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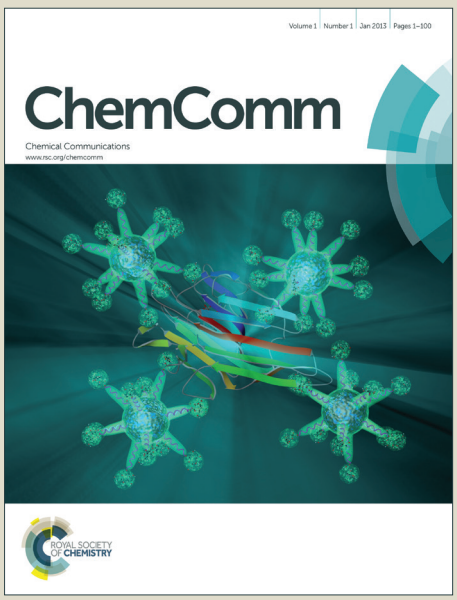

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FEATURE ARTICLE

Stereodefined acyclic trisubstituted metal enolates towards the asymmetric formation of quaternary carbon stereocentres†

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Reactions that involve metal enolate species are amongst the most versatile carbon–carbon bond forming processes available to synthetic chemists. Enolate species are involved in a multitude of powerful applications in asymmetric organic synthesis, but the generation of fully substituted enolates in a geometrically defined form is not easily achieved especially in acyclic systems. In this Feature Article we focus on the most prominent examples reported in the literature describing the formation of highly diastereo- and enantiomerically enriched quaternary stereocentres in acyclic molecules derived from stereodefined non-cyclic trisubstituted metal enolates.

Introduction

The past several decades have witnessed an impressive progress in the field of stereoselective organic synthesis, and countless efficient and elegant synthetic transformations have appeared in the literature.[1] In this context, the development of new strategies leading to the enantioselective creation of quaternary stereocentres, *i.e.* carbon atoms asymmetrically bonded to four different non-hydrogen substituents, have blossomed in the last few years.[2–4] Indeed, σ-bonding to four different carbon substituents represented a particular case of high molecular complexity that generated vivid scientific interests. Taking into consideration the fact that this molecular fragment is found in a plethora of natural products,[5,6] one can realize the significance of new efficient methods allowing for a rapid access to such stereogenic centres.[2,5–12] Since the carbon–carbon bond forming event leading to the creation of a quaternary stereocentre is often complicated by steric congestion between the approaching carbon substituents in the transition state, the state-of-the-art is the enantioselective construction of quaternary carbon stereocentres in acyclic systems that is considerably more difficult due to the number of degrees of freedom associated with these structures.[13] Several attractive methods based on asymmetric catalysis have therefore been developed in the recent years.[5,7–9]

As one can realize, the structure and reactivity of the intermediate involved in the key carbon–carbon bond-forming step is of extreme importance. Therefore, reactions that involve metal enolate species represent one of the most versatile carbon–carbon bond forming processes available to synthetic chemists,[14] and are involved in a multitude of powerful applications in asymmetric organic synthesis. However, the generation of stereodefined trisubstituted enolate in acyclic systems is still not a trivial task and has been the focus of only a few independent studies, first in racemic and then in enantiomerically enriched forms.

In this Feature Article we focus on the most prominent reported examples leading to the formation of highly diastereo- and enantiomerically enriched quaternary stereocentres in acyclic molecules derived from stereodefined non-cyclic trisubstituted metal enolates. Indeed, taking into consideration the significance of enolates as valuable intermediates in asymmetric organic synthesis (alkylation, aldol, Mannich and related reactions), one can evaluate the consequence to develop efficient methods to the direct access of trisubstituted metal enolates. Alternative stoichiometric and catalytic

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† Dedicated to my dear friend and colleague Prof. Zeev Gross on the occasion of his 60th birthday.

Yury Minko

Yury Minko was born in Nizhny Novgorod (Russia) in 1984. He completed undergraduate studies in chemistry at the Nizhny Novgorod State University in 2007 before moving to the Technion – Israel Institute of Technology, Schulich Faculty of Chemistry for his MSc followed by a direct route to PhD studies with Professor Ilan Marek. Yury is currently completing his PhD research in the Marek group working on the development of new synthetic methodologies allowing for the asymmetric formation of quaternary stereogenic centers in acyclic systems.

methodologies that do not include the formation of stereodefined enolate species,[15–18] employing enolate equivalents,[19,20] or using kinetic resolution of diastereomeric (*E*/*Z*) mixtures of trisubstituted enolates[21] and silylenol ethers,[22,23] but still leading to a quaternary-branched carbonyl moiety, constitute a separate broad topic *per se*, and therefore, are not covered here.

General stereochemical aspects of classic enolization reactions

Generally speaking, stereochemical aspects of the enolate formation include regio- and stereoselectivity (*E vs. Z* configuration) that determine the isomeric ratio of the final product formed by a reaction with an electrophile. Indeed, unsymmetrical ketones possessing protons in both α-positions are potentially able to produce the two isomeric enolates. In this case, kinetic and thermodynamic factors in the deprotonation step are crucial to determine the enolate regiochemistry. Thus, kinetically favored enolates are formed by deprotonation in the position with the least steric hindrance in the α- and β-positions, while the most substituted enolates are favored by thermodynamic factors.[24,25] In the case of non-cyclic carbonyl compounds, the formation of either the (*Z*)- or (*E*)-enolate isomer needs to be controlled in addition to thermodynamic and kinetic products. Common methods to control enolate geometry are usually based on the steric bulk variations of the substituents on the metal amide base and the nature of the linear carbonyl compound. Ireland, in his pioneering studies, rationalized the observed stereochemical outcomes by considering a chair-like six-membered cyclic transition state for the deprotonation step.[26,27]

Thus, increased steric bulk of the metal amide generally favors the formation of (*Z*)-enolate, while favored formation of the (*E*)-isomer of the enolate is possible in the presence of a steric hindrance caused by the R^2 substituent in the substrate. Following this logical assumption, the formation of (*Z*)-enolates is favored in the case of tertiary amides while *E*-enolates are predominantly formed from the corresponding ester substrates.

To be successfully abstracted by a base, the $\sigma_{C–H}$ orbital of the proton being removed must be in 0° dihedral angle alignment with the $\pi^*_{C=O}$ orbital (105° between the C–H and C=O bond) to maximize the overlap with the larger lobe of the antibonding orbital of the carbonyl, and therefore, allow for the maximum electron delocalization during the proton transfer event (Fig. 1(b)).[28]

In acyclic systems, the proton of the α-branched carbonyl compounds can be abstracted only when one of the two suitable conformers is reached that ultimately lead to additional difficulties for controlling the stereochemistry of the enolate. If selectively formed, the corresponding enolate becomes a pro-chiral species with two π-stereofaces equally accessible, and as a consequence, one additional factor leading to enantioselectivity is the reaction of this enolate with an electrophilic counterpart.

Thus, all three modes of selectivity summarized in Fig. 1 must be carefully controlled at the same time to form a single stereochemically pure functionalized carbonyl product bearing a quaternary stereogenic centre.

Ilan Marek

Ilan Marek, FRSC, born in Haifa in 1963 but educated in France, moved to the Technion – Israel Institute of Technology in 1997. He is Professor of chemistry and since 2005 he has been holding the Sir Michael and Lady Sobell Academic Chair. The research group of Prof. Ilan Marek is primarily concerned with the design and development of new and efficient stereo- and enantioselective strategies that do not have precedent in classical organic chemistry for the synthesis of important complex molecular structures. His vision is that challenging synthetic problems should be answered with efficiency and elegance. Prof. Marek heads the Mallat Family Laboratory of Organic Chemistry and has been Fellow of the Royal Society of Chemistry since 2011. He has received several major international awards over the years including the 2013 Moore Distinguished Scholar Appointment from California Institute of Technology, the 2012 Janssen Award for creativity in organic synthesis, the 2012 Israel Chemical Society Award for Academic excellence, the 2011 Royal Society Chemistry Organometallic Award, the 2011 Taiwan National Science Council Visiting Scholar, the 2010 German-Technion Award for Academic Excellence and Scientific Collaborations, the 2009 Henry Taub Prize for Academic Excellence, the 2005 Bessel Award of the Humboldt Foundation, the 2004 Merck Sharpe and Dohm Lecturer, the 2003 Prize for Excellent Young Chemist from The Israel Chemical Society and the 2002 Michael Bruno Memorial Award 2002, administrated by the Rothschild Foundation. He has received several awards for excellence in teaching. Prof. Marek also serves on the Advisory board of international leading journals such as Chemical Communications, Organic and Biomolecular Chemistry, Chemistry A European Journal, Angewandte Chemie International Edition, Synlett, Synthesis, Advancd Synthesis and Catalysis, European Journal of Organic Chemistry and The Chemical record. He also serves as Associate Editor of Beilstein Journal of Organic Chemistry, Associate Editor of Israel Journal of Chemistry and senior-editor of the Patai's series. He is chairman of the organic division of the European Association of Chemical and Molecular Sciences (EUCHEM) organic Division.

Formation of stereodefined trisubstituted enolates by deprotonation of branched carbonyl compounds

As followed from the prior discussion, it is crucial to control the free rotation along the $\sigma_{C–C}$ bond of α-branched carbonyl compounds for the successful formation of a single geometrical isomer of acyclic trisubstituted enolate.

In some cases, the generated enolate species should possess additional stereochemical information for the subsequent

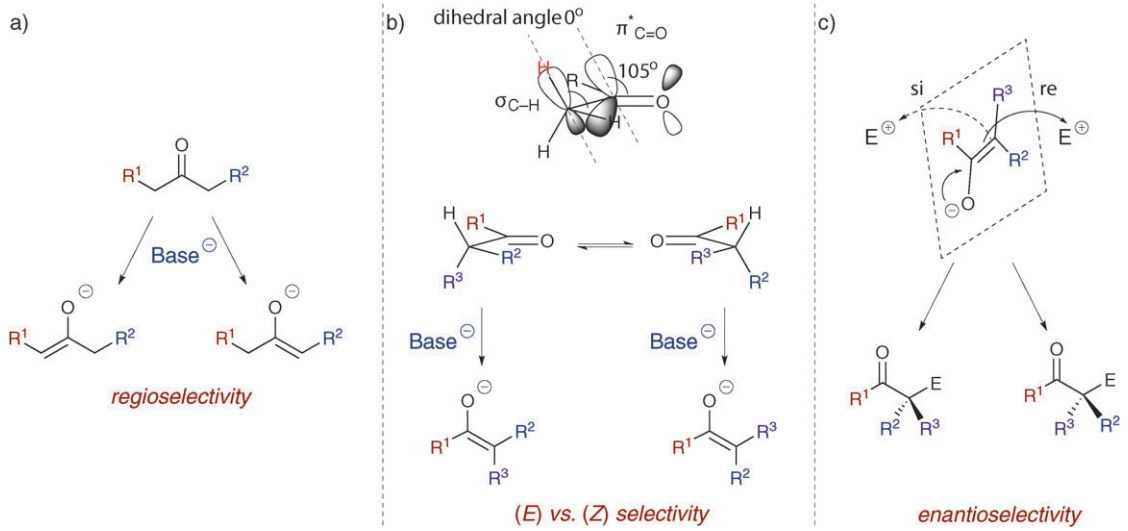


Fig. 1 Three modes of selectivity that need to be controlled in the reactions involving trisubstituted metal enolates.

diastereoselective formation of a quaternary stereocentre. The use of chiral auxiliaries to control both the stereochemistry of the enolization process as well as the reaction with the electrophile is still one of the most reliable strategies.[29]

Although this feature article deals with the preparation of acyclic trisubstituted enolates, the pioneering and important contribution of Meyers should be described as it shows the complexity of the problem. In this particular work, the preparation of α-quaternary branched carbonyl compounds was based on the sequential deprotonation–alkylation–alcoholysis of bicyclic lactams followed by cleavage and opening to linear γ-ketoester (Scheme 1).[30–32]

Early studies on the formation of polysubstituted enolates show that these entities easily undergo an α-elimination into ketenes. To address this issue, Boeckman and coworkers developed a class of camphor-derived lactam auxiliaries that allowed highly stereoselective formation of trisubstituted enolates.[33] Following this strategy, α-branched amides were formed by deprotonation of linear precursors with LDA at low temperature and a further alkylation reaction (Scheme 2(a)).

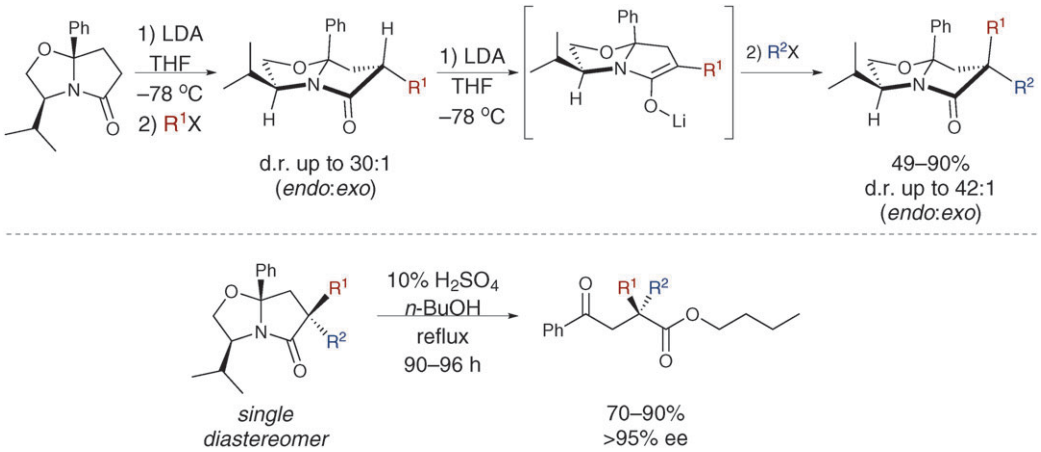
This alkylation reaction afforded α-branched amides in exceptional levels of diastereoselectivity. It was confirmed that deprotonation of linear amides with LDA provided the lithium enolate in high yield, and the enolization reaction was highly *Z*-selective according to nOe analysis of the corresponding silylenol ether.[33] However, the alkylation reaction led to the product with low yield and diastereoselectivity. To explain such outcome the authors proposed that the lack of selectivity originates from steric factors. On the other hand, deprotonation of the same α-branched amides with sodium diisopropylamide (NDA) afforded the more ionic sodium enolates with excellent diastereoselectivity (>49 : 1 *Z* : *E* ratio).[33] Moreover, these sodium enolates led to the alkylated products, upon reaction with allyl iodide, with very high diastereomeric ratios in moderate to good yields (Scheme 2(b)). Based on molecular mechanics calculations, the authors assumed that the orientation of sodium enolate is perpendicular to the endocyclic π-system of the lactam that prevents unfavorable electronic interactions.[33] The approach of an electrophilic alkylating reagent then occurs from the least sterically hindered enolate stereoface. Cleavage of the chiral auxiliary has been achieved by transesterification with LiOBn and proceeds with an almost quantitative recovery of the lactam, leading to the α-quaternary benzyl ester in 80% yield (Scheme 3).[33]

Myers and coworkers reported one of the most prominent examples of highly stereospecific enolization of acyclic α-alkylbutyramides with LDA in the presence of lithium chloride under mild conditions. Thus, pseudoephedrine-based α-branched amides selectively formed *Z*- and *E*-enolates upon deprotonation, as confirmed from the nOe spectra of the corresponding cyclic siloxane derivatives (Scheme 4).[34]

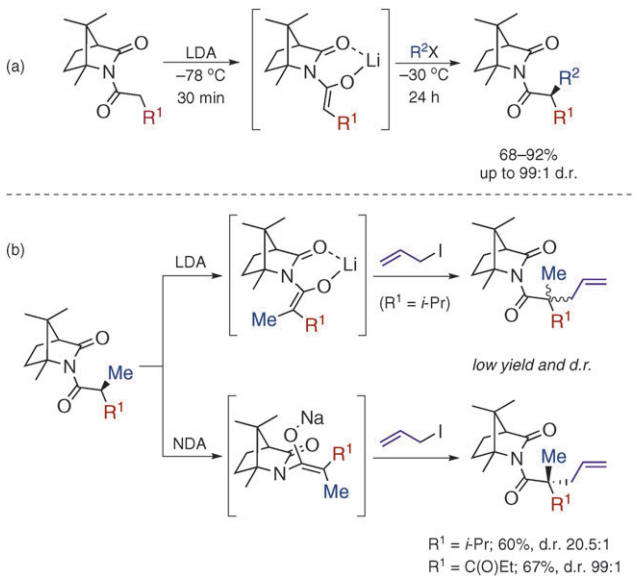
The rationalization for the favored pre-transition state suggested that the solvated lithium alkoxide side chain and the base are positioned on opposite faces of the forming enolate, with the R–C–H bond suitably aligned for deprotonation (Fig. 2).[34]

Alkylation of these stereodefined enolate species with an excess of benzyl bromide is also stereospecific suggesting that *Z*- and *E*-trisubstituted pseudoephedrine amide enolates are alkylated preferentially from the same diastereoface (Scheme 5).[34] The sense of alkylation in this case is in good agreement with the general stereoinduction of alkylation of linear pseudoephedrine amides,[35–37] approach of the alkylating agent from the less sterically hindered enolate π-face.

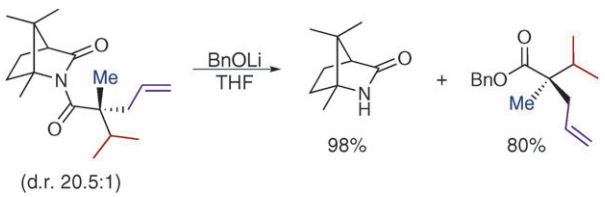
However, it should be noted that benzylation of the (*Z*)-enolate is more diastereoselective and occurs more rapidly ($k_1/k_2 > 4$) than the analogous reaction of the (*E*)-enolate.[34] The observed decrease in the diastereomeric ratio of the benzylated product led the authors to suggest that a small amount of (*E*)-enolate, formed during the deprotonation of amide, is alkylated less rapidly, and with opposite diastereoselectivity to the (*Z*)-enolate. Consequently, the diastereoselectivity of these reactions was achieved by using a slight excess of



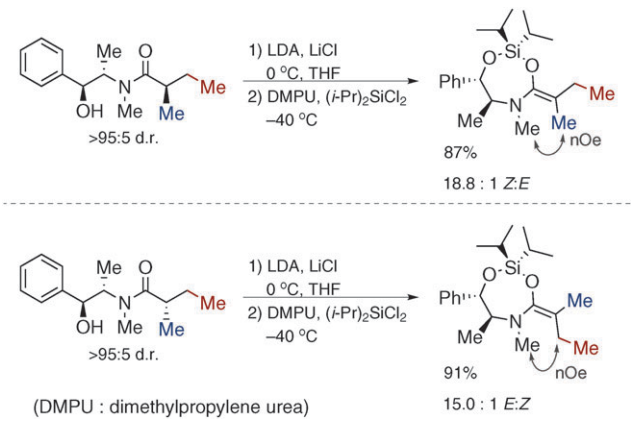
Scheme 1 Formation of γ-ketoester possessing a quaternary stereocentre by using a chiral bicyclic lactam auxiliary.



Scheme 2 One of the first examples of stereocontrolled formation of acyclic trisubstituted enolates.



Scheme 3 Cleavage of the camphor-derived lactam auxiliary.



Scheme 4 Using pseudoephedrine auxiliary for highly selective enolization leading to the formation of trisubstituted acyclic enolates.

enolate (1.25 equiv.), with the electrophile as a limiting reagent. Thus, under these optimized conditions, the diastereoselectivity of benzylation of pseudoephedrine-based amides increased to 19 : 1 with no decrease in yield, and a range of different electrophiles (including unactivated alkyl halides) reacted efficiently and diastereoselectively with various α,α-disubstituted enolates (Scheme 6).[34]

The practicality of the pseudoephedrine chiral auxiliary has been demonstrated by subsequent transformation of α-quaternary amides into a variety of enantiomerically enriched carboxylic acids, ketones, and aldehydes (Scheme 7).[34]

Despite these excellent results, the application of pseudoephedrine as a chiral auxiliary in organic synthesis is restricted in many countries since pseudoephedrine can be transformed into methamphetamine and other illegal drugs that complicate its use in industrial and academic research. To address this legal issue, Myers and coworkers developed and synthesized in their further studies, an alternative pseudoephenamine auxiliary.[38,39]

This superseding analogue of pseudoephedrine auxiliary was successfully applied toward the alkylative construction of quaternary stereogenic centres providing comparable, and, in some cases, better results in terms of diastereoselectivity (Scheme 8).[39]

A recent application of Myers' alkylative quaternization methodology was demonstrated in the concise total synthesis of several aspidosperma alkaloids reported by Medley and Movassaghi,[40] where pseudoephenamine auxiliary was successfully used to control trisubstituted enolate formation, and, eventually, the alkylative asymmetric construction of the C-5 quaternary carbon stereocentre of this class of natural compounds.

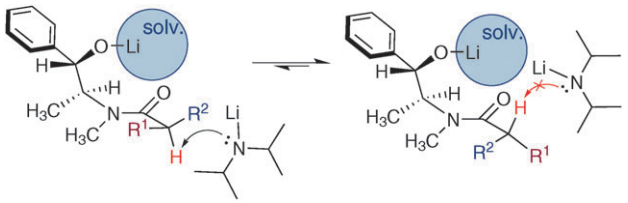


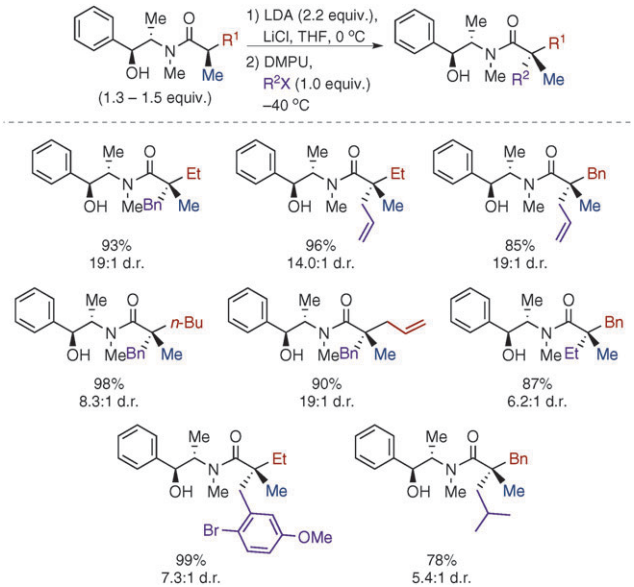
Fig. 2 Proposed model confirming the high diastereoselectivity of the deprotonation of branched pseudoephedrine amides by LDA.

[3,3]-Sigmatropic rearrangements belong to the most well-developed methods affording the formation of all-carbon stereogenic centres in structurally complex cyclic molecules.[41] One of the most versatile and thoroughly studied variant of the [3,3]-sigmatropic reactions is the Ireland enolate–Claisen rearrangements. This class of transformations enables introduction of sterically encumbered quaternary stereogenic centres. Nevertheless, complications accompanying the enolization of α-branched esters (poor control of enolate geometry) limited the applicability of the Ireland–Claisen methodology to acyclic substrates for a long time.

This issue was resolved when Zakarian and coworkers reported the diastereoselective Ireland–Claisen rearrangement through an unprecedented stereoselective enolization of α,α-disubstituted allylic esters.[42] The highly stereoselective formation of trisubstituted enolates in this case was achieved by using a double stereodifferentiation in the deprotonation of chiral enantiomerically enriched α-branched allylic esters with enantiomerically pure chiral lithium amides (Scheme 9).[42]

Although substituents have essentially no difference in terms of steric volume, the corresponding *Z*- and *E*-enolates were produced with high levels of selectivity only when the matching enantiomer of a chiral lithium base was used for deprotonation.[42] In control experiments, when achiral bases (LDA or LDE) were used, the enolates were obtained with low selectivity (*Z*/*E* = 2/1), as confirmed by trapping the mixture of enolates with Me_3SiCl and analysis of the nOe spectra of the corresponding silylenol ethers.

The origin of this outstanding stereoselectivity of the enolization process is not completely elucidated by the authors but they suggested that the enolate configuration is determined by

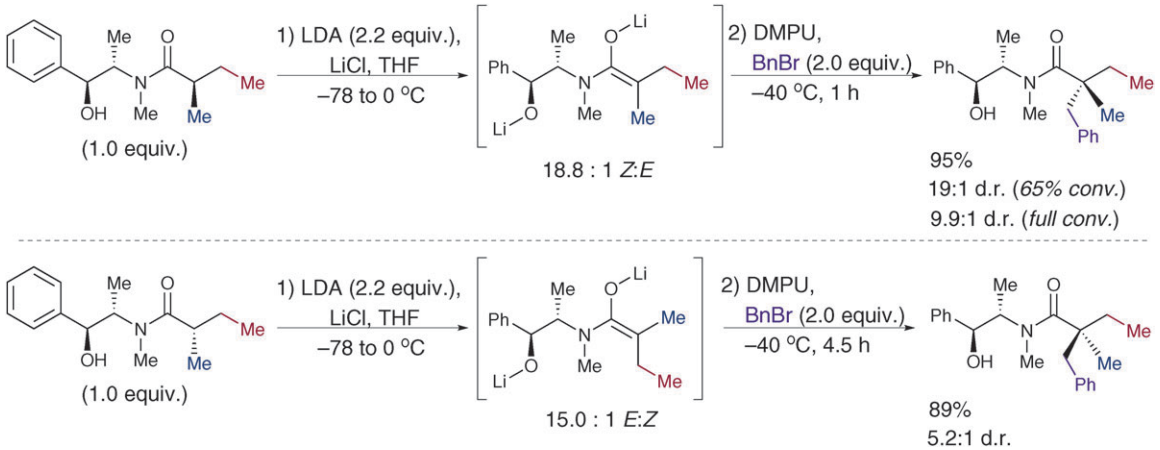


Scheme 6 Selected examples of diastereoselective alkylative construction of quaternary stereocentres in acyclic systems using Myers' pseudoephedrine auxiliary.

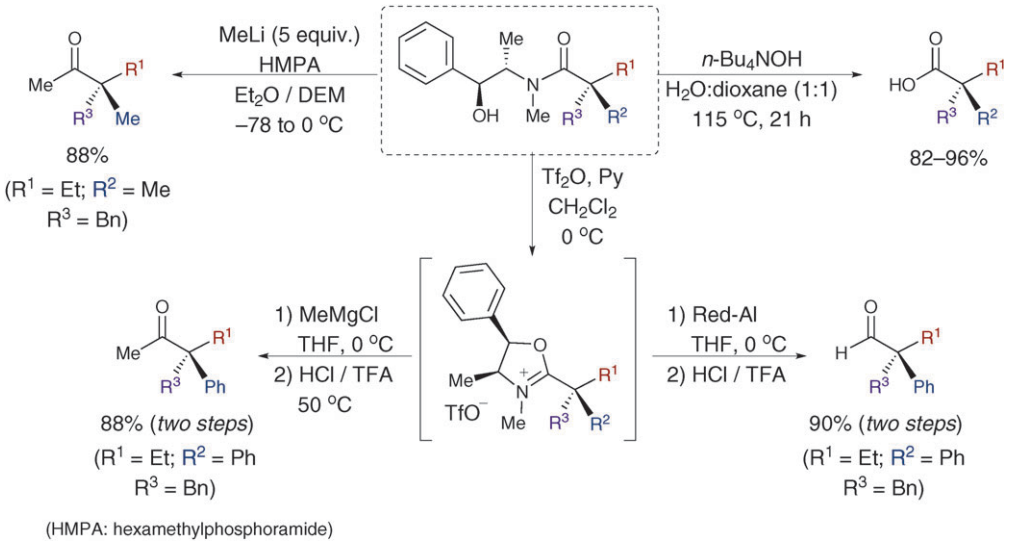
highly organized transition states similar to the ones proposed by Ireland (Scheme 10).[42]

According to this hypothesis, chiral substituents on the amide nitrogen atom have a significant effect on the relative energies of cyclic transition states, and the presence of such substituents provides selectivity of enolization. However, it is not completely clear whether either groups R^1 and R^2 have an influence or if a certain transition state is more energetically favorable due to the double stereodifferentiation. Thus, an empirical model consistent with experimental observations was proposed to rationalize the stereoselectivity of the enolization step (Scheme 10).[42]

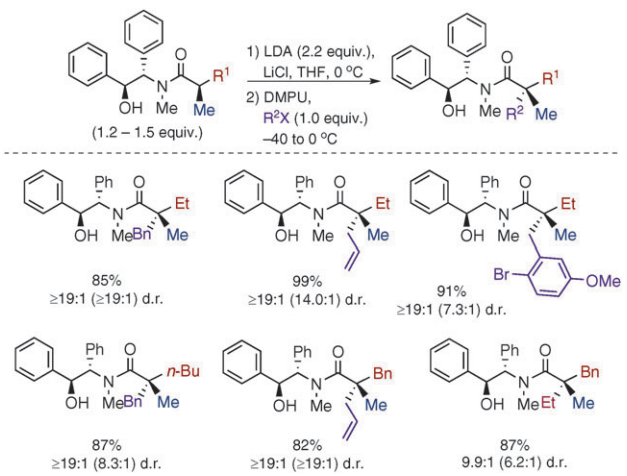
The application of this stereoselective enolization was exemplified by the subsequent Ireland–Claisen rearrangement of enantiomerically enriched allylic esters in the presence of chiral base B2. Particularly, α-branched esters bearing a disubstituted



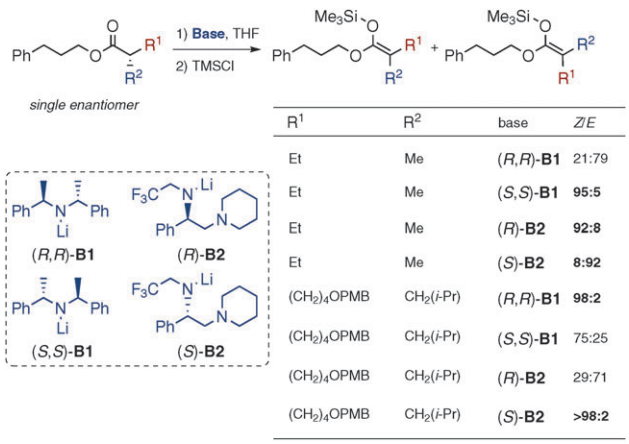
Scheme 5 Diastereodivergent benzylation of pseudoephedrine-derived trisubstituted lithium enolates.



Scheme 7 Further transformations of α-quaternary branched pseudoephedrine amides into valuable non-cyclic building blocks possessing all-carbon quaternary stereocentres.



Scheme 8 Myers' pseudoephenamine auxiliary for the alkylative formation of acyclic all-carbon quaternary stereocenters.



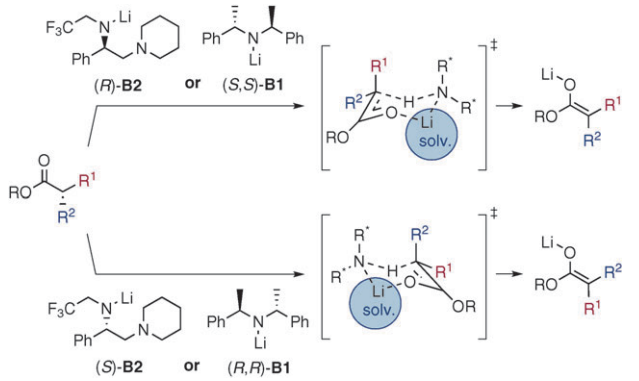
R1	R2	base	Z/E
Et	Me	(R,R)-B1	21:79
Et	Me	(S,S)-B1	95:5
Et	Me	(R)-B2	92:8
Et	Me	(S)-B2	8:92
$(CH_2)_4OPMB$	$CH_2(i\text{-}Pr)$	(R,R)-B1	98:2
$(CH_2)_4OPMB$	$CH_2(i\text{-}Pr)$	(S,S)-B1	75:25
$(CH_2)_4OPMB$	$CH_2(i\text{-}Pr)$	(R)-B2	29:71
$(CH_2)_4OPMB$	$CH_2(i\text{-}Pr)$	(S)-B2	>98:2

Scheme 9 Double stereodifferentiation in the deprotonation of enantiomerically pure branched esters by chiral lithium amide bases.

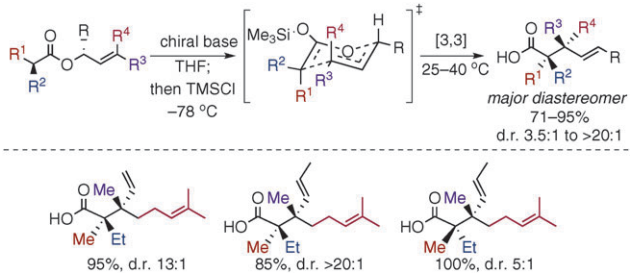
terminal double bond involved in the sigmatropic rearrangement gave products with two adjacent all-carbon quaternary stereogenic centres with moderate to high diastereoselectivity (Scheme 11).

This strategy allows for an efficient relay of chirality from readily accessible chiral allylic esters of α-branched carboxylic acids to new stereogenic centres through the Ireland–Claisen rearrangement en route to the spiroimine core of gymnodimine,[42] and more recently, to the total synthesis of (+)-pinnatoxin A (Scheme 12).[43]

One of the most widely used class of auxiliary groups is the chiral oxazolidinones, initially developed by Evans.[44] This class of chiral imide auxiliaries has been intensively studied in a variety of asymmetric transformations and the methodology developed has been applied to the stereoselective construction of many different chiral building blocks, natural products, and biologically active compounds.[45,46] Despite their efficiency in asymmetric synthesis, the α-branched imides bearing Evans' auxiliary, to the best of our knowledge, were not reported as substrates used for the second stereoselective deprotonation–alkylation sequence to form products with quaternary stereocentres. At some level of approximation, the monoalkylated (branched) carbonyl substrate domain attached to the chiral auxiliary can indeed be considered as the analogous starting material to the pseudoephedrine-derived one developed and studied by Myers, as discussed previously.[34,39] However, the only known strategy to produce stereodefined trisubstituted enolates by using Evans' oxazolidinone auxiliary with good stereochemical control was based on deprotonation of α,β-unsaturated conjugated imides. Thus, Kobayashi and coworkers while working on the synthesis of cyclopentenedione core of madindolines A and B developed a highly stereoselective alkylation of trisubstituted conjugated enolates (Scheme 13).[47]



Scheme 10 Proposed favorable transition states for the deprotonation of enantiomerically pure branched esters by chiral lithium amide bases.



Scheme 11 Stereoselective formation of trisubstituted silylenol ethers followed by [3,3]-sigmatropic rearrangement provides acyclic molecular scaffolds with two adjacent quaternary stereocentres.

Preliminary optimizations were performed using tiglic acid derivatives that underwent highly (*E*)-selective enolization as was confirmed by nOe experiment on the corresponding silylenol ether. Conjugate deprotonation followed by alkylation with alkoxymethyl chlorides provided products bearing the quaternary stereocentre in moderate yields but with a good level of diastereoselectivity (Scheme 13). This approach was further investigated, and the scope was further expanded to various substrates (Scheme 14).[48]

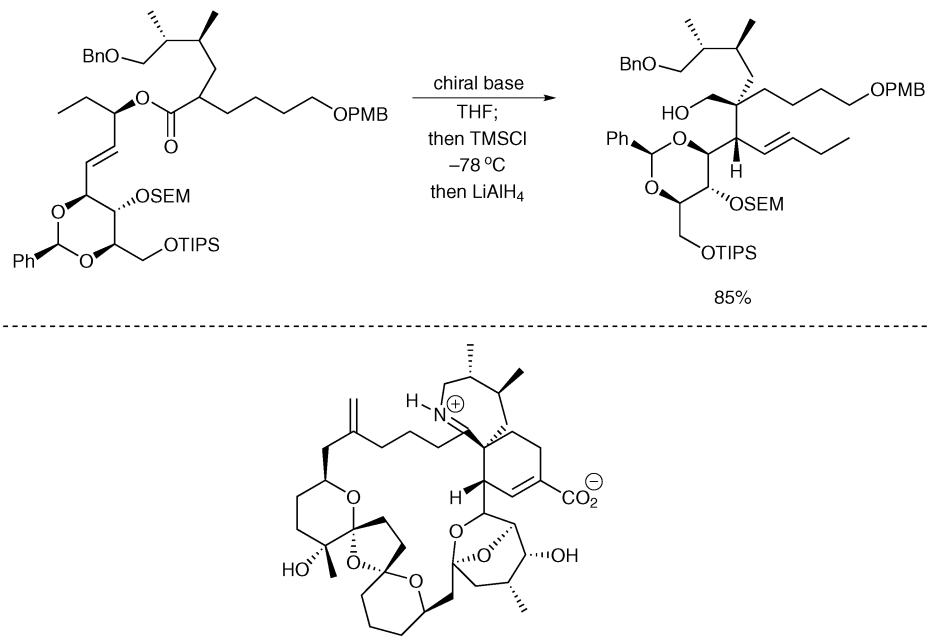
In all cases stereoselective alkylation of trisubstituted sodium enolates provided products in good yields and excellent diastereomeric ratios. This approach to generate chiral enolates bearing Evans' auxiliary allowed the authors to develop a concise total synthesis of succinimide anticonvulsant (+)-ethosuximide, a compound commonly used in treatment of epilepsy (Scheme 15).[48]

Hug and Bochet applied this strategy to construct the quaternary carbon stereogenic centre of the challenging (*R*)-[$^{2}H_1$, $^{2}H_2$, $^{2}H_3$]-neopentane, a molecule that represents the archetype of chiral molecules where the asymmetry results from a dissymmetric mass distribution (number of neutrons) (Scheme 16).[49]

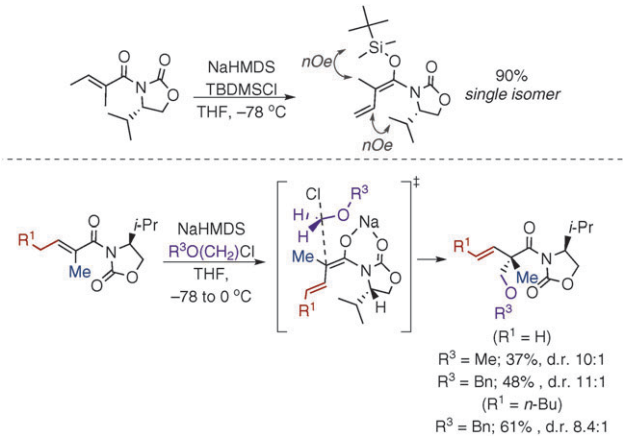
The absolute configuration of this molecule has been determined by Raman spectroscopy.[49]

Stereodefined acyclic trisubstituted enolates by methodologies not involving a deprotonation step

Dunitz, Seebach and coworkers pioneered the formal generation of stereodefined trisubstituted lithium enolates by the *in situ* generation and trapping of ketene intermediates.[50,51] According to this strategy, it was proposed that ketene or



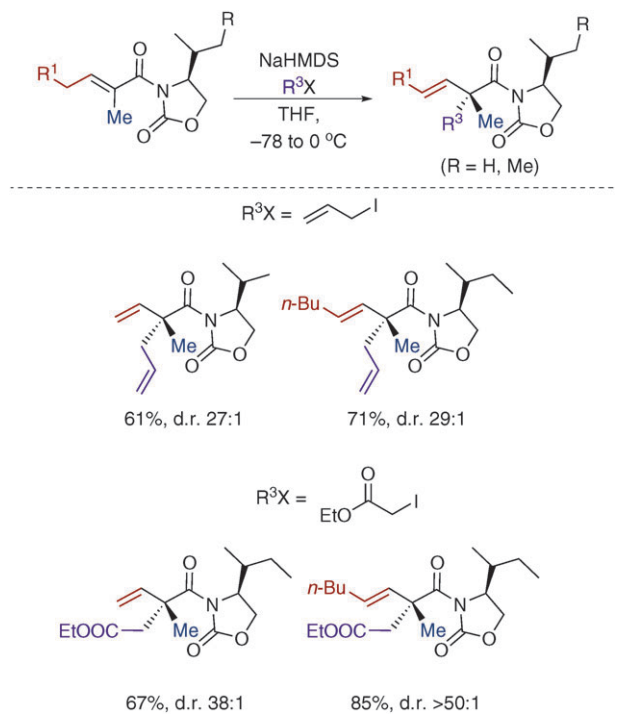
Scheme 12 Stereoselective formation of trisubstituted silylenol ethers followed by [3,3]-sigmatropic rearrangement en route to the total synthesis of pinnatoxin A.



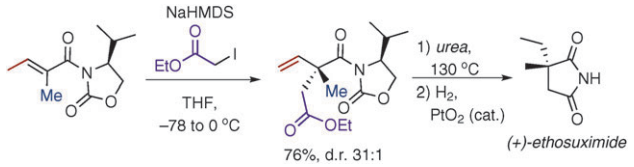
Scheme 13 Formation of stereodefined trisubstituted enolates by conjugate deprotonation of α,β-unsaturated Evans' auxiliary-based imides.

ketene-like intermediate species, produced by elimination reaction from BHT ester lithium enolates upon slow warming from −78 °C to temperatures above *ca.* −20 °C, were trapped by methyllithium to lead to the diastereoselective formation of ketone enolates (Scheme 17).[51]

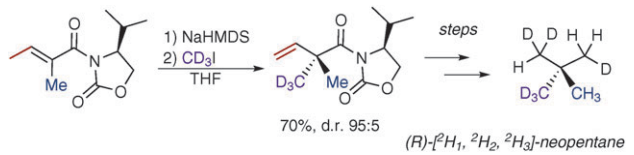
It was shown that the *Z*/*E* ratio improves with increased difference in steric bulk between the two substituents on the ketene intermediate, methyllithium reacting from the less sterically encumbered stereoface. Based on these observations, the authors extended the scope of this method and trisubstituted enolate species were used for the diastereoselective aldol addition reactions (Scheme 18).[51]



Scheme 14 Selected examples for the formation of quaternary centres in acyclic systems by the method developed by Kobayashi.



Scheme 15 Concise total synthesis of an anticonvulsant (+)-ethosuximide.



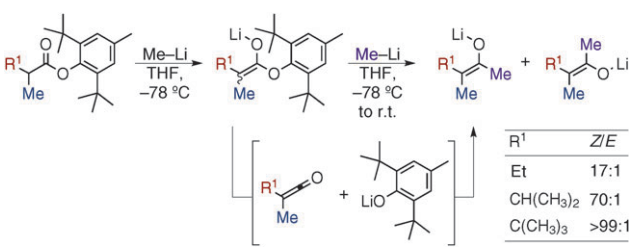
Scheme 16 Application towards the stereoselective synthesis of a challenging quaternary stereocentre of (*R*)-[$^2H_1$, $^2H_2$, $^2H_3$]-neopentane.

It should be mentioned that attempts to generate ketone enolates, under the same experimental conditions, were not successful from analogous branched methyl and *tert*-butyl esters as well as from asymmetric anhydride $R_2CHC(O)OC(O)t$-Bu.[51]

Myers reported an alternative strategy for the stereocontrolled generation of enolates *via* a stereoselective alkylation reaction of α,α-disubstituted pseudoephedrines amides. Following this approach, the initial conjugate addition of organolithium reagents to unsaturated carbonyl substrates led to the selective formation of *Z*- and *E*-enolates (Scheme 19).[34]

These enolates were successfully alkylated from a common diastereoface, providing diastereomerically enriched adducts with a variety of substitution patterns at the quaternary carbon centres (Scheme 20(a)).[34] In the following studies, α-alkyl-α,β-unsaturated pseudoephenamine amides were similarly subjected to the conjugate addition–alkylation. Diastereoselectivities observed for the alkylated products were significantly enhanced in all cases compared to the prior method using a pseudoephedrine auxiliary (Scheme 20(b)).[39]

Yields of conjugate addition–alkylation products are slightly reduced when the conjugate addition was performed with primary alkyllithium reagents as competitive 1,2-addition to the amide substrate may occur. Further transformations of pseudoephedrine amides bearing the α-quaternary carbon centres into synthetically valuable carboxylic acids, methyl ketones, primary alcohols, and aldehydes are then easily accessible following standard cleavage procedures.



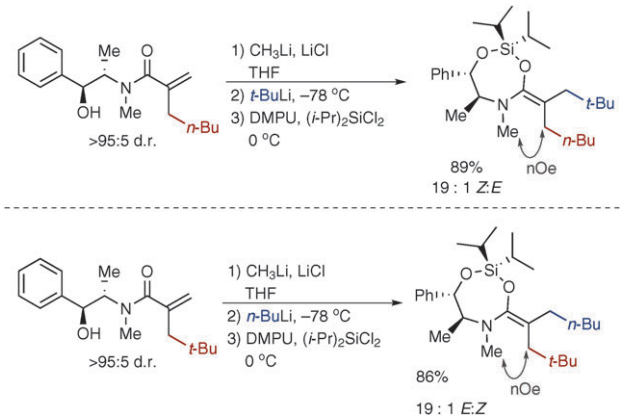
Scheme 17 Diastereoselective formation of trisubstituted acyclic *Z*-enolates from branched BHT-esters.

Manthorpe and Gleason reported a noteworthy strategy for the stereoselective generation of trisubstituted enolates by reductive ring opening of bicyclic thioglycolate lactams.[52,53] Both (*E*)- and (*Z*)-amide enolates could be prepared from the corresponding α,α-disubstituted bicyclic system showing in some cases excellent levels of stereocontrol (Scheme 21).[53]

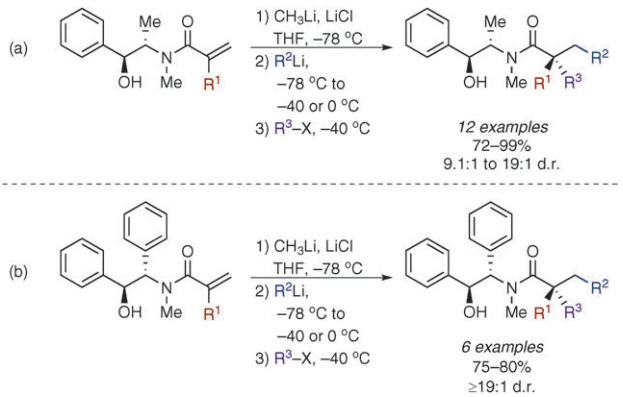
This method is based on a simple mechanistic model where the thiolactam system is holding the sulfur atom exclusively on one stereoface of the carbonyl plane with the O–C–C–S dihedral angle at the maximum proximity to 90° due to the interconversion inability of the rigid bicyclic system (Scheme 21). The two-electron reduction under standard Birch-type conditions facilitates the selective carbon–sulfur bond cleavage.

The *E*/*Z* stereocontrol of this enolate is pre-determined by the absolute configuration at the α-quaternary centre in the starting bis-alkylated lactam, and therefore, the complementary enantiomer can be easily formed by inverting the order of alkylation followed by cleavage of the cyclic system. This strategy was successfully applied, first to form alkylated products with a quaternary stereocentre and then aldol adducts upon reaction with aldehydes (Scheme 22).[52,54]

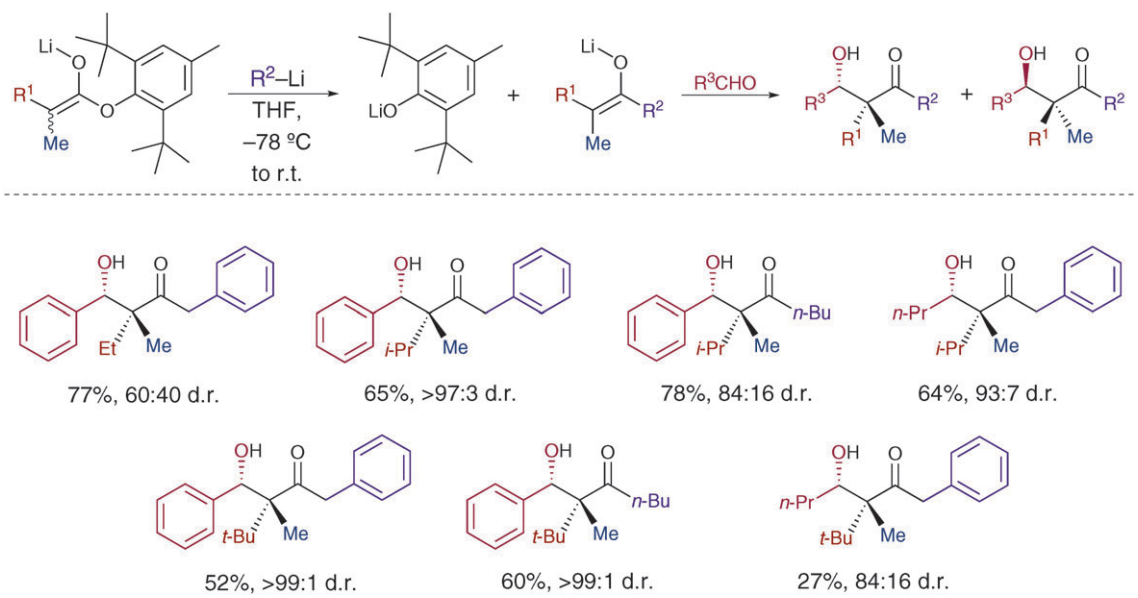
The initially reported system, however, had several significant drawbacks such as poor selectivity in the alkylation of *E*-configured enolates, inability to produce carboxylic acids by direct hydrolysis of the chiral auxiliary, and a ten-step synthesis of the starting chiral bicyclic lactam that could not be recovered under the cleavage reaction conditions.[52] These shortcomings were addressed in the following work reported by Gleason and coworkers where an improved second-generation of bicyclic lactam could be prepared on a large scale using a concise strategy that does not involve chromatographic purification of the intermediate precursors.[55] This more practical chiral thioglycolate lactam was then employed in the alkylative



Scheme 19 Formation of stereodefined trisubstituted lithium enolates by conjugate addition of alkyllithium reagents to pseudoephedrine-derived unsaturated amides.

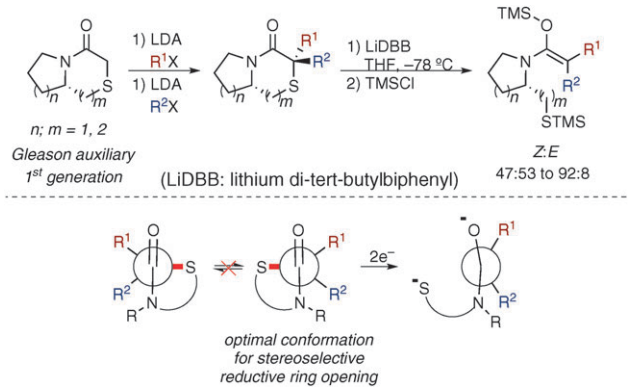


Scheme 20 Comparing efficiency of pseudoephedrine (a) and pseudoephenamine (b) auxiliaries in the alkylative construction of all-carbon quaternary stereocentres in acyclic systems.



Scheme 18 Diastereoselective aldol addition reaction of trisubstituted acyclic (*Z*)-enolates derived from trisubstituted BHT-ester lithium enolates.

construction of quaternary stereocentres and in the asymmetric Mannich reactions (Scheme 23).[55,56]

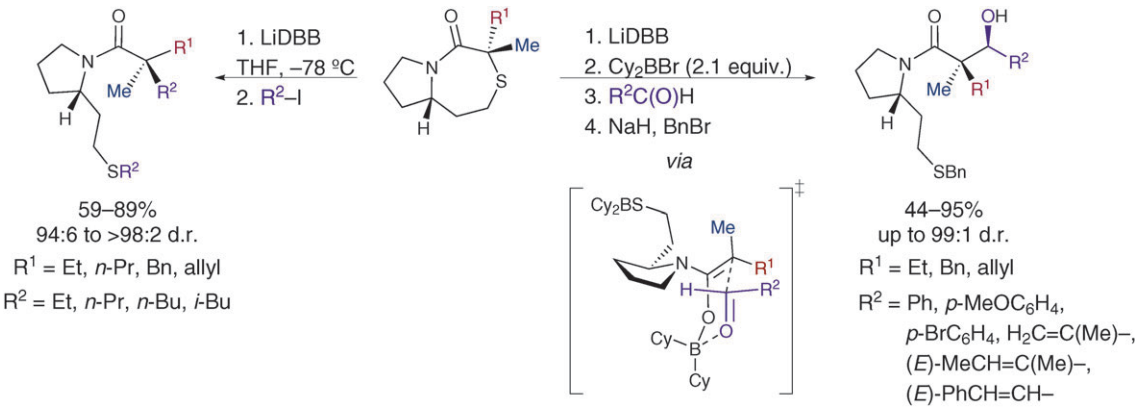


Scheme 21 Chiral bicyclic thioglycolate lactam auxiliary and a proposed model explaining the stereoselective reductive cleavage of the carbon–sulfur bond.

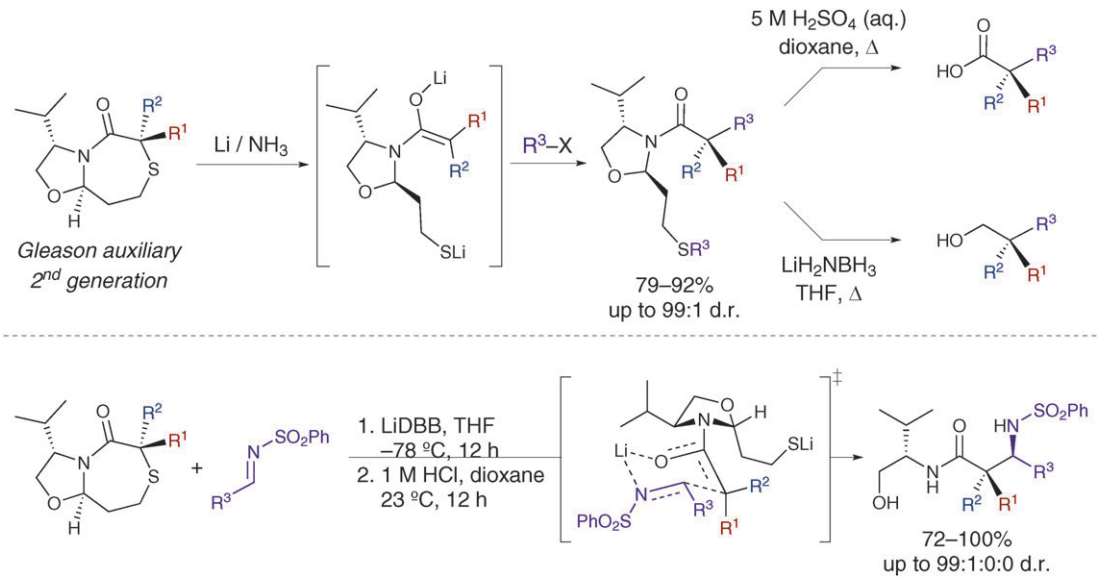
The application of the second generation of the Gleason auxiliary has been demonstrated in the recent and concise total synthesis of (*R*)-puraquinonic acid, where this class of thioglycolate lactams was used to control the enantioselective formation of the all-carbon quaternary stereocentre (Scheme 24).[57]

Existing methods for the creation of quaternary stereocentres in acyclic systems through the formation of stereodefined enolate structures covered so far clearly demonstrate the extraordinary levels of sophistication reached in synthetic organic chemistry with respect to the creation of *one* carbon–carbon bond *per* chemical step.

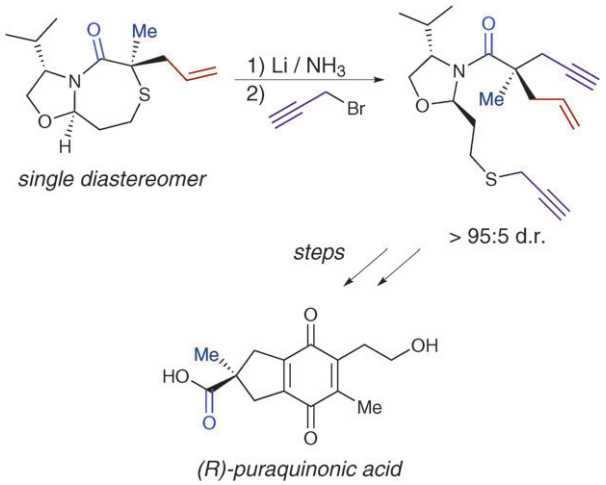
However, if one can develop concise synthetic methodologies allowing for the concomitant formation of several new carbon–carbon bonds and several stereogenic centres, including the acyclic all-carbon quaternary through the formation of stereodefined trisubstituted enolates, it would undoubtedly be a significant improvement in terms of efficiency and be a valuable addition to the existing tools in synthetic methodologies.



Scheme 22 Stereoselective formation of quaternary stereogenic centres based on the first generation of the Gleason chiral auxiliary.



Scheme 23 Application of the second generation of bicyclic thioglycolate auxiliary towards the formation of quaternary stereocentres by alkylation and Mannich-type reactions of stereochemically defined lithium enolates.



Scheme 24 Stereoselective construction of the quaternary stereocentre of (*R*)-puraquinonic acid using Gleason auxiliary.

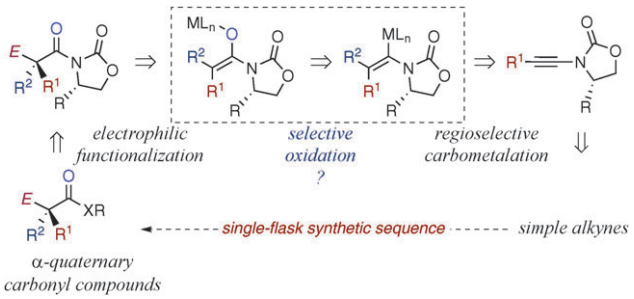


Fig. 3 Revised retrosynthetic analysis for the generation of stereochemically defined trisubstituted metal enolates from functionalized alkyne starting substrates in a single-flask protocol.

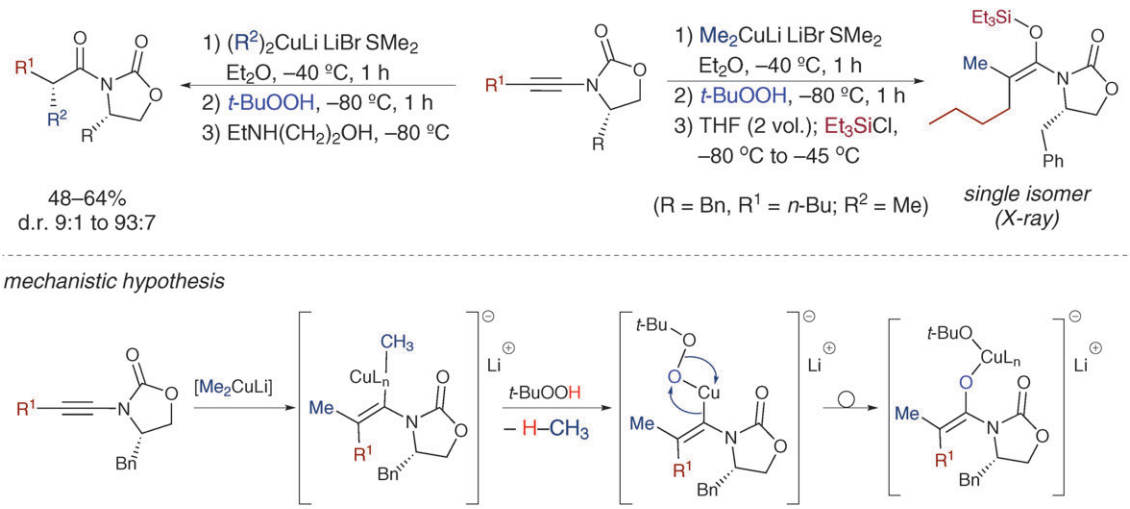
During the past several years, we have contributed to the development of such synthetic strategies,[58–61] and have initially disclosed a simple approach to the formation of aldol surrogates possessing the all-carbon quaternary carbon stereocentres in a single-pot operation from simple starting materials through the formation of trisubstituted allylmetal species.[62] In the following studies, the same authors have reported the formation of stereodefined substituted metal enolates through manipulation of easily accessible ynamides.

Since the regio- and stereoselective formation of configurationally defined vinyl copper species by a carbocupration reaction of ynamides has been reported,[63,64] the formation of stereodefined enolates could logically result from an oxidation reaction of these vinyl copper species (Fig. 3).[65]

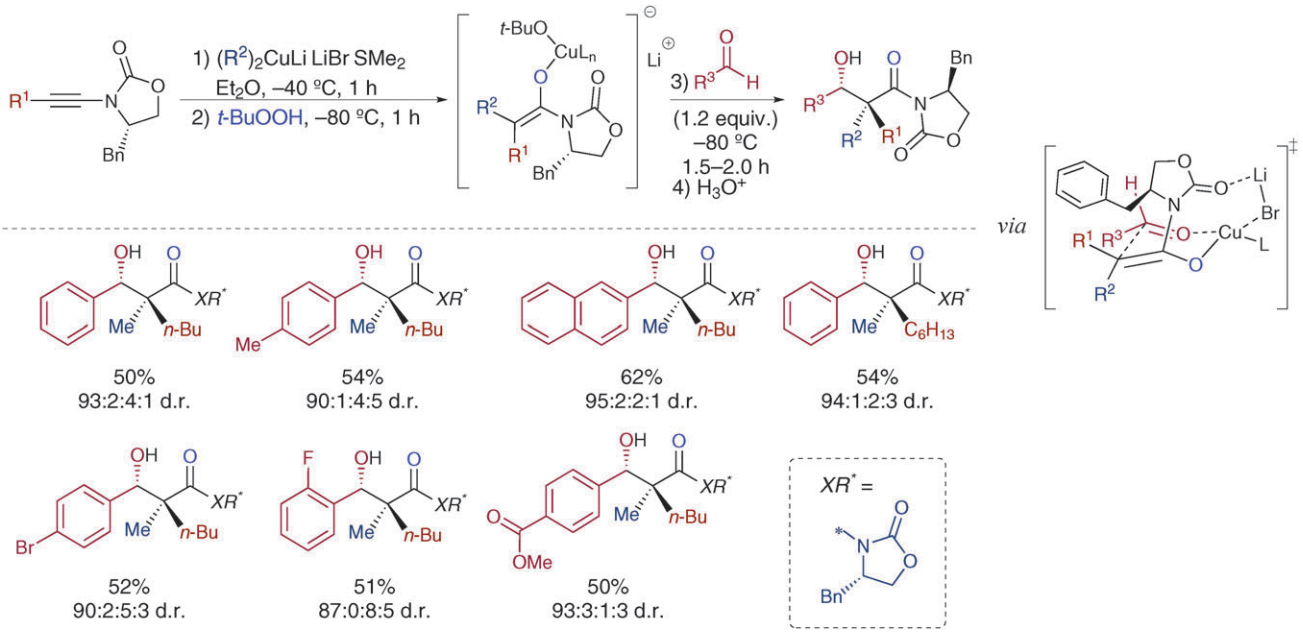
According to this concept, if the key step (Fig. 3, framed) of this retrosynthetic analysis is successfully performed, the overall strategy outlined above should be successful. In this case, the formation of the target carbonyl product bearing an α-quaternary stereogenic centre would be virtually possible from simple alkynyl substrates.

Following previous studies, where the insertion of a methylene unit into a C(sp^2)–M bond was successfully achieved by the use of carbenoid reagents,[62,66–68] the insertion of an oxygen unit into the same C(sp^2)–M bond should be obtained by reaction with oxenoids with general structure M–O–LG.[69] The electrophilic nature of these species was the subject of several studies and was summarized in a few reviews[66,69,70] and research papers. Usually, oxenoids oxidize vinyl metal into metal enolates with retention of configuration of the initial stereochemistry.[71–73] However, all examples reported in the literature were related to a lower substitution pattern of the enolate.

The possibility to employ oxenoids for the generation of stereodefined trisubstituted chiral enolates was originally checked by oxidation of the vinylcopper intermediates, easily obtained by carbocupration of ynamides with a separately prepared THF solution of oxenoid *t*-BuOOLi at low temperature.[65] Despite this reaction provided the expected enolate intermediate in an efficient manner, a simple modification of the carbocupration step using Gilman-type organocuprates[74,75] $R_2CuLi{\cdot}LiX$ instead of organocopper reagents $RCu{\cdot}MX_n$ allowed the authors to perform the direct and selective oxidation by



Scheme 25 Formation of stereodefined trisubstituted copper enolates by the direct oxidation of alkyl vinyl cuprates with *t*-BuOOH.

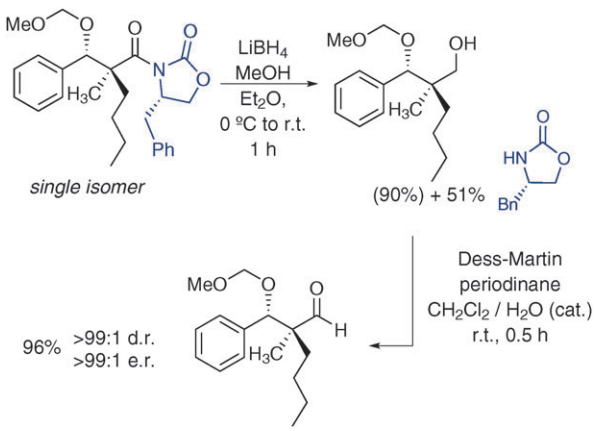


Scheme 26 A single-flask sequence for the stereoselective formation of aldol adducts possessing quaternary carbon stereogenic centres in acyclic systems.

commercially available *t*-BuOOH (Scheme 25).[65,76] Thus, it was found that the oxidation reaction proceeds with a complete retention of configuration initially obtained during the carbocupration reaction, as determined by X-ray crystallographic analysis of the stereochemistry of the silylenol ether obtained by reaction of the copper enolate with triethylchlorosilane.[77,78] Therefore, this combined approach of a carbometalation reaction of ynamides followed by stereospecific oxidation either with oxenoid or directly with *t*-BuOOH leads to the formation of stereodefined trisubstituted copper enolate (Scheme 25).[65] The direct oxidation in this case is possible due to the formation of mixed alkyl vinyl cuprate that provides an additional basic centre capable of an *in situ* deprotonation of the hydroperoxide counterpart. Indeed, an alkyl organometallic species (C(sp^3)–M) is more basic than a vinyl metal species (C(sp^2)–M), and therefore the addition of *t*-BuOOH led to a fast *in situ* deprotonation of the peroxide by the alkyl group present on the copper (in the case of $R^2 = CH_3$ this process was expected to be thermodynamically favorable as liberation of CH_4 happens) with concomitant formation of the intermediate peroxocopper. The latter undergo a 1,2-metalate rearrangement to result in the copper enolate bearing Evans' chiral auxiliary.

This conceptual single-flask synthetic strategy to the synthesis of stereodefined trisubstituted metal enolates has finally allowed for the development and study of aldol and Mannich-type addition reactions. Accordingly, the acyclic aldol adducts were formed in good yields (based on the starting ynamides) and high diastereomeric ratios (Scheme 26).[65,76]

The absolute configuration in the formation of the respective aldol adducts in this case is determined by a Zimmerman–Traxler cyclic transition state[79] (Scheme 26).[65] The six-membered highly organized cyclic transition state adopts a chair-like conformation,



Scheme 27 Reductive cleavage and recovery of the chiral oxazolidinone auxiliary.

the carbonyl of the oxazolidinone auxiliary chelates copper or, more likely, associated lithium salts, and the benzyl substituent shields one stereoface in the chelated six-membered ring.

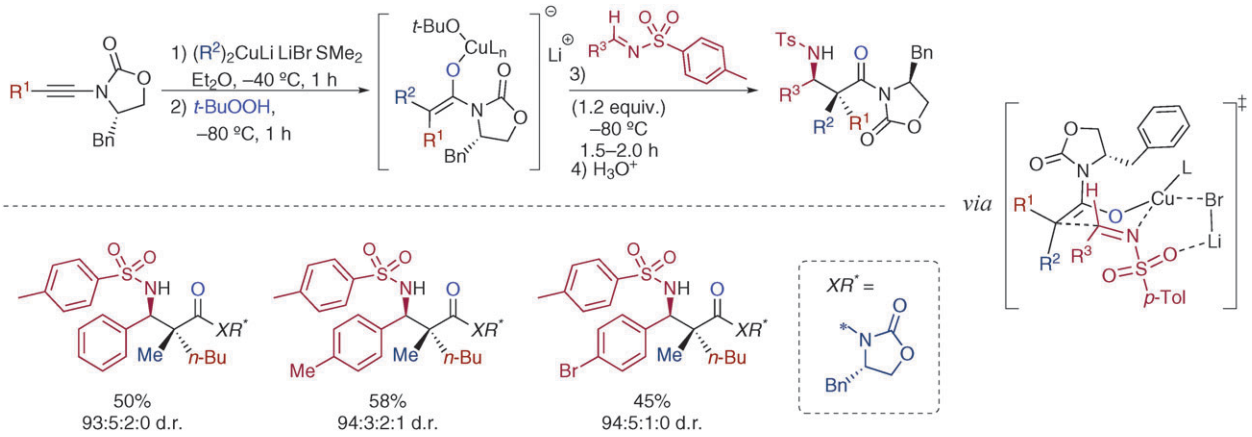
As a consequence, the aldehyde approaches the enolate *anti* to this shielding group, with its R^3 substituent in a pseudo-equatorial position. The major diastereoisomer of the aldol adducts could easily be separated by simple column chromatography on silica gel, and the stereochemical outcome was confirmed by X-ray crystallographic analysis.[65]

Despite the fact that aldol adducts could not be straightforwardly converted into the corresponding carboxylic acids, it was cleanly reduced into the corresponding monoprotected diol with recovery of the chiral auxiliary. The following water-accelerated Dess–Martin oxidation[80] led to the acyclic aldol adduct bearing a quaternary carbon stereocentre in high yield (Scheme 27).[65]

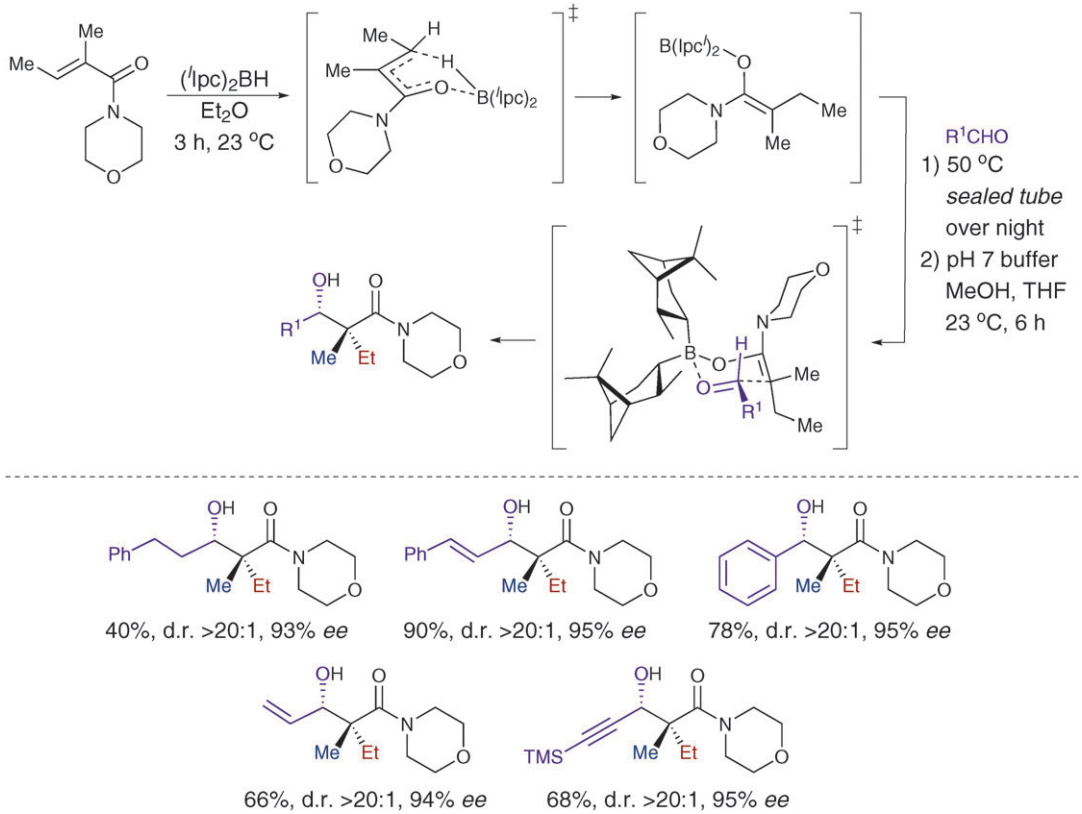
In subsequent experiments, it was found that these trisubstituted stereodefined enolates could react with *N*-sulfonyl imines to generate Mannich-type adducts with similar diastereomeric ratios and isolated yields (Scheme 28).[65,76]

The absolute configuration of the Mannich adducts was determined by X-ray crystallographic analysis and was consistent with a Zimmerman–Traxler transition state[79] with approach of the electrophilic imine from the stereoface opposite of the benzyl group of oxazolidinone. However, in this case the barrier of planar *E* to *Z* inversion of *N*-sulphonyl imines is low,[81] and steric factors most probably account for the favorable formation of the *Z*-isomer (the *E*-isomer of *N*-sulphonyl imine would generate 1,4-diaxial steric interactions with the chiral unit) in the six-membered transition state (Scheme 28).

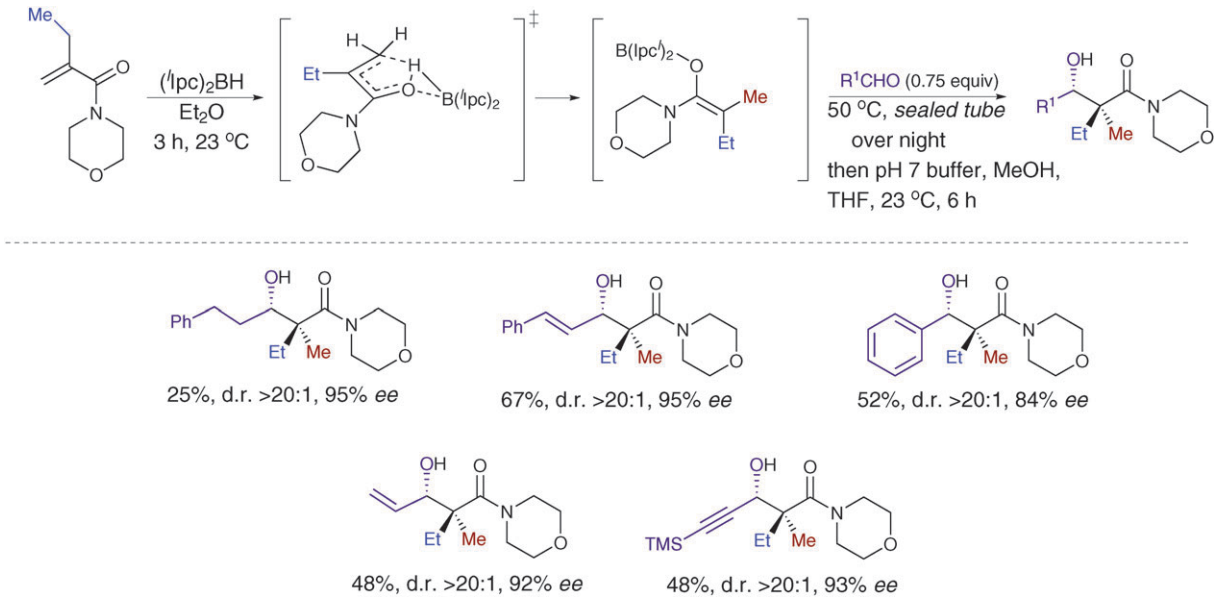
In their recent work Roush and coworkers disclosed a simple procedure to the stereocontrolled formation of trisubstituted enolborinates through a 1,4-hydroboration reaction of unsaturated morpholine carboxamides. These chiral trisubstituted boron eno-



Scheme 28 A single-flask sequence for the stereoselective formation of Mannich-type adducts possessing quaternary carbon stereogenic centres in acyclic systems.



Scheme 29 Highly diastereo- and enantioselective formation of α-quaternary aldol adducts from stereodefined trisubstituted enolborinates generated by 1,4-hydroboration reactions of unsaturated morpholine carboxamides.



Scheme 30 Reductive aldol reactions of α-ethyl acrylamide.

late species undergo highly enantio- and diastereoselective aldol reactions with a range of non-chiral aldehydes (Scheme 29).[82]

In all cases, the stereoselectivity observed for the formation of the enolate species and the corresponding aldol adducts was controlled by highly organized cyclic transition states. Complementary diastereodivergency at the quaternary centre formation can easily be achieved by a proper modification of the reacting morpholine amide and more particularly by using α-ethyl acrylamide as a substrate for the 1,4-hydroboration reaction (Scheme 30).[82]

Conclusions

During the past decades, we have witnessed the development of new efficient methodologies for selective formation of metal enolates. Selective access to configurationally defined fully substituted metal enolate species has opened new horizons in stereoselective organic synthesis. In this context, use of acyclic stereodefined trisubstituted enolates is especially valuable for the construction of acyclic scaffolds bearing all-carbon quaternary stereogenic centres. Despite that a variety of efficient and elegant methodologies appeared in the recent literature, most of these methodologies employ stoichiometric chiral auxiliaries. Taking into consideration recent advances and the rapid evolution of asymmetric catalytic methods, it is expected that more methodologies for the generation of stereodefined trisubstituted metal enolates will soon appear in the literature and lead to beautiful transformations.

Acknowledgements

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