Enantioselective Construction of Quaternary Stereocenters

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The stereoselective formation of C–C bonds is of great importance for the synthesis of enantiomerically pure natural products and pharmaceuticals. A broad repertoire of chiral auxiliaries, reagents, and catalysts can be utilized for the reliable generation of tertiary stereocenters. In contrast, the synthesis of organic compounds with quaternary stereocenters is a much more demanding and challenging task. Every enantioselective synthetic method can demonstrate its value through the generation of a fully substituted carbon center. In this Minireview examples of newer stoichiometric and catalytic methods are summarized which have proved their suitability for the enantioselective construction of quaternary stereocenters.

1. Introduction

In the past twenty years impressive progress has been made in the field of organic synthesis.[1] The basis for this development was the enlargement and improvement of the repertoire of transformations available for synthetic organic chemists. In particular, the development of stereoselective[2] and atom-economic[3] techniques for efficient syntheses of enantiomerically pure compounds has been of central importance in this context. Methods for the direct asymmetric coupling of C–C bonds nowadays play a key role in the preparation of complex natural products and pharmaceuticals. The enantioselective construction of carbon centers with four non-hydrogen substituents, that is, quaternary carbon centers, is still a challenge.

The latter problem has been the subject of a number of review articles,[4] and catalytic asymmetric reactions were summarized by Corey and Guzman-Perez a few years ago.[4a] This Minireview collects recent work that has been published since then. Completeness is not claimed, but examples were subjectively selected according to their originality. Moreover, this review focuses on quaternary carbon centers without any heteroatom substituents. Apart from catalytic asymmetric procedures, which are commonly of central interest, the use of chiral auxiliaries is also considered, since they are—despite their stoichiometric application—of great practical relevance.[5]

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2. Alkylations

Asymmetric alkylations with chiral auxiliaries or catalysts are frequently used and are reliable reactions for the synthesis of quaternary carbon centers. The enantioselective construction of two vicinal quaternary stereocenters, however, is very difficult.

Recently, Overman et al. reported on a new synthesis of the indole alkaloids *meso*-chimonanthine (**5**) and (+)-chimonanthine (**6**) as basic representatives of polypyrroloindoline alkaloids with a hexacyclic 3a,3a′-bispyrrolidino[2,3-*b*]indoline substructure (Scheme 1).[6] The key synthetic step is the dialkylation of dihydroisoindigo **1** (prepared from oxoindole and isatin)[6c] with the chiral bistriflate **2** derived from tartaric acid. Double deprotonation of **1**, followed by alkylation of the achiral dienolate with the dielectrophile **2** furnished two quaternary centers in a single step. The relative configuration of the two stereocenters was tuned by the proper choice of the metal dienolate counterion and the solvent system: With Na^+ as the counterion a chelated intermediate yielded the *cis* product **3**. The use of 1,3-dimethylhexahydro-2-pyrimidinone (DMPU) as cosolvent prevented the chelation of the corresponding lithium enolate and furnished the *trans* product **4**. The generation of two vicinal quaternary stereocenters in one step and the control of their relative configuration make this example particularly striking.

A completely different approach to the synthesis of carbonyl compounds with a chiral quaternary α-center was reported by Spino and Beaulieu.[7] Common strategies for the generation of such carbon centers are the alkylation of chiral enolates or the application of chiral electrophiles. In contrast, this auxiliary-based method utilizes an allylic-substitution reaction (Scheme 2). The auxiliary **8** was prepared in two steps by Wittig olefination of (–)-menthone with methoxymethylphosphonium ylide and subsequent acidic hydrolysis. The sequence started with the synthesis of allylic alcohol **9** by vinylation of aldehyde **8** with a vinylalane derived from alkyne **7** by zirconium-catalyzed carboalumination.[8] The addition

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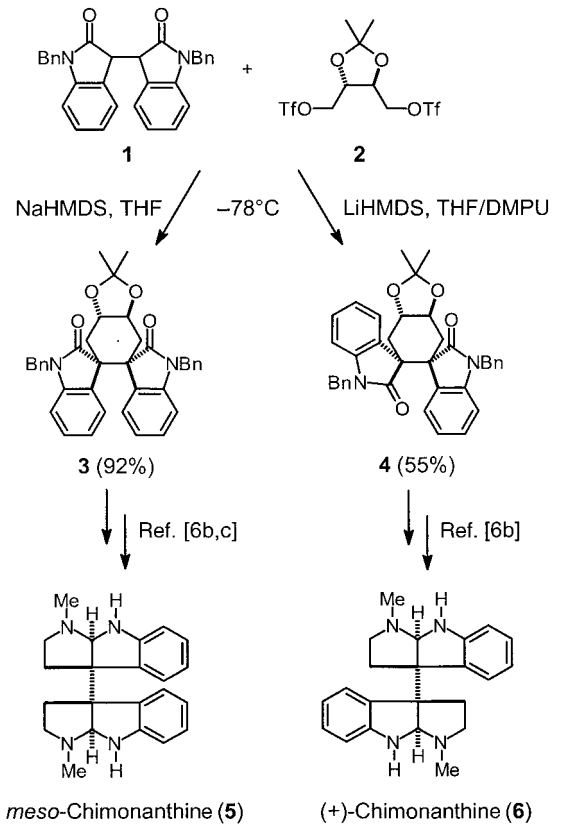
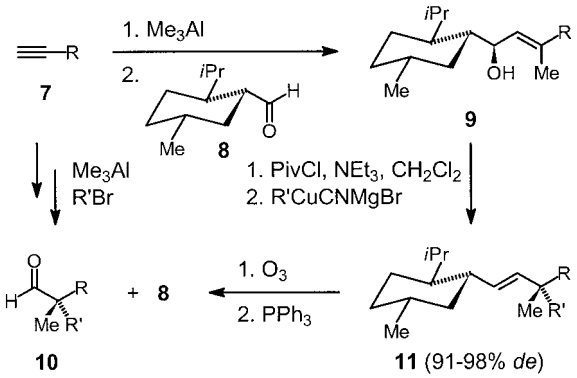


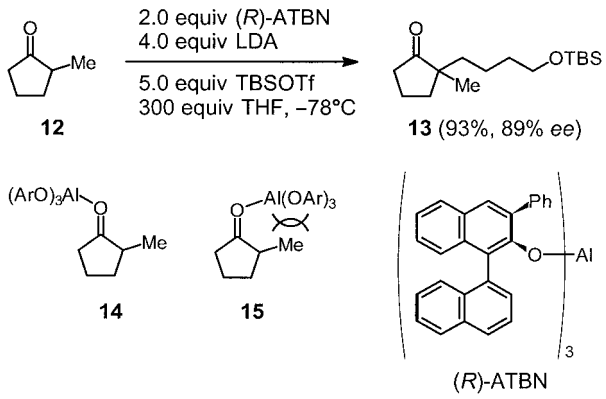
Scheme 1. Construction of vicinal quaternary stereocenters by dialkylation with an optically active dielectrophile. Bn = benzyl; OTf = triflate = trifluoromethanesulfonate; HMDS = 1,1,1,3,3,3-hexamethyldisilazanide; DMPU = 1,3-dimethylhexahydro-2-pyrimidone.



Scheme 2. Auxiliary-mediated synthesis of α-chiral aldehydes by allylic substitution. Piv = pivaloyl = Me_3CCO.

resulted in Felkin product **9** in good yield and diastereoselectivity after separation from the minor diastereoisomer by chromatography. Allylic alcohol **9** was activated as the pivaloate and converted with alkylcuprates of the general type R′CuCNMgBr (R′ = Alkyl) to yield the quaternary stereocenter in the S_N2' products **11** in very good yields and with high diastereoselectivities. Subsequent ozonolysis afforded aldehydes **10** and regenerated auxiliary **8**.

Another methodology for the stereoselective generation of carbonyl compounds with quaternary α-chiral centers was developed by Yamamoto and co-workers (Scheme 3).[9a,b] After precomplexation of the cyclopentanone **12** by the chiral



Scheme 3. α-Alkylation of cycloalkanones with THF/TBSOTf in the presence of a chiral Lewis acid. LDA = lithium diisopropylamide; TBS = *tert*-butyldimethylsilyl.

Lewis acid aluminum (*R*)-tris(3-phenyl-1,1′-binaphthoxide-2) ((*R*)-ATBN)[9c,d] and subsequent generation of the enolate, a regioselective alkylation with TBSOTf-activated THF at the sterically more hindered α-site took place. The alkylating reagent TBSOTf/THF had previously been used by Lohray and Enders for the diastereoselective formation of tertiary α-centers by using (*S*)- and (*R*)-*N*-amino-2-methoxymethylpyrrolidine hydrazones (SAMP and RAMP hydrazones, respectively).[10] *O*-Silyltetrahydrofuranium triflate was postulated to be the actual alkylating species. The largeness of the Lewis acid and the resulting steric hindrance in the complexed intermediate **15** was used to explain the high regioselectivity of the reaction ($\geq$20:1). The more stable conformer **14** is siloxybutylated to yield product **13**. In a similar concept, γ-aldolizations of α,β-unsaturated carbonyl compounds ("directed aldol reaction") were successfully achieved by applying an achiral aluminum Lewis acid.[11] The best example out of the original publication is shown in Scheme 3. A variation in the ring size significantly lowered the yields and enantioselectivities. The use of an excess of the chiral reagent currently prevents a broad application and offers an incentive for further improvement of this method.

3. Allylations

Apart from new asymmetric palladium-catalyzed vinylations[12a] and arylations,[12b] particularly of keto-enolates, palladium-catalyzed allylic substitution has become a flexible and established reaction to give quaternary carbon centers.[13] Recently, Hoveyda and co-workers reported on the first copper-catalyzed, enantioselective allylic substitution for the synthesis of quaternary centers (Scheme 4).[14] Modular, nonsymmetric pyridyl-dipeptides, such as **17**, with an aldimine moiety were identified as suitable chiral ligands by multistage parallel screening of ligand libraries. The potential of structurally related compounds as ligands in transition metal catalysis, for example, in asymmetric Strecker reactions or in 1,4-additions to cyclic enones, has already been proved.[15] Di- or trisubstituted allylphosphates such as **16** were used as substrates, and dialkylzinc compounds such as **18**, namely non-stabilized ("hard") alkylation reagents,[16] were used as

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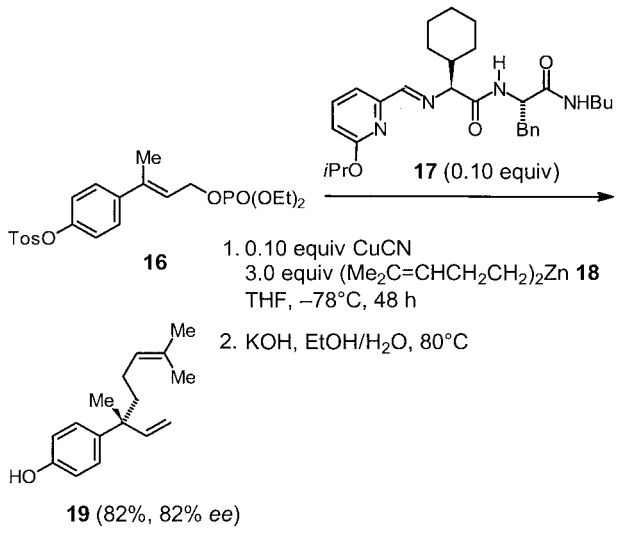
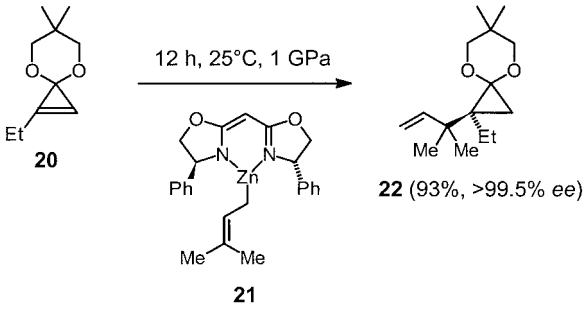


Scheme 4. Copper-catalyzed allylic substitution. Tos = *p*-tosyl = *p*-toluenesulfonyl.

nucleophiles. In this way, tertiary centers were generated with 66–75% *ee* and quaternary centers with 78–90% *ee*. The synthesis of the fish deterrent (−)-sporochnol (**19**) is shown as an example in Scheme 4.

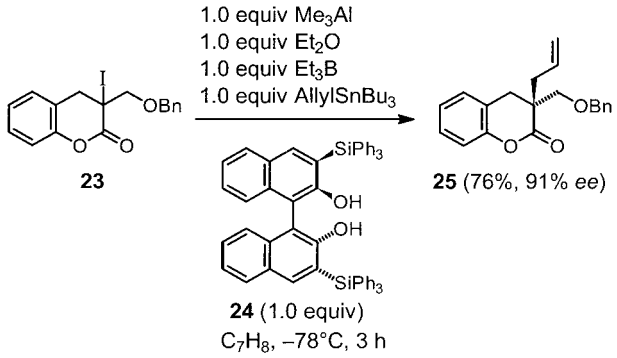
There are to date very few examples of enantioselective allylmetalations of isolated double bonds. As recently reported by Nakamura et al., quaternary stereocenters are generated by allylzincation of the olefin moiety of cyclopropenonacetals such as **20** with excellent enantioselectivities at ambient temperature (Scheme 5).[17] The chiral allylzinc



Scheme 5. Auxiliary-mediated allylzincation.

reagent **21** was prepared in situ by conversion of the corresponding allylzinc bromide, with an anionic bisoxazoline ligand (BOX)[18] being an auxiliary in this case. The ligand-controlled allylzincation of **20** took place regioselectively at the higher substituted carbon atom of the cyclopropene unit. Two vicinal quaternary carbon centers in compound **22** were obtained by application of the prenylzinc derivative **21** and subsequent hydrolysis. At ambient pressure the carbometalation proceeded very slowly, but with good selectivity (for **22** at 1 atm, 72 h: 19% yield, >99.5% *ee*). Application of a high-pressure technique accelerated the process and resulted in an improved yield together with an excellent stereoselectivity.

Although asymmetric C–C bond formations by radical processes have received increasing attention in the past few years, they are still relatively rare compared to other methods.[19] Besides chiral auxiliaries or chiral organotin compounds, chiral Lewis acids play an important role in this field. To date, the only radical reaction for the generation of a quaternary carbon center was introduced by Hoshino and co-workers (Scheme 6).[20] Products such as **25** were obtained in good yield (75–85%) and with high enantioselectivity (75–91% *ee*) by the conversion of α-alkyl-α-iodolactones such as **23** with allyltributylstannane at −78 °C in the presence of a stoichiometric amount of a chiral Lewis acid. Scheme 6 illustrates the best example of the original publication. The Lewis acid was generated in situ from $AlMe_3$ and the binaphthol derivative **24** in the presence of Et_2O as an



Scheme 6. Asymmetric radical-mediated allylation.

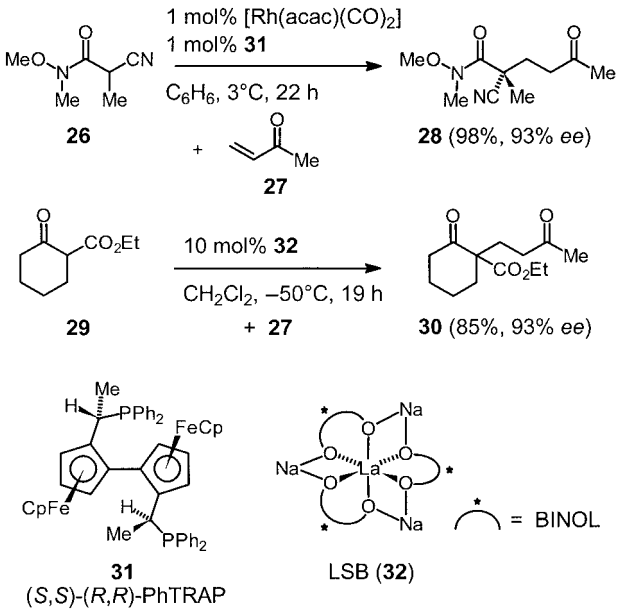
additive, with triethylborane used to initiate the reaction. As was shown by the authors, conversion also proceeded with a catalytic amount of the Lewis acid, but with lower selectivity (for **25** with 0.1 equiv catalyst: 78% yield, 71% *ee*).

4. Conjugate Additions

4.1. Asymmetric Catalysis

Conjugate additions (1,4-additions) of carbon nucleophiles to acceptor-activated C–C multiple bonds belong to the most important and versatile reactions for the synthesis of quaternary and tertiary carbon centers.[21] Recently, such catalytic enantioselective Michael reactions have been the subject of a detailed review article.[21a] Therefore, only two important examples are discussed here.

As early as 1992 Ito and co-workers reported on rhodium-catalyzed Michael reactions of α-methyl-substituted cyanoacetates with vinyl ketones and acrolein.[22b,c] The rhodium catalyst was generated in situ from $[RhH(CO)(PPh_3)_3]$ and the chiral bis(ferrocenylphosphane) ligand 2,2′′-bis[1-(diphenylphosphanyl)ethyl]-1,1′′-biferrocene ((*S*,*S*)-(*R*,*R*)-PhTRAP, **31**).[22a] This diphosphane, bearing planar as well as central stereogenic elements, forms *trans* chelate complexes with rhodium. Cyanoacetamides such as **26** (Weinreb amide)[23] which acted as Michael donors were reported to be alkylated in the α-position by vinyl ketones or acrolein under the reaction conditions used.[22d] Scheme 7 shows the conversion with methyl vinyl ketone (**27**) as an example. In this case, the



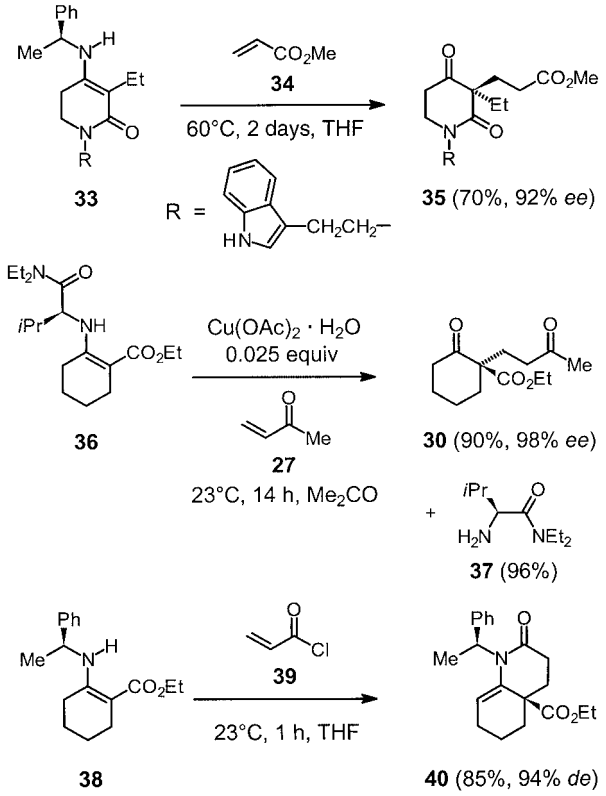
Scheme 7. Rhodium- and heterobimetal-catalyzed Michael reactions. acac = acetyl acetonate; Cp = cyclopentadienyl.

catalyst was generated in situ from the phosphane-free $[Rh(acac)(CO)_2]$ complex. The product **28** was obtained in excellent yield and selectivity, and can be readily transformed into other carbonyl derivatives.

The actual breakthrough in the field of catalytic enantioselective Michael reactions was achieved in 1994 by Shibasaki and co-workers. They introduced a new class of heterobimetallic catalysts, which also turned out to be very versatile for a number of other C–C bond-forming reactions.[21, 24] Tertiary, as well as quaternary stereocenters, are generated with high enantioselectivity by the conversion of different Michael donors with cyclic or open-chain Michael acceptors when catalyzed by a lanthanum-sodium-BINOL complex (LSB, **32**), prepared from $La(OiPr)_3$ and three equivalents each of BINOL (2,2′-dihydroxy-1,1′-binaphthyl) and NaO*t*Bu. In the course of the reaction the acceptor is activated by coordination to the Lewis acidic metal center (La^{3+}), while the Brönstedt basic Na-BINOLate moiety deprotonates and coordinates to the Michael donor. The actual C–C bond-forming step takes place in the coordination sphere of the metal center. Whereas tertiary carbon centers are constructed with high enantioselectivities at ambient temperature, the synthesis of quaternary centers requires lower reaction temperatures, as shown in Scheme 7 for the conversion of the cyclic β-keto ester **29** with methyl vinyl ketone (**27**).[25]

4.2. Application of Chiral Auxiliaries

Auxiliary-mediated asymmetric Michael reactions are also significant since they often tolerate a broad range of substrates and functional groups, and proceed under comparatively mild and neutral reaction conditions.[26] The use of 1-phenylethylamine (first reported in 1985 by Pfau and d'Angelo) as a readily available and universal auxiliary is established in this field.[26b] The new C–C bond is formed from an enamine–Michael reaction, with a cyclic transition state being mechanistically related to an aza–ene reaction.[26a] In some cases, increased reaction temperatures are required, and in particular for the conversion of simple vinyl ketones that are acting as Michael acceptors, a stoichiometric amount of a Lewis acid or high-pressure techniques are necessary.[27] The key intermediate **35** for the total synthesis of (+)-vincamin, the main alkaloid of periwinkle with cerebroprotective activity, was prepared by d'Angelo and co-workers as shown in Scheme 8.[28] Enaminolactam **33** was converted at elevated temperature with two equivalents of methyl acrylate (**34**) to yield the Michael product **35** in 70% yield and with an enantiomeric excess of 92% after cleavage of the auxiliary.



Scheme 8. Asymmetric Michael reactions of optically active enamines.

α-Aminocarboxamides such as **37** were recently introduced as an alternative to phenylethylamine in copper-catalyzed asymmetric Michael reactions.[29, 30] The conversion of the corresponding enamines (for example, **36**) with simple vinyl ketones such as **27** proceeds in the presence of a catalytic amount of $Cu(OAc)_2 \cdot H_2O$ at ambient temperature in acetone (Scheme 8). Products such as **30** were obtained with selectivities up to 99% *ee* after cleavage of the auxiliary. Similar enantioselectivities were achieved with open-chain 1,3-dicarbonyl compounds as donors.[31] The auxiliaries, such as **37**, are readily prepared from natural α-amino acids and can be recovered almost quantitatively after workup. In contrast to other transition metal catalyzed reactions, quaternary stereocenters are generated at ambient temperature in excellent selectivities and high yields under very mild reaction conditions by applying this procedure.

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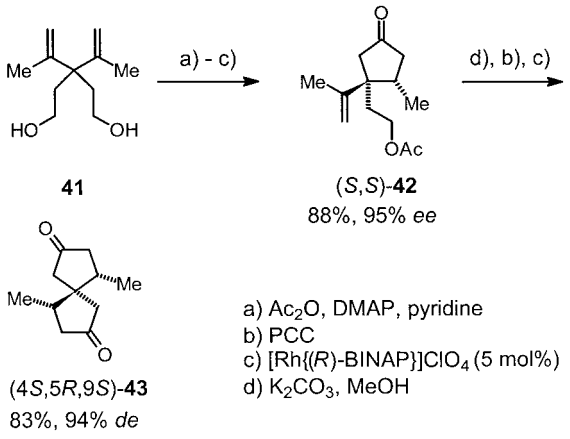
A sequence of N-acylation of the enamino ester **38** with acryloyl chloride (**39**) and subsequent intramolecular enamine–Michael reaction was reported by Stille and coworkers to access δ-lactam derivatives such as **40** (Scheme 8).[32] Phenylethylamine was used as a chiral auxiliary for the enamine–Michael reaction and, moreover, as the nitrogen source of the lactam moiety.[32c] The aza-annulation product **40** was obtained in good yield (85%) and with good diastereoselectivity (94% *de*).

5. Rhodium-Catalyzed Hydroacylation

Rhodium-catalyzed intramolecular asymmetric hydroacylations of γ,δ-unsaturated aldehydes[33] provide access to optically active cyclopentanones bearing a quaternary and a vicinal tertiary carbon center.[34a,b] Tanaka, Suemune, and coworkers developed a remarkable strategy consisting of a double intramolecular hydroacylation of a bispentenal to synthesize chiral asymmetric spirocycles (Scheme 9).[34c] Intramolecular hydroacylation of a prochiral 4-pentenal, prepared from precursor **41**, in the presence of [Rh{(*R*)-BINAP}]ClO_4 as the catalyst yielded the cyclopentanone **42** at room temperature in 95% *ee* and 88% yield. The spiro[4.4]nonane **43** was obtained with very high stereoselectivity after saponification of the ester and subsequent oxidation of the resulting alcohol in a second hydroacylation step. The introduced sequence provides flexible access to spirocenters with two vicinal tertiary stereocenters.



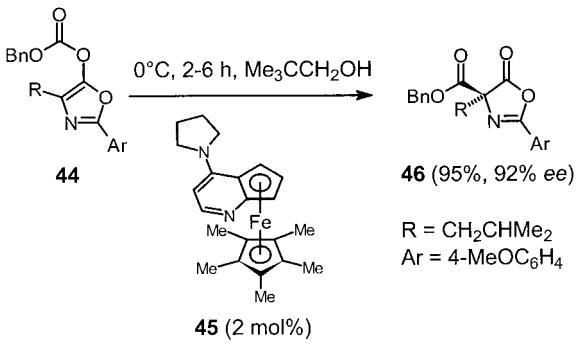
Scheme 9. Synthesis of chiral spiro compounds by double intramolecular rhodium-catalyzed hydroacylation (the yields refer to step c). DMAP = 4-dimethylaminopyridine; PCC = pyridinium chlorochromate.

6. Rearrangements

Rearrangements belong to the most important C–C bond-formating reactions in organic synthesis. Together with cycloaddition reactions, they are definitively atom-economic processes. Since most sigmatropic rearrangements proceed via a well-defined cyclic transition state, they are highly stereospecific and stereoselective.[35] Consequently, such processes provide excellent preconditions for the concurrent construction of more than one stereocenter.

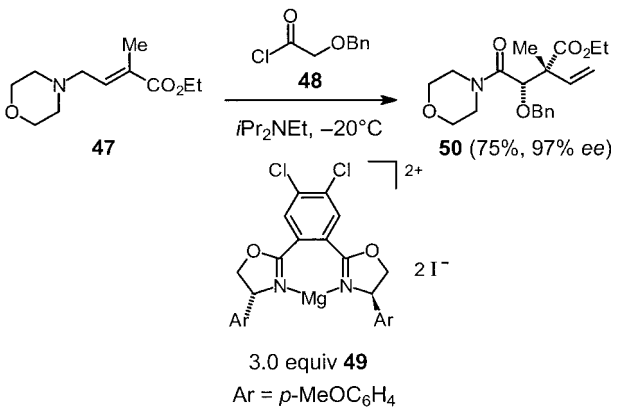
6.1. Asymmetric Catalysis

As already shown by Steglich and Höfle in 1970, the rearrangement of O-acylated azlactones to the corresponding C-acylated oxazolinones is catalyzed by 4-dimethylaminopyridine (DMAP).[36] The first asymmetric version of this 1,2-acyl shift was introduced by Ruble and Fu (Scheme 10).[37a] Substrates such as **44** are converted in the presence of the planar-chiral DMAP derivative **45** (PPY), which acts as the nucleophilic catalyst, in very good yield (93-95%) and with high enantioselectivity (88–92% *ee*) into the oxazoline derivatives **46**, which are interesting precursors for α,α-dialkylated α-aminocarboxylic acid derivatives. Analogous pyrido-annulated ferrocene derivatives with planar chirality were used by the same authors for the stereoselective synthesis of tertiary stereocenters by kinetic resolutions of secondary alcohols and for the additions of alcohols to ketenes.[37b]



Scheme 10. Steglich rearrangement catalyzed by planar-chiral DMAP.

Recently, MacMillan and co-workers reported on the first Lewis acid catalyzed asymmetric version of an acyl–Claisen rearrangement (Scheme 11).[38] The substrates were *N*-allylmorpholine derivatives, such as **47**, which were acylated with a ketene generated in situ from benzyloxyacetyl chloride **48** and iPr_2NEt. The resulting intermediate underwent a [3,3] sigma-

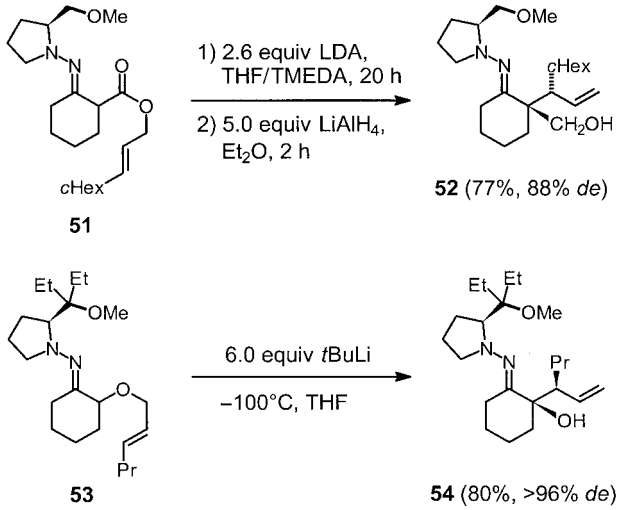


Scheme 11. Acyl–Claisen rearrangement catalyzed by a chiral Lewis acid.

tropic rearrangement to **50** in the presence of the optically active Lewis acid **49**. The *syn* diastereomer (*syn*:*anti* = 94:6) was obtained with high enantioselectivity (97% *ee*) and in good yield (75%). A vicinal tertiary carbon center was generated in addition to the quaternary stereocenter. MgI_2 in combination with a C_2-symmetrical bisoxazoline ligand (Arbox ligand) was used to generate the chiral Lewis acid **49**. An excess amount of the Lewis acid (three equivalents) is required, which thus prevents a broader application of this method.

6.2. Application of Chiral Auxiliaries

Since sigmatropic rearrangements proceed mostly with high stereospecifity, the conversion of enantiomerically pure substrates with tertiary carbon centers can result in the generation of quaternary carbon centers in the product. Consequently, the application of chiral auxiliaries is an attractive strategy.[5, 35] An asymmetric version of the Carroll rearrangement was published by Enders et al. (Scheme 12).[39] The



Scheme 12. Carroll rearrangement and [2,3] Wittig-rearrangement with optically active methoxymethylpyrrolidine derivatives as auxiliaries. *c*-Hex = cyclohexyl; TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.

pyrrolidine derivative (*S*)-*N*-amino-2-methoxymethylpyrrolidine (SAMP) served as the auxiliary. This auxiliary belongs to a class of chiral *N*-aminopyrrolidine derivatives developed by Enders et al. which has proved its versatility in a number of C–C bond-forming reactions.[40] After deprotonation, the SAMP hydrazones, such as **51**, derived from β-keto esters underwent a [3,3] sigmatropic rearrangement. Alcohols **52** were obtained with good diastereoselectivity (94:0:6) after reduction of the carboxylic acid moiety. The auxiliary was cleaved from **52** and the keto function regenerated by ozonolysis. This sequence allows the synthesis of a cycloalkanone with a quaternary α and a tertiary β stereocenter starting from a β-keto allyl ester.

Enders and co-workers also reported on the preparation of chiral α-hydroxy ketones by [2,3] Wittig rearrangements using the optically active pyrrolidine derivative (*S*)-*N*-amino-2-(1-ethyl-1-methoxypropyl)pyrrolidine (SAEP).[41a,b] Quaternary products were obtained starting from an α-allyloxycyclohexanone to give the corresponding SAEP hydrazone **53** (Scheme 12).[41c] The homoallyl alcohol **54** was obtained as the *anti* product (*anti*:*syn* = 91:9) from a [2,3] sigmatropic rearrangement after deprotonation of the starting material **53** with an excess of *t*BuLi. The auxiliary was cleaved from the product **54** by ozonolysis to yield a carbonyl compound with a quaternary O-substituted center and a vicinal tertiary stereocenter.

7. Conclusion

Several new methods and strategies for the enantioselective synthesis of quaternary carbon centers have been developed in the recent years. Only a small selection from a very active area of research has been presented. Despite these new developments, there is still a great demand for new processes and for optimization of the known ones, since they do not always meet the requirements of modern synthetic organic chemistry. In particular, flexibility and versatility with regard to substrates and functional groups, atom-economy, efficiency, and simple performance are standards a modern synthetic method ought to fulfill. Moreover, chiral auxiliaries and ligands should be readily accessible. The development of catalytic asymmetric reactions suitable for the generation of quaternary stereocenters remains a particular challenge.

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