for 2 h after which the aqueous layer was extracted with EtOAc (3×20 mL). The combined organic extracts were dried over Na_2SO_4 and filtered and the filtrate was concentrated under reduced pressure. The residue was purified by silica-gel flash chromatography to yield the corresponding HVMAR adduct of type **3**, **5**, **7**, or **9**.

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Keywords: aldol reaction · amides · asymmetric synthesis · vinylogy · oxindoles

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[15] The reactivity profiles of diene nucleophiles **4a** and **4b** proved strictly dependent on the reaction under scrutiny. When similar ethenyl siloxyindoles were coupled to activated nitrobenzaldehydes under the catalysis of **I** at −78 °C, the corresponding aldol products were isolated in modest 37 – 45% yields. See ref. [11]. In contrast, vinylogous Mannich addition to *N*-Boc imine acceptors under TMSOTf catalysis proved successful. See: B. Ranieri, A. Sartori, C. Curti, L. Battistini, G. Rassu, G. Pelosi, G. Casiraghi, F. Zanardi, *Org. Lett.* **2014**, *16*, 932 – 935.

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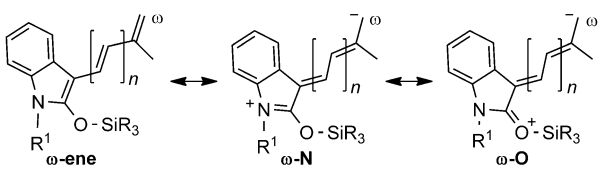
[18] In valency bonding terms, the neutral general structure of polyenyl 2-silyloxyindoles (**ω-ene**, see inserted figure) may be flanked by two alternative limiting resonance structures, **ω-N** and **ω-O**, where a negative charge is explicit at the C-ω position. The higher the stabilizing electron-donating effect of R′ on the nitrogen positive charge, the greater the role played by the **ω-N** structure.



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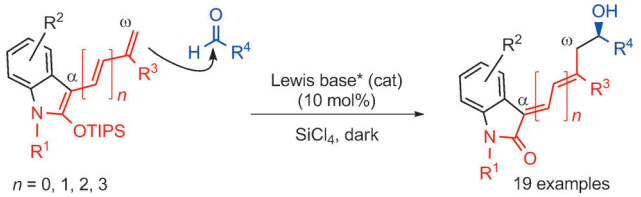

Asymmetric Synthesis

C. Curti, A. Sartori, L. Battistini, N. Brindani, G. Rassu, G. Pelosi, A. Lodola, M. Mor, G. Casiraghi, F. Zanardi**

■■ – ■■

Hypervinylogous is better: The first example of catalytic, enantioselective hypervinylogous Mukaiyama aldol reaction (HVMAR) involving polyunsaturated 2-silyloxyindoles is reported. The reaction provides the simultaneous installation of up to four conjugated olefins and one carbinol center delivering 3-polyenylidene 2-oxindole products with extraordinary levels of regio-, enantio-, and geometrical selectivity.

Pushing the Boundaries of Vinylogous Reactivity: Catalytic Enantioselective Mukaiyama Aldol Reactions of Highly Unsaturated 2-Silyloxyindoles

On the road…
…to hypervinylogy. On a dark cloudy day, lightning strikes a straight road at a distant point on the horizon. This scene represents how various aldehydes add at the most distant ω-point of the polyene chain of 3-polyalkenyl-2-oxindole nucleophiles through a catalytic, hypervinylogous Mukaiyama aldol reaction, as described by C. Curti, F. Zanardi et al. in their Full Paper on page ■■ ff.