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Enantioselective Synthesis of Vicinal Tertiary and Quaternary Stereocenters in Open-Chain Structures

• Dr. **David Pierrot**
Department of Chemistry, University of Strasbourg, Strasbourg, France

• Prof. **Dr. Ilan Marek**
Department of Chemistry, Technion – Israel Institute of Technology, Haifa, Israel

Abstract: Exceeding the inherent difficulty to prepare quaternary carbon stereogenic centers, the diastereo- and enantioselective preparation of acyclic carbon backbone possessing vicinal quaternary and tertiary stereogenic centers (i.e. in a 1,2-relationship) causes distorted geometries and represents a very acute problem in organic synthesis. Several approaches are discussed in this minireview underlining the challenges illustrated by the rather limited number of approaches available to practitioners.

1. Introduction

Nature is an immense source of inspiration as it provides sophisticated targets and underlines potential biomimetic routes.[1] The subsequent *in vitro* preparation of naturally occurring molecular backbones enabled organic chemists to validate the developed strategies and eventually improve the biological activities by preparing more potent analogues.[2] The enantioselective preparation of quaternary carbon stereogenic centers in acyclic molecules, present in many natural products, [3] was considered until recently, as one remaining challenging transformation. Since then, chemists have elaborated various efficient strategies to achieve this goal.[4] However, the diastereo- and enantioselective preparation of *vicinal (1,2) quaternary and tertiary carbon stereogenic centers in acyclic system* is much more difficult and examples are scarce in the literature as limited strategies are available to the practitioners (Figure 1). Reasons for the paucity of methods result from the i) rotational freedom of acyclic molecules complicating the enantio- and diastereodiscrimination; ii) absence of polar functional groups narrowing the potential existing methodologies; iii) presence in close proximity of bulky alkyl chains causing distorted geometries along the carbon backbone.[5] On the other hand, modern standards in the field of chemical synthesis implies the development of strategies that would allow the preparation of all possible enantio- or diastereomers at will, constantly challenging the ingenuity of chemists.[6]

In this short review, the state of the art for the stereodefined preparation of acyclic compounds possessing enantioenriched vicinal tertiary and quaternary carbon stereogenic centers is presented. The discussion is organized by general reaction types as described in Figure 1 where substrate-controlled (diastereoselective) and catalytic (enantioselective) approaches will be discussed. The probably easiest strategy relies on the enantioselective allylic substitution (also called allylic alkylation, Figure 1a) and conjugated addition (Figure 1b). In both cases, the quaternary stereocenter arise either from the nucleophilic or the electrophilic partner. An additional approach consists in the sigmatropic rearrangement of substituted allyl vinyl ethers (Figure 1c) and can also be divided into two sub-classes in which the polysubstitution would either be on the enol ether or on the allyl fragments. Finally, one final major approach uses the exergonic ring-opening reactions of strained rings (figure 1d) through selective carbon-carbon bonds cleavage. Additional minor strategies are represented in a separate section (Miscellaneous) and include kinetic resolutions, desymmetrization and 1,2-migrations.

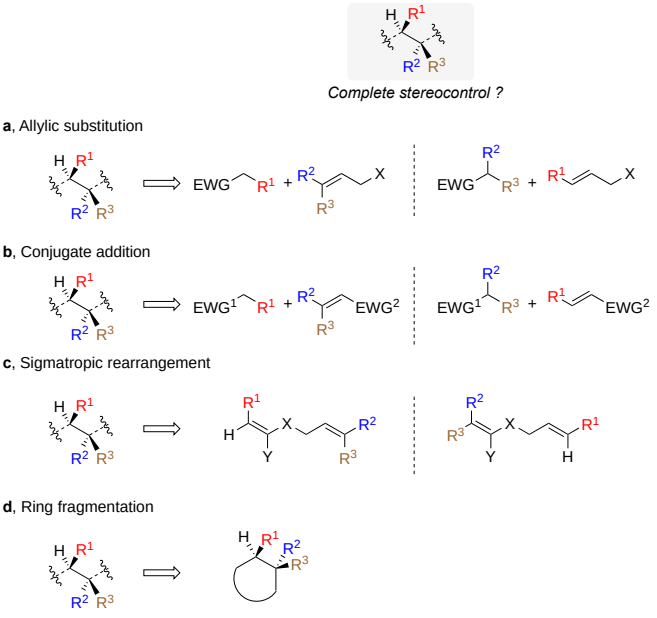


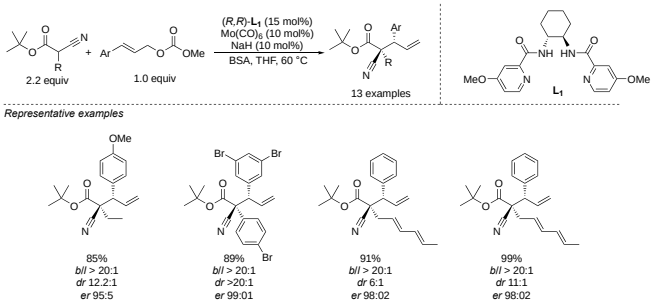
Figure 1. Main strategies for the enantioselective preparation of vicinal tertiary and quaternary stereocenters in acyclic systems

2. Allylic substitution

The enantioselective formation of an acyclic molecular backbone possessing vicinal tertiary and quaternary carbon stereogenic centers via allylic substitution implies the reaction between either a mono- or disubstituted allylic electrophiles and a mono- or disubstituted nucleophile respectively (Figure 1**a**).

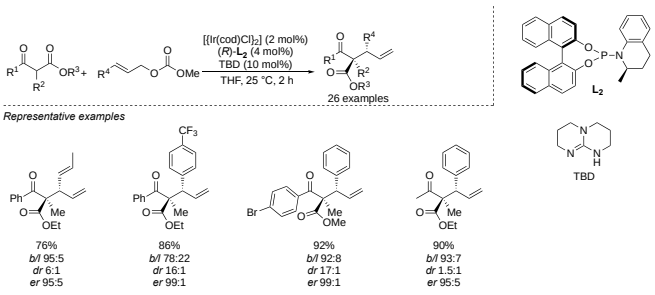
2.1. Metal-Catalyzed Processes

An efficient Mo-catalyzed regio- and enantioselective allylic alkylation of α-cyanoester nucleophiles with carbonate derivatives has recently been reported (Scheme 1).[7] Only the branched isomers were obtained potentially providing a new route to β-amino acid derivatives. Several molybdenum catalysts were tested and fortunately, the commercially available and easily handled $Mo(CO)_6$ was found to be the most reliable catalyst. The method is highly regio, diastereo- and enantioselective owing to a postulated "Claisen-like" transition state.[8] Chiral ligand **L₁** discriminates the two faces of the electrophile and only one face of the *(Z)*-enolate reacts for steric reasons.



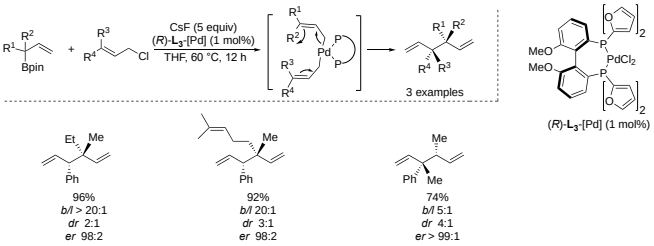
Scheme 1. Mo-catalyzed allylic alkylation

Based on previous reports demonstrating the power of Ir-*N*-arylphosphoramidite catalysis to access cyclic vicinal quaternary and tertiary carbon stereogenic centers,[9] the strategy was extended to acyclic systems by using ketoesters with substituted carbonates in the presence of **L₂** (Scheme 2).[10] The electronic nature of the substituent R^4 on the carbonate has an effect on the regioselectivity of the allylation as electron-deficient groups favor the linear product whereas vinyl and electron-rich aromatic groups produce the branched products. Overall the method is very general with good to excellent regio-, diastereo- and enantiocontrol while keeping a broad functional group tolerance.



Scheme 2. Ir-N-arylphosphoramidite catalyzed allylic alkylation

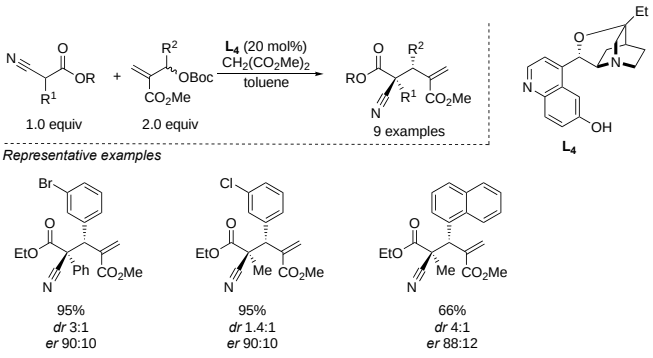
Unlike iridium and molybdenum catalysts, palladium has a natural propensity to form linear allylation products.[11] However, it was reported that small-bite-angle ligands drive the allylpalladium equilibrium towards the formation of primary organopalladium species[12] and this observation was cleverly used for the preparation of stereodefined vicinal tertiary and quaternary carbon stereogenic centers with BYPHEP **L₃** as ligand (Scheme 3).[13] Using substituted allylboronic esters and allyl chloride derivatives, the method proceeds with excellent regio- and enantiocontrol yet with a modest diastereoselectivity. Unlike the other approaches whose products contain a carbonyl functional group, this method leads to the formation of hydrocarbons possessing the expected stereogenic centers.



Scheme 3. Pd-Catalyzed allyl-allyl cross-coupling reaction

2.2. Organocatalysis

The Morita-Baylis-Hillman (MBH) reaction has constantly attracted a lot of attention in stereoselective synthesis and recent reports have described the possibility to operate this reaction via a tandem S_N2' reaction in which the MBH intermediate becomes a substrate for enantioselective allylic substitution.[14] The same concept has been used between a carbonate as precursor of the MBH intermediate and a cyanoester using modified *cinchona* alkaloids (Scheme 4).[15] The allylic carbonate reacts with the catalyst **L₄** via a conjugate addition to form a Michael acceptor, with one shielded face. The *in-situ* generated *tert*-butoxide anion deprotonates the cyanoacetate, which reacts with the Michael acceptor to provide the products in decent enantioselectivities but modest diastereoisomeric ratios. When the cyanoester was used in excess, the stereochemical outcome remained unchanged, ruling out a possible kinetic resolution.

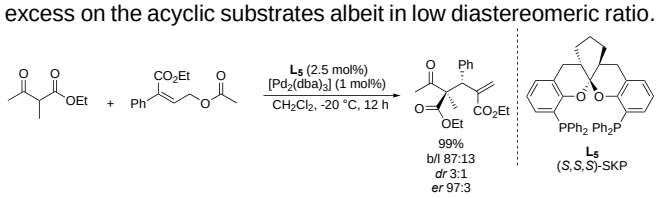


Scheme 4. Organocatalytic allylic alkylation of Morita-Baylis-Hillman carbonates

2.3. Dual Catalysis

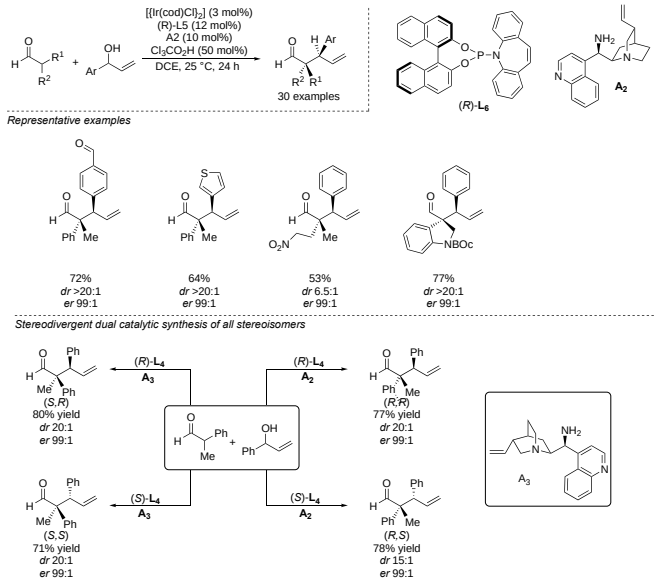
One example of enantioenriched acyclic product possessing tertiary and quaternary carbon stereogenic centers was recently reported by condensation of a ketoester with a Morita-Baylis-Hillmann-type substrate (Scheme 5).[16] The

catalytic system is composed of a chiral spiroketal-based diphosphine **L5** acting both as a Lewis base and as a ligand of palladium. The electrophile is first activated by the diphosphine by nucleophilic substitution of the acetate and the resulting cationic allylic intermediate is subsequently exchanged with the palladium to form a π-allyl Pd-species which is intercepted by the enolate. The methodology enables a good regiocontrol and enantiomeric excess on the acyclic substrates albeit in low diastereomeric ratio.



Scheme 5. Pd-Catalyzed allylation of β-ketocarbonyl with a Morita-Baylis-Hillman intermediate

Finally, a remarkable enantio- and diastereodivergent synthesis of γ,δ–unsaturated aldehydes has recently been reported by concurrently combining two chiral catalysts that independently dictate the configuration of each stereogenic centers in the product. This dual catalysis combines the reaction of an enantiomerically enriched catalytic π-allyl Ir-complex bearing the phosphoramidite ligand **L6** with a catalytic chiral enamine species formed by the condensation of **A2** on the aldehyde (Scheme 6).



Scheme 6. Enantio- and diastereodivergent dual catalysis for the α-allylation of branched aldehydes

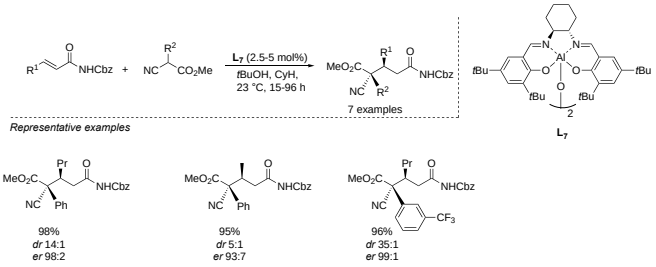
The main asset of this methodology comes from the compatibility between both catalytic systems, allowing the access to all enantio and diastereomers of this dyad with good yields and diastereomeric ratios and excellent enantio and regiocontrol (Scheme 6).[17]

3. Conjugate Additions

The conjugate addition follows the same synthetic disconnection than the allylic substitution and therefore shares identical challenges associated to the dual stereofacial approaches of the nucleophile and electrophile. For the sake of simplicity, four subcategories are described below.

3.1. Lewis Acid Activation

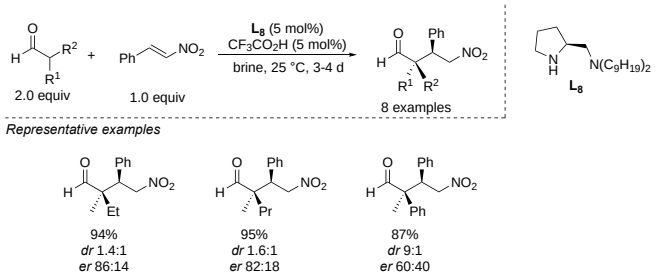
The addition of methyl phenylcyanoacetate to α,β-unsaturated amides in the presence of the μ-oxo-dimer **L7** (5 mol%) provides the product in good diastereoselectivity and excellent enantiomeric ratio (Scheme 7).[18] The one-point binding Lewis acid aluminum based catalyst increases the amide electrophilicity while the chiral salen ligand **L7** shields one enantiotopic face of the enamide. This catalytic system is well designed to this substrate class and leads to excellent enantiomeric ratios. A stoichiometric amount of *tert*-butanol is crucial to maintain the efficiency of the reaction in non-polar solvent.[19]



Scheme 7. Enantioselective Michael additions to α,β-unsaturated imides catalyzed by salen-Al complexes

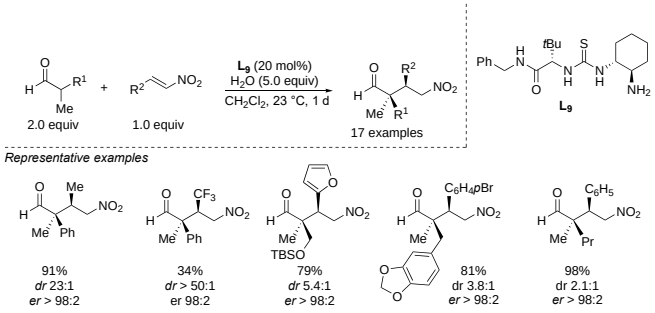
3.2. Organocatalysis

The first organocatalytic enantioselective synthesis of acyclic compounds possessing vicinal tertiary and quaternary carbon stereogenic centers using a bifunctional proline-based catalyst **L8** relied on the Michael addition of various α,α-disubstituted aldehydes with nitrostyrene.[20] A catalytic amount of trifluoroacetic acid was necessary to accelerate the reaction by facilitating the enamine formation. The expected aldehydes are obtained with moderate enantioselectivities but as two diastereomers in almost equal proportions (Scheme 8) illustrating the difficulty to control the stereochemistry of the β,β'-disubstituted enamine intermediate.

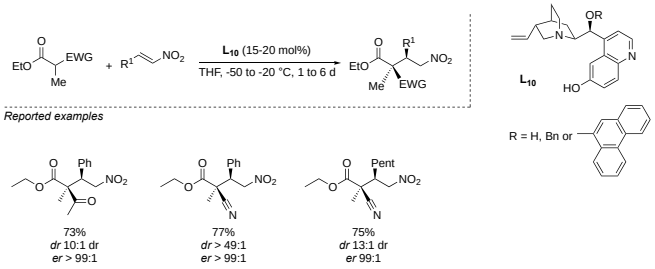


Scheme 8. Enantioselective organocatalytic Michael reactions of α,α-disubstituted aldehydes with β-nitrosyrene

By replacing the proline-based catalyst by a less sterically demanding primary amine-based bifunctional catalytic system **L$_9$**, improved results were obtained.[21] A wide range of α,α-disubstituted aldehyde/nitroalkene combinations were surveyed and excellent enantioselectivities were usually observed (Scheme 9). The diastereoselectivity ranged from moderate to very good depending on the aptitude to *in-situ* prepare stereodefined polysubstituted enamines as single isomers. The method tolerates several functional groups and is not limited to nitrostyrene as alkyl substituted nitroolefins were also successfully engaged in this transformation (Scheme 9). Nitroolefins were also used as electrophiles with enolizable esters through a different activation mode with bifunctional catalysts **L$_{10}$** derived from *cinchona* alkaloids.[22] High diastereoselectivity and enantioselectivity could also be obtained with trisubstituted nucleophiles that are not dicarbonyl compounds as long as a chelated model controls the stereochemistry of the intermediate Michael donor (Scheme 10).

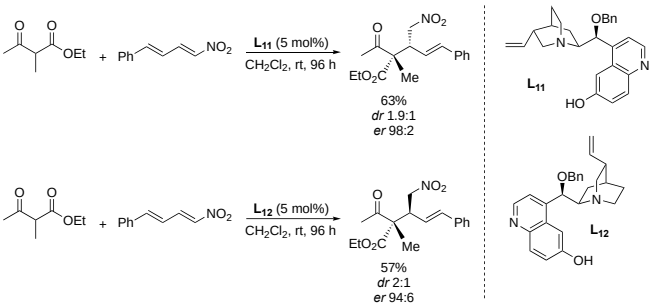


Scheme 9. Chiral primary amine thiourea catalyst for the highly enantioselective direct conjugate addition of α,α-disubstituted aldehydes to nitroalkenes



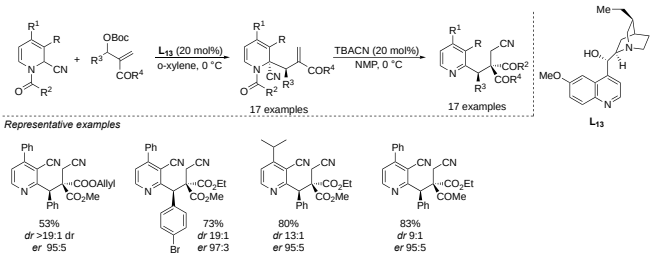
Scheme 10. Stereocontrolled creation of adjacent quaternary and tertiary stereogenic centers by a catalytic conjugate addition

The organocatalyzed enantioselective conjugate addition of 1,3-dicarbonyl derivatives on nitrodienes has also been reported using *cinchona* alkaloid-derived catalysts **L$_{11}$** and **L$_{12}$**.[23] Although the study was mainly focused on cyclic nucleophiles, two examples involving acyclic β-ketoesters were reported with good enantioselectivity albeit moderate diastereoselectivity. Changing the *cinchona* alkaloid-derived catalyst to its *pseudo*enantiomer **L$_{12}$** leads to the formation of the other diastereomer as the major product (Scheme 11).



Scheme 11. Regio- and stereoselective Michael addition to nitrodiene

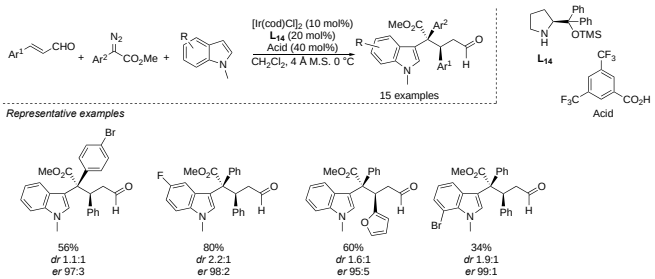
Other bifunctional organocatalysts **L$_{13}$** promote the condensation of enolisable cyanoesters to nitroolefins albeit with lower selectivities.[24] An elegant two-step enantioselective synthesis of adjacent stereogenic centers was reported from α-cyanodihydropyridine. An initial organocatalytic enantioselective allylic alkylation of allylic carbonates with dihydropyridines allows the formation of the two contiguous stereogenic centers with high selectivities. Then, a cyanide-catalyzed domino sequence composed by a Morita-Baylis-Hillman reaction where the terminal olefin undergoes the nucleophilic addition of the cyanide leading to the formation of an enolate. Finally, a diastereoselective acyl migration occurs triggering a final aromatization by elimination of the tertiary cyanide moiety (Scheme 12).[25]



Scheme 12. Enantioselective construction of functionalized 1,2- pyridine derivatives with adjacent stereogenic centers via unified metal-free catalytic approach

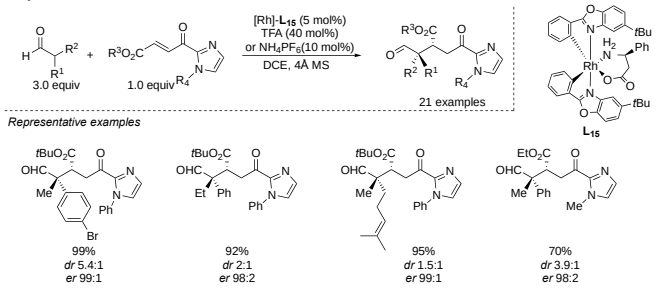
3.3. Dual catalysis

A multicomponent catalytic process started with the Ir-catalyzed decomposition of a diazoester reacting with *N*-methyl indole to provide the iridium enolate. The latter reacts with a chiral eniminium ion formed by the Hayashi-Jørgensen catalyst **L$_{14}$** and an α,β-unsaturated aldehyde.[26] The expected products are obtained with an excellent enantioselectivity yet with moderate diastereocontrol (Scheme 13).



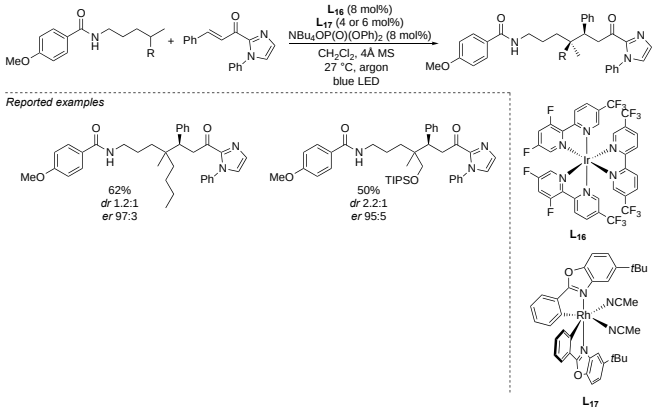
Scheme 13. Enantioselective catalytic three-component reaction of diazoacetates with indoles and α,β-unsaturated aldehydes

A mechanistically noticeable variant originates from the enantioselective addition of aldehydes to conjugated acyl imidazoles. In this case, the latter replaces the chiral β-amino acid on the rhodium catalyst **L15** releasing the chiral β-amino acid derivative that in-situ forms an enamine with the aldehyde. This new intermediate then reacts with the rhodium-activated α,β-unsaturated 2-acyl imidazole. Despite the excellent enantioselectivity and functional group tolerance, the method suffers from a poor to moderate diastereoselectivity (Scheme 14).[27]



Scheme 14. Enantioselective dual catalysis via fragmentation of a single Rh-complex

An interesting approach to create vicinal stereogenic centers relied on a radical translocation of acylamines.[28] For this purpose, an iridium-based photosensitizer **L16** generates a *N*-centered radical on the acylamine which rapidly undergoes a 1,5-radical transfer. The formed tertiary radical intermediate then attacks the α,β-unsaturated 2-acyl imidazole activated by the chiral rhodium catalyst **L17**. Although the diastereoselectivity of the product is poor, the enantioselectivity is consistently excellent and more importantly, it represents a new approach to create remote stereogenic centers (Scheme 15).[28]

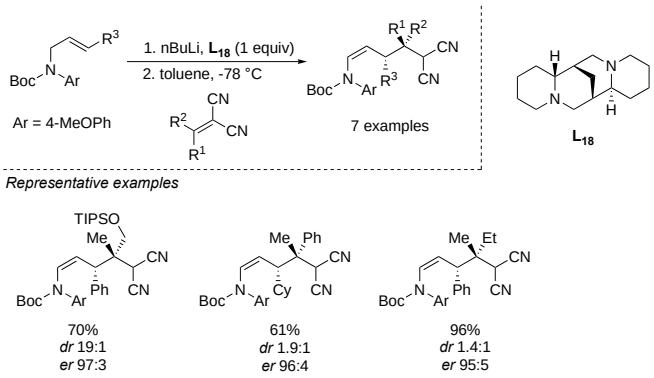


Scheme 15. Enantioselective alkylation of remote C(sp^3)-H bonds by combining proton-coupled electron transfer with chiral Lewis acid catalysis

3.4. Miscellaneous

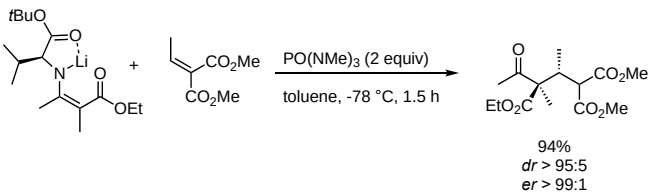
One example of vicinal quaternary and tertiary stereocenter synthesis was originally reported in the synthesis of vitamin B_{12}.[29] The strategy was based on the preparation of enantioenriched propargylic quaternary stereocenter by resolution with (+)- or (-)-α-phenylethylamine and subsequent modifications.

Although not catalytic, the reaction of enantioenriched α-*N*-substituted allyllithium species, in-situ generated by enantioselective deprotonation with *n*-BuLi/(-) sparteine **L18**, with doubly activated electrophile produced the vicinal quaternary and tertiary carbon stereocenters with moderate to excellent diastereomeric and overall good enantiomeric ratios (Scheme 16).[30]



Scheme 16. Conjugate additions of chiral organolithium nucleophiles to α,α-dinitrile β,β-disubstituted olefins

Using a labile amino acid-based chiral auxiliary, a β-ketoester could be deprotonated with a lithiated base and condensed to a Michael acceptor leading to the formation of a single example of vicinal tertiary and quaternary stereocenters with excellent diastereo- and enantioselectivity (Scheme 17).[31]

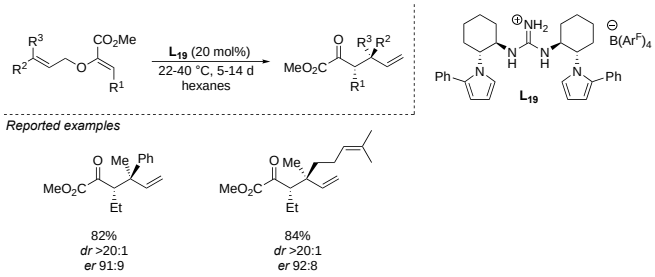


Scheme 17. Conjugate addition of chiral lithiated enamine nucleophile to malonate-derived Michael acceptor

4. Sigmatropic Rearrangements

4.1. Claisen

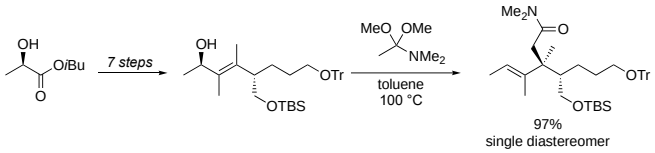
A guanidinium-based hydrogen-bonding catalyst **L19** enabling the enantioselective Claisen rearrangement of allyl vinyl ethers has been successfully reported as source of vicinal tertiary and quaternary stereogenic centers in acyclic systems.[32] Despite relatively long reaction times, the transformation is highly enantioselective when hexane was used as solvent even though the low catalyst's solubility (Scheme 18).



Scheme 18. Enantioselective Claisen rearrangements with a hydrogen-bond donor catalyst

4.2. Eschenmoser-Claisen

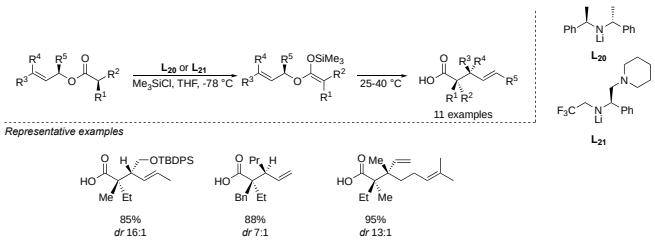
Through more traditional transformations, (*R*)-isobutyl lactate could be transformed into a key-substrate that undergo the stereospecific Eschenmoser-Claisen rearrangement to provide, after subsequent modifications, the desired cyclic molecular fragment of Vitamine B_{12} semicorrin (Scheme 19).[33]



Scheme 19. Towards the stereocontrolled synthesis of a nonracemic vitamin B_{12} A-B-semicorrin.

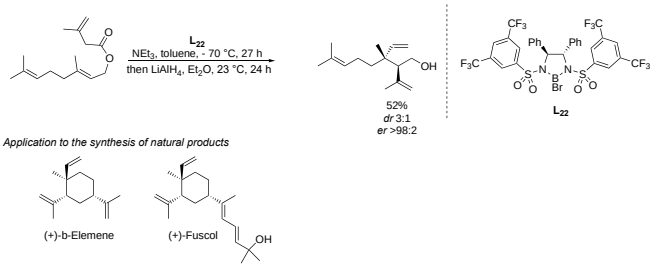
4.3. Ireland-Claisen

In all the above discussed sigmatropic rearrangements, the quaternary stereocenter originates from the presence of a disubstituted double bond at the allylic position. The stereochemistry of the quaternary stereocenter coming from the enol ether is much more challenging as one needs to control the stereochemistry of fully substituted enol ethers. Few key studies have been reported by using the stereodefined formation of enol ethers followed by the Ireland-Claisen rearrangement. In this context, the stereoselective formation of polysubstituted enol ethers has been reported by an original enantioselective deprotonation of α-chiral ester (Scheme 20).[34] Although the base (**L20** or **L21**) needs to be reoptimized for each substrate, the transformation occurs efficiently under mild conditions. The subsequent control of the diastereoselectivity during the Claisen-rearrangement is trouble less as classically controlled by the α-branched ester. Remarkably this study is still one of the rare approaches allowing the preparation of acyclic molecular backbone possessing two enantioenriched vicinal quaternary stereogenic centers.



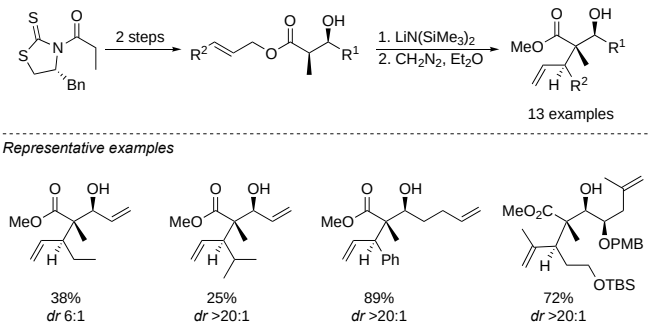
Scheme 20. Acyclic stereocontrol in the Ireland-Claisen rearrangement of α-branched esters.

This approach was applied to the synthesis of the natural product (+)-pinnatoxin A[35] and a fragment of spirolide C.[36] In these particular two cases, a Koga-type chiral lithiated base[37] was used to obtain the stereodefined polysubstituted enolate, therefore ensuring the efficiency of the subsequent rearrangement. Two additional natural products containing a vicinal tertiary and quaternary stereogenic centers, β-elemene and fuscol, were also reported through a Ireland-Claisen rearrangement.[38] In this approach, a stoichiometric amount of chiral boron reagent **L22** controls the stereochemistry of the mono-substituted enolate but also controls its stereofacial approach. The product is obtained with a moderate diastereoselectivity but both diastereomers could be separated after reduction (Scheme 21).



Scheme 21. Enantioselective total synthesis of β-elemene and fuscol based on an enantiocontrolled Ireland-Claisen rearrangement

In an approach towards the total synthesis of brassinosteroids, an enantioenriched allylic carboxylate precursor, originating from the (*R*)-Roche ester, underwent a diastereoselective Ireland-Claisen rearrangement upon activation with LDA.[39] α-Tertiary and a β-quaternary stereogenic centers were formed again with a poor diastereoselectivity due to the lack of stereocontrol in the enolate formation. However, using the oxazolidinone chiral auxiliary, enantioenriched allylic carboxylate derivatives underwent a dianionic Ireland-Claisen rearrangement providing an efficient access to these desired vicinal stereogenic centers (Scheme 22).[40] The diastereoselectivity of the transformation improves with the steric bulk of the substituents R^1 and R^2. Using this method, up to four contiguous stereogenic centers were obtained including the quaternary and the tertiary carbon stereogenic centers in acyclic compounds. This approach was later applied to the synthesis of the briarthein A core.[41]

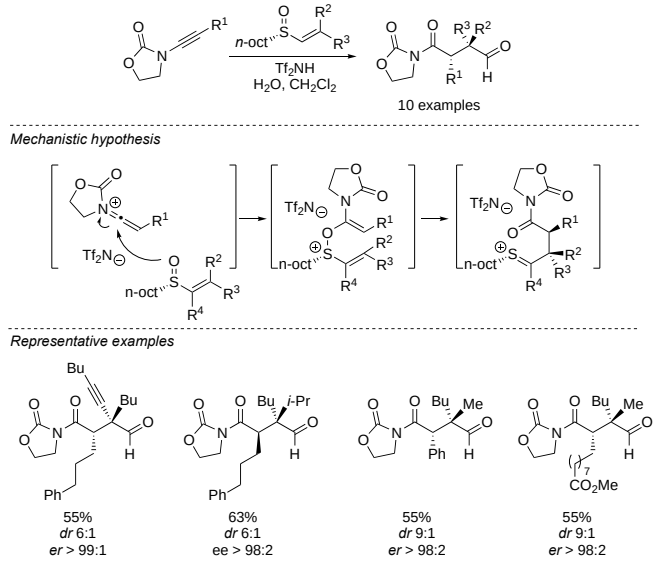


Scheme 22. Approach to the synthesis of briarane diterpenes

4.4. Other Sigmatropic Rearrangements

Recently, a diastereodivergent enantioselective synthesis of 1-4-dicarbonyl derivatives possessing a vicinal acyclic tertiary and

quaternary carbon stereogenic centers was achieved via a charge accelerated sulfonium rearrangement.[42] This approach combines the use of enantioenriched alkenylsulfoxides with activated ynamides by a Brønstedt acid catalyst. Through the proton-activation of the ynamide into the keteniminium intermediate followed by the addition of a stereodefined enantioenriched β,β'-disubstituted alkenylsulfoxide derivatives, the sulfonium thus generated undergoes a charge-accelerated sigmatropic rearrangement. 1-4-Dicarbonyl derivative possessing vicinal acyclic carbon stereogenic centers are obtained with excellent selectivities (Scheme 23). The absolute configuration is set by the chirality of the sulfur atom while the relative configuration depends on the olefin geometry. By changing the absolute configuration of the sulfoxide and the olefin geometry, all possible diastereo- and enantiomers of the product could be similarly accessed.



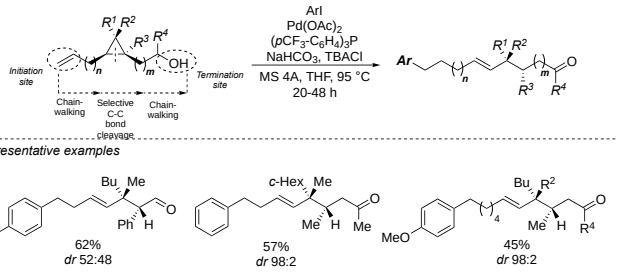
Scheme 23. Stereodivergent synthesis of 1,4-dicarbonyls by traceless charge-accelerated sulfonium rearrangement

5. Ring Opening

An alternative approach for the creation of vicinal stereogenic centers in acyclic systems relies on the initial diastereo- and enantioselective preparation of stereogenic centers on cyclic systems followed by a selective carbon-carbon bond cleavage. Among all possible ring sizes, cyclopropanes possess the ideal structural element and are frequently used as starting materials for selective carbon-carbon cleavage. If one can design an easy access to polysubstituted cyclopropanes from easily available starting materials followed by a subsequent selective rupture of the molecular backbone, the formation of these vicinal tertiary and quaternary stereogenic centers should become straightforward.

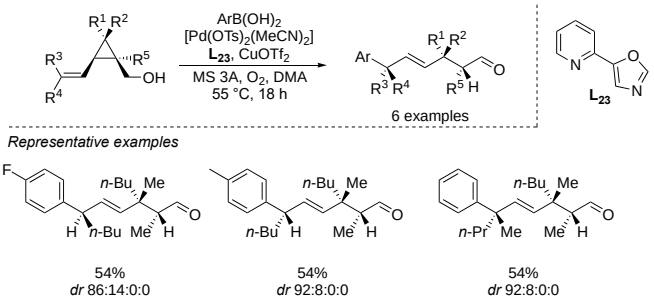
5.1. Cyclopropane Ring Fragmentation

The thermodynamically favored cyclopropane ring opening was achieved by a Pd-catalyzed remote functionalization[43] of ω-ene polysubstituted cyclopropanes.[44] In an initial step, a Heck-type carbopalladation reaction was performed triggering a subsequent Pd-walk by successive addition-elimination reactions along the hydrocarbon chain. The directionality of the walk is driven by the selective ring-opening of the cyclopropyl ring and is catalytically productive by transforming the terminus alcohol into a carbonyl group. The ability of the palladium to isomerize along the carbon chain while preserving the inherent stereochemistry enabled a diastereoretentive ring opening event suggesting that the Pd does not disengage during the process and migrates on the same stereoface (Scheme 24).[45] This Pd-catalyzed unfolding of the strained cycle remarkably proved its efficiency and versatility, as the reaction proceeded regardless of the molecular distance between the initiation (double bond) and termination (alcohol) sites (Scheme 24).



Scheme 24. Pd-Catalyzed Heck arylation as a remote trigger for cyclopropane selective ring-opening

Based on these results, the oxidative Heck reaction conditions could convert alkenyl cyclopropyl methanol derivatives into the corresponding aldehydes through a similar cascade of carbopalladation – selective ring opening – Pd-walk (Scheme 25).[46]



Scheme 25. Stereodivergent synthesis of unsaturated acyclic fragments bearing contiguous stereogenic elements

The strategy allows the formation of up to two quaternary and one a tertiary stereogenic centers in acyclic system with excellent diastereocontrol. The alcohol moiety is once again crucial in this transformation as it directs both the carbopalladation and the selectivity of the carbon-carbon bond cleavage. Importantly, this approach allows the formation of all possible diastereo- and enantiomers of a given product.

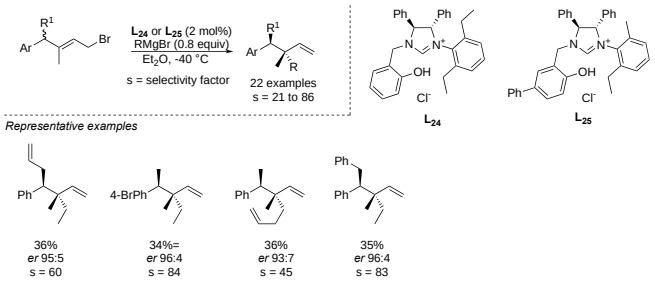
5.2. Other Fragmentations

Apart from the ring cleavage of strain rings, more classical strategies have been reported that include the oxidative cleavage of olefins, vicinal diols or ring-opening of lactones. In all these cases, the vicinal stereocenters are created in chemical steps that are not related to the fragmentation (or cleavage) steps. The stereocenters in acyclic systems are only revealed subsequently. Such strategies were applied towards the synthesis of various natural products such as vitamin B_{12},[47] cobyric acid,[48] phomactins,[49] vitamin D_3,[50] and glycinoeclepin A.[51]

6. Miscellaneous

6.1. Kinetic Resolution

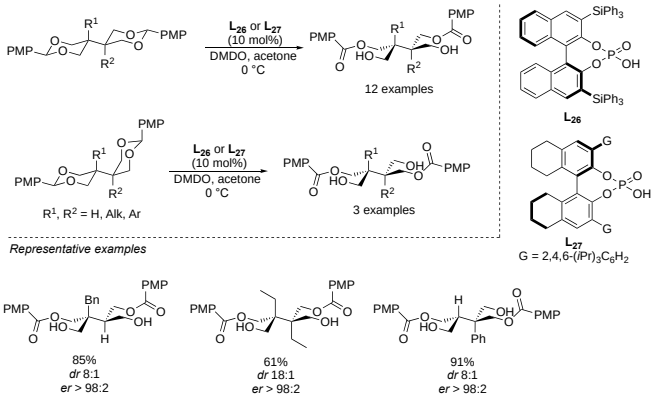
The enantioselective preparation of acyclic compounds with these stereogenic centers was reported through the asymmetric copper-catalyzed allylic alkylation of racemic allyl bromide. Using chiral NHC ligands **L$_{24}$** or **L$_{25}$**, high levels of enantioselectivity could be achieved in this kinetic resolution. Another asset of this approach relies on the ability to access the opposite enantiomer after recovering the remaining starting material (Scheme 26).[52]



Scheme 26. Construction of vicinal stereogenic centers via kinetic resolution.

6.2. Desymmetrization

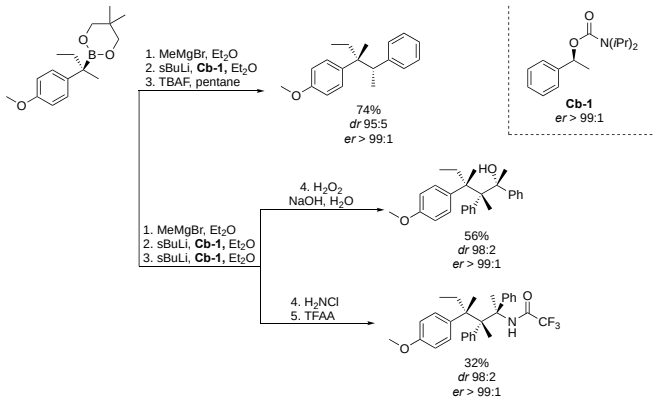
The BINOL-derived phosphoric acid **L$_{26}$** or **L$_{27}$** catalyzed enantioselective desymmetrization of tetrol-derived acetals was reported.[53] Using these conditions, with dimethyldioxirane as oxidant, several acetals could be converted into diacylated tetrols with excellent enantio-enrichments and good diastereomeric ratios (Scheme 27). It should be noted that this approach is one of the rare enantioselective preparations that also allow the preparation of two quaternary stereogenic centers within an acyclic chain along with the approach described in Schemes 20 and 28.



Scheme 27. Enantioselective approach to tetrol bearing vicinal stereogenic centers

6.3. 1,2-Rearrangement of Organoboron Species

The 1,2-metallate rearrangement of organoboron species was successfully applied to the preparation of enantioenriched vicinal tertiary and quaternary and even quaternary-quaternary carbon stereogenic centers. In the first step, a tertiary anion generated by deprotonation of the corresponding enantioenriched tertiary carbamate **Cb-1** is condensed with a trialkylborane to form an ate-complex intermediate. Upon 1,2-migration, the expected tertiary borane. Is obtained. It should be noted that the initial addition of MeMgBr allows the transformation of boronic esters into the more reactive borane derivatives. The subsequent treatment with TBAF leads to the acyclic vicinal stereogenic centers while the addition of a second tertiary lithiated carbamate **Cb-1** followed by oxidative cleavage of the carbon-boron bond leads to the formation of vicinal contiguous tetrasubstituted stereogenic centers (Scheme 28).[54]



Scheme 28. Construction of vicinal stereogenic centers by lithiation-borylation

7. Conclusion and Perspectives

Exceeding the difficulty to prepare enantioenriched quaternary carbon stereogenic centers in acyclic molecules, the diastereo- and enantioselective preparation of vicinal quaternary and tertiary carbon stereogenic centers (i.e. in a 1,2-relationship) in acyclic system remains one of the most acute problem in organic synthesis and examples are scarce in the literature as limited strategies are available to the practitioners. Four main approaches have been described using either allylic displacement, conjugated addition, rearrangement and ring opening. Owing to the potential in synthesis of these transformations combined with the plethora of available and newly developed catalysts, this field will surely grow continuously, and more appealing transformations are expected to appear in the years to come. We are convinced that organic chemists will grasp the importance of controlling the stereochemistry of vicinal stereocenters possessing at least one quaternary carbon stereogenic center and cleverly integrate it into the development of natural products. Despite this progress, the preparation of their vicinal two quaternary analogs remains an almost pristine challenge.

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Keywords: tertiary • quaternary • stereogenic centers • vicinal • diastereodivergent

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