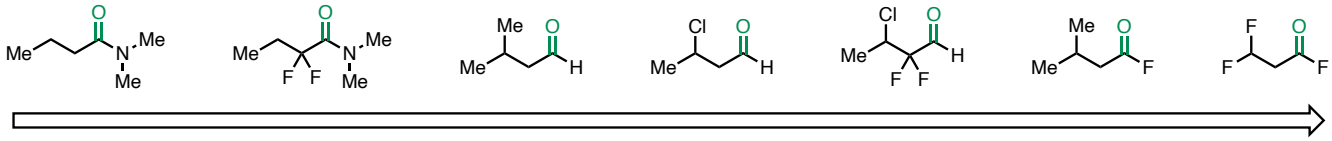
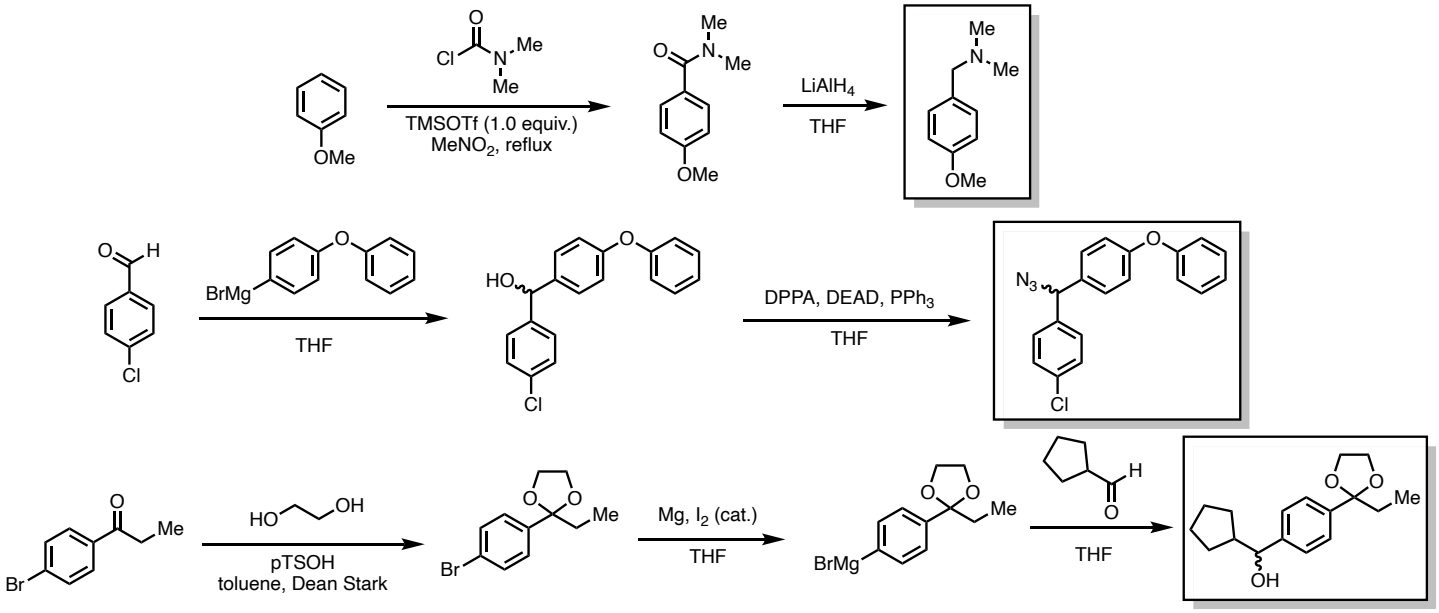
1. Order the following carbonyl compounds according to increasing electrophilicity [★]



We categorize first the different carbonyl groups, namely amides, aldehydes, and acyl fluorides. Amides are among the least electrophilic carbonyl compounds, due to the strong contribution of the N-lone pair to resonance. Aldehydes are substantially more electrophilic, and acyl halides are the most electrophilic. This is due to the strong inductive effect exerted by halide substituents, which are also prone to elimination from the tetrahedral intermediate. Among the amides, α-fluorination renders the carbonyl more electrophilic (inductive effect). By the same token, β-chlorination of aldehydes renders the carbonyl more electrophilic, but the effect is larger in the presence of α-fluorination. β-Fluorination in acyl fluorides has a significant impact on their electrophilicity.

2. Suggest a synthetic strategy based on carbonyl compounds for each of the following molecules. [★★]



The two-step conversion of anisole into its *N,N*-dimethylbenzylamine derivative can take advantage of the *ortho*/*para* directing effect of the methoxy substituent (electrophilic aromatic substitution). Friedel-Crafts acylation represents an excellent means of installing a group without the risk of over-acylation (when compared to the corresponding alkylation reaction, which renders the arene more electron-rich and therefore more susceptible to consecutive substitutions). The use of N,N-dimethylchloroformate with Lewis acid activation (*Eur. J. Org. Chem.* **2019**, 46–49) could form a substituted amide, which successively undergoes hydride reduction to the corresponding amine. Other possible reduction conditions (specific to benzylic amides) involve the use of siloxanes (*Angew. Chem. Int. Ed.* **2009**, *48*, 9511–9514) or zinc hydrides (*Angew. Chem. Int. Ed.* **2019**, *58*, 4992-4997).

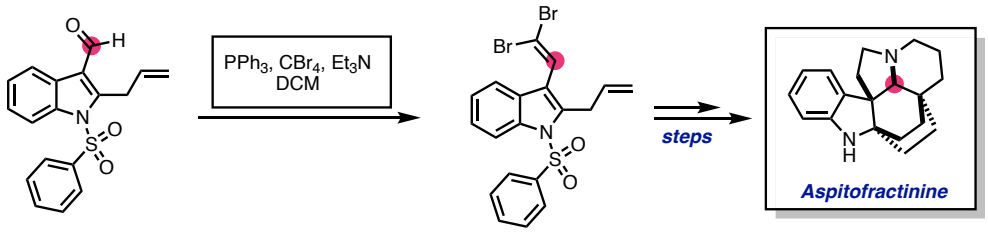
The two-step conversion of 4-chlorobenzaldehyde into the secondary azide can be achieved *via* final functional group interconversion of an alcohol, which originates from Grignard addition. Typical conditions involve the slow addition of Grignard reagent (in this case diphenylether 4-magnesium chloride or bromide) to the electrophile in ethereal solvent (THF, Et_2O, 1,4-dioxane, MTBE). Mitsunobu reaction using diphenylphosphoryl azide (DPPA) as azide source, diethylazodicarboxylate (DEAD) as electrophilic activator and triphenylphosphine can easily convert alcohols into azides (original publication: *Austr. J. Chem.* **1973**, *26*, 1591-1593).

Created by Peter Bellotti, PhD

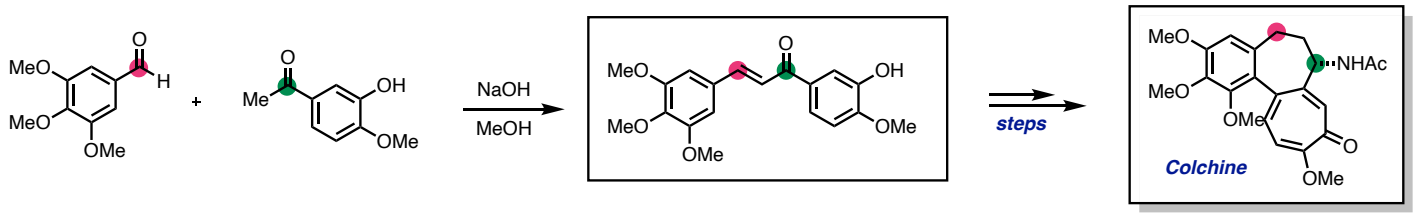
The three-step synthesis of the secondary alcohol from 4-bromophenylethylketone require two fundamental operations: (1) alkylation of the bromo-position; (2) protection of the ketone moiety as acetal. Strategically, the first reaction is the acetal formation, which can shield the ketone from undesired alkylation. Common conditions involve refluxing the ketone with ethylene glycol in the presence of an acidic catalyst (*e.g. para*-toluenesulfonic acid) and water removal using a Dean-Stark apparatus, in order to drive the equilibrium reaction towards the product (see for example: *Eur. J. Org. Chem.* **2002**, 1677–1684). The following step involves the conversion of the aryl bromide into a Grignard reagent. Elemental magnesium, activated by a small amount of iodine to remove the passivating oxide layer, can undergo formal oxidative addition (is it believed to involve single-electron oxidation, see *Coord. Chem. Rev.* **2004**, *248*, 623-652) to generate the corresponding Grignard reagent as a solution in ethereal solvent. Cyclopentancarbaldehyde can be reacted with the Grignard reagent to afford the corresponding racemic alcohol.

3. Complete the following reaction schemes concerning the total synthesis of aspidofractinine (*J. Org. Chem.* **2009**, *74*, 16, 6035–6041), colchine (*Pure & Appl. Chem.* **1996**, *68*, 539-542), and leuconoxine (*Chem. Eur. J.* **2015**, *21*, 6355-6357). [★★]

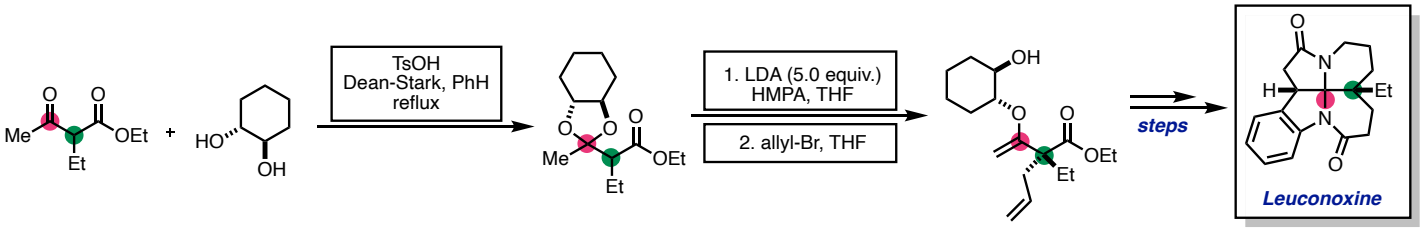
a. Total synthesis of aspidofractinine



b. Total synthesis of colchine



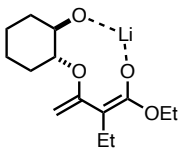
c. Total synthesis of leuconoxine



a. The one-step conversion of an aldehyde into a homologated vinyldibromide involves an *in-situ* Wittig reaction as part of the Corey-Fuchs alkyne synthesis (original paper: *Tetrahedron Lett.* **1972**, *13*, 3769–3772). The reaction requires carbon tetrabromide and triphenylphosphine, which can immediately react to form the corresponding sulfonium salt (Br_3C-PPh_3^+ Br^-), which upon bromide elimination generates an ylide. In Wittig reaction fashion, the nucleophilic ylide attacks the carbonyl compound, generates the intermediate oxaphosphetane, and undergoes triphenylphosphine oxide elimination to deliver the final product.

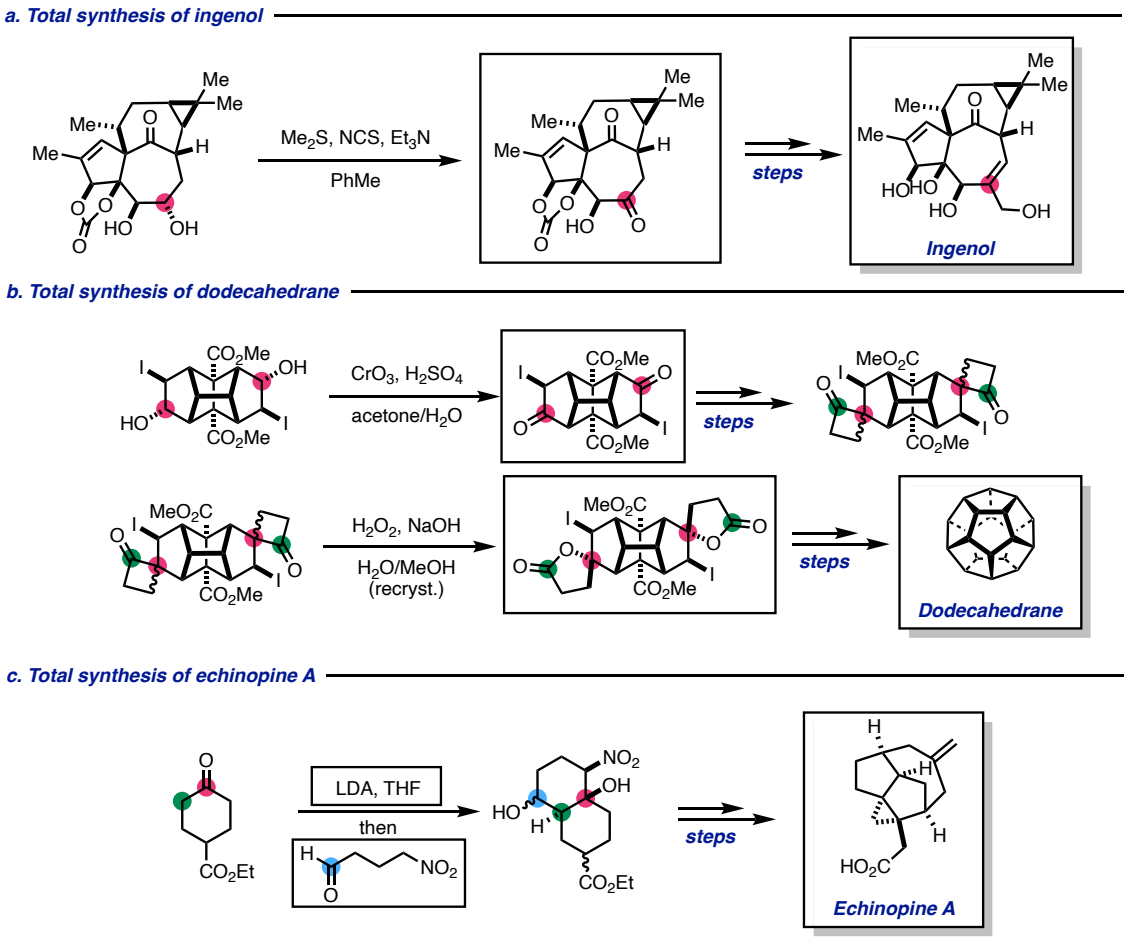
b. In the total synthesis of colchine by Banwell, the basic treatment of a mixture of a non-enolizable aldehyde (2,3,4-trimethoxybenzaldehyde) and an enolizable ketone triggers an aldol condensation to the corresponding chalcone.

c. The total synthesis approach to leuconoxine by Gaich and co-workers involves the generation of an a chiral auxiliary-bearing ketal *via* condensation. Treatment of the carbonyl compound and enantiopure alcohol with a sulfonic acid at



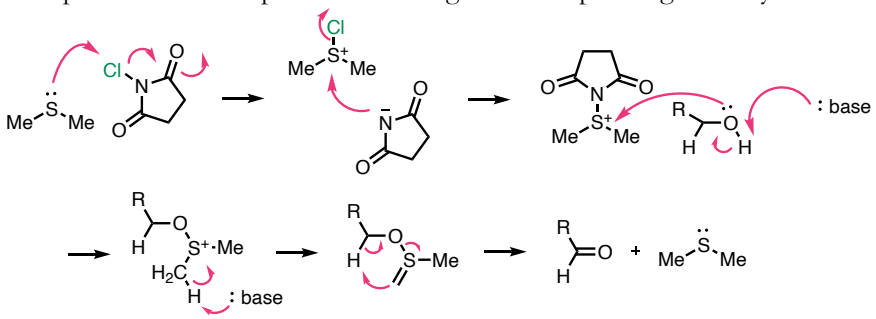
reflux in toluene (with water removal using a Dean-Stark apparatus) generates the ketal. The second step is an diastereoselective enolate allylation/enol ether formation (report by Tanaka, Suemune and co-workers: *J. Org. Chem.* **2001**, *66*, 2667-2673): upon treatment with excess LDA (lithium di*iso*propylamine), double deprotonation generates a chelate enol-ether/enolate (see structure on the right) which possesses a more sterically accessible face to electrophiles. While double enolates usually first react *via* the more reactive terminus, the trapping of the enolate as stable enol ether renders the more substituted position the only reactive one.

4. Complete the reaction schemes. Regarding the total synthesis of ingenol (*J. Am. Chem. Soc.* **2003**, *125*, 1498–1500): (a) propose a mechanism for the Corey-Kim oxidation reaction; (b) suggest a reason for the selectivity. Regarding the total synthesis of dodecahedrane (*J. Org. Chem.* **1979**, *44*, 3616–3630): (a) rationalize the selectivity in the migration step of the Baeyer-Villiger oxidation. Regarding the total synthesis of echinopine A (*Org. Lett.* **2013**, *15*, 1978–1981): (a) suggest a mechanism for the cascade reaction; (b) what is the name reaction involved? [★★] [NCS, *N*-chlorosuccinimide]

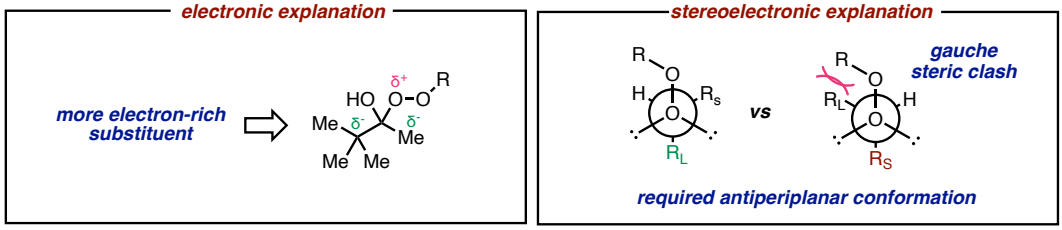


a. The advanced intermediate towards ingenol undergoes selective Corey-Kim oxidation at the least substituted secondary alcohol. Since the other secondary alcohol points at the same face of the proximal cyclic carbonate system, substantial steric bulk prevents its oxidation. The Corey-Kim oxidation (original paper*: J. Am. Chem. Soc.* **1972**, *94*, 7586–7587) involves a substantially similar mechanism to Swern-type oxidations. Instead of using dimethylsulfoxide as terminal oxidant and various activating agents (*i.e.* oxalyl chloride, Swern; DCC, Pfizner-Moffatt; SO_3-pyridine, Parikh-Doering; acetic anhydride, Albright-Goldman), the electrophilic sulfonium species is generated from *N*-chlorosuccinimide (terminal oxidant) and dimethylsulfide. Initial nucleophilic attack of dimethylsulfide to *N*-chlorosuccinimide generate *S*-Cl-dimethylsulfonium species, which undergoes attack from the succinimide to form the corresponding N-S sulfonium. The alcohol substrate can now act as nucleophile and

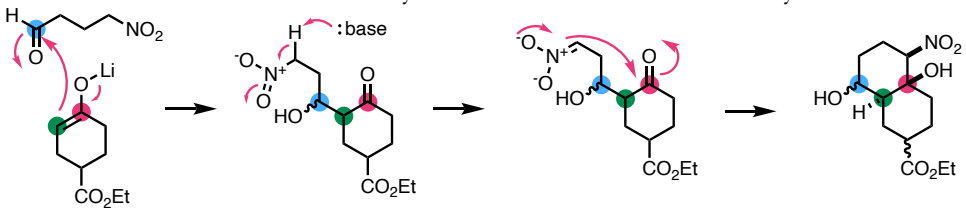
displace succinimide, generating an O-S sulfonium intermediate, which upon deprotonation generates an ylide. The ylide deprotonate the proximal alcohol position releasing the corresponding carbonyl and volatile dimethylsulfide.



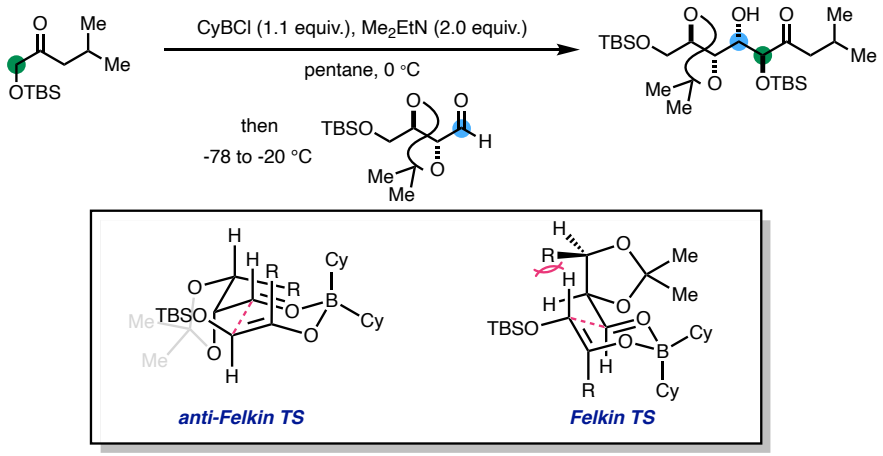
b. The total synthesis of dodecahedrane features a Jones oxidation (CrO_3 under acidic conditions), which converts the secondary alcohols into the corresponding ketones. In a following step, the bis-cyclobutanone is converted into the corresponding bis-lactone *via* Baeyer-Villiger oxidation. The selectivity in the migration is in accordance with the empirical rule that secondary tertiary alkyl groups migrate more easily than secondary and primary. There are two invoked explanations for this effect: (1) Since the Criegee intermediate is characterized by positive charge buildup at the peroxide oxygen, more electron-rich substituents are more energetically favorable (lower TS); (2) the migrating group is required to be antiperiplanar to the O-O bond (stereoelectronic requirement). More bulky tertiary groups preferentially adopt an antiperiplanar conformation to avoid gauche steric interactions, and therefore the reactive conformation is more easily adopted by tertiary alkyl substituents.



c. The reaction in part c of the scheme requires both the alkylation of the α-carbonyl position and the addition to the carbonyl carbon to form an alcohol (see scheme below). This could be achieved *via* deprotonation to generate an enolate, followed by addition to the aldehyde. The aldehyde contains a nitro group to undergo subsequent α-deprotonation and addition to the ketone moiety. This reaction is called the Henry reaction.

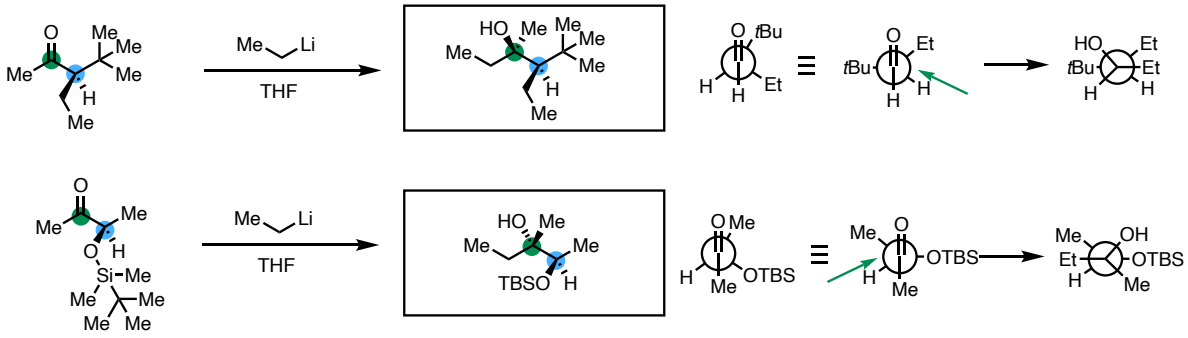


5. In the context of the total synthesis of aflastatin A (*J. Am. Chem. Soc.* **2022**, *144*, 19953-19972), Beiger and co-workers observed the following stereoselectivity in the following aldol reaction. Rationalize the stereochemical outcome. [★★★] [Suggestion: the reaction proceeds *via* (*E*)-enolate.] [TBS, *tert*-butyldimethylsilyl]



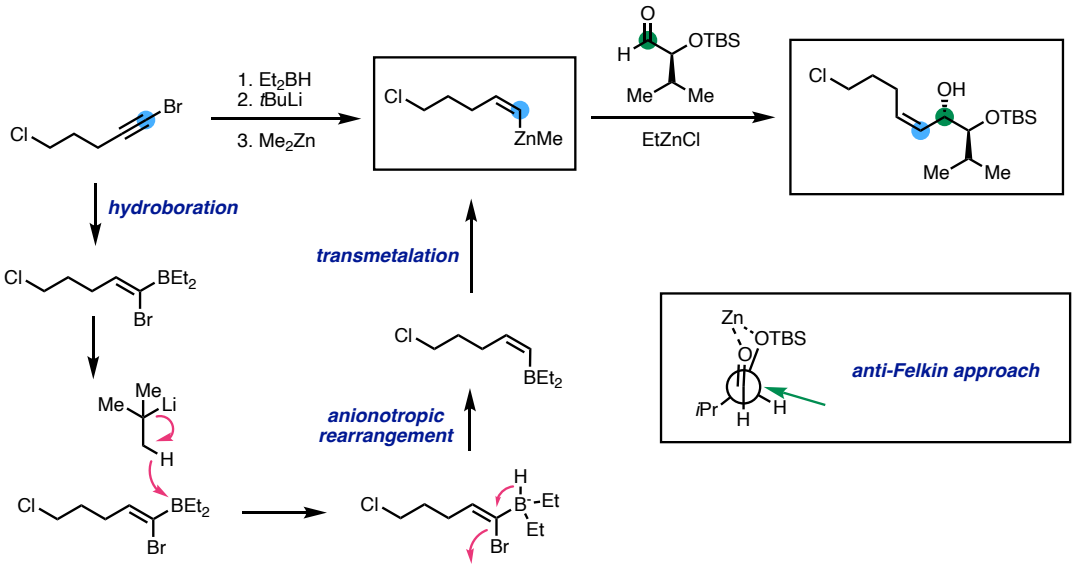
Since the geometry of the enolate intermediate can impact the stereoselectivity of aldol reaction, *E*/*Z* selectivity control is fundamental. Brown observed that boron enolates can be selectively formed as *E* or *Z* isomers upon careful selection of the boron-capping alkyl groups, leaving group, and base (*J. Am. Chem. Soc.* **1989**, *111*, 3441-3442). For instance, 9-BBN-BOTf (9-BBN, 9-borabicyclo(3.3.1)nonyl) with DIPEA as base can selectively afford the *Z*-isomer (*E*/*Z* > 1:99), while CyBOTf with DIPEA selectively afford the *E*-isomer (*E*/*Z* > 99:1). It is believed that highly sterically encumbered boron substituents (*i.e.* cyclohexyl) favor the formation of *E*-isomer (*J. Am. Chem. Soc.* **1979**, *101*, 6120–6123). In the reported reaction, *E*-boron enolate formation defines the relative stereochemistry between the α-position of the enolate component and the carbonyl carbon of the electrophile. In this case, the absolute stereochemistry is enforced by stereoinduction of the adjacent acetonide system (electrophile). Normally, a Felkin-Ahn model approach would determine the stereochemical outcome of the process (as the authors observed in the case of a ring-open system), but in this case an anti-Felkin-Ahn approach is more favorable. Since aldol reactions of boron-enolates proceed *via* a Zimmerman-Traxler transition state, we can analyze the two possible TSs. In the case of the Felkin approach, steric clash between the incoming enolate axial proton and the side acetonide chain renders the TS less favorable than an anti-Felkin approach, where this interaction is suppressed.

6. Predict the major diastereoisomer of the following carbonyl addition reactions and rationalize it according to the Felkin-Ahn model. [★★]



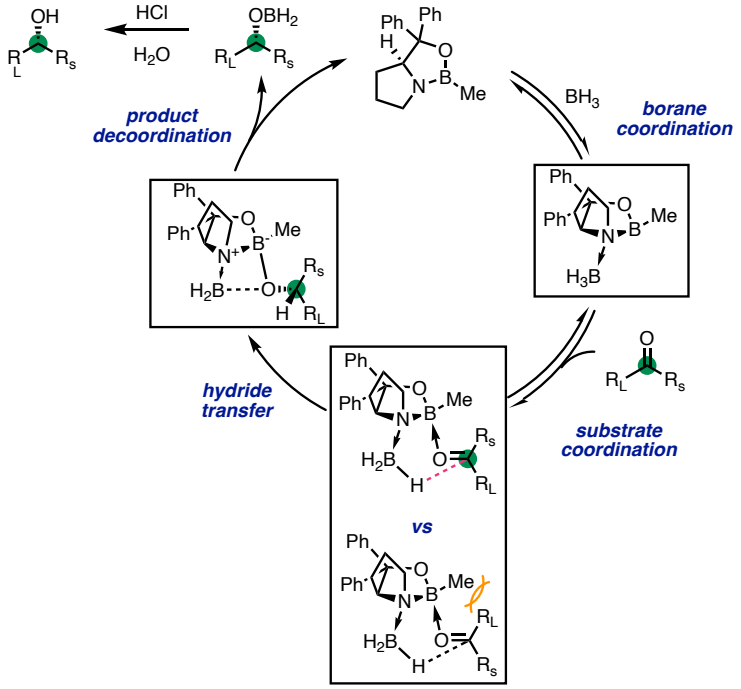
According to the Felkin-Ahn model for carbonyl addition, the conformation at the transition state can be approximated as staggered (lower steric clash than eclipsed, as in the Cram model), with an early (reactant-like) transition state. The main steric interaction occurs at the α-carbon, and the biggest substituent must lay perpendicular to the carbonyl. The incoming nucleophile approaches with a Bürgi–Dunitz angle towards the substituent with the minimum steric bulk. In the first case, the *tert*-butyl group is perpendicular, and the incoming nucleophile follows a trajectory close to the least sterically demanding hydrogen atom. In the second case, the most sterically demanding OTBS group is perpendicular, and again the incoming nucleophile follows a trajectory close to the least sterically demanding hydrogen atom.

7. Walsh and co-workers reported the following carbonyl addition (*J. Am. Chem. Soc.* **2010**, *132*, 4399-4408). Complete the reaction scheme and rationalize the stereoinduction. [★★] [TBS, *tert*-butyldimethylsilyl]



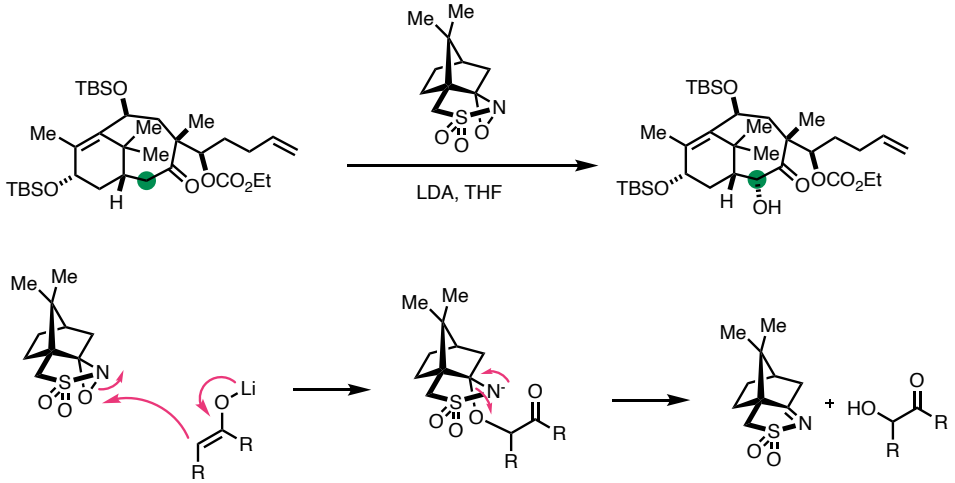
The initial treatment of the alkyne with diethylborane triggers *syn*-hydroboration, which is followed by formal hydride Zweifel rearrangement (original paper: *J. Am. Chem. Soc.* **1967**, *89*, 5086–5088) by *tert*-butyl lithium treatment (*J. Organomet. Chem.* **1978**, *156*, 71-79), an anionotropic rearrangement that selectively generates *Z*-vinylboron species. Transmetalation with dimethylzinc completes the first part of the process. The nucleophilic addition to aldehydes occurs in anti-Felkin fashion: strong coordination between the silyl-ether, the carbonyl, and the zinc center promotes an eclipsed conformation, which results in the *anti*-stereochemistry.

8. Complete the stereoinduction model for the Corey-Bakshi–Shibata reduction and suggests which step is decisive for enantioinduction (*J. Am. Chem. Soc.* **1987**, *109*, 5551-5553). [★★] [R_L, large substituent; R_S, small substituent]



The Corey-Bakshi–Shibata reduction system is based on a chiral oxazaborolidine (derived from either enantiomer of proline) and borane as stoichiometric hydride source. The reaction involves initial coordination between borane and the nitrogen atom, followed by substrate coordination to the Lewis acidic boron center. This coordination both increases the carbonyl electrophilicity and renders the two diastereotopic carbonylic faces distinguishable. In particular, the geometry is more energetically favorable when the large substituent is pointing away from the oxazaborolidine system, thus generating a specific enantiomer *via* six-membered TS hydride transfer. Upon product de-coordination and O-B bond hydrolysis, the product is released.

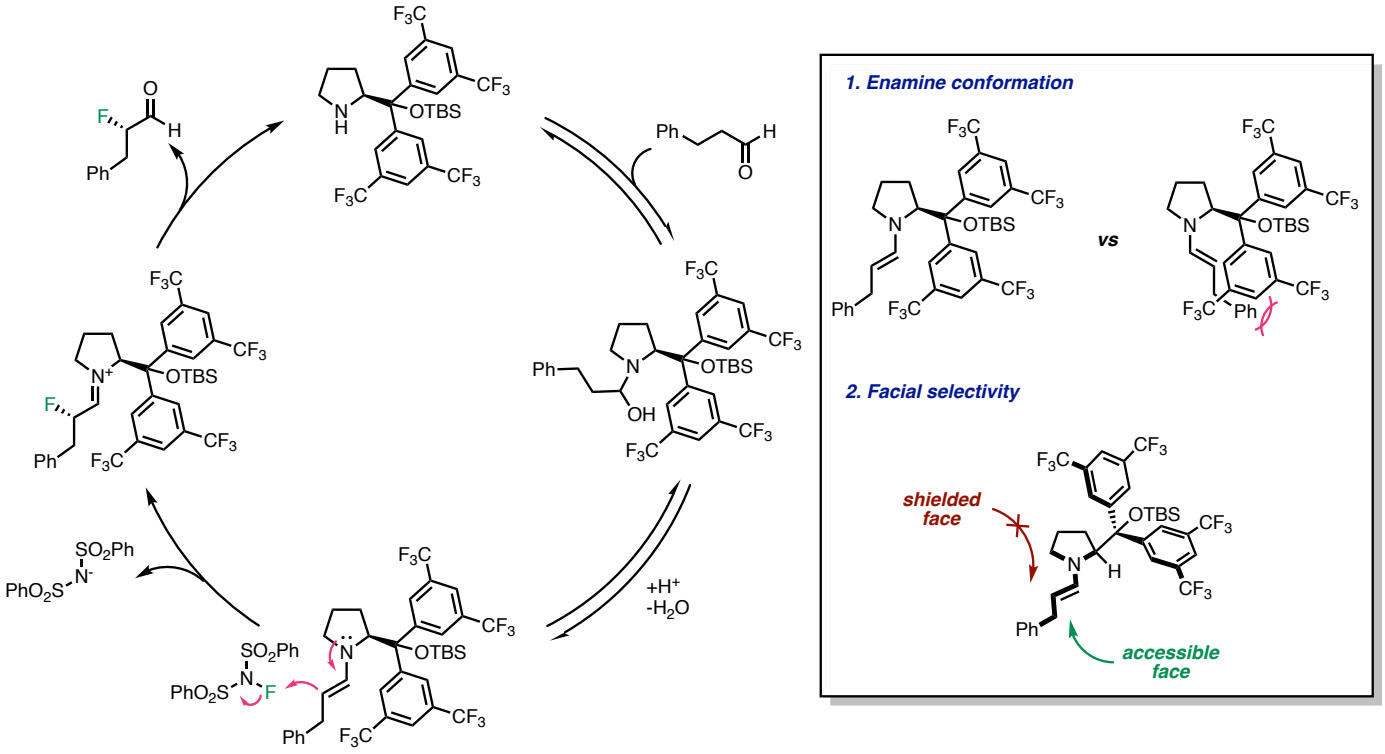
9. Suggest a mechanism for the following transformation (*J. Am. Chem. Soc.* **1994**, *116*, 1597-1598). What is the name of the transformation? [★★]



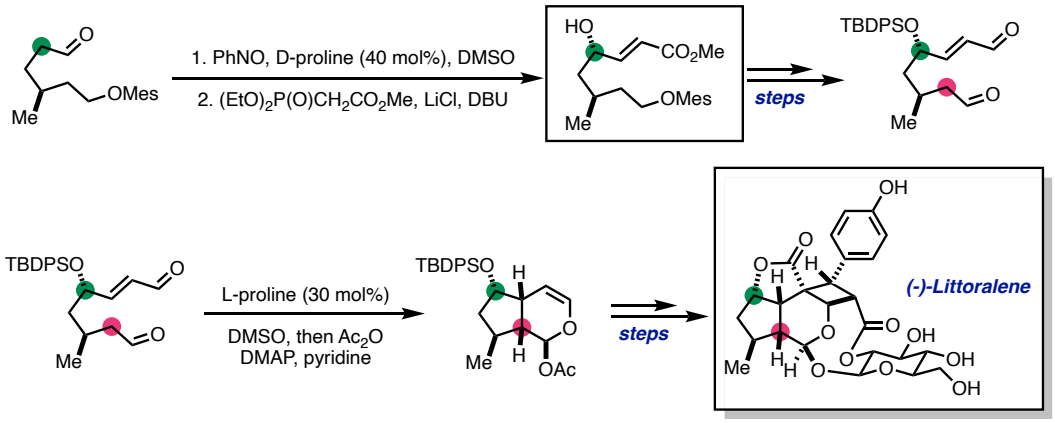
The oxidation of an enolate using a sulfonyl oxaziridine is called Davis oxidation, and camphor derived oxaziridine are privileged scaffold for the enantioselective enolate oxidation (*J. Org. Chem.* **1986**, 51, 2402–2404). Mechanistically, the reaction is initiated by enolate formation, which undergoes nucleophilic attack onto the oxaziridine electrophilic oxygen. The corresponding N-O bond-scission intermediate (a tetrahedral intermediate) undergoes facile fragmentation to a sulfinimine and the corresponding hydroxycarbonyl compound.

10. In 2005, Jørgensen and co-workes (*Angew. Chem. Int. Ed.* **2005**, *44*, 3703-3706). published the following enantioselective fluorination of aldehydes. Propose a mechanism and the origin of enantioselectivity. [TBS, *tert*-butyl-dimethylsilyl; MTBE, metyl-*tert*-butyl ether] [★★]

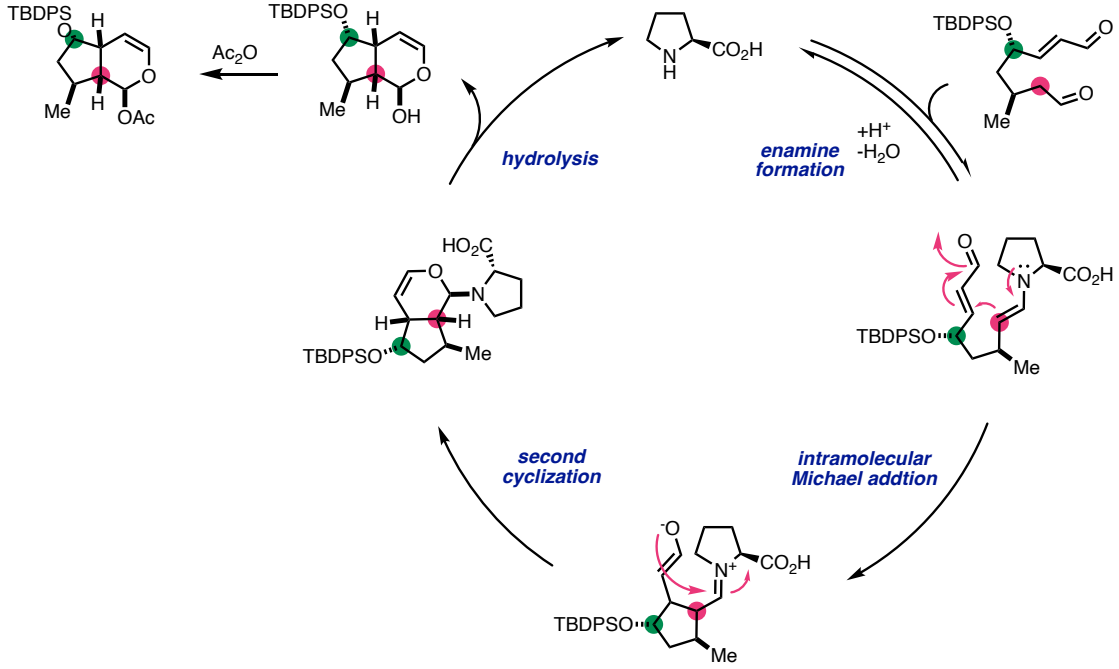
The general mechanistic pathway is typical of proline/prolinol-based organocatalytic reaction relying on enamine intermediates (HOMO-raised activation mode, for an excellent review by Benjamin List, see: *Chem. Rev.* **2007**, *107*, 5471-5569). Hydrocinnamaldehyde undergoes reversible condensation with the Jørgensen-Hayashi prolinol catalyst to generate an enamine species, which undergoes electrophilic fluorination at the α-carbonyl position. Hydrolysis of the corresponding iminium species releases the final product and turns-over the reactive prolinol species. We have to define two important aspects of enantioinduction: (1) the configuration and conformation of the enamine system; (2) facial selectivity. Regarding the first aspect, the enamine adopts a preferential *E*-configuration and *s-trans* conformation (pointing away from the bulky prolinol substituents), in order to minimize the steric clash between the aldehydic backbone and the sterically encumbered prolinol system. The rigid conformation of the intermediate ensures excellent stereochemical transfer. The upper face of the intermediate is sterically inaccessible, while NFSI approach from the bottom faces a much lower energetic barrier, and therefore leads to the predominant enantiomer.



11. MacMillan and co-workers reported the total synthesis of littoralisone (*J. Am. Chem. Soc.* **2005,** *127*, 3696-3697) using multiple organocatalyzed transformations. Complete the reaction scheme and provide a mechanistic hypothesis for the second reaction. [TBDPS, *tert*-butyl-diphenylsilyl; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene, DMAP, *N,N*-dimethylaminopyridine] [★★]

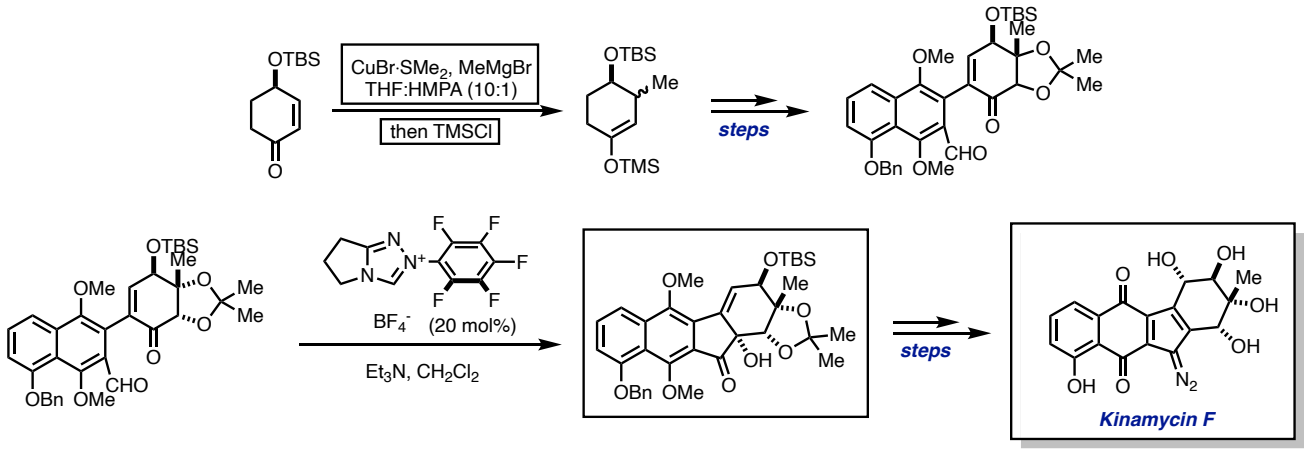


Similarly to the previous example, the first reaction is a proline-catalyzed enantioselective α-hydroxylation of alkdehydes. Nitrosobenzene acts as oxidizing agent on the electron-rich enamine intermediate (the reaction was previously developed by the MacMillan's lab: *J. Am. Chem. Soc.* **2003**, *125*, 10808–10809). The second step involves a Horner-Wadsworth-Emmons reaction to convert the aldehyde into an α,β-unsaturated ester.

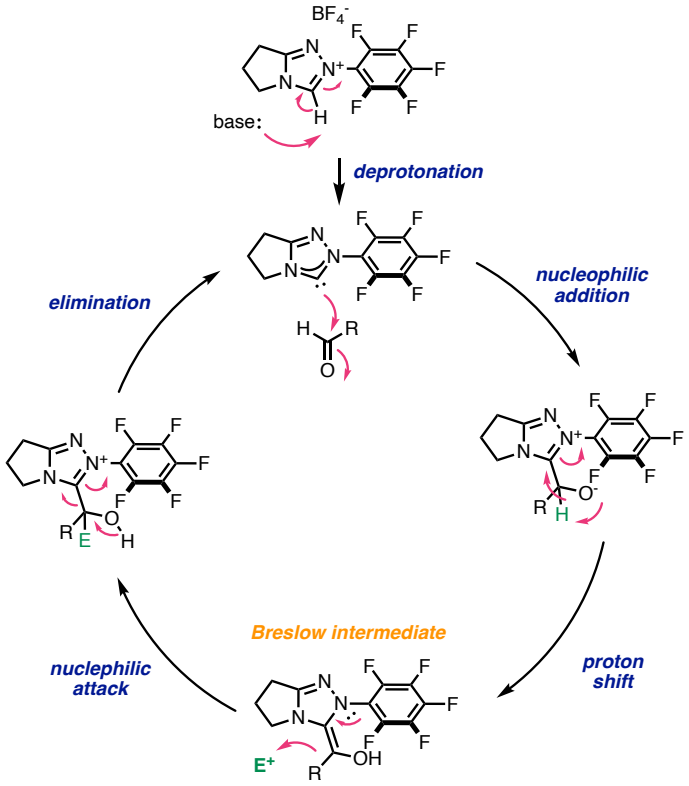


Mechanistically, the second proline-catalyzed reaction involves the initial formation of an enamine species, which undergoes Michael attack onto the attached α,β-unsaturated aldehyde to give an iminium-enolate, which cyclizes to an intermediate hemiaminal. The hemiaminal species undergoes facile hydrolysis to the hemiacetal product and releases back proline. The kinetic hemiaminal is particularly prone to hydrolysis and epimerization at the bridgehead positions, and it is therefore immediately acylated with acetic anhydride.

12. Complete the following reaction scheme, part of the total synthesis approach towards Kinamycin F by Nicolaou and co-workers (*J. Am. Chem. Soc.* **2007**, *129*, 10356-10357). [TBS, *tert*-butyl-dimethylsilyl; TMS, trimethylsilyl] [★★]



The initial step features conjugate cuprate (Gilman reagent) addition to the cyclic α,β-unsaturated ketone, immediately followed by enolate trapping with trimethylsilylchloride, which generates a silyl enol ether species. The second step involves a catalytic amount of triazolium salt, which *in situ* generates an N-heterocyclic carbene. N-heterocyclic carbenes (see a recent general review: *Nat. Rev. Chem.* **2021**, *5*, 711-725) can catalyze the umpolung of aldehydes, rendering the carbon atom electrophilic *via* Breslow-type intermediates. According to the mechanisms in figure, initial depronation causes the pre-catalytic triazolium species to enter the catalytic cycle, which commences with nucleophilic attack of an aldehyde. A proton shift from the betaine intermediate to the neutral Breslow intermediate (a resonance with a negative charge on the aldehydic carbon can be drawn), which can intercept an electrophilic species (e.g. another carbonyl). The ensuing intermediate can be considered analogous to a tetrahedal intermediate, whereby the cationic triazolium substituents can be eliminated to deliver the product and the catalytically active carbene. For selected reviews regarding NHC-organocatalysis, the reader can consult: (1) *Chem. Rev.* **2015**, *115*, 9307–9387; (2) *Chem. Soc. Rev.* **2012**, *41*, 3511-3522; (3) *Chem. Rev.* **2007**, *107*, 5606–5655; (4) *Chem. Soc. Rev.* **2015**, *44*, 5040-5052; (5) *ACS Catal.* **2020**, *10*, 6862–6869.



In the example, the napthylaldehyde moiety can give its Breslow intermediate, which undergoes cyclative nucleophilic attack to the appended α,β-unsaturated ketone and generates the corresponding α-hydroxyketone. Facial selectivity, which is eventually inconsequential for the product, is likely enforced by the ketone substituents.

13. Complete the following scheme, which summarizes some steps of the total synthesis of retigeranic acid by Corey and co-workers (*J. Am. Chem. Soc.* **1985**, *107*, 4339-4341). What is the name of the last reaction? [★★★]

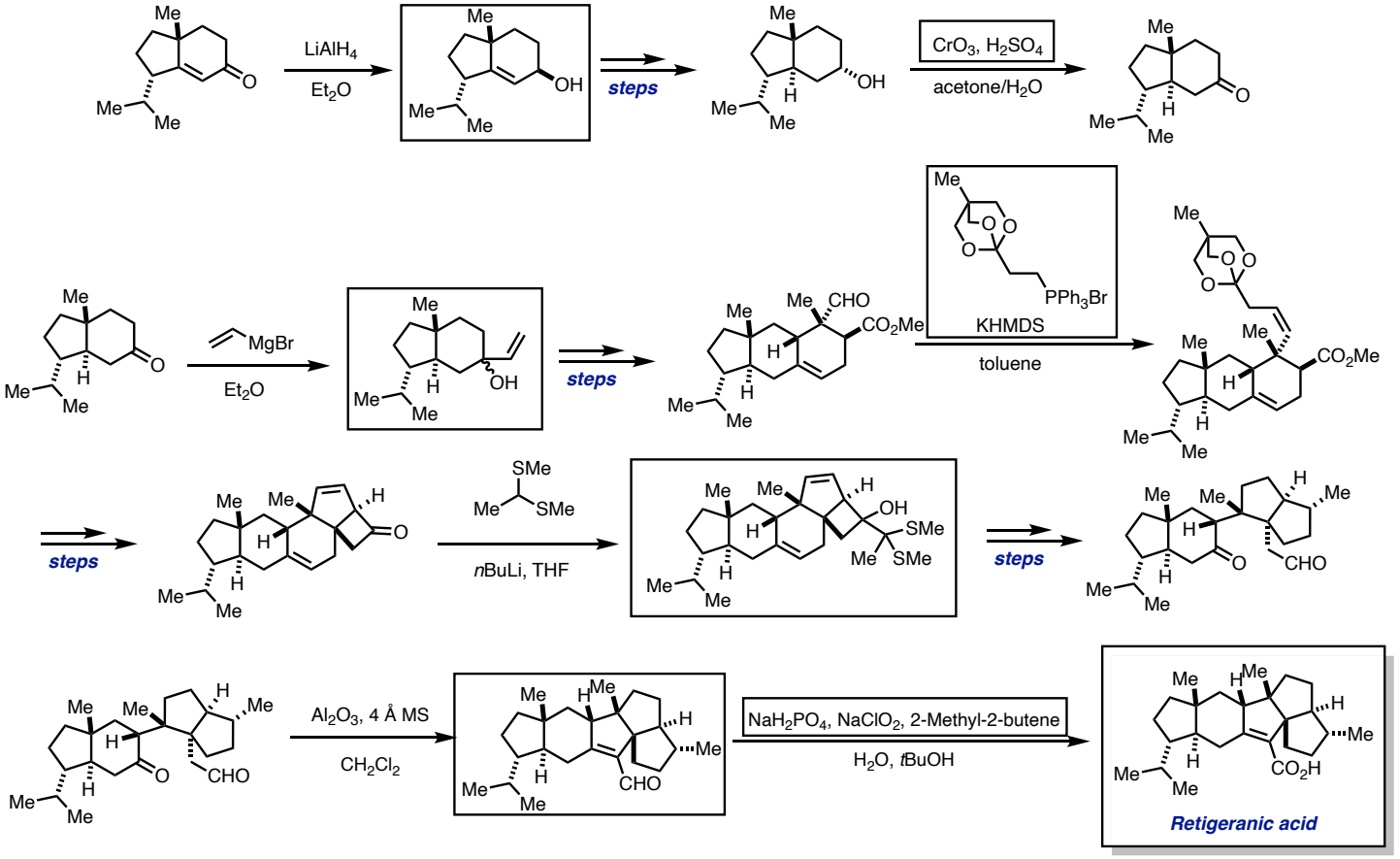
The initial step involves reduction of the cyclic α,β-unsaturated ketone to the corresponding allylic alcohol. Contrary to common wisdom, α,β-unsaturated ketones almost never undergo conjugate reduction using $LiAlH_4$ (*J. Chem. Educ.* **1981**, *58,* 628-630, with the possible exception of cinnamyl systems).

Following intermediate steps to establish the bridgehead stereocenter, the oxidation of secondary alcohol to ketone was achieved *via* Jones oxidation (chromic anhydride, sulfuric acid). Since the synthesis was published in 1985, milder, less toxic, and environmentally friendly oxidation protocols for alcohols have become preferential, for instance Dess-Martin periodinane oxidation (*J. Org. Chem.* **1983**, *48*, 4155–4156), Swern-type oxidation (*Chem. Rev.* **1967**, *67*, 247–260), TPAP oxidation (*Synthesis*

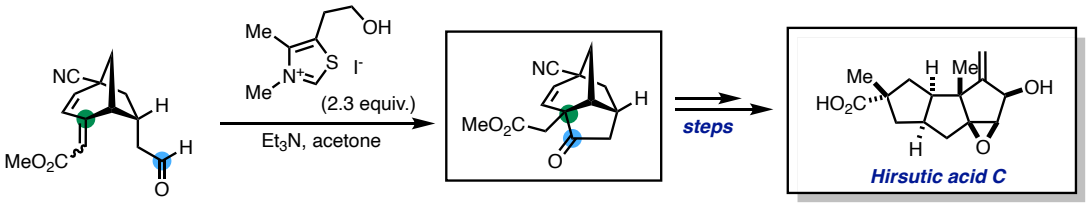
1994, *7*, 639-666), TEMPO-based oxidations (e.g. TEMPO/TCCA: *J. Org. Chem.* **2003**, *68*, 4999–5001; TEMPO/bleach: *Org. Process Res. Dev.* **2005**, *9*, 577–582), and many others.

Addition of vinyl magnesium bromide to the ketone generate the corresponding allyl alcohol. The authors reported no significant control of the diastereoselectivity. The authors elaborated the bicyclic fragment to achieve a tricyclic aldehyde. Wittig reaction using an orthoester-protected phosphonium salt produces the intermediate alkene with *Z*-selectivity, which can be anticipated on kinetic arguments (non-stabilized ylide). The authors used the strong base KHMDS to promote the deprotonation of the phosphonium salt.

The next reaction features the deprotonation of acetaldehyde dithiane (a formal carbonyl umpolung), followed by addition to the cyclobutanone portion of the intermediate. The following synthetic step is an acid-catalyzed cyclative aldol condensation between the ketone portion (electrophile) and α-position of the aldehyde portion (nucleophile). The generation of a thermodynamically stable 5-membered ring, over medium-sized rings (II α-ketone position as enolate) or spirocyclic products (III α-ketone position as enolate), accounts for the observed regioselectivity. The endgame reaction requires the oxidation of the α,β-unsaturated aldehyde to the corresponding carboxylic acid. Typical conditions for the Pinnick oxidation (*Tetrahedron* **1981**, *37*, 2191-2196) use sodium chlorite as stoichiometric oxidant under buffered conditions. Since sodium hypochlorite byproducts can promote undesired oxidation reactions, electron-rich 2-methyl-2-butene is added as scavenger. Scavenger oxidation generates the corresponding chlorohydrin.

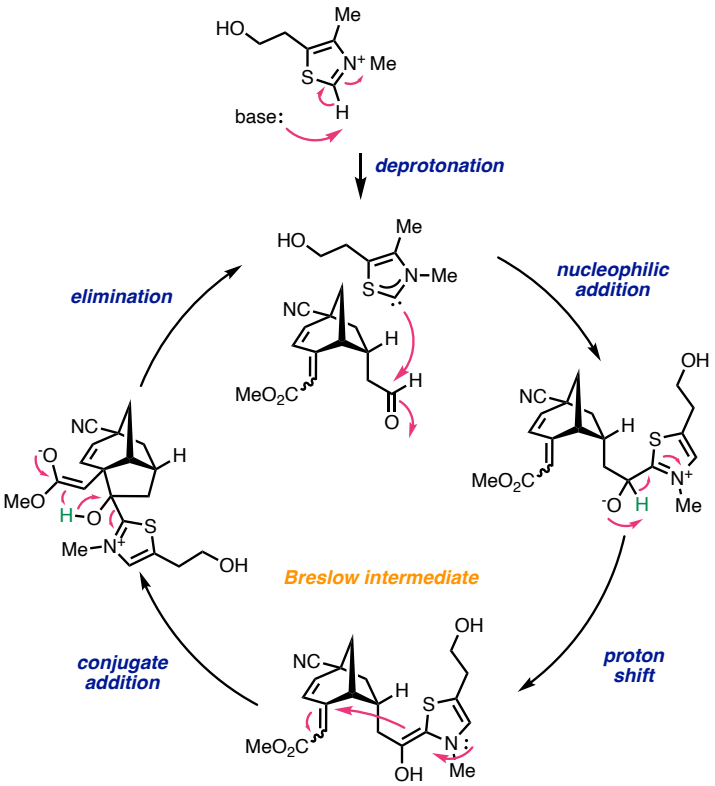


14. Complete the following scheme, part of the racemic total synthesis of hirsutic acid C by Trost and co-workers (*J. Am. Chem. Soc.* **1979**, *101*, 1284-1285) and propose the reaction mechanism. [★★]

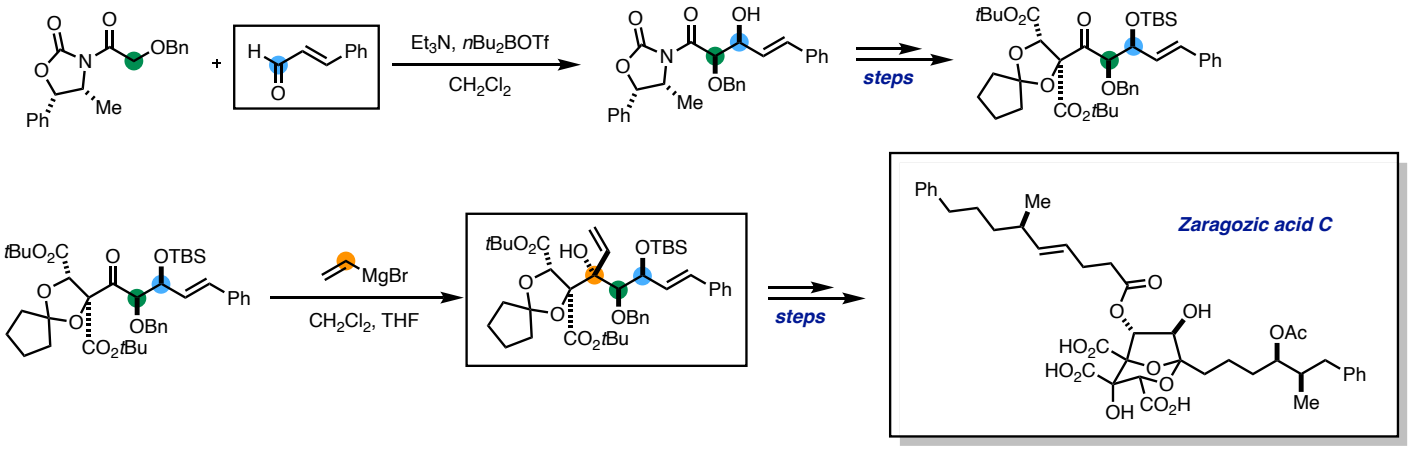


The reaction is an organocatalytic generation of 1,4-dicarbonyl *via* NHC-based umpolung, also known as Stetter reaction (original paper: *Angew. Chem. Int. Ed.* **1976**, *15*, 639-647). This reaction is particularly significative, since 1,4-dicarbonyls cannot be synthesized using the normal polarity of carbonyl compounds.

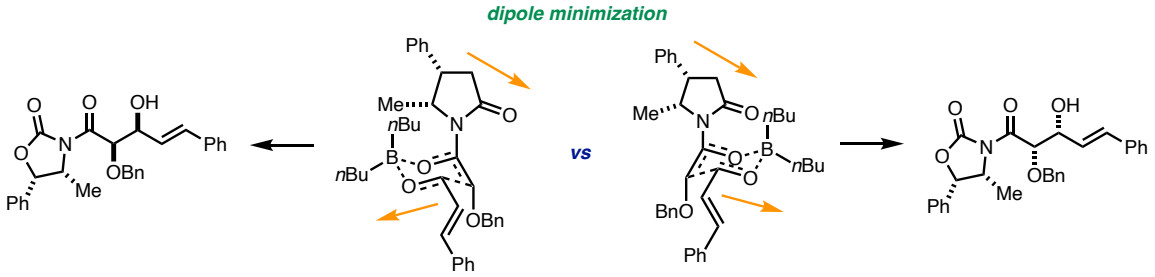
Analogously to all NHC-organocatalytic reactions, the pre-catalytic thiazolium salt undergoes deprotonation to generate the catalytically active N-heterocyclic carbene. The nucleophilic carbene can add to the electrophilic aldehyde portion to yield a tetrahedral intermediate, which undergoes proton shift to yield a Breslow intermediate. We can draw the eponymous intermediate as resonance structure with a negative charge on the aldehydic carbon, and this account to the nucleophility of the once-aldehydic carbon. Michael addition to the α,β-unsaturated ester generates the five-membered ring. The ensuing intermediate can be considered analogous to a tetrahedal intermediate, and the thiazolium substituent can be eliminated to deliver the product and the catalytically active carbene. For selected reviews regarding NHC-organocatalysis, the reader can consult: (1) *Chem. Rev.* **2015**, *115*, 9307–9387; (2) *Chem. Soc. Rev.* **2012**, *41*, 3511-3522; (3) *Chem. Rev.* **2007**, *107*, 5606–5655; (4) *Chem. Soc. Rev.* **2015**, *44*, 5040-5052; (5) *ACS Catal.* **2020**, *10*, 6862–6869.



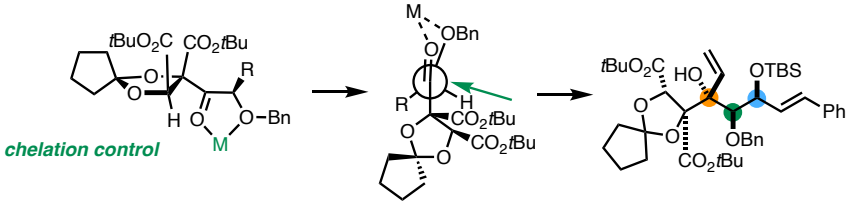
15. In 1994, Evans and co-workers achieved the total synthesis of zaragozic acid C (*J. Am. Chem. Soc.* **1994**, *116*, 12111-12112). Please complete the following scheme and propose two models for the diastereoinduction observed at each step. [★★★]



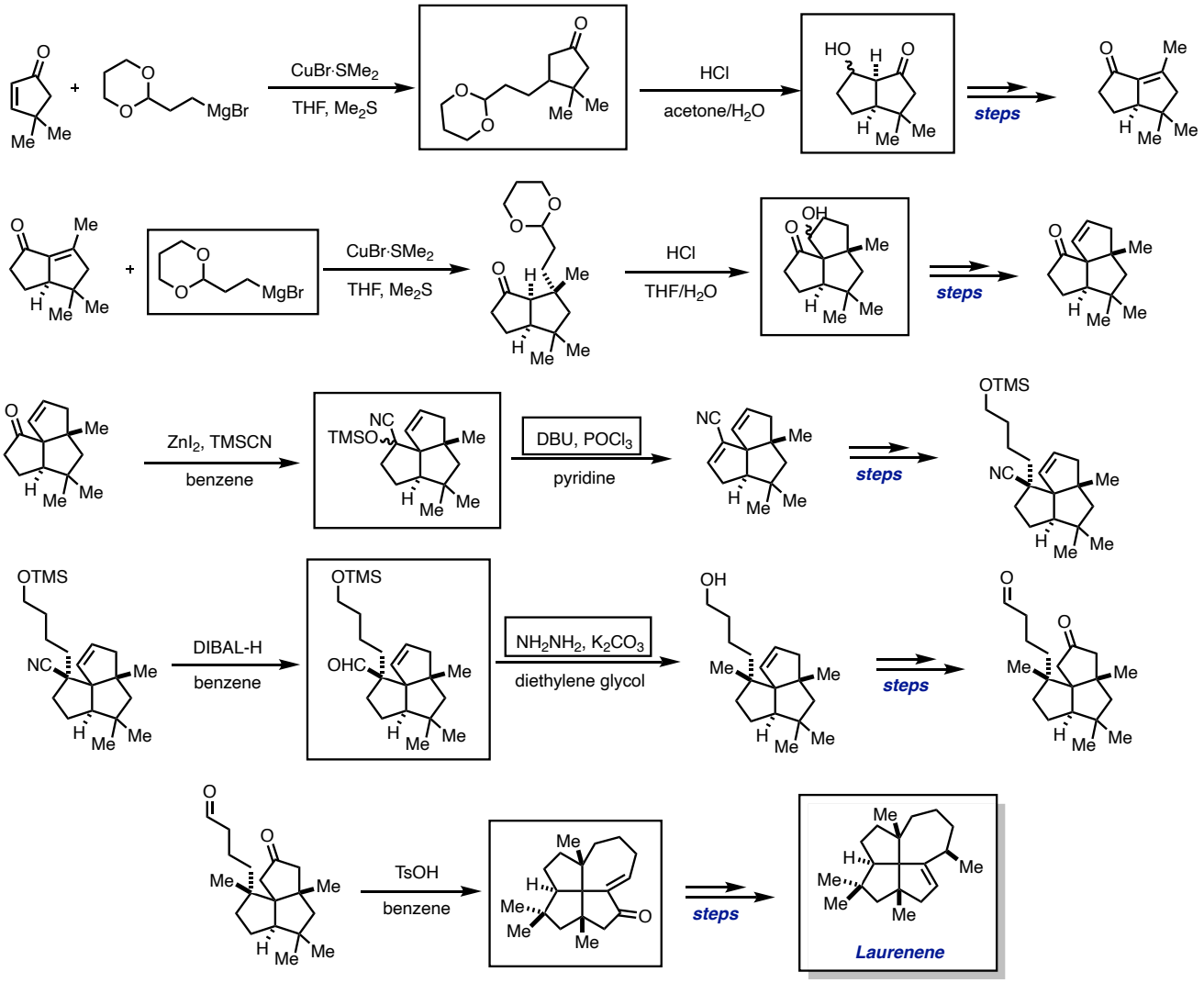
The first step involves a directed aldol reaction between an amide bearing Evans auxiliary (nucleophile) and cinnamaldehyde (electrophile). Similarly to exercise 5, the geometry of the enolate intermediate can impact the stereoselectivity of aldol reaction and *E*/*Z* selectivity control is fundamental. Brown observed that boron enolates can be selectively formed as *E* or *Z* isomers upon careful selection of the boron-capping alkyl groups, leaving group, and base (*J. Am. Chem. Soc.* **1989**, *111*, 3441-3442). In this case, *n*Bu$_2$BOTf can selectively generate *Z*-enolate. It is believed that more sterically encumbered boron substituents (*i.e.* cyclohexyl) favor the formation of *E*-isomer (*J. Am. Chem. Soc.* **1979**, *101*, 6120–6123).
Aldol reactions of boron-enolates proceed *via* a Zimmerman-Traxler transition state, which decides the relative stereochemistry of the aldol product (substituents arrange in a more stable equatorial position to minimize 1,3-diaxial interactions). The absolute stereochemistry is enforced by the facial approach selectivity enforced by the Evans auxiliary-decorated enolate.



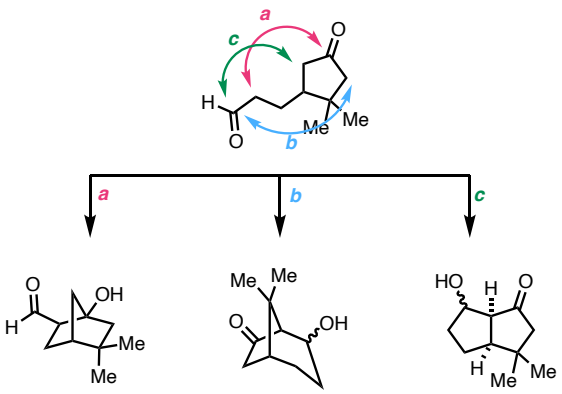
The second step involves a diastereoselective carbonyl addition of vinyl magnesium bromide to the ketone intermediate. Given the presence of numerous α-heteroatom substituents, chelation control, instead of Felkin-Ahn control, could be anticipated. Chelation preferentially occurs at the benzyl-ether substituent, since the sterically encumbered spirocyclic acetal adopts the most sterically favorable conformation and does not engage in chelation.



16. Complete the following formal total synthesis of laurenene by Paquette and co-workers (*J. Org. Chem.* **1988**, *53*, 477-481). [★★★] [DIBAL-H, di*iso*butylaluminum hydride; TMS, trimethylsilyl]



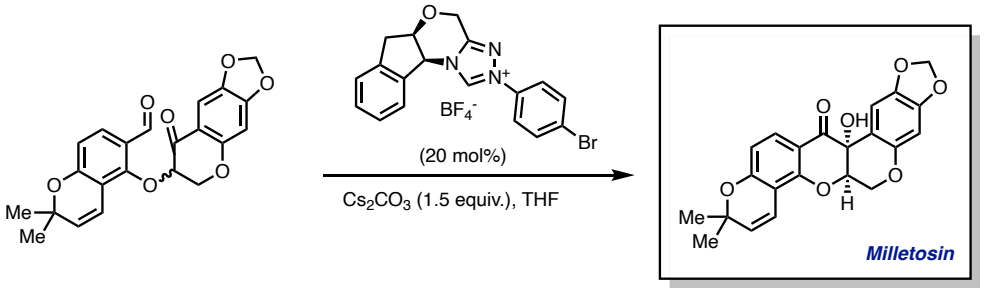
The initial reaction involves the conjugate cuprate (Gilman reagent) addition (obtained *in situ* from Mg/Cu transmetalation) to the cyclic α,β-unsaturated ketone. Acidic treatment of the ensuing ketal liberates the aldehyde, which spontaneously undergoes aldol reaction with the appended ketone. Three possible nucleophile-electrophile combination can be conceived. According to the Baldwin cyclization rules for enolates (*J. Chem. Soc., Chem. Commun.* **1977**, 233-235; *Tetrahedron* **1982**, *38*, 2939-2947), the pathways can be classified as *5-enolexo-exo-trig, 6-enolexo-exo-trig,* and *5-enolexo-exo-trig*, and therefore possible. Nonetheless, only pathway c is observed, since it gives rise to a *cis*-fused unstrained system (*vs* two bridgehead systems).



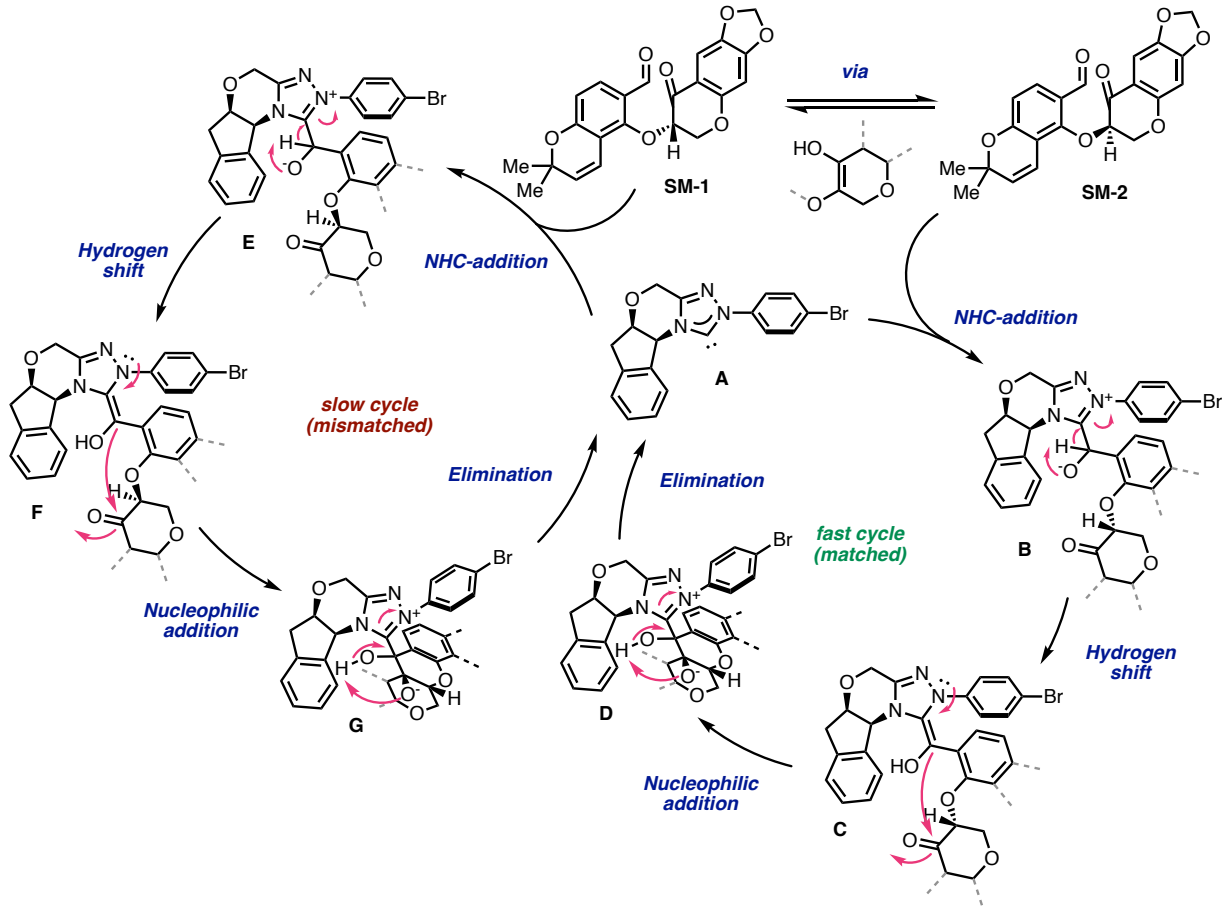
Having created the bicyclic system, another Michael-type addition of acetal-protected Grignard reagent elongates the chain for the ensuing aldol cyclization. The addition diastereoselectivity occurs at the less sterically congested *exo* face. The aldol reaction selectivity can be derived from considerations analogous to the abovementioned.

The intermediate tricyclic ketone is treated with TMSCN and ZnI_2 as Lewis acid to afford the corresponding TMS-protected cyanohydrin. Treatment of this intermediate with strongly dehydrating $POCl_3$ and DBU as base provided the corresponding acrylonitrile.
The next reaction step involves the treatment of the nitrile intermediate with DIBAL-H, which can selectively reduce it to the corresponding aldehyde. The stoichiometry could be controlled to deliver a single hydride and thus prevents overreduction. The conversion of the aldehyde to the corresponding methyl can be achieved *via* Wolff–Kishner reduction (in this case the Huang Minlon modification is used: *Helv. Chim. Acta* **1979**, *62*, 1120-1128), which concomitantly cleaves the labile TMS-ether. Interestingly, the Wolff–Kishner reduction occurs *via* intermediate hydrazone formation, followed by two-fold deprotonation to trigger dinitrogen release (for mechanistic detail: *Angew. Chem. Int. Ed.* **1968**, *7*, 120-128; for a general reference work: 10.1002/9780470638859.conrr683). The endgame cyclization reaction under acidic treatment involves an aldol condensation, with the pendant aldehyde acting as electrophile.

17. Fang and co-workers reported the total synthesis of milletosin (*Commun. Chem.* **2019**, *2*, 8). Propose a mechanism for the transformation. Explain why the yield of the transformation is higher than 50% (60%). [★★]

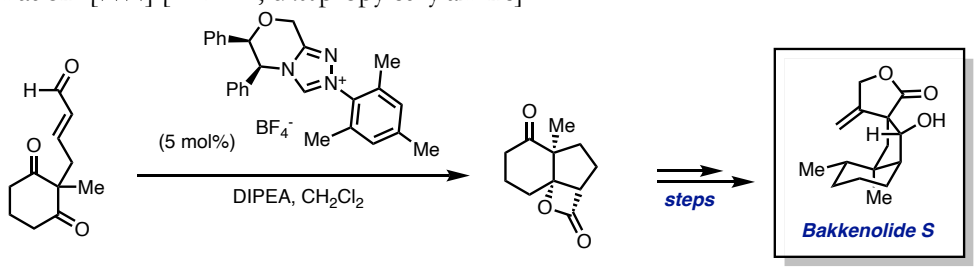


The transformation is analogous to exercise 12 and generates α-keto-alcohols *via* cyclization. In this case, the use of a chiral NHC species imparts enantioselectivity to the transformation (the starting material is racemic). The reaction can be seen as a dynamic kinetic resolution (hence the higher than 50% yield), since the existing stereocenter easily epimerizes *via* keto-enol tautomerism. A total of four stereoisomers consisting in two diastereomeric *cis-trans* pairs can be produced. We limit the discussion to the *cis*-enantiomeric pair, but analogous considerations can be drawn for the other pair. These isomers are not observed likely to their reduced thermodynamic stability *vs cis*-isomers.



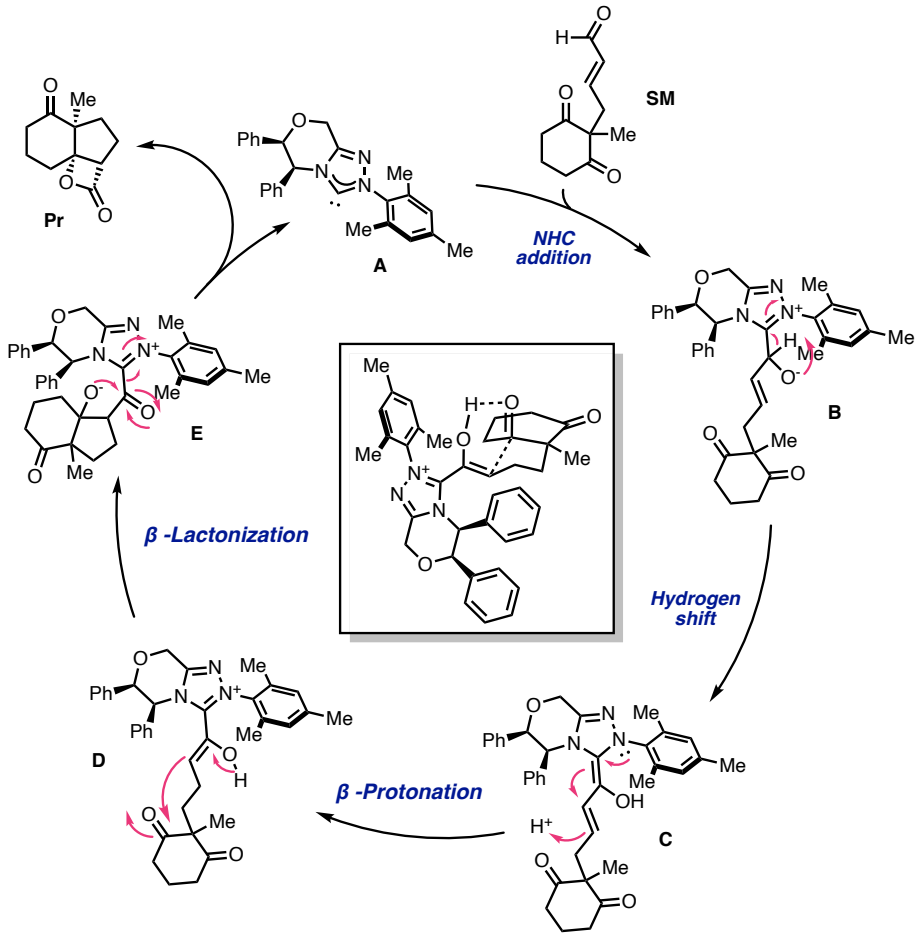
The outlined reaction mechanism is typical of NHC-catalyzed benzoin condensations. NHC species **A** undergoes addition to substrate **SM-1** or **SM-2** to generate tetrahedral intermediate **B** or **E**, respectively. These intermediates (and all the ones following in the catalytic cycle) are diastereoisomeric couples, and therefore their free Gibbs energies (and the ones of their TSs) are different. This renders the productive cycle (matched) faster than the parasitic cycle (mismatched) and ultimately leads to the enantioselection. The tetrahedral intermediates **B**-**E** undergo hydrogen shift to the corresponding Breslow intermediates (**C** and **F**, respectively). Nucleophilic addition of the aldehydic carbon to the ketone generates the second stereocenter by cyclization, and the resulting tetrahedral intermediate (**D** or **G**) can undergo elimination to release the final product and turnover the active NHC-species **A**. While it is not clear which step is enantioselectivity determining, the involvement of diastereoisomeric intermediates/TSs is key to achieve enantioselectivity.

18. Scheidt and co-workers reported the total synthesis of bakkenolide S (*Org. Lett.* **2010**, *12*, 2830-2833). Propose a mechanism for the transformation. [★★] [DIPEA, di*iso*propylethylamine]

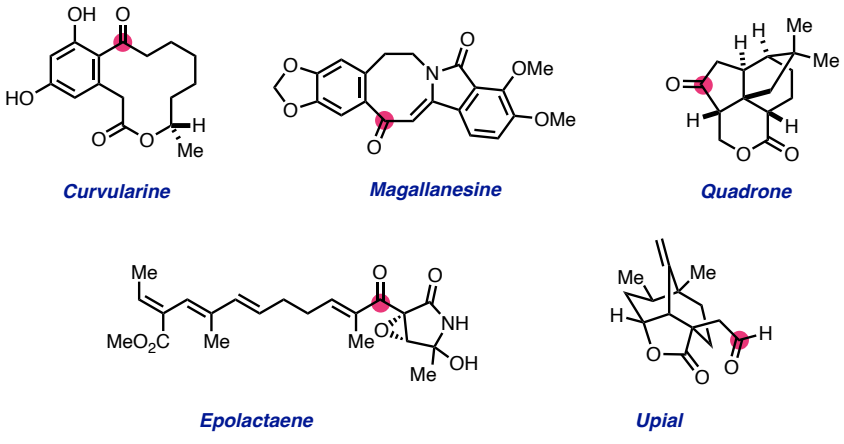


From a topological perspective, the α-aldehyde carbon forms a new C–C bond with the ketone carbon, followed by lactonization. From a prochiral substrate, the reaction generates three new stereocenters (see the synthetic strategy developed by Scheidt and co-workers: *J. Am. Chem. Soc.* **2007**, *129*, 10098–10099). The catalytic cycle commences with NHC-species **A** (generated *via in situ* deprotonation) undergoing addition to the α,β-unsaturated aldehyde to generate tetrahedral intermediate **B**. Hydrogen shift

produces a Breslow-type d³ homoenolate **C**. This species, upon β-protonation, produces an azolium enolate (for reviews on the chemistry of azolium enolates: *Synthesis* **2012**, *44*, 2295-2309; *Chem. Rec.* **2022**, *22*, e202200054), which can undergo aldol-type addition to one of the two ketone moieties to produce the new five-membered ring. Intermediate aldol **E** undergoes lactonization by ejecting the azolium species and turns-over catalytically active species **A**. The authors propose an enantioselection model (see box in figure) based on a compact six-membered transition state facilitated by hydrogen-bond. The compact structure enforces selective shielding of one face of **D**, giving high enantioselectivity.



19. Highlight the carbonyl group that is the most susceptible to nucleophilic addition in the following molecules. [★★]



For curvularine, the ketone moiety is more susceptible to nucleophilic attack compared to the ester moiety. For magallasenine, the α,β-unsaturated ketone and amide carbonyl groups must be considered. Ketones (and α,β-unsaturated ketones even more so) are substantially more electrophilic than amides, which are markedly unreactive due to lone-pare resonance to reduce their electrophilicity. For quadrone, the cyclic ketone moiety is more electrophilic than the lactone system. Analogous considerations apply to epolactaene, where an ester, a ketone, and an amide are present. Both the ester and the ketone are α,β-unsaturated, and therefore their most electrophilic position is the β-carbon. For upial, the acyclic aldehyde moiety is the most electrophilic carbon, followed by the lactone system.