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[3,3]-Sigmatropic rearrangements: a variety of methods and recent advances

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The systematic review integrates and analyzes data on [3,3]-sigmatropic rearrangements published in the past decade. The main types of [3,3]-sigmatropic rearrangements are highlighted, optimal catalytic systems for various types of transformations and for various classes of compounds are considered. Examples are given for the use of such reactions in the synthesis of structurally complex, biologically active, natural and practically valuable compounds. For a number of processes, general mechanistic features of their behaviour, the geometry of transition states and the structures of inermediates are discussed.
The bibliography includes 533 references.

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1. Introduction

Sigmatropic rearrangements are a powerful tool for the construction of new chemical bonds. Their use significantly expands the scope of preparative organic chemistry. A large number of papers on the synthetic applications of sigmatropic rearrangements published in recent years is evidence of the relevance of such studies. However, a review [1] considering such rearrangements in most details was published back in 2004. Since many fundamental investigations on this transformation are continuously evolving, the present review aims to systematically summarize the data published mainly after 2010.

The field of organic chemistry associated with sigmatropic rearrangements is quite extensive. The huge body of data available on this topic has a simple and obvious advantage. Thus, if the synthesis requires the use of a sigmatropic rearrangement, it is highly probable that a procedure has already been developed that includes the necessary or similar reaction or describes the nuances of the transformation of the related compounds. Meanwhile, despite this advantage, the accumulated large volume of data becomes the main obstacle to considering this information in a summarizing review. Therefore, when writing reviews on rearrangements, priority is given to reactions, which are either typical of one class of compounds or are implemented for a particular target. As examples of reviews addressing specific classes of compounds and(or) reactions, mention should be made of the study [2] on the transformation of allyl sulfoxides into allyl sulfenates and its application in various reactions, the review [3] of rearrangements of *N*-oxyenamines, and earlier review publications [4, 5] on rearrangements of fluorinated compounds and the use of the aza-Cope rearrangement in organic synthesis, respectively.

In some cases, rearrangements represent one of the components of a synthetic toolkit designed for a specific purpose, *e.g.*, for the preparation of indolizidine and pyrrolizidine alkaloids.[6] This also includes a review [7] published in 2021 and considering the use of sigmatropic rearrangements in the synthesis of heterocyclic compounds.

Finally, a separate category of works concerns the mechanistic aspects of particular reactions or implementations of particular computational methods for the analysis of chemical transfomations. These include, for example, a

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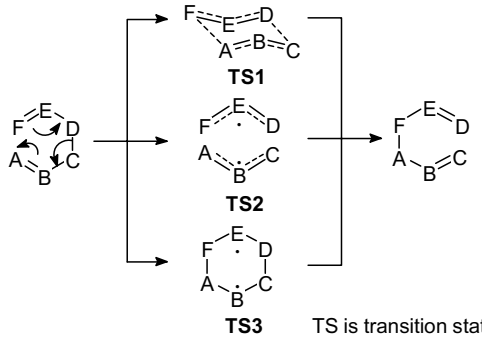
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review[8] on the use of URVA (Unified Reaction Valley Approach) to study catalytic reactions including some rearrangements or the summarizing paper[9] on the mechanisms of rearrangements characteristic of cyclopolyene systems.

The most common studies were those addressing [2,3]- and [3,3]-sigmatropic rearrangemens involved in various reactions; less often, [1,3]-rearrangemens; very rare publications highlighted [1,2]-, [1,5]- and [3,5]-rearrangemens. Therefore, among the variety of possible rearrangements, the authors focused on [3,3]-sigmatropic rearrangemens as the most common and most-employed.

Scheme 1 outlines the pathways of [3,3]-sigmatropic rearrangement of a bis(allyl) system. The formation of an energetically more favourable structure is generally the driving force behind this process, which is achieved by the formation of stronger bonds.

Scheme 1



Quite often, such processes involve the formation of C—C bonds (the bond dissociation energy (E_d) in ethane is 90 kcal mol^{-1}) and cleavage of weaker bonds, *e.g.*, N—N or N—O (E_d = 38 and 48 kcal mol^{-1}, respectively). In this case, the structure of the transition state and the reaction mechanism are largerly determined both by the nature of substituents in the molecule and the reaction conditions such as the use of a polar or apolar solvent, carrying out the reaction in solution or in the gas phase, the structure and the type of the catalyst, *etc*. Hypothetically, the [3,3]-sigmatropic rearrangement can proceed *via* a synchronous concerted pathway (transition state **TS1**), follow a stepwise mechanism through the intermediate formation of a bis(allyl) derivative (transition state **TS2**) or occur in a stepwise manner through the formation of a 1,4-diyl system (transition state **TS3**). The first variant is the most common in literature, since aromaticity of the transition state **TS1** provides the energy gain compared to the other two variants. Transition states **TS2** and **TS3** are also possible, however, they usually occur under exotic conditions, for example, in photo-impulsive reactions.[10,11] A significant benefit of the sigmatropic rearrangement occurring *via* the step of **TS1** formation is the stereochemical outcome. A chair-like conformation provides predictability for the stereo configuration of the products, since an intermediate with the lowest steric hindrance is almost always formed. This fact makes it possible to design the highly stereoselective synthesis, which is very important for the production of natural compounds and their derivatives.

Stereo- and enantioselectivity of these transformations can be further improved by introducing small rings into the molecules to be rearranged. This not only provides energy compensation in the reaction due to relief of strain in three- or four-membered rings (one more driving force of the process) but can additionally increase the selectivity of the reaction due to the spatial fixation of certain bonds or functionalities relative to the plane of a small ring. This method is applied most often in procedures involving the Cope rearrangement.

In some cases, rearrangements occur under thermal conditions, although a large number of catalytic [3,3]-sigmatropic rearrangements are also known. The nature and structure of the catalyst are selected for each particular case; this can be electrophilic catalysis,[12] transition-metal catalysis, metal complex catalysis (including that with chiral ligands or lanthanide compounds), *etc*. Even biocatalysis is possible, which is usually not confined to chemical laboratories and bioreactors: in living nature, enzymes also catalyze [3,3]-sigmatropic rearrangements. For example, the enzyme chorismate mutase catalyzing the Claisen rearrangement is responsible for the formation of phenylalanine and tyrosine.† The application field of sigmatropic rearrangements is rather wide. Examples of their involvement in various cascade transformations are also known.[13]

A wide variety of compounds can serve as substrates for rearrangements, so it is rather difficult to classify these reactions and(or) reagents according to a single criterium. In the present review, the classification is based on the structure of the moiety that forms part of a molecule to be rearranged. The review discusses only selected cases of the Cope rearrangement (most often its aza-version) for two reasons. First, the consideration of this transformation would significantly increase its scope. Second, a clear line can be drawn between the Cope and Claisen rearrangements (as well as between numerous versions of the latter). Thus, the former rearrangement occurs exclusively in the systems containing six carbon atoms, whereas the latter one allows heteroatoms to be present in the structure, which makes it more flexible and more common in synthetic chemistry. Scheme 2 illustrates the main types of rearrangements related to named reactions[14] and also a general pattern of the Cope rearrangement.[15] (The aromatic version of Claisen rearrangements is considered in detail in Section 3.1).

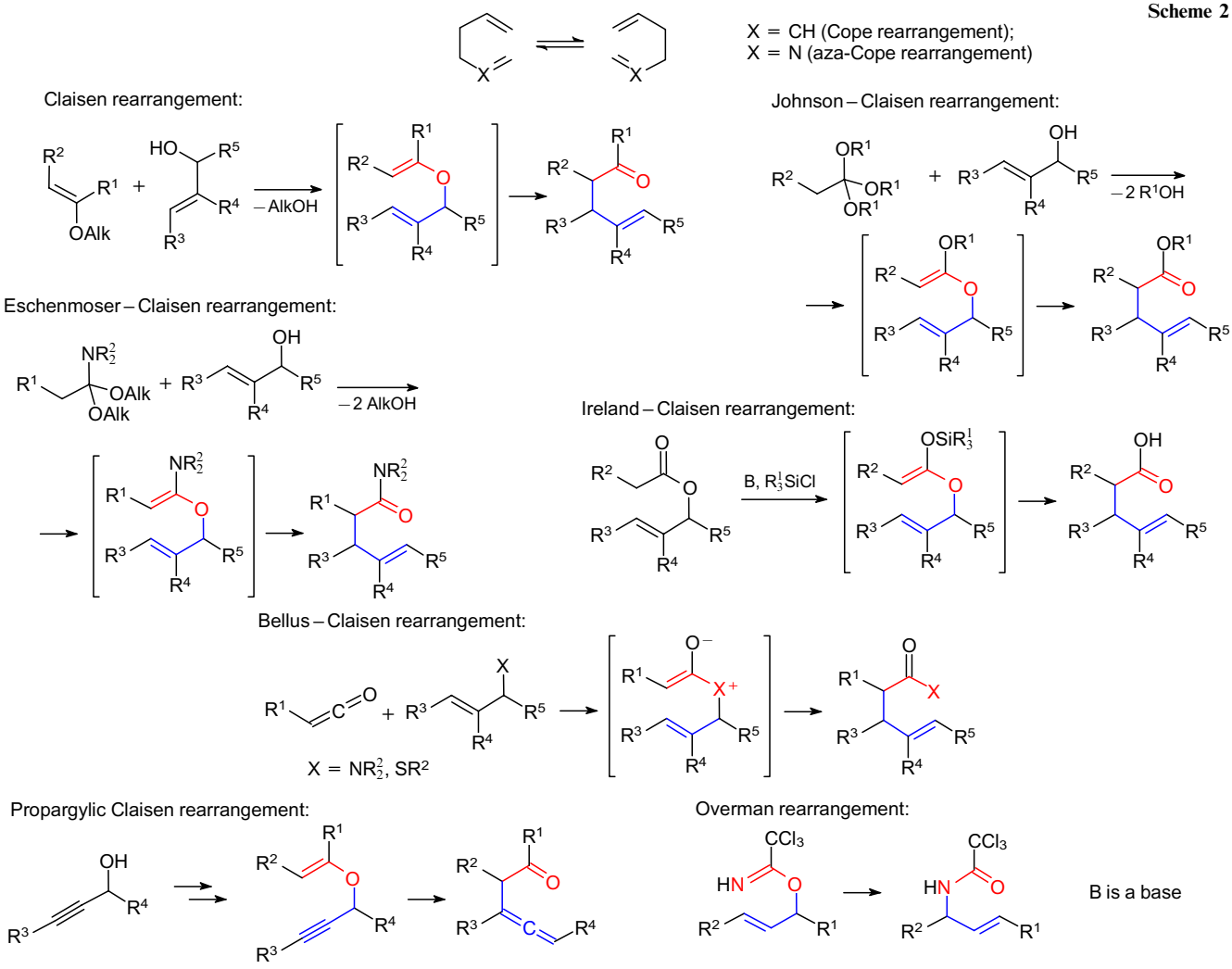
Rearrangements as depicted in Scheme 2 usually have a six-membered transition state and differ in the resulting products, belonging to different classes such as γ,δ-unsaturated ketones, esters, amides, acids, thiols, allenes, trichlor-

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Translation: N.M.Vinogradova, T.N.Safonova

† See B.Hamberger, J.Ehlting, B.Barbazuk, C.J.Douglas. In *Integrative Plant Biochemistry. (Ser. Recent Advances in Phytochemistry. Vol. 40)*. (Ed. J.T.Romeo). (Amsterdam: Elseiver, 2006). P. 88

Scheme 2



oacetamides. Specific features of these named reactions are discussed in the relevant sections.

Note that the present review focuses on the diversity of transformations involving [3,3]-sigmatropic rearrangements due to a large body of accumulated knowledge. Reactions presented in the cited original publications differ significantly from each other, which gives an idea of an enormous synthetic potential of [3,3]-sigmatropic rearrangements in organic chemistry.

2. [3,3]-Rearrangements promoted by small-ring strain

In this Section, only the most interesting examples of reactions are considered, using the small-ring strain as a factor facilitating the rearrangement.‡ In some cases, the classical Cope rearrangement is discussed; in others, its versions, in which the vinyl moiety of the substrate is linked to a heteroatom (oxygen or nitrogen). A [3,3]-sigmatropic rearrangement can be used for ring expansion in various molecules, *e.g.*, in the synthesis of tetrahydrocyclohepta[*b*]indoles **1** (Ref. 17) and dihydrocyclohepta[*c*,*d*]indoles **2**.[18] Such rearrangements can also occur in living organisms.[19] An important prerequisite for the preparation of products **1** is the presence of the hydrogen atom in the α-position of the substituent at the C(2) atom of indole. In the absence of the hydrogen atom in the said position, the reaction occurs *via* the [1,3]-sigmatropic rearrangement to give spiroindoles (Scheme 3).

For the second reaction to be successfully completed and products **2** to be formed, it is essential that both vinyl arms of the cyclopropane moiety in the intermediate **A**,§ have a *syn* orientation. Otherwise, the orbital overlap between the vinyl group and the aromatic ring becomes impossible and the rearrengement does not occur. An important driving force of this transformation is the strain relief in the molecule due to the three-membered ring opening (see Scheme 3).

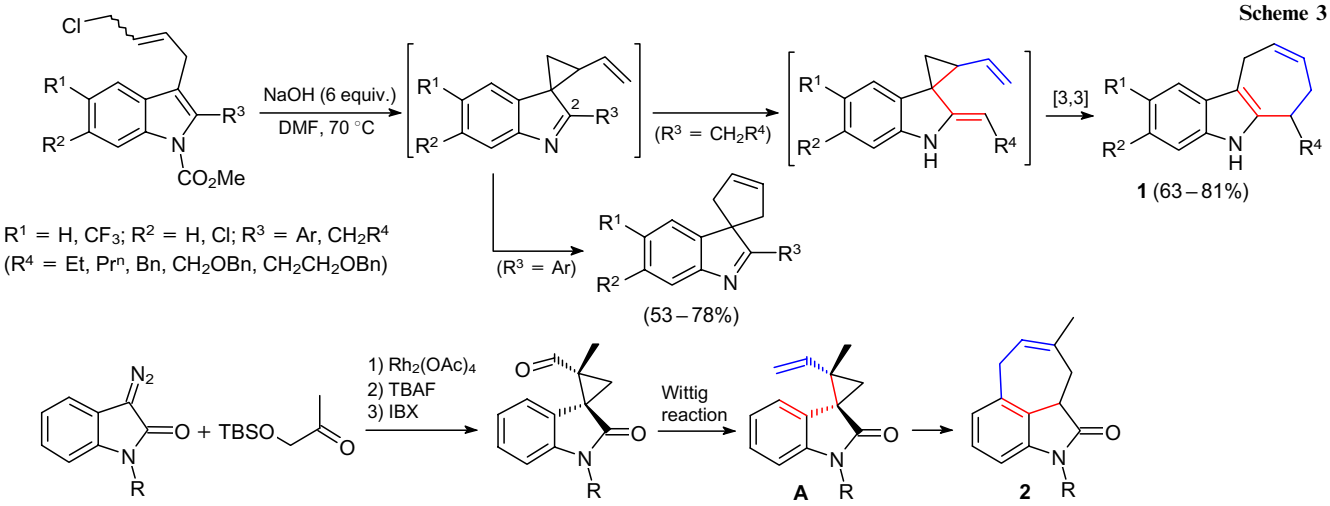
1-Aryl-2-vinyl cyclopropanes **3** can also enter the ring-expansion reactions under appropriate conditions (Scheme 4).[20] The aryl vinyl cyclopropane Cope rearrangement allows the construction of the benzocycloheptene scaffold, which is commonly found in natural compounds.

The spatial fixation of vinyl groups with the help of the cyclopropane backbone was used in the synthesis of 2,5-dihydrooxepines **4**.[21] Metastable bicyclic 2,5-dihydrooxepines were obtained from cyclic 1,3-diketones and 1,4-dibromobut-2-enes by the rearrangement of the intermedi-

‡ Such transformations were partially considered in the review [16].

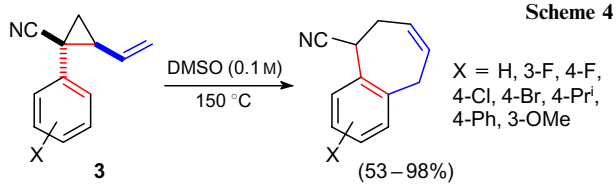
§ In the present review, intermediates are designated with Latin letters within the same Scheme, while for ligands (L^n) and catalysts (Latin numbers), continuous numbering is used.

Scheme 3



R = H, Bn; TBS is *tert*-butyldimethylsilyl, TBAF is tetra-n-butylammonium fluoride, IBX is 2-iodoxybenzoic acid

Scheme 4

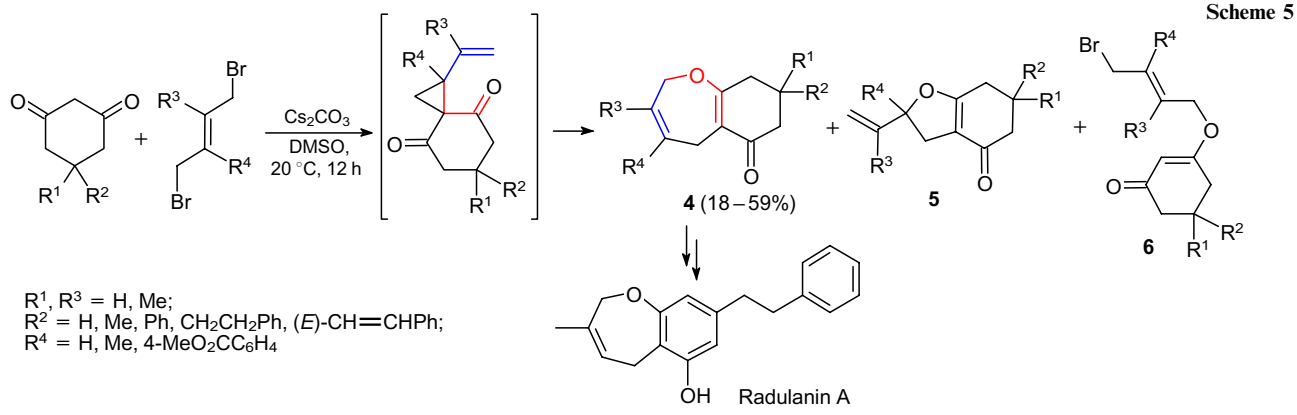


ate products, *syn*-2-vinylcyclopropyl diketones. Quantum chemical calculations indicate a significant effect of temperature on the reaction pathway. The same was also confirmed by experimental data. Thus, product **4** is predominantly formed at low temperatures (not above 20 °C), and its purification by column chromatography requires further cooling of the column (< 10 °C). When these requirements are not met, significant amounts of an undesirable by-product, dihydrofuran **5**, are formed (the **4**:**5** ratio varies from 84:16 to 39:61). It should be noted that the use of tertiary amines as bases significantly increases the fraction of dihydrofurans **5**, and the replacement of the solvent with an alcohol or an ether shifts the equilibrium towards O-alkylation products **6**. This reaction has been successfully applied in the total synthesis of natural 2,5-dihydrobenzoxepine radulanin A (Scheme 5). The authors subsequently published a small review[22] on the use of vinylcyclopropylcarbonyl compounds in organic synthesis.

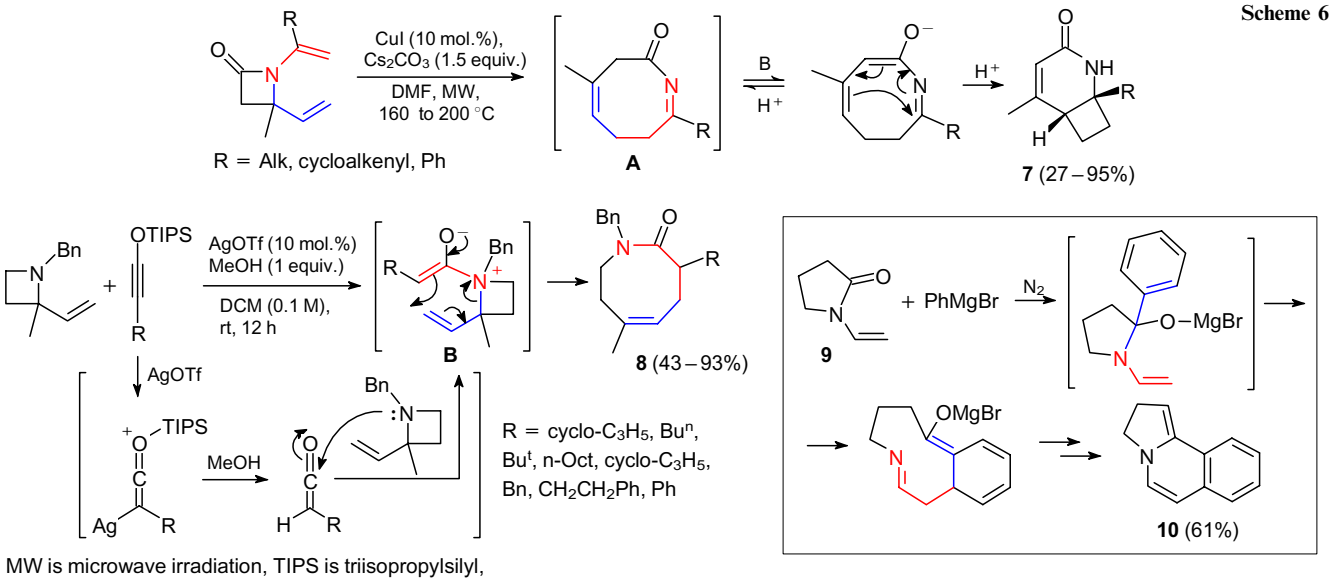
Under certain conditions, the relief of strain in nitrogen-containing four-membered heterocycles provides an approach to obtain 2-azabicyclo[4.2.0]octen-3-ones **7** (see Ref. 23) and eight-membered lactams **8** (Scheme 6).[24] For products **7** to be formed, the salts such as CuI and Cs_2CO_3 should present in the reaction mixture. In their absence, the reaction is terminated with the isomerization of the initially formed intermediate **A** into a non-reactive enamide (not shown in Scheme 6). When CuI and Cs_2CO_3 are added to this enamide, then after a certain period of time, only starting enamide and no traces of fused cyclobutanes can be detected in the reaction mixture. The catalytic system CuI–Cs_2CO_3 was proposed on the basis that deprotonation of the enol form of the eight-membered intermediate **A** occurs faster than its tautomerization to enamide. Therefore, the addition of a base shifts the equilibrium (which was proved during the experiment) towards the formation of the desired cyclobutane **7**. Adding more CuI further promotes this process, facilitating the abstraction of the amide α-hydrogen atom (it is assumed that cuprous iodide acts as a Lewis acid and is either coordinated to the carbonyl oxygen atom, or forms a chelate structure involving oxygen and nitrogen atoms).

The process for obtaining lactams **8** comprises the formation of the intermediate **B** derived from the starting β-lactam and ketene, generated from alkyne under the action of silver triflate. The implementation of this pathway was confirmed by the replacement of the solvent, namely,

Scheme 5



Scheme 6



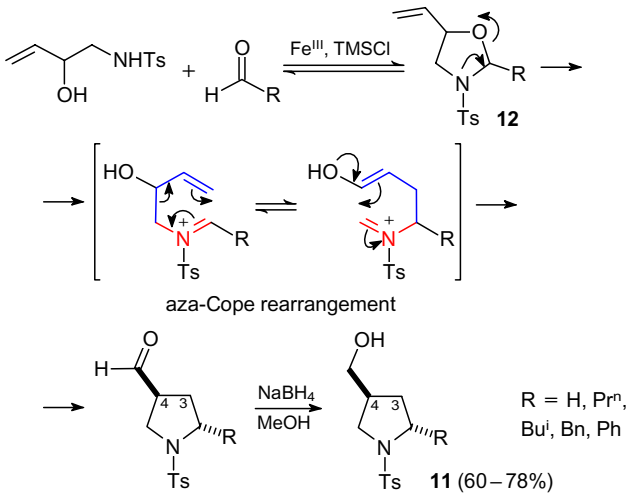
MW is microwave irradiation, TIPS is triisopropylsilyl,
Tf is trifluoromethanesulfonyl (triflyl), DCM is dichoromethane, rt is room temperature, Oct is octyl

methanol with its deuterated analogue: 92% of the resulting product contains the deuterium atom in the α-position to the carbonyl moiety. The evidence for the involvement of ketene intermediates enabled the use of acyl chlorides in place of alkynes. In this case, there is no need to use transition metals as catalysts. Moreover, this method can be employed to obtain α,α-disubstituted lactams, while reactions with alkynes afford only monosubstituted lactams.

In addition to the strain relief through the small-ring opening, other versions of the rearrangement can also be implemented. For instance, the driving force for the reaction of *N*-vinyl derivative **9**, which is the starting material in the synthesis of 3,4-dihydropyrrolo[2,1-*a*]isoquinolines **10**, is the possibility to convert the enol form into the corresponding ketone (see Scheme 6).[25] The reaction with phenylmagnesium bromide is employed to initiate the cascade reactions affording the final product. In the aza-Cope rearrangement, the π-bonds of the phenyl moiety and vinyl group are involved, which assemble the hexa-1,5-diene system necessary for the [3,3]-sigmatropic rearrangement to occur.

The methodology for the ring formation of pyrrolidines **11** using the aza-Cope rearrangement of derivatives **12** (Scheme 7) was reported by Carballo *et al.*[26] Alcohols and aldehydes were used as the starting materials (the Mannich reaction). If propargyl alcohol rather than allyl alcohol is involved in the process, the bond between the C(3) and C(4) atoms of the pyrrolidine ring becomes double. The rearrangement is catalyzed by iron compounds and affords products in 60–78% yields. The process is based on the sequential generation of γ-unsaturated iminium ion, the [3,3]-sigmatropic rearrangement and the subsequent intramolecular Mannich reaction. It was also demonstrated that iron(III) salts are efficient catalysts for the aza-Cope–Mannich cyclization.

Scheme 7



Ts is *p*-toluenesulfonyl, TMS is trimethylsilyl

3. Rearrangements of allyl vinyl ethers and their structural analogues

Examples of sigmatropic rearrangments of allyl compounds such as allyl vinyl or allyl aryl ethers are most abundant in the literature. Rearrangements involving allyl moieties have already been mentioned in the reviews published in the past 10 years. Among them are studies on the direct [1,3]-transposition of functionalities in allylic alcohols and silyl ethers,[27] asymmetric synthesis of allylamines[28] and tandem reactions involving the Michael addition followed by the rearrangement.[29]

3.1. Classical Claisen rearrangement

Rearrangements of allyl phenyl ether were first described by Claisen in 1912.¶ This reaction became common in the synthesis of various compounds of practical value and has not yet lost its relevance. Later, the range of its application was expanded and extended to aliphatic substrates, thus made it possible to find the optimal conditions for a specific synthetic purpose.

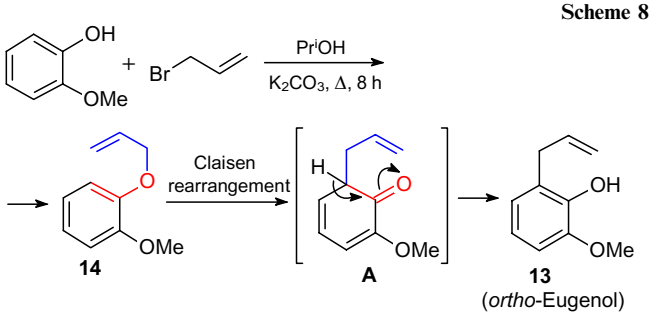
A distinctive feature of the classical Claisen rearrangement is the loss of aromaticity of a molecule during the

¶ See L.Claisen. *Ber. Dtsch. Chem. Ges.*, **45**, 3157 (1912).

bond rearrangement. Due to the formation of a keto group, the rearangement can be followed by a rapid tautomeric proton shift and recovery of the aromaticity. This favourably distinguishes this reaction from the aromatic Cope rearrangement (see Introduction) and makes the process for unsubstituted allyl phenyl ethers possible in principle. Nevertheless, the energy barrier of such a rearrangement is ~35 kcal mol^{-1} (in the gas phase),[30] resulting in the necessity to increase the temperature to ~180–225 °C or to use special catalysts. It is reported[31] that the transformation can be accelerated and the temperature can be decreased by carrying out the reaction in an aqueous medium (presumably, water molecules stabilize the transition state due to hydrogen bonding).

The synthesis of natural *ortho*-eugenol (2-allyl-6-methoxyphenol, **13**) can be considered the closest to the classical Claisen rearrangement. This product was obtained *via* the sigmatropic rearrangement of compound **14** (Scheme 8). The initial formation of intermediate **A** results in the loss of aromaticity; however, after the rearrangement the aromatic system is restored due to the strong shift of the keto-enol equilibrium to the right. Compound **13** was used

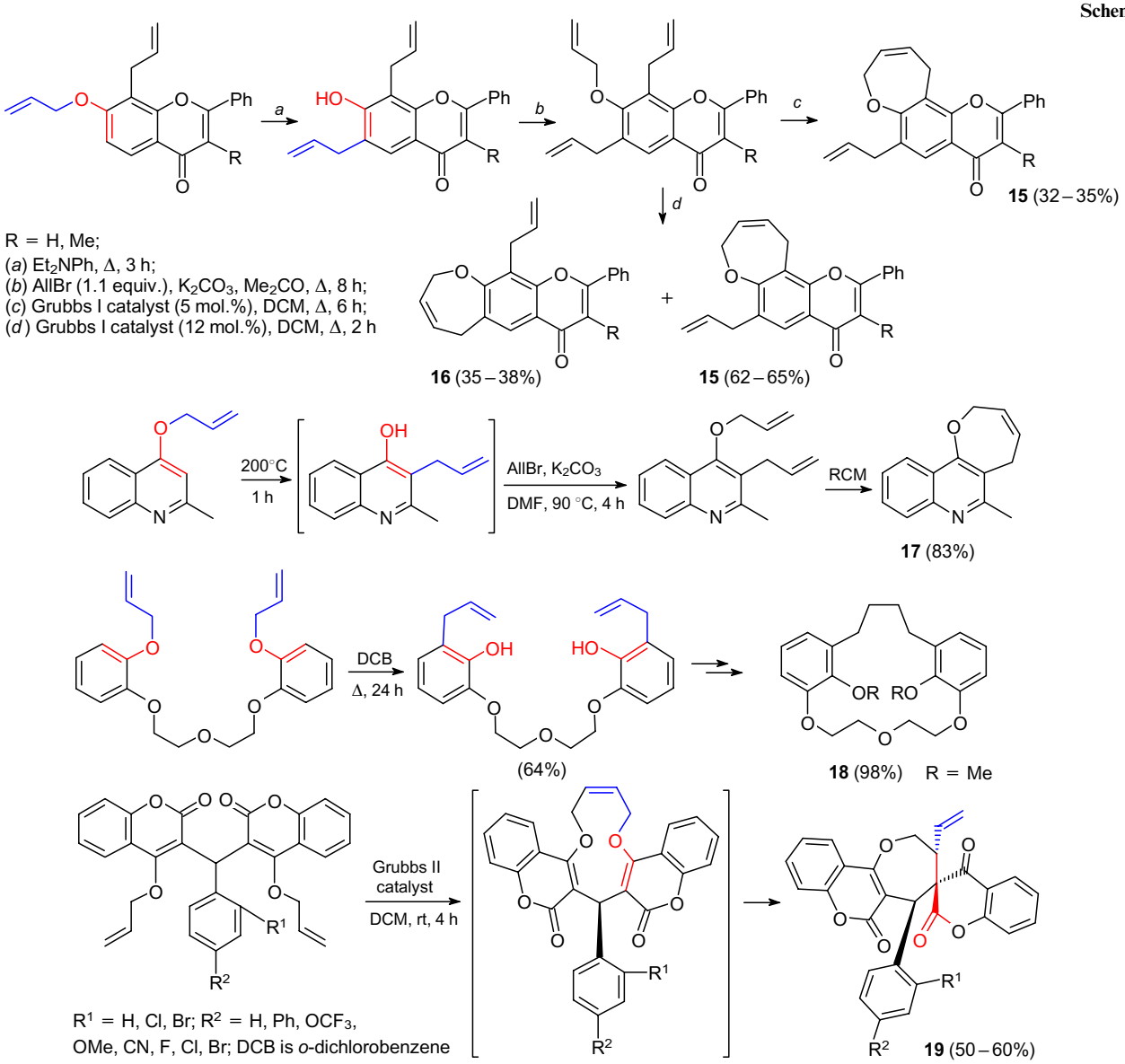
Scheme 8



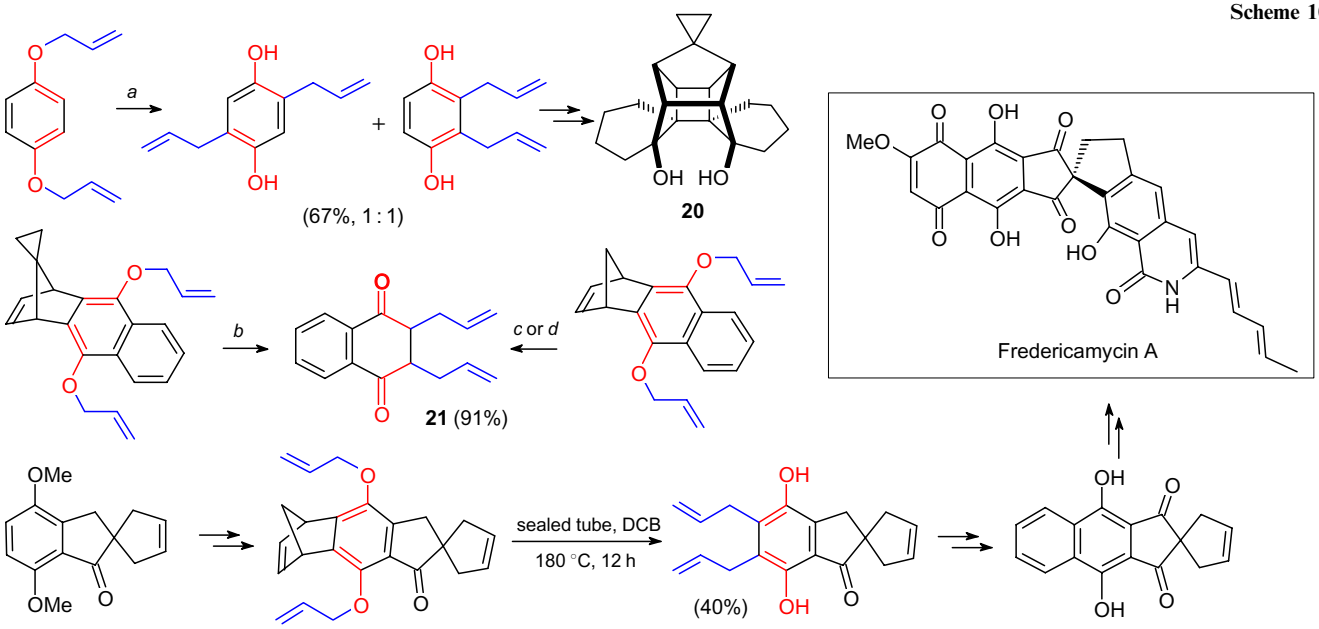
to produce functionalized alkenes by the ruthenium-catalyzed cross-metathesis reaction involving electron-deficient alkenes (methyl acrylate, arylonitrile and acrylamides).[32]

The combination of the Claisen rearrangement and the ring-closing metathesis (RCM) provided an access to flavonoid systems **15** and **16** (including the microwave-assisted methods[33]), annulated with oxepine, oxocine and dioxocine rings (Scheme 9).[34,35] A similar approach was used to obtain ethyleneoxy-bridged fused derivatives of quinoline

Scheme 9



Scheme 10



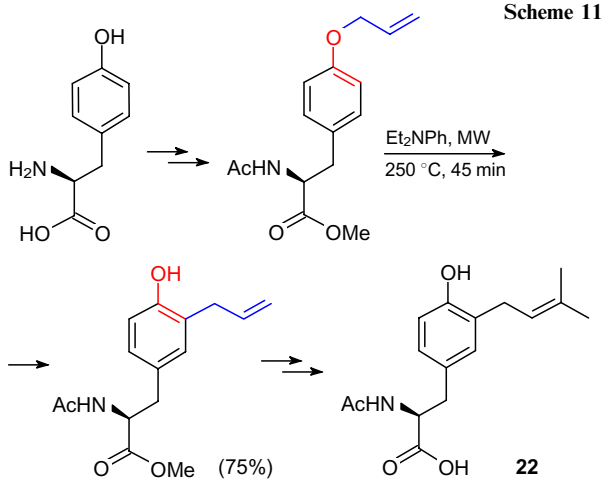
(*a*) neat, 160 – 165 °C; (*b*) sealed tube, DCB, 180 °C, 4 h; (*c*) sealed tube, DCB, 180 °C, 4 h (97%); (*d*) DCB, MW, 120 °C, 3 h (92%)

17 (see Ref. 36) and cyclophanes **18** (*via* the double Claisen rearrangement and ring-closing metathesis),[37] and also for the synthesis of spirocyclic compounds **19**.[38]

An effective strategy for the synthesis of the C_2-symmetric bisannulated octacyclic cage **20** from easily accessible 1,4-hydroquinone was implemented in 8 steps (Scheme 10). The sequence of transformations included the Claisen rearrangement, the Diels – Alder reaction, intramolecular [2 + 2]-photocycloaddition and ring-closing metathesis. The structure of product **20** was confirmed by X-ray diffraction analysis.[39,40] A similar synthetic approach yielded derivatives of 2,3-diallyl-1,4-quinone **21**. In this case, the straightforward Diels – Alder reaction, the Claisen rearrangement and the retro-Diels – Alder reactions were carried out. This approach was applied for the synthesis of the ABCD ring system of the anticancer agent fredericamycin A (NSC-305263).[41,42]

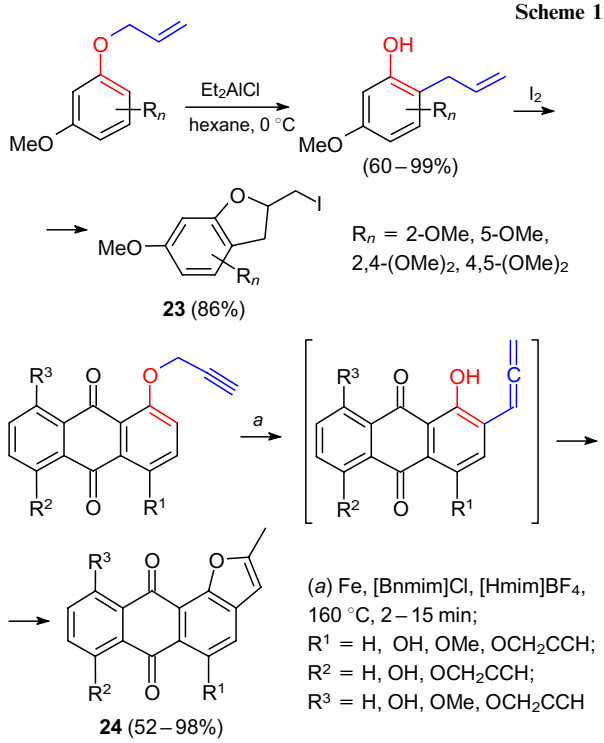
The ligand TRAIL relates to cytokines of the tumour necrosis factor (TNF) family, which binds to the death receptors DR4 and DR5, selectively activating apoptosis in tumour cells, and, therefore, is a promising therapeutic agent. Compound **22** isolated from *Streptomyces* sp. IFM 10937 showed activity in overcoming TRAIL resistance in human gastric adenocarcinoma (AGS) cell lines. The synthesis of compound **22** from L-tyrosine comprised the Claisen rearrangement and cross-metathesis as key steps (Scheme 11).[43]

Scheme 11

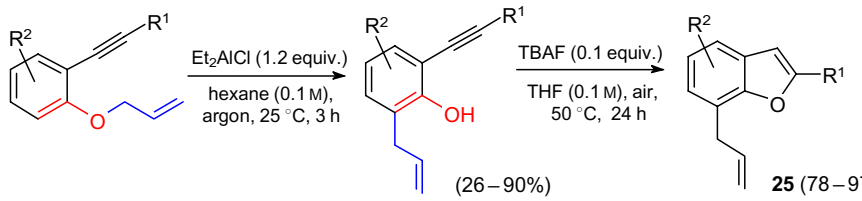


Another tandem transformation, which has become popular lately, is based on the Claisen rearrangement followed by cyclization. For example, the synthesis of benzofuran derivatives involved the step of formation of the *o*-allylphenolic moiety through the Et_2AlCl-catalyzed Claisen rearrangement (Scheme 12).[44] The subsequent electrophilic cyclization gave rise to partially hydrogenated

Scheme 12

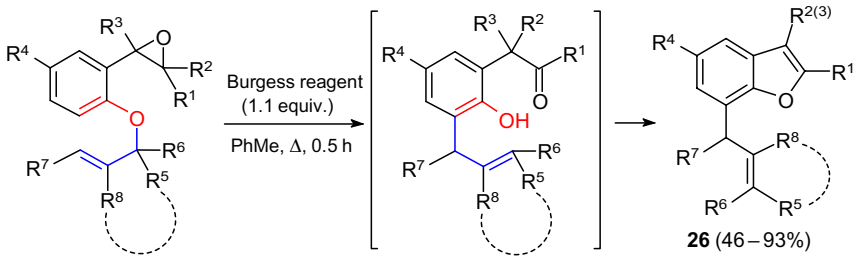


Scheme 13



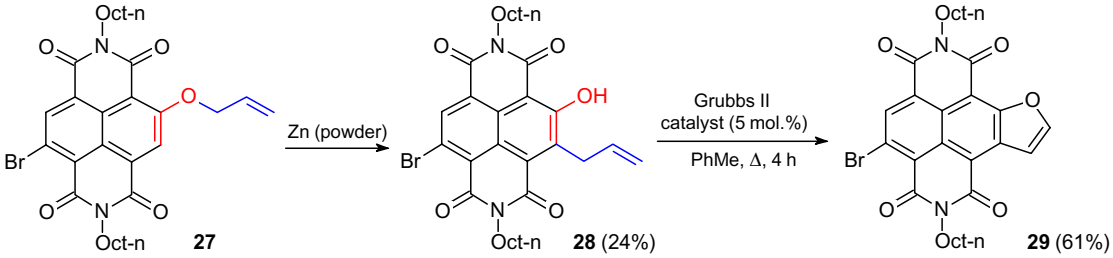
R^1 = Ph, 4-MeC_6H_4, 3-MeC_6H_4, 2-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4; R^2 = H, 4-Me, 4-OMe, 4-Cl, 5-OMe (the position of a substituent in the substrate is indicated)

Scheme 14



R^1 = Et, Bu^t, Bn, Ph, Bz, vinyl; R^2, R^3 = Me, Ph; R^1–R^3 = $(CH_2)_3$, $(CH_2)_4$; R^4 = H, F, Me, OMe; R^5, R^6, R^7, R^8 = H, Me; R^5–R^7 = $(CH_2)_3$, R^5–R^8 = $(CH_2)_4$

Scheme 15



benzofurans **23**. Structurally similar dihydrobenzofurans were obtained from allyl aryl ethers in the presence of the $FeCl_3$–silicate MCM-41 catalytic system.[45] Powdered iron in the mixture of ionic liquids, such as 1-methylimidazolium tetrafluoroborate (Hmim) and 1-benzyl-3-methylimidazolium chloride (Bnmim), proved to be another efficient catalytic system to perform the Claisen rearrangement, which helped to reduce the reaction time.[46] The rearrangement of propargyloxyanthraquinones affords furan derivatives **24**. In case, when any of the substituents is a $OCH_2C{\equiv}CH$ group, while the other two are hydrogen atoms, the annulation of the second furan ring is possible (not shown in the Scheme, but the mechanism for their formation is the same).[47] An alternative way to accelerate the rearrangement is to carry it out in near-critical water.[48]

The Claisen rearrangement mediated by Et_2AlCl was a key step in the synthesis of 7-allylbenzofurans **25**.[49] 1-Allyloxy-2-ethynylbenzene derivatives were used as the starting materials (Scheme 13). The annulation of the rearranged product was found to occur under mild conditions in the presence of a catalytic amount of TBAF. Tetra-n-butylammonium fluoride acts as a base in the second step of the formation of benzofurans. The annulation is initiated with the deprotonation of the hydroxy group. This transformation can be carried out as a one-pot procedure. Similar products are also available *via* a microwave-assisted process.[50]

Another one-pot cascade approach using the Burgess reagent [methyl *N*-(triethylammoniumsulfonyl)carbamate] provides an access to polysubstituted benzofurans **26**.[51] The reaction sequence includes the Claisen rearrangement, the Meinwald rearrangement and heterocyclization (Scheme 14). In an earlier study,[52] the authors applied the same approach to prepare 2*H*-chromenes using the aromatic Claisen rearrangement through the intermediate formation of *o*-quinone methides.

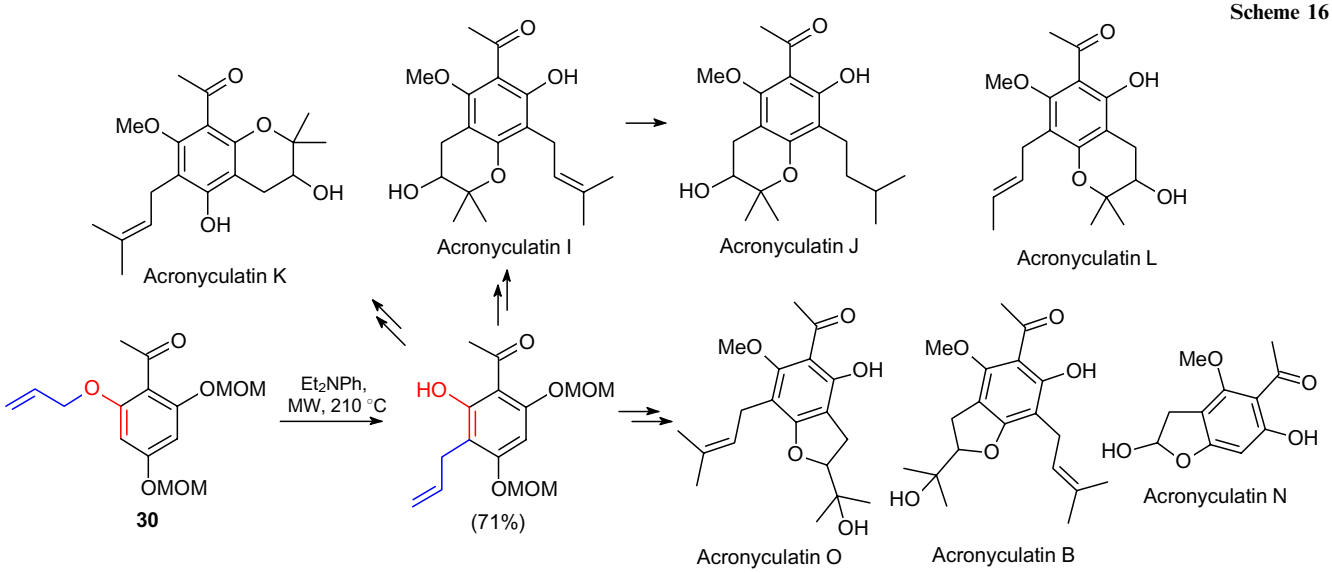
Under certain conditions, naphthalimide allyl ether **27** also undergoes [3,3]-sigmatropic rearrangements (Scheme 15).[53] Product **28** is converted into annulated furan **29** in the presence of the Grubbs II generation catalyst.

Six analogues of natural acronyculatin B, namely, acronyculatins I, J, K, L, N and O, having anticancer activity, were isolated from *Acronychia trifoliolata*. The synthesis of these compounds was accomplished through the rearrangement of allylic ethers of acetophenone **30** (Scheme 16).[54] Trihydroxyacetophenone was converted into target compounds *via* various reaction sequences including the protection of the hydroxy group, allylation or prenylation and epoxydation followed by cyclization. C-Prenylation was carried out by the direct addition of the prenyl group or through [1,3]- or [3,3]-sigmatropic rearrangement. All resulting compounds significantly inhibited the Epstein–Barr virus activation.

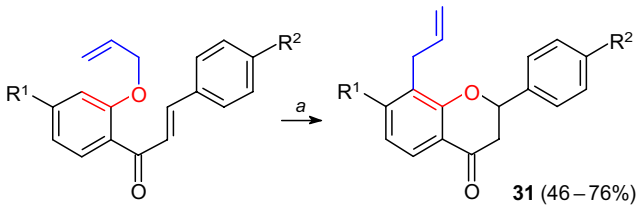
An unusual tandem Claisen rearrangement and 6-*endo*-*trig*-cyclization of *ortho*-allyloxy chalcones provides a simple way to flavanones **31** in a one-pot manner. These products also include natural compounds (Scheme 17).[55–57]

In 2021, the enantioselective *para*-Claisen rearrangement was achieved for the first time.[58] (−)-Illicinole was used as a model substrate, which was converted into (−)-illicinone A. The final product obtained under optimized catalytic conditions using chiral Lewis acid **I** had an enantiomeric ratio (*er*) of 87 : 13. In this case, an unexpected by-product (+)-**32** with a 93 : 7 enantiomeric ratio was obtained, and upon completion of the reaction, 34% of unreacted illicinole was recovered. The authors have not fully clarified the mechanism of this transformation; never-

Scheme 16



Scheme 17



(*a*) 1) PhMe (0.15 M), MW, 250 °C, 1 h; 2) NaOAc (10 equiv.), MeOH, MW, 100 °C, 1 h; R^1 = H, OMOM; R^2 = H, OMe, Cl, Br, NO_2, OMOM; MOM is methoxymethyl

theless, they hypothesized two putative reaction pathways *via* the Claisen and Cope rearrangement sequence to give the Hurd–Pollack intermediate **A** or *via* the dissociative mechanism to afford the Dewar intermediate **B** followed by recombination. The mechanism for the formation of by-product **32** was also not elucidated (Scheme 18).

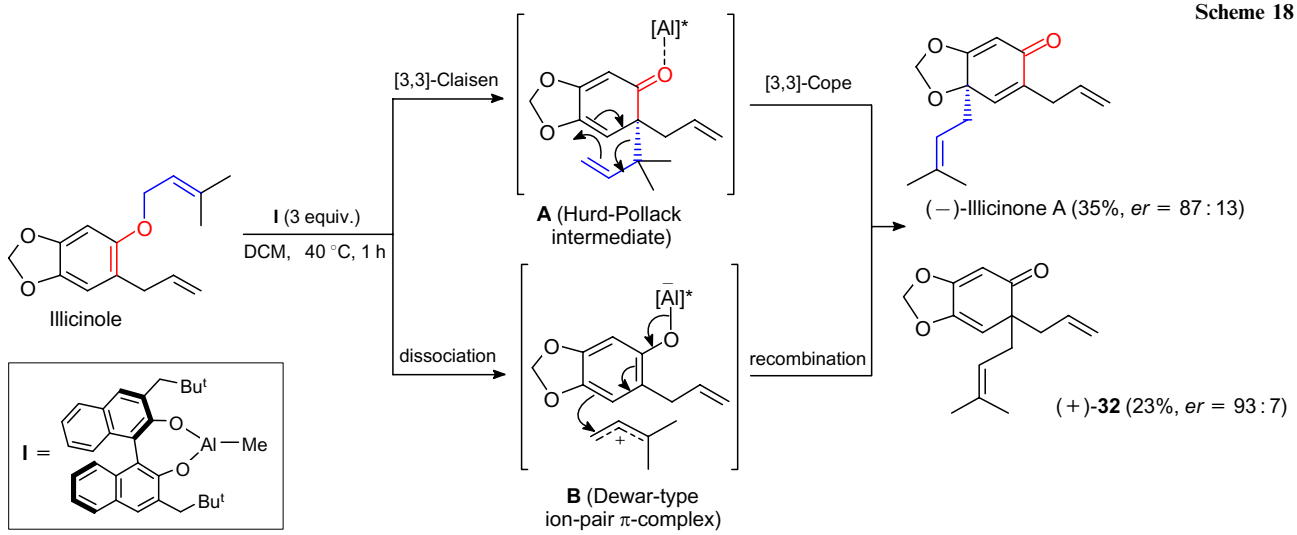
The rearrangement of allyl ethers **33** in the presence of a combined Pd- and Cu-based catalyst furnishes dihydrocoumarins **34** (Scheme 19).[59] The process occurs regio- and stereoselectively to give the target products in yields of up to 83%. The mechanism for the reaction with naphthalene derivatives has not yet been established but the authors suggested that it is similar to that for the classical Claisen rearrangement.

The double Claisen rearrangement of allyl ether of 2,5-dichloro-1,4-hydroquinone **35** followed by alkene isomerization, oxidation and double substitution of chlorine with azide afforded 2,5-diazido-3,6-dipropenyl-1,4-benzoquinone.[60] Upon its heating, nitrene undergoes double cyclization to give pyrrolo[2,3-*f*]indole-4,8-dione system **36** (Scheme 20). The products of the double Claisen rearrangement are often used in the synthesis of novel polymers.[61]

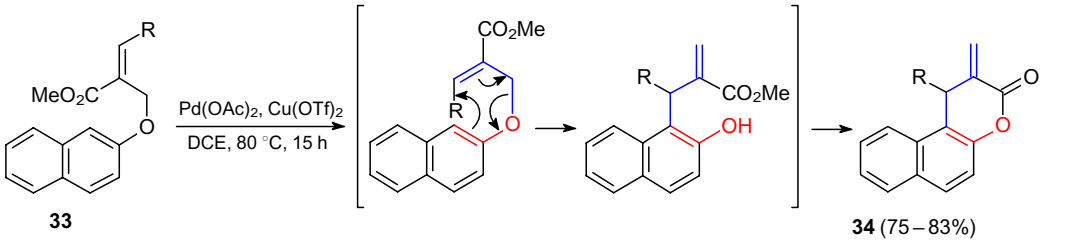
An example of the one-step synthesis of isoprenyl-substituted coumarin **37** (cedrelopsin) based on the rearrangement of compound **38** was reported (Scheme 21).[62] This transformation represents a domino sequence including the Wittig reaction, 3,3-sigmatropic rearrangement, heterocyclization and removal of a prenyl moiety.

An effective method was elaborated for the synthesis of novel phosphorus-containing fused heterocycles **39** bearing an eight-membered ring.[63] The Claisen rearrangement is followed by the coupling reactions with allyl or vinyl phosphonate and ring-closing metathesis (Scheme 22). All

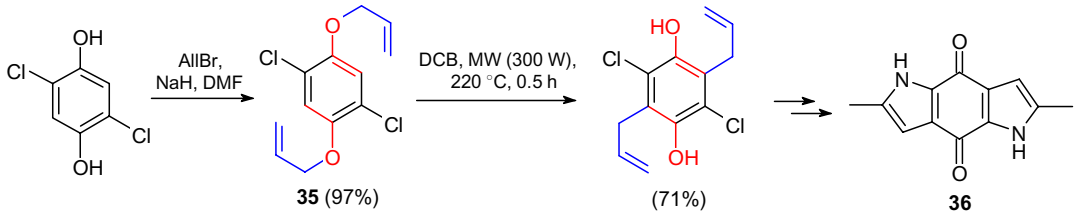
Scheme 18



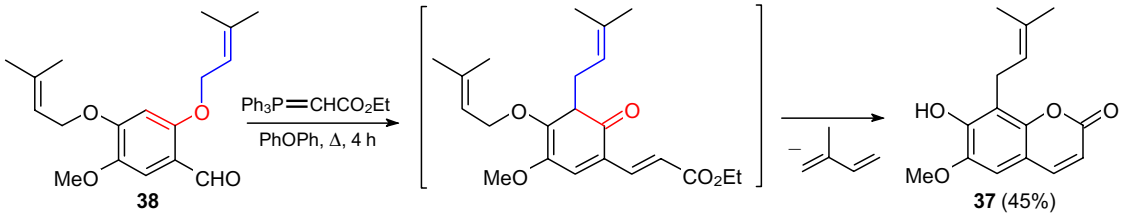
Scheme 19



Scheme 20



Scheme 21

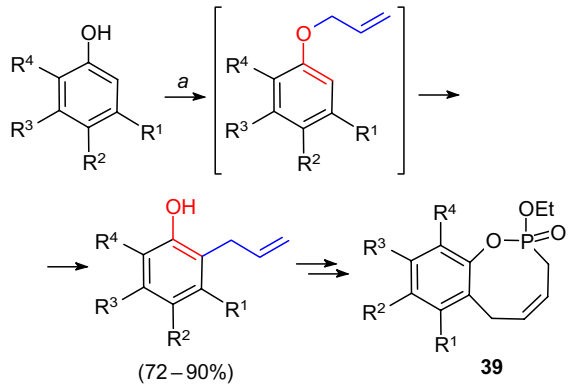


transformations occur at room temperature and furnish products in yields of up to 90%.

The Claisen rearrangement is actively implemented as a key step in many synthetic approaches to construct natural molecules for example, in the 19-step synthesis of termicalcicolanone A, which is an anticancer xanthone natural product (Scheme 23).[64] Prenylation was perfomed in the final steps using the regioselective version of this rearrangement.

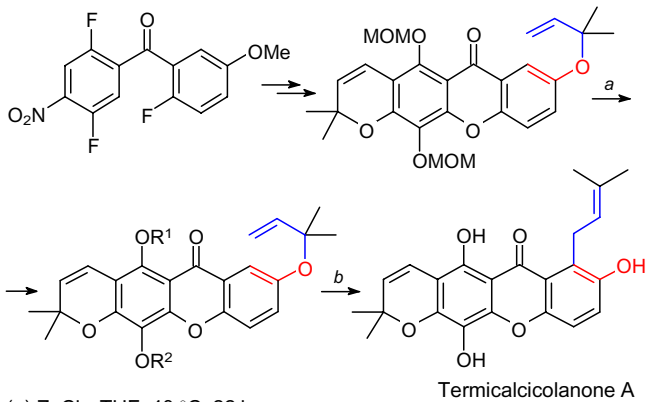
It should be noted that in the past decades, the chemistry of fluorine-containing compounds has been rapidly evolving, since the presence of a fluorine atom determines certain unique physical and(or) chemical properties of the molecule.[65] Thus, the total synthesis of natural xanthone garcinone A bearing two prenyl moieties was accomplished using 1,3-difluoroxanthone derivative **40** (Scheme 24). The use of

Scheme 22



(*a*) 1) AllBr, K_2CO_3, Me_2CO (dry), Δ, 8 h;
2) DCB, Δ, h; R^1, R^3, R^4 = H; R^1–R^2, R^2–R^3, R^3–R^4 — benzo;
R^2 = H, Me, Br, OMe, Bu^t, NO_2

Scheme 23



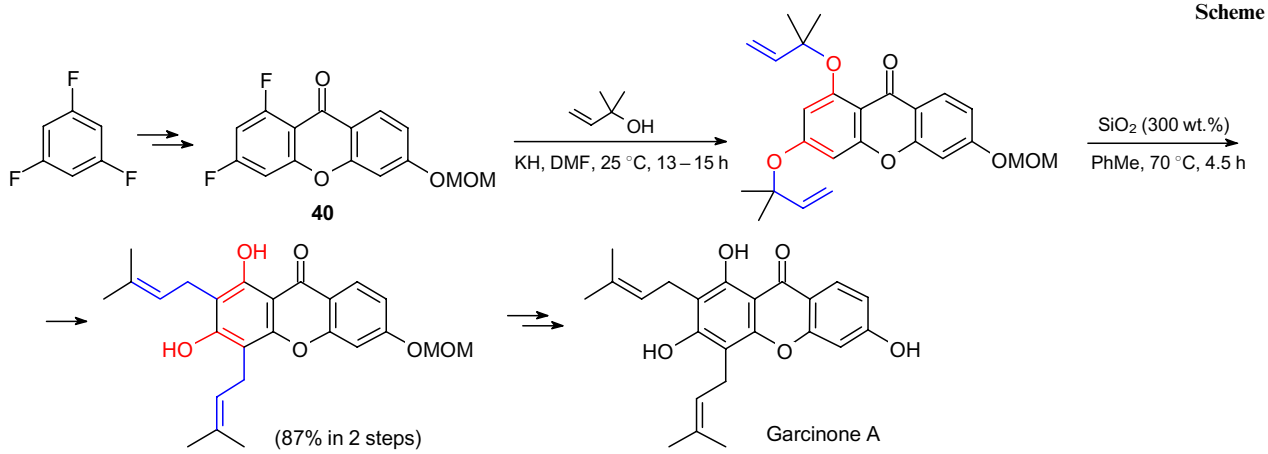
(*a*) $ZnCl_2$, THF, 40 °C, 22 h;
(*b*) 1) PhMe, 100 °C, 5 h; 2) TsOH, EtOH, DCM, Δ, 4 h; R^1 = H, R^2 = MOM or R^1 = MOM, R^2 = H

the Claisen rearrangement enables the selective introduction of the target substituents into the desired positions of the molecule.[66] A similar double rearrangement was applied in the synthesis of amorfrutin C.[67]

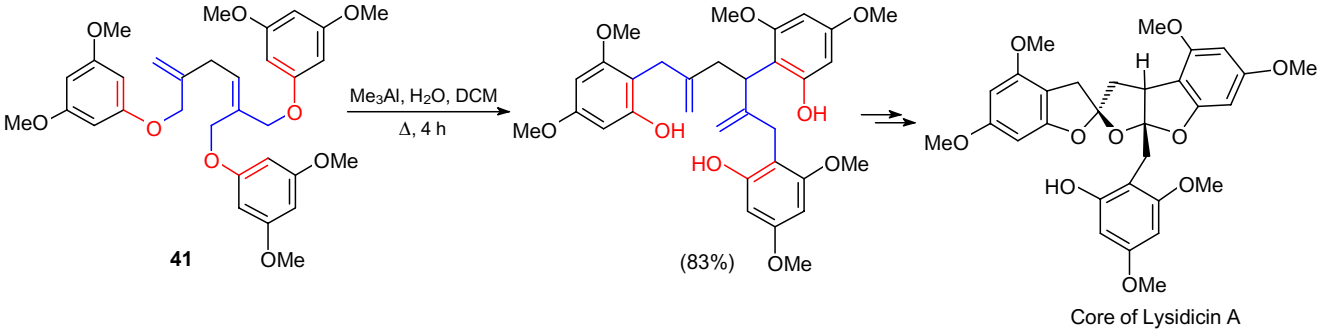
A triple Claisen rearrangement of phloroglucinol ether **41** produced a tricyclic core of lysidicin A isolated as a racemate (Scheme 25).[68] All three steps of the rearrangement can be carried out in one reactor.

A tandem Claisen rearrangement and the Diels–Alder reaction was used in the synthesis of natural compounds isolated from the *Garcinia* plants and containing a unique 4-oxatricyclo[4.3.1.$0^{3,7}$]decan-2-one scaffold (Scheme 26).[69] These plants are known for their antibacterial and cytotoxic properties, so that they are frequently used in traditional medicine. Forbesione and cluvenone as well as their two

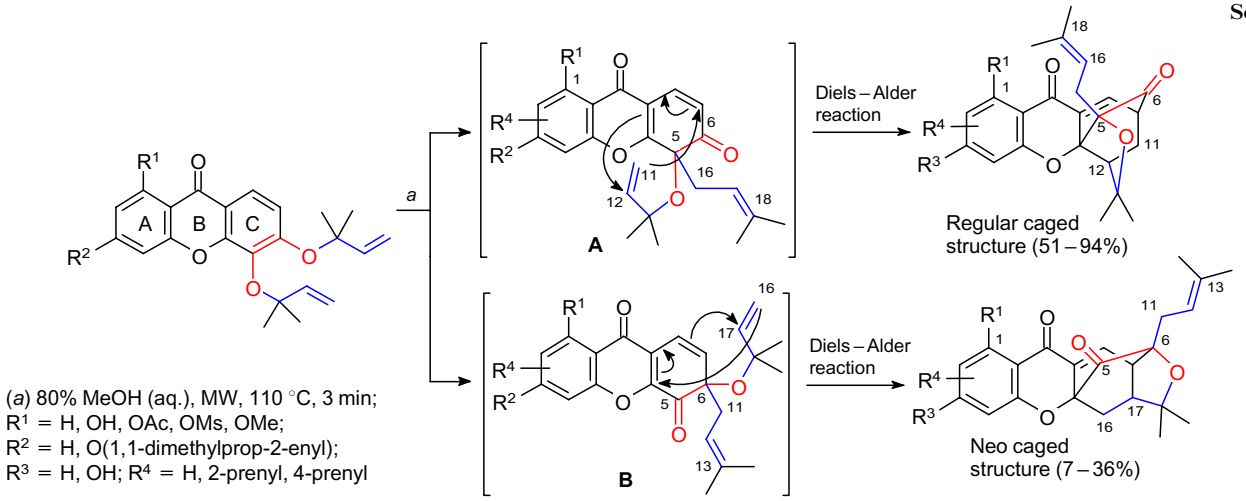
Scheme 24



Scheme 25



Scheme 26



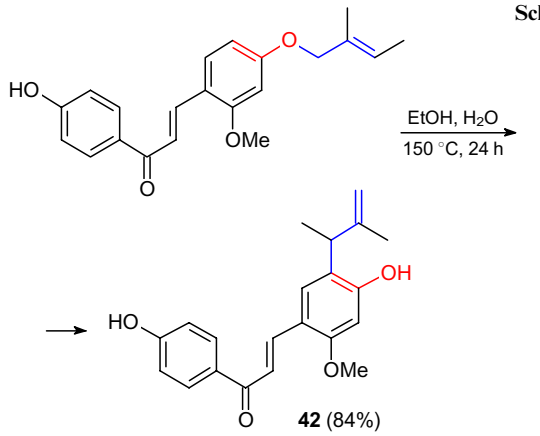
novel and six known caged analogues were obtained based on xanthone and chromone. Two pathways are possible for this reaction. In the first step, two Claisen rearrangement occur, the first one in the ring A by the mechanism similar to that for the classical Claisen rearrangements (not shown in the Scheme), while the second one in the ring C, which is responsible for the further course of the process. Allylation at the C(5) atom yields intermediate **A** followed by the Diels – Alder reaction involving the C(11) – C(12) bond as a dienophile to afford the so-called regular caged scaffolds. Allylation at the C(6) atom gives intermediate **B**, which, after the Diels – Alder reaction involving the C(16) – C(17) bond as a dienophile, produces neo caged scaffolds. Microwave activation substantially reduces the reaction time and improves the product yields.

Licochalcones, isolated from the roots of liquorice (*Glycyrrhiza inflata*), have anticancer, antiparasitic, antileishmanial, antioxidant, antibacterial and other biological activities. Licochalcone E (**42**) was obtained through the rearrangement of the corresponding allyl aryl ether (Scheme 27).[70] Several similar modifications of this transformation were described, also carried out in an aqueous alcohol medium.[71 – 76]

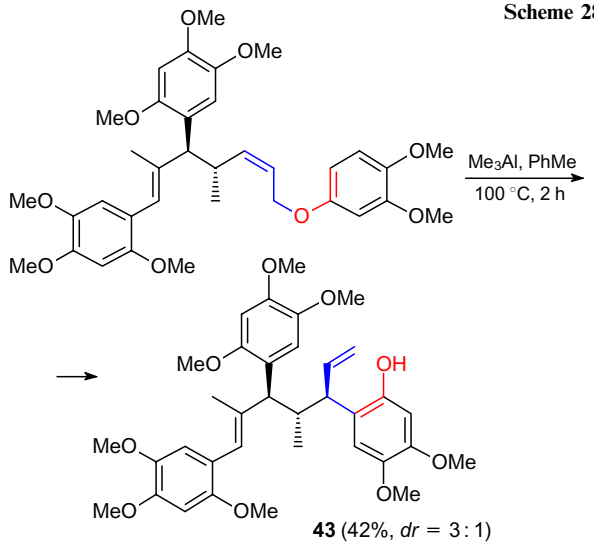
Tatanans belong to sesquilignans, which are a new class of complex natural compounds isolated in 2011 from the rhizomes of *Acorus tatarinowii* plants.[††] These derivatives turned out to be potent glucokinase activators, and their

[††] See G.Ni, Z.-F.Shen, Y.Lu, Y.-H.Wang, Y.-B.Tang, R.-Y.Chen, Z.-Y.Hao, D.-Q.Yu. *J. Org. Chem.*, **76**, 2056 (2011).

Scheme 27



Scheme 28



dr is diastereomeric ratio

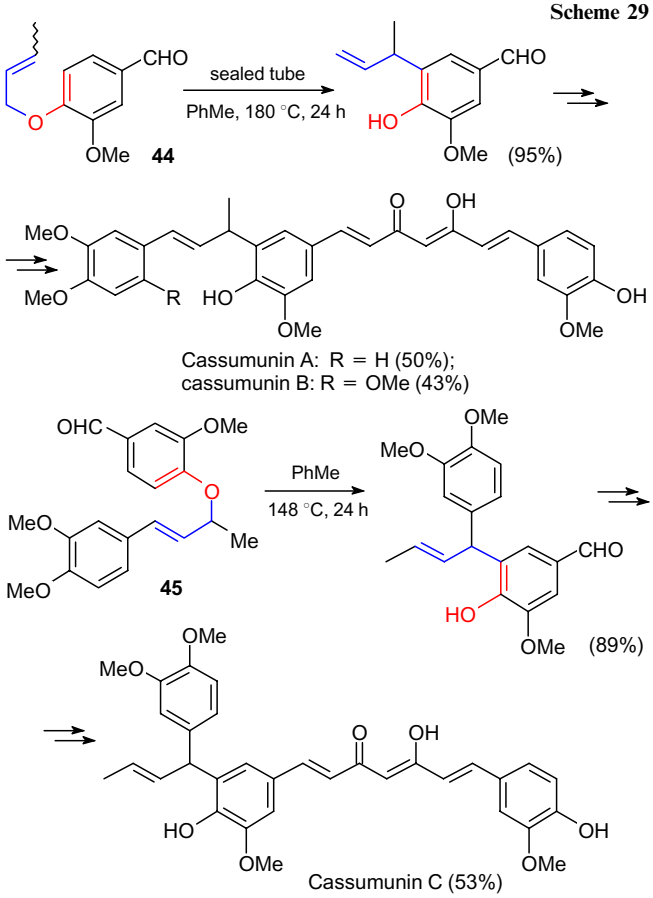
in vitro activity exceeded that of known synthetic antidiabetic agents. A series of sequential [3,3]-sigmatropic rearrangements produced tatanan A (13 steps, 13% overall yield) along with its analogues, tatanans B and C.[77] One of the rearrangements affording intermediate **43** is depicted in Scheme 28.

Natural cassumunins A, B and C possess significant antioxidant and anti-inflammatory properties. The total synthesis of cassumunins A and B was accomplished in five linear steps from available 4-hydroxy-3-methoxybenzaldehyde in a moderate overall yield.[78] The key transformations were the Claisen rearrangement and the Heck reaction. The total synthesis of cassumunin C from the known alcohol, 1-(3,4-dimethoxyphenyl)but-2-enol, comprises three steps, namely, a tandem [3,3]-sigmatropic shift, the S_N2' reaction and an aldol condensation. A total of eighteen symmetrical and unsymmetrical analogues of natural curcumin were synthesized. The sigmatropic rearrangement of compounds **44** and **45**, occurring in different steps of the synthesis of cassumunins A, B and C, is illustrated in Scheme 29.

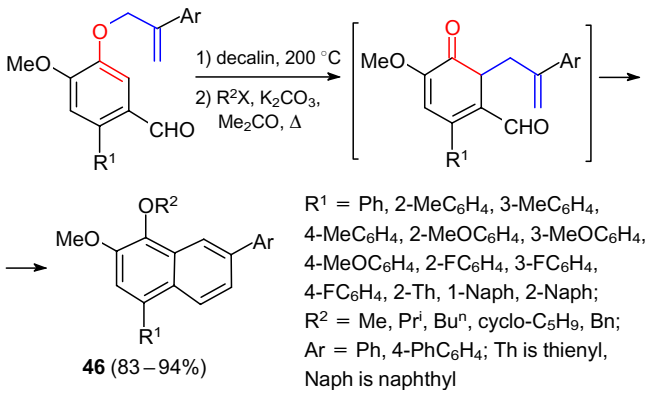
Polysubstituted naphthalenes **46** were obtained starting from commercially available isovanillin and its derivatives (Scheme 30).[79] Alkylation of the phenol moiety with styryl bromide, the subsequent Claisen rearrangement, the ene reaction and final O-alkylation provided the corresponding compounds in high yields.

Recently, more and more examples of the implementation of transition metal compounds for the catalysis of the Claisen rearrangement along with its tandem version with various cross-coupling reactions have appeared. A rearrangement of bromo-substituted allylic alcohols **47**,[80] which is a europium(III)—catalyzed Claisen rearrangement, offers interesting synthetic possibilities. Aryl ether deivatives were prepared from bromo-substituted allylic alcohols by the Mitsunobu reaction *via* copper(II)-catalyzed arylation using potassium aryltrifluoroborate or the nucleophilic aromatic substitution (S_NAr). In this case, the bromoalkenyl moiety remains intact indicating a possibility of the migration of C—O and C—C σ-bonds in synthetically relevant compounds, which furnishes compounds **48**. Exam-

Scheme 29

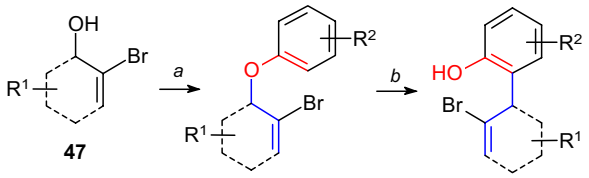


Scheme 30



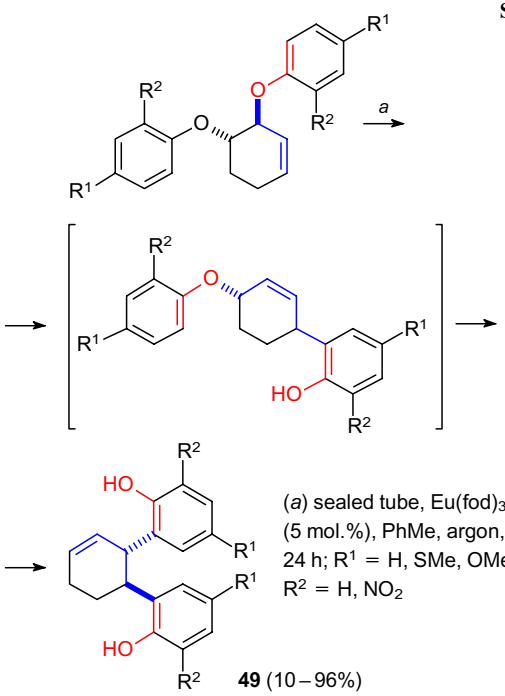
R^1 = Ph, 2-MeC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4, 2-$MeOC_6H_4$, 3-$MeOC_6H_4$, 4-$MeOC_6H_4$, 2-FC_6H_4, 3-FC_6H_4, 4-FC_6H_4, 2-Th, 1-Naph, 2-Naph;
R^2 = Me, Pr^i, Bu^n, cyclo-C_5H_9, Bn;
Ar = Ph, 4-PhC_6H_4; Th is thienyl, Naph is naphthyl

Scheme 31



(*a*) $R^2C_6H_4BF_3K$, $Cu(OAc)_2 \cdot H_2O$, DMAP, MS 4A, DCM, O_2, rt, 60–72 h; (*b*) sealed tube, $Eu(fod)_3$, PhMe, argon, 120–130 °C, 24 h; R^1 = $(CH_2)_2$, $(CH_2)_3$, $(CH_2)_4$; R^2 = H, 4-OMe, 4-F, 2-NO_2, 4-NO_2; DMAP is dimethylaminopyridine, fod is 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyloctane-3,5-dionate, MS are molecular sieves

Scheme 32

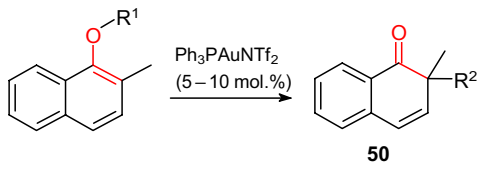


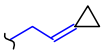
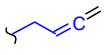
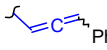
(*a*) sealed tube, $Eu(fod)_3$ (5 mol.%), PhMe, argon, 120 °C, 24 h; R^1 = H, SMe, OMe, F, NO_2; R^2 = H, NO_2

49 (10–96%)

ples of rearrangements of both cyclic and aliphatic allylic alcohols are known. Subsequent O-alkylation of *o*-(2-bromoallyl)phenol or C-arylation–alkenylation *via* Suzuki–Miyaura cross-coupling provide a route to a variety of densely functionalized molecules (Scheme 31).

Scheme 33



R^1	R^2	*T*, °C	Solvent	Yield (%)
		50	DCE	61
		50	DCE	78
		rt	PhMe	63
		rt	PhMe	90 (*dr* = 1.5 : 1)

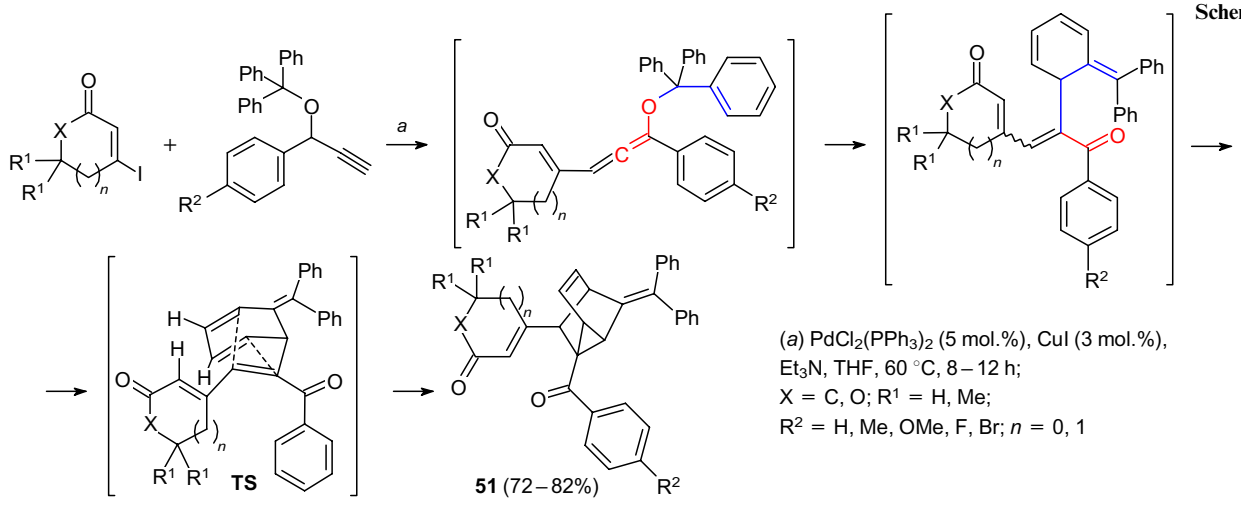
Ramadhar *et al.*[81] elaborated a procedure to construct $C(sp^3)-C(Ar)$ bonds by the lanthanide-catalyzed sigmatropic rearrangement (Scheme 32). The domino sequence includes the Claisen [3,3]-sigmatropic rearrangement, which can be carried out with a high yield of product **49** using $M(fod)_3$ complexes (where M = Eu, Er, Yb, Pr) as catalysts. Europium(III) compounds proved to be most effective in this reaction. Diaryl ethers were derived from the corresponding diols *via* the double arylation using the copper-catalyzed coupling of aryltrifluoroborate salts or the S_NAr reaction. Similar procedures are suitable to convert bromo-substituted allylic alcohols.[80]

The $Ph_3PAuNTf_2$-catalyzed Claisen rearrangement of allyl ethers of α-naphthol provides an access to enones **50** containing quaternary carbon atoms (Scheme 33).[82] Due to the presence of a methyl group in the *ortho* position of the product, the reaction stops at the enone formation since the further tautomerization becomes impossible.

The study[83] describes an interesting reaction sequence including the Sonogashira coupling, propargyl–allenyl isomerization, allenyl–benzyl Claisen rearrangement and [4 + 2]-cycloaddition (Scheme 34). This sequence provides, *e.g.*, a successful synthesis of fused tricyclo[3.2.1.$0^{2,7}$]oct-3-enes **51**.

There are several possible pathways for the reaction of phenols **52** with primary or secondary anilines depending on

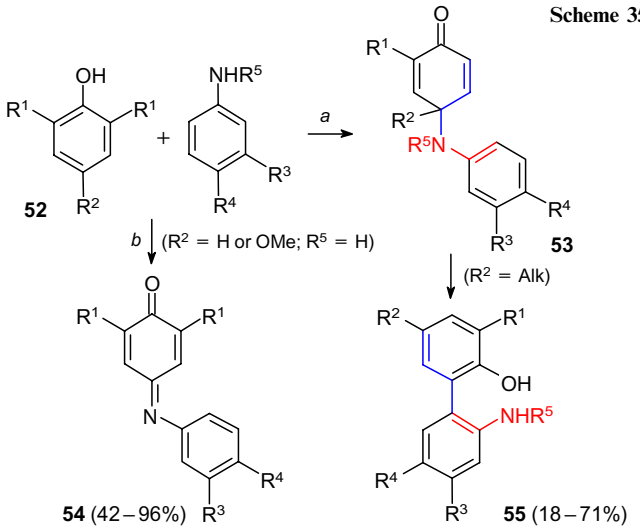
Scheme 34



(*a*) $PdCl_2(PPh_3)_2$ (5 mol.%), CuI (3 mol.%), Et_3N, THF, 60 °C, 8–12 h; X = C, O; R^1 = H, Me; R^2 = H, Me, OMe, F, Br; *n* = 0, 1

51 (72–82%)

Scheme 35

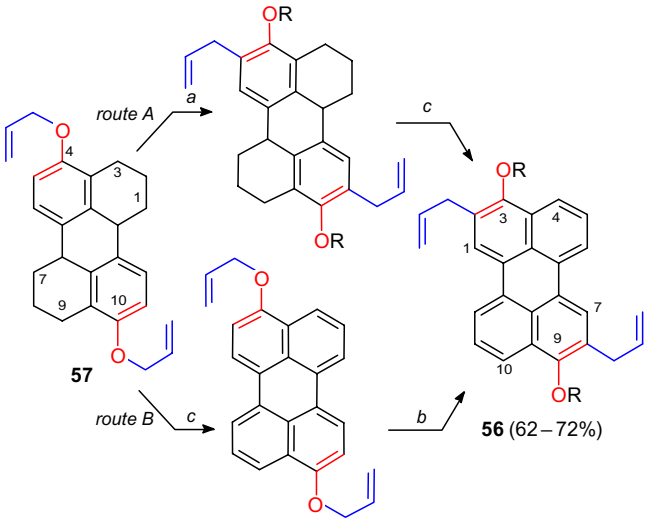


(*a*) Mn[TPP]Cl (1 mol.%), UHP, HFIP, overnight, rt;
(*b*) Fe[TPP]Cl (1 mol.%), Bu^{t}OOH, HFIP, overnight, rt;
R^1 = Me, Bu^t, OMe; R^2 = H, Me, OMe, All;
R^3 = H, OMe, Me; R^4 = OMe, OH, NMe_2;
R^5 = H, Me; UHP is carbamide peroxide (urea hydrogen peroxide clathrate)

the nature of the substituent R^2 (Scheme 35).[84] The rearrangement of intermediates **53** occurs if R^2 is an alkyl group. When the substituent R^2 is a hydrogen atom, dehydrogenation takes place, while with R = OMe, elimination occurs to afford Schiff bases **54**. These reactions are catalyzed by *meso*-tetraphenylporphyrin (TPP) complexes of metal (Fe, Mn, Co) chlorides. Compounds **55** are formed through oxidative amination and a [3,3]-sigmatropic rearrangement of quinone amine **53**.

A combined strategy based on the Friedel–Crafts annulation and the Claisen rearrangement was employed to prepare tetrasubstituted perylenes **56** from di(allyloxy)octahydroperylene **57** (Scheme 36).[85] This result shows that allyloxyperylene readily undergoes the Claisen rearrangement, whereas its partially hydrogenated analogue produces several products under the same conditions.

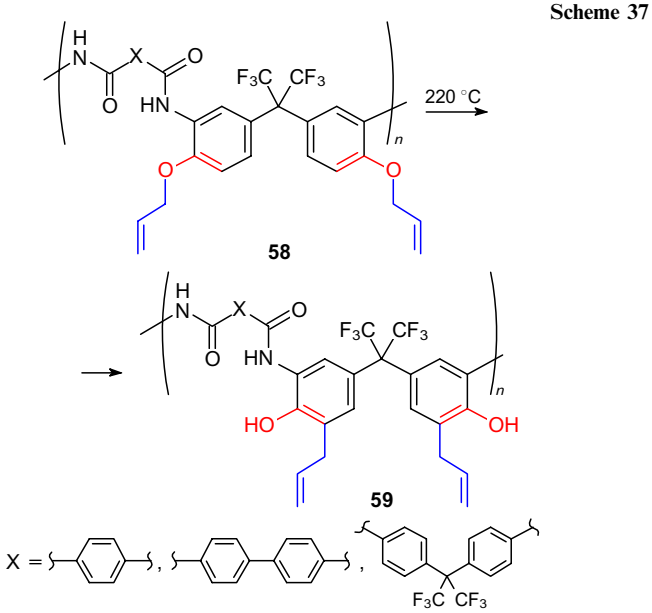
Scheme 36



(*a*) neat, 190 °C; (*b*) Me_2PEG, 180 °C;
2) n-$C_7H_{14}C(O)Cl$, Py, 0 °C to rt; (*c*) chloroanil, PhMe, rt; R = H, $C(O)C_7H_{14}$-n; Me_2PEG is polyethylene glycol dimethyl ether

In recent years, there has been a growing interest in the application of the Claisen rearrangement in the synthesis of modified polymers. It turned out that the rearrangement of polyamide **58** affording compound **59** can occur even in solid state (Scheme 37).[86] As a result, a new method was developed for the synthesis of monomers based on the Claisen rearrangement. The procedure was applied to the preparation of three polyamides and three allylic derivatives bearing various functionalities and of various rigidity. This study demonstrates a great potential of the approach providing the facile and well-established functionalization of the polymer backbone with the aim of creating novel high-performance materials for various appliations.

Scheme 37

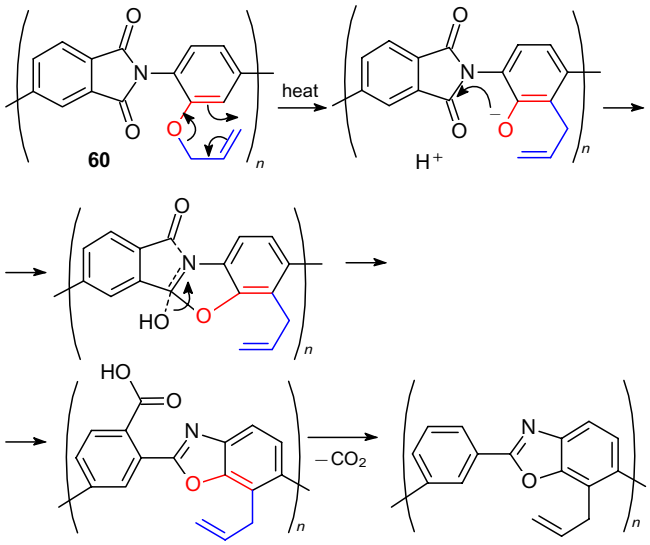


Another specific feature of thermaly rearranged polymers is the prospects of their use in the development of new-generation membrane materials. Such polymers can be prepared by a [3,3]-sigmatropic rearrangement of compound **60** (Scheme 38).[87] At 200 °C, the conversion of functionalized polyimide into polybenzoxazole of more than 97% was achieved. This mechanically stable material is 5 times more permeable than the reference polymer processed under the same conditions.[86]

The Claisen rearrangement of benzyl vinyl ethers is much less known than the rearrangement of allyl ethers, and their synthetic applications remain poorly studied. For instance, the presence of the α-alkoxy substituent in a vinyl moiety is known to facilitate the Claisen rearrangement of benzyl vinyl ether **61**, thus providing an access to diversely substituted phenylacetic acids **62**.[88] Scheme 39 represents two synthetic routes to these products.

A new cascade benzyl-Claisen rearrangement was performed using keteniminium salts.[89] When the benzene ring contains no strong electron-donating or electron-withdrawing substituents R^1, the reaction proceeds *via* the [3,3]-sigmatropic rearrangement to generate an intermediate oxonium ion **A**. The sequence of transformations leads to the formation of α-arylated lactones **63** (Scheme 40). However, if R^1 is, *e.g.*, a strong electron-donating (EDG) or electron-withdrawing (EWG) group, there were no traces of

Scheme 38



rearrangement products **63** in the reaction mixture upon the completion of the reaction. Instead, alkylation products **64a** or **64b** were isolated. The mechanism for the formation of compound **64a** might involve the dissociation of an oxonium intermediate to generate two species, which undergo further recombination. Product **64b** is probably also formed as a result of fragmentation of the oxonium ion; however, in this case, the electron-poor benzylic moiety generates uncharged intermediates.

3.1.1. Aliphatic version

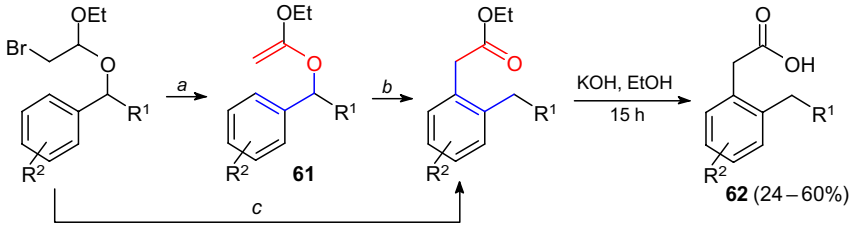
The Claisen rearrangement of allyl vinyl ethers and structurally similar systems is to a certain extent equivalent to the rearrangement of allyl aryl ethers. However, in this case the vinyl moiety is no longer a part of a benzene ring, which provides more options for its influence on the reaction stereoselectivity. Thus, a small number of enantioselective *ortho*-Claisen rearrangement protocols were reported: two studies [90,91] of the last decade concerned with indole compounds (see Schemes 87 and 226 below), and the sole example of an enantioselective *para*-Claisen rearrangement (see Scheme 18). Not to mention that studies are currently underway on tandem transformations based on the Claisen rearrangement involving allyl vinyl ether and novel similar structures, the asymmetric version being particularly actively explored.

The nucleophilic substitution reaction of (*Z*)-2*H*-nonafluoropent-2-ene with the corresponding allylic alcohols gives polyfluorinated allyl vinyl ethers **65**. The latter compounds undergo the Claisen rearrangement at moderate temperatures to afford polyfluorinated homoallylic ketones **66** in quantitative yields (Scheme 41).[92]

Based on tandem transformation including double allylation, ring-closing metathesis and Claisen rearrangement, an effective method to obtain functionalized vinylcyclopropanes **67** has been developed.[93] The reaction begins with O-allylation of α-allyl-α-sulfonyl ketones (Scheme 42).

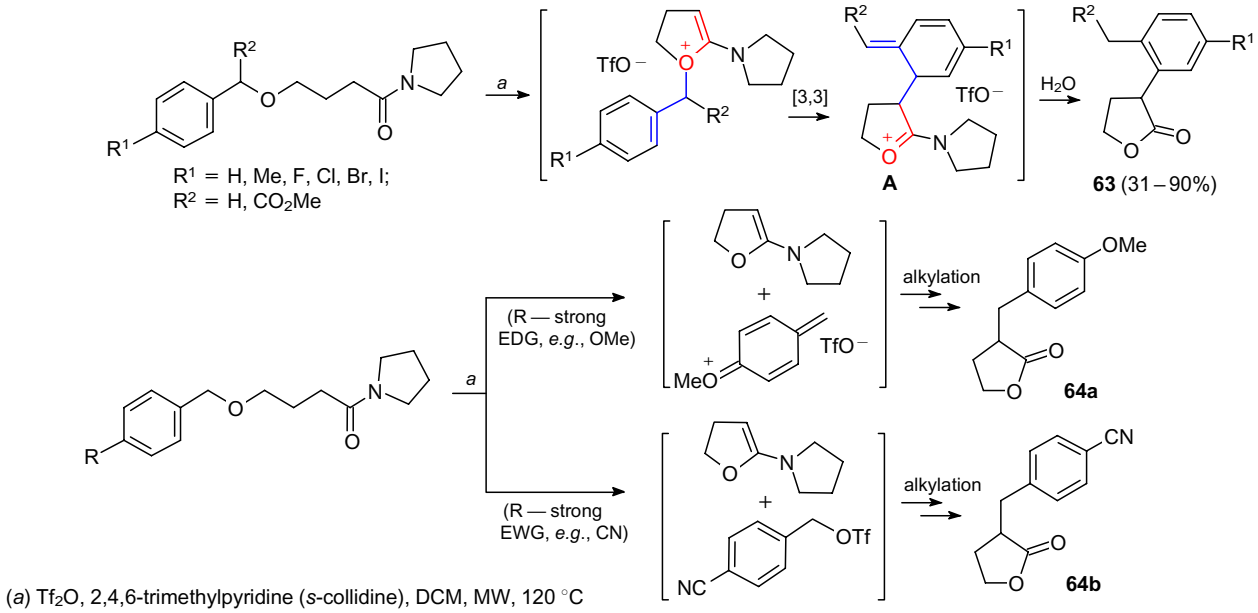
Publications [94–96] describe a new version of the indium-mediated Reformatsky–Claisen tandem rearrangement carried out under ultrasonication (US). In its classical version, this transformation represents the reaction of allyl α-bro-

Scheme 39



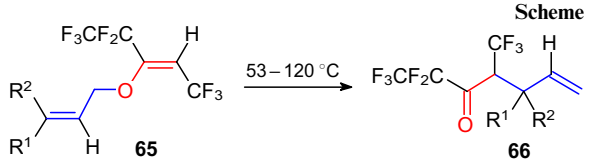
Method A: (*a*) KOBu^t (1.5 equiv.), THF, Δ, 1 h; (*b*) DMF or diglyme, Δ, 15 h;
method B: (*c*) 1) KOBu^t (1.5 equiv.), DMF or diglyme, rt, 0.5 h; 2) DMF or diglyme, 155 °C (oil bath temperature), 15 h; R^1 = H, Me; R^2 = H, Me, Ph, F, Cl, Br, OMe, SMe

Scheme 40



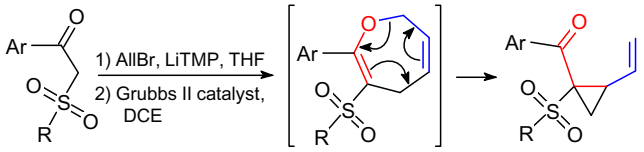
(*a*) Tf_2O, 2,4,6-trimethylpyridine (*s*-collidine), DCM, MW, 120 °C

Scheme 41



R^1 = H, Me; R^2 = Me, Ph

Scheme 42



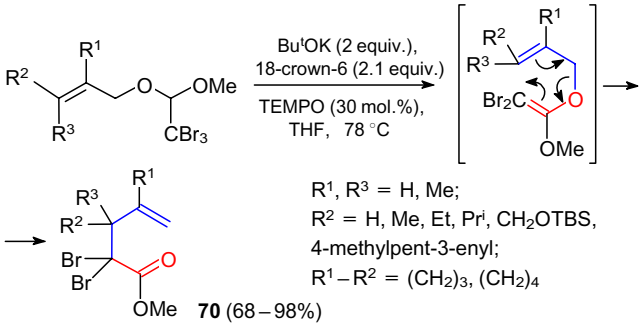
67 (70–84%)

Ar = Ph, 4-PhC_6H_4, 4-FC_6H_4, 2,5-$(MeO)_2C_6H_3$, 4-$O_2NC_6H_4$, 4-MeC_6H_4, 4-$MeOC_6H_4$; R = Me, Ph, 4-MeC_6H_4, 3-MeC_6H_4, 4-FC_6H_4, 4-$Bu^nC_6H_4$, 4-$Bu^tC_6H_4$; LiTMP is lithium 2,2,6,6-tetramethylpiperidide

moacetates with the zinc dust and makes it possible to produce unsaturated carboxylic acids **68** and **69** (compounds with a reduced C–Br bond are formed as minor products). In the non-classical version of the reaction, indium metal and its chloride are used. In the reaction medium they generate monovalent InCl, which immediately reacts with the starting α-bromoacetate. The intermediate **A** can be reduced by another molecule of InCl to monovalent α-indium acetate **B**. Both intermediates can be converted into indium enolate, which is further transformed into silyl ketene acetal. The latter undergoes a rearrangement already at room temperature. Since no rearrangement products were detected in the reaction mixture without the addition of TMSCl and triethylamine, the direct rearrangement of indium enolates can be regarded as unlikely. The Reformatsky–Claisen rearrangement is used to prepare (–)-dihydrosporothriolide (the indium version is depicted in Scheme 43) and 2′,3′-dideoxy-6′-fluorocarbocyclic nucleosides, which are carbovir and abacavir analogues (the classical zinc version).[97]

The transformation of allylic alcohols into mixed acetals followed by the Claisen rearrangement is applicable to the preparation of γ,δ-unsaturated α,α-dibromo-substituted esters **70**. A combination of potassium *tert*-butoxide with 18-crown-6 provides necessary conditions for dehydrobromination, which gives rise to ketene acetal required for the rearrangement (Scheme 44).[98] To avoid the undesirable radical debromination of the starting material, the reaction mixture is supplemented with (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO).

Scheme 44



R^1, R^3 = H, Me;
R^2 = H, Me, Et, Pr^i, CH_2OTBS, 4-methylpent-3-enyl;
R^1–R^2 = $(CH_2)_3$, $(CH_2)_4$

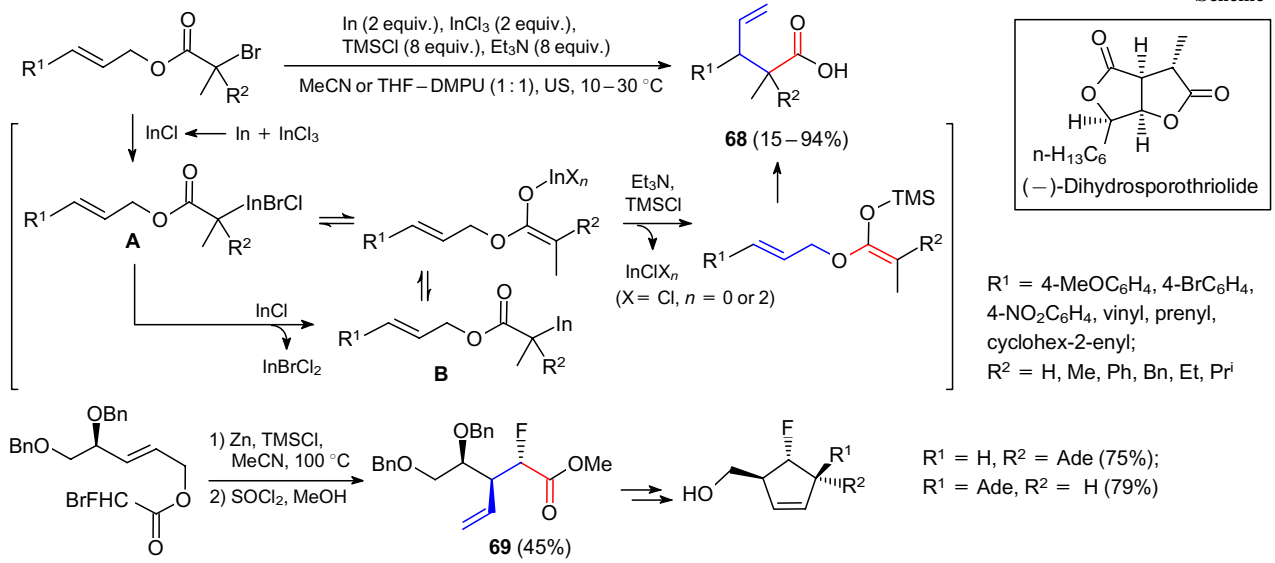
70 (68–98%)

Monosilylated divinyl ethers **71** can be isomerized under the action of a cationic iridium catalyst to afford compounds for the subsequent thermal Claisen rearrangement. As a result, allyl silane derivatives **72** were produced in yields of up to 91% and diastereoselectivity of up to *dr* = 97 : 3 (Scheme 45).[99]

The divergent synthesis of functionalized 2,3-dihydrofurans **73** and 2,3-dihydropyrroles is based on the reaction sequence consisting of a Lewis base-catalyzed hydroalkoxylation (to afford intermediate **A**), the subsequent Claisen rearrangement and the final oxa(aza)-Michael addition (Scheme 46).[100] This tandem process reduces the number of steps and provides the target products in 33–90% yields from readily available allylic cyanohydrins and activated alkynes.

An effective method was developed for the synthesis of 3-methylquinoline-4-carbaldehyde **74** based on the succes-

Scheme 43



68 (15–94%)

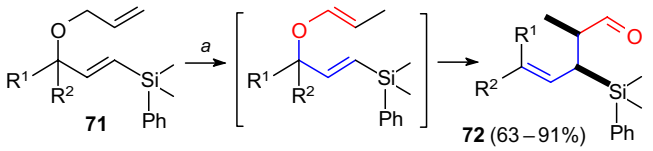
R^1 = 4-$MeOC_6H_4$, 4-BrC_6H_4, 4-$NO_2C_6H_4$, vinyl, prenyl, cyclohex-2-enyl;
R^2 = H, Me, Ph, Bn, Et, Pr^i

(–)-Dihydrosporothriolide

69 (45%)

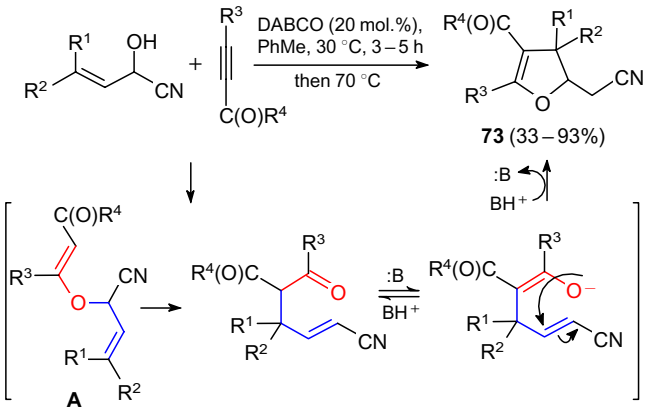
R^1 = H, R^2 = Ade (75%);
R^1 = Ade, R^2 = H (79%)

Scheme 45



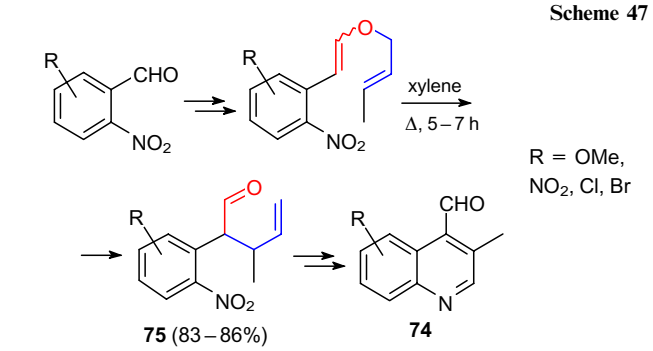
(*a*) 1) $[Ir(COE)_2Cl]_2$, PCy_3, $NaBPh_4$, PhCl; 2) PPh_3, 90 °C;
R^1 = H, Me, Ph; R^2 = Me, Ph, Bu^n, Bu^i, Cy;
R^1–R^2 = $(CH_2)_4$, $(CH_2)_5$, $(CH_2)_2O(CH_2)_2$; Cy is cyclohexyl, COE is cyclooctene

Scheme 46



R^1 = Me, Et, Ph; R^2 = H, Me, Et, Ph; R^1–R^2 = $(CH_2)_4$, $(CH_2)_3$;
R^3 = H, CO_2Me, CO_2Et; R^4 = Ph, OMe, OEt, OBu^t, OBn, (−)-menthyloxy, morpholino; DABCO is diazabicyclo[2.2.2]octane

Scheme 47



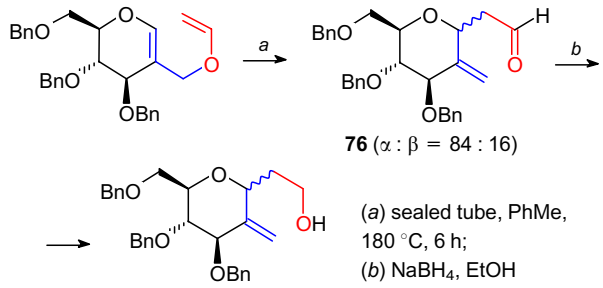
R = OMe, NO_2, Cl, Br

sive Wittig reaction and the Claisen rearrangement.[101] *o*-Nitrobenzaldehydes were used as the starting material. The Claisen rearrangement furnishes 4-pentenals **75**, the subsequent oxidation of the double bond and reductive cyclization afford the final products **74** (Scheme 47). Cyclohexene carbaldehydes can be produced under similar conditions.[102]

An effective approach to the stereoselective synthesis of C(2)-methylene-α- and C(2)-methylene-β-C-glycosides **76** *via* the rearrangement of 2-vinyloxymethyl glycal derivatives is depicted in Scheme 48. Later, this methodology was extended to the diastereoselective synthesis of C(2)-methyl-C-glycosides.[103]

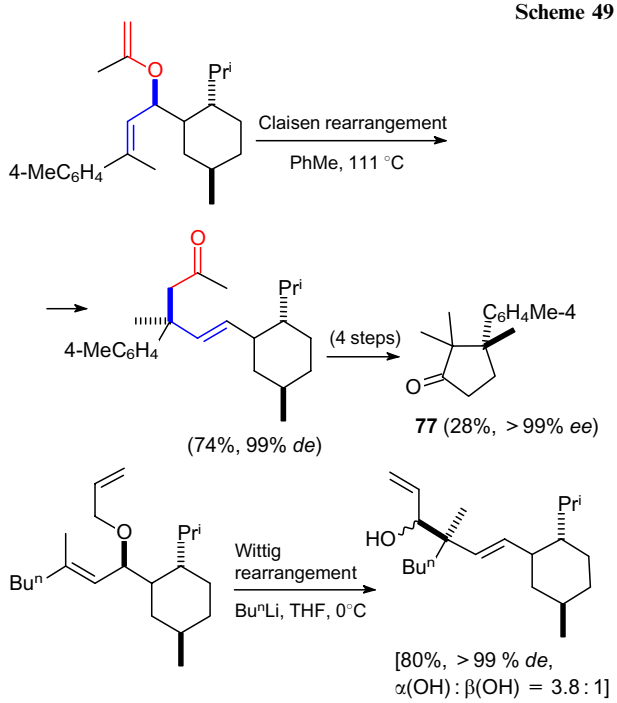
The reaction of menthone and *p*-menthyl-3-carboxaldehyde gave rise to a series of chiral polysubstituted carbonyl compounds, *e.g.*, (+)-cuparenone **77**.[104] In this process, the authors used Claisen and Wittig rearrangements, as illustrated in Scheme 49.

Scheme 48



(*a*) sealed tube, PhMe, 180 °C, 6 h;
(*b*) $NaBH_4$, EtOH

Scheme 49

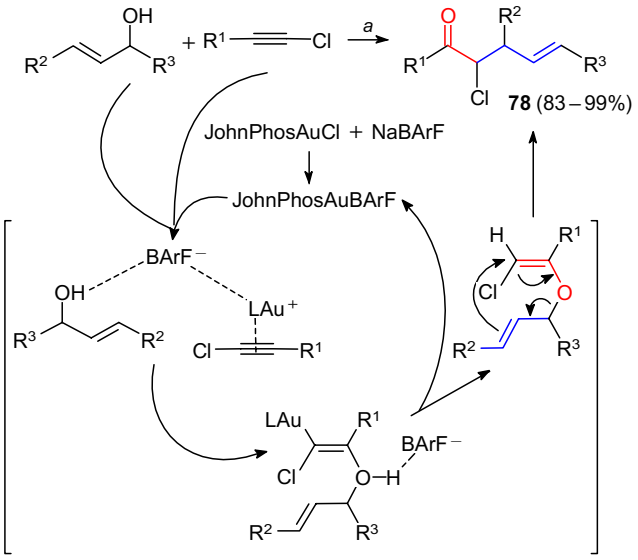


de is diastereomeric excess, *ee* is enantiomeric excess

A current trend in this field of chemistry is the extensive use of gold-containing catalysts.[105–107] This can be exemplified by a recently developed efficient method for the synthesis of γ,δ-unsaturated chloroketones **78**. It is based on a tandem transformation catalyzed by a mixture of JohnPhosAuCl [JohnPhos is 2-(di-*tert*-butylphosphino)biphenyl] and sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBArF). The key steps are the reaction of allylic alcohols with chloroacetylenes followed by the Claisen rearrangement (Scheme 50).[108] It is possible to obtain target products **78** in yields of up to 99% with high stereoselectivity.

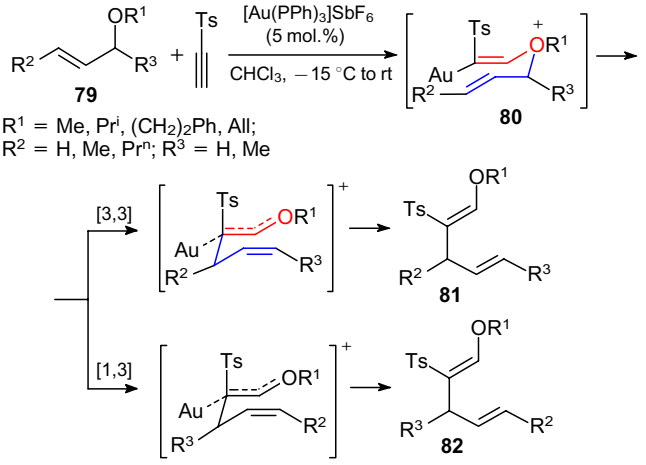
The reaction of allyl ethers **79** with sulfonylacetylenes is catalyzed by gold compounds (Scheme 51).[109] As a result, the products of the rearrangement of intermediate **80** can be formed, such as compound **81** and **82**. A sigmatropic rearrangement can occur through various pathways ([3,3] or [1,3]), with the product ratio as well as the predominant process being determined by the position and structure of substituents in the allyl ether. A cooperative polarization of alkynes by an Au catalyst and a sulfonyl substituent results in an efficient intermolecular tandem carboalkoxylation.

Scheme 50



(*a*) JohnPhosAuCl (1 mol.%), $NaBAr^F_4$ (1 mol.%), DCE, 40 °C;
R^1 = Bu^n, XC_6H_4 (X = 4-Me, 4-Ph, 4-Cl, 4-Br, 3-Br, 2-Br);
R^2 = H, Me, Pr^n, Ph; R^3 = H, Ph, 2-ClC_6H_4, 4-MeC_6H_4, Cy, Bu^i

Scheme 51



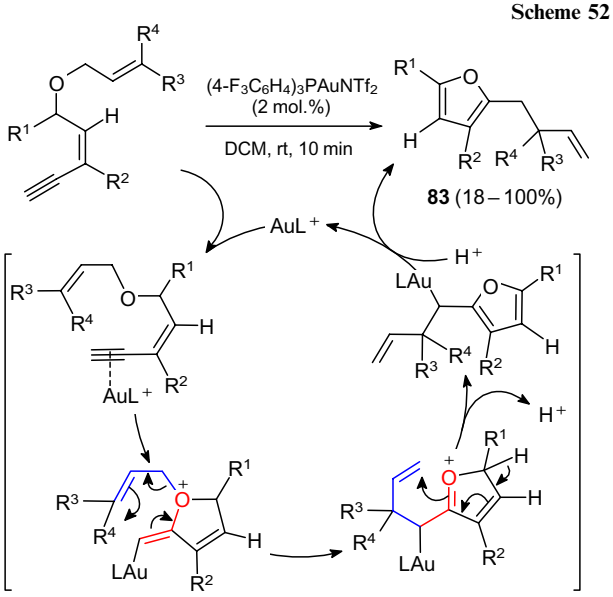
R^1 = Me, Pr^i, $(CH_2)_2Ph$, All;
R^2 = H, Me, Pr^n; R^3 = H, Me

For linear allyl ethers, the rearrangement follows the [3,3]-sigmatropic mechanism, whereas branched allyl ethers, due to the formation of an ion–dipole pair, produce a mixture of [3,3]- and [1,3]-rearrangement products in 18–75% overall yield and a **81**:**82** ratio from 1:1.7 to >20:1.

A series of allyl ethers, bearing an enyne moiety, were converted into polysubstituted furans **83** using a gold-containing catalyst (Scheme 52).[110] It is assumed that this process involves a Claisen-type rearrangement, which allows the efficient generation of quaternary carbon centres under mild conditions.

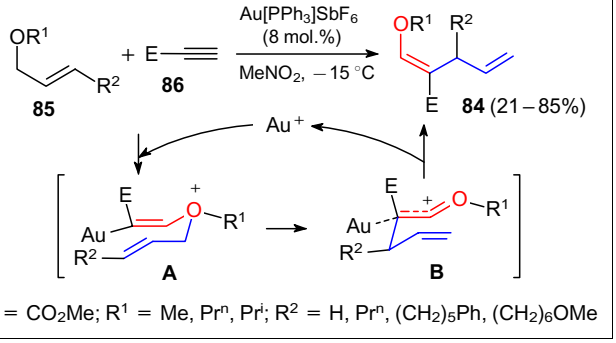
β-Alkoxyacrylates **84** were synthesized by the reaction of allyl ethers **85** with alkynoates **86** (Scheme 53).[111] The process is gold-catalyzed; its plausible mechanism involves the formation of a key intermediate **A**, which rearranges into alkene **B**. Interesting features of this reaction are high *Z*-selectivity and complete chemoselectivity. Thus, no coupling products of alkynes and alkenes were detected in the reaction mixture.

Scheme 52



L is ligand; R^1 = H, Et, Pr^i, Bu^t, vinyl, Ph; R^2 = Me, n-C_5H_{11}, Ph;
R^3 = H, Me, 5-(2-methylpent-2-en)yl, $(CH_2)_2Ph$; R^4 = H, Me;
R^3–R^4 = $(CH_2)_n$ (*n* = 4, 5)

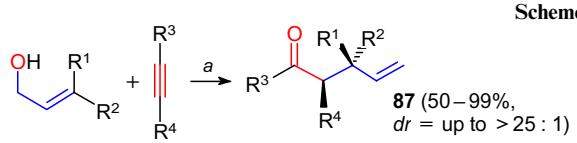
Scheme 53



E = CO_2Me; R^1 = Me, Pr^n, Pr^i; R^2 = H, Pr^n, $(CH_2)_5Ph$, $(CH_2)_6OMe$

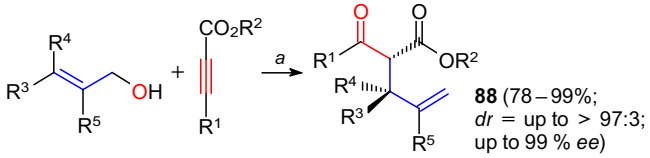
γ,δ-Unsaturated ketones **87** became available using hydroalkoxylation of alkynes with allylic alcohols.[112] Under catalysis with monovalent gold compounds, this reaction affords allyl vinyl ethers, which further undergo a Claisen rearrangement (Scheme 54). Regioselectivity of the process is governed by the nature of substituents in the alkyne. With electron-withdrawing substituents in a molecule, α-aryl ketones (R^4 = Ar) are produced as the major products, whereas with electron-donating substituents, on the contrary, ketones with R^3 = Ar are formed. A similar transformation was later implemented in an asymmetric version. A cascade reaction of alkynyl ethers with allylic alcohols is catalyzed by gold(I) and chiral nickel(II) complexes.[113] A series of acyclic keto esters **88** were obtained in high yields (up to 99%) with high diastereoselectivity (up to 97:3) and enantioselectivity (up to 99% *ee*) under mild conditions. A need for nickel complexes stems from the fact that the monocatalysis with gold compounds will only lead to the coordination of the gold atom by the oxygen atom, resulting in poor enantioselectivity, since the reaction centre is distant from the chiral ligand. The monocatalysis also requires higher temperature (*e.g.*, 120 °C for product **87**). In this case, a catalyst-free side thermal Claisen rearrangement occurs, which adversely affects the reaction selectivity. Both of these drawbacks can be avoided by

Scheme 54



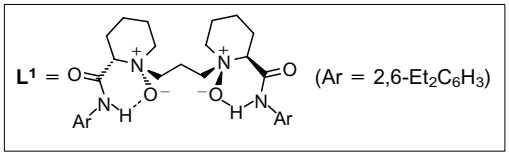
87 (50–99%, *dr* = up to > 25 : 1)

(*a*) IPrAuCl–$AgBF_4$ (5 mol.%), THF, 65 °C, 15 h; then 120 °C, 6 h;
R^1 = H, Me, $CH_2OTBDPS$; R^2 = Me, Ph, n-Oct, prenyl;
R^3 = Me, Et, n-C_6H_{13}, Ph, 4-$MeOC_6H_4$; R^4 = n-C_6H_{13}, Ph, 4-$O_2NC_6H_4$, $(CH_2)_2OMe$, $(CH_2)_2OAc$, $CH_2C(O)CF_3$, CH_2NPhth



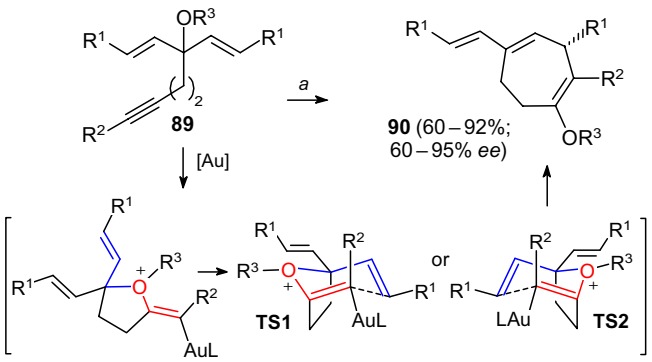
88 (78–99%; *dr* = up to > 97:3; up to 99 % *ee*)

(*a*) IPrAuCl (1 mol.%), $AgSbF_6$ (1.5 mol.%), $Ni(ClO_4)_2 \cdot 6H_2O$ (2.5 mol.%), **L¹** (2.5 mol.%), DCE, 35 °C, 48 h;
R^1 = Ph, 2-FC_6H_4, 3-FC_6H_4, 4-FC_6H_4, 2-$MeOC_6H_4$, 3-$MeOC_6H_4$, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4, 4-NCC_6H_4, 4-PhC_6H_4, 1-Naph, 2-Th; R^2 = Me, Et, Bu^t, Bn; R^3 = H, Me, Cy, 2-$O_2NC_6H_4$, 2-ClC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 2-MeC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-FC_6H_4, 4-BrC_6H_4, 1-Naph, 2-Naph, 2-Th; R^4, R^5 = H, Me;
IPr is 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene,
TBDPS is *tert*-butyldiphenylsilyl, NPhth is phthalimido



introducing a carbonyl moiety into an alyne molecule and supplying the reaction mixture with a chiral Lewis acid (**L**¹) and a source of nickel ions ($NiClO_4$). Then, due to coordination of the carbonyl moiety to the newly formed Ni catalyst, the reaction centre will be located closer to the chiral ligand, which enhance the stereocontrol of the reaction. Moreover, such coordination will further decrease the energy barrier, thus enabling the reaction to occur at a lower temperature.

Scheme 55



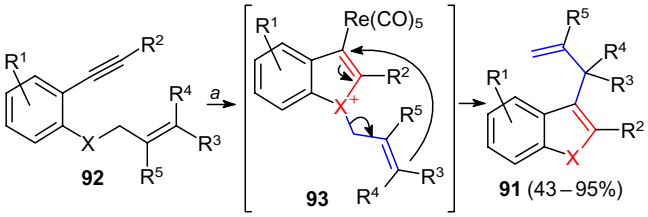
(*S*)-**L²** = (Ar = 3,5-Bu^t_2-4-$MeOC_6H_2$)

(*a*) (*S*)-**L²**$(AuCl)_2$ (3 mol.%), $AgBF_4$ (20 mol.%), MS 4A, PhMe, PhH, −20 °C; R^1 = Me, Bu^t, Ph, 2-MeC_6H_4, 4-MeC_6H_4, 3-$MeOC_6H_4$, 2-$MeOC_6H_4$, 2-FC_6H_4, 2-ClC_6H_4, 1-Naph, 2-Fu; R^2 = CO_2Me, CO_2Bn, CO_2All; R^3 = Me, All; Fu is furyl

A combination of the enantioselective alkoxylation and the Claisen rearrangement produces substituted cycloheptenes in high yields with high enantioselectivity (Scheme 55).[114] A tandem of these reactions was achieved through desymmetrization of 1,4-dienes **89** using the catalytic system (*S*)-DTBM-Segphos$(AuCl)_2$–$AgBF_4$, where (*S*)-DTBM-Segphos is (*S*)-(+)-5,5′-bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole. The reaction can occur *via* either of the two transition states, **TS1** or **TS2**. Under the optimal conditions, compound **90** is formed as the major product; however, the replacement of the solvent with dichloromethane reverses the selectivity (optical antipode of compound **90** is formed in 61% *ee*). With R^1 = Me, the enantioselectivity decreases to 60% *ee*, suggesting a decisive influence of spatial interactions between the catalyst and the substituent R^1 on the resulting stereoconfiguration of the product.

In the past decade, a large number of examples of various transition metal-catalyzed transformations involving sigmatropic rearrangements were reported in the literature. Since transition metals by now proved to be extremely efficient catalysts for hydrofunctionalization of unsaturated carbon bonds,[115–117] metathesis reactions (including the construction of bridged azabicycles[118]) and acetylene–azide click macrocyclization of peptides,[119] the development of synthetic approaches to transition metal-catalyzed sigmatropic rearrangements was quite expected. Thus, indoles and benzofurans **91** were synthesized from compounds **92** using rhenium compounds.[120] This transformation involves a rearrangement of allylic intermediate **93** (Scheme 56). Mechanistic studies revealed that rhenium serves as a π-acidic catalyst to activate alkynes followed by a [3,3]-sigmatropic rearrangement.

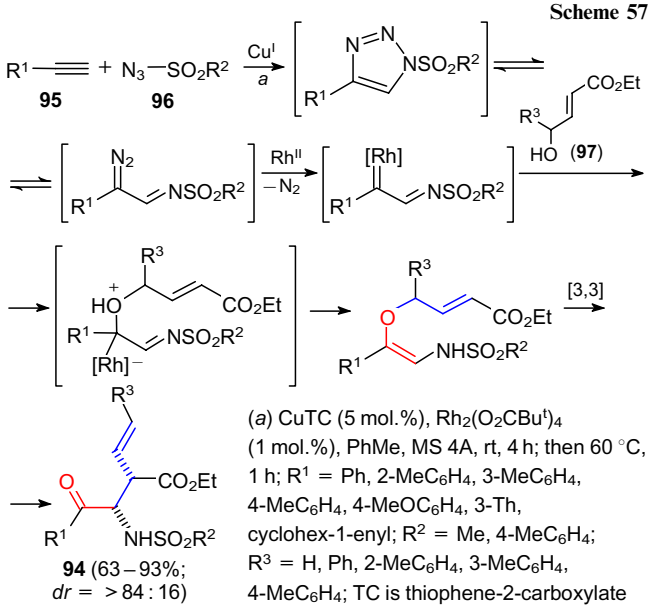
Scheme 56



(*a*) $Re(CO)_5Br$ (5 mol.%), cyclohexane, 70 °C, 15 h;
X = O, NR (R = Me, Bn, CO_2Me); R^1 = H, 6-F, 6-CF_3, 6-Me, 6-CO_2Me (the position of a substituent in the substrate is indicated);
R^2 = H, Me, Bu^n, 4-BrC_6H_4, 3,5-$Cl_2C_6H_3$, 4-MeC_6H_4; R^3 = H, Me;
R^4 = Me, Ph, 2-MeC_6H_4, 4-BrC_6H_4, 3-Th, Pr^n, Bu^i; R^5 = H, Me, Ph

A sigmatropic rearrangement can be used in a one-pot synthesis of polysubstituted γ-oxo-β-amino esters **94** from alkynes **95**, sulfonyl azides **96** and γ-hydroxy-α,β-unsaturated esters **97** catalyzed by copper and rhodium compounds (Scheme 57).[121] The reaction proceeds with high regio- and stereoselectivities. In this catalytic triad, CuI selectively catalyzes cycloaddition of terminal alkyne and sulfonyl azide to give the corresponding 1-sulfonyl-1,2,3-triazole. Following the triazole-ring opening, a rhodium α-iminocarbenoid is generated, which reacts with γ-hydroxy-α,β-unsaturated esters **97** affording allyl vinyl ethers. A rapid [3,3]-sigmatropic rearrangement affords target products **94** in high yields with high diastereoselectivity.

Scheme 57



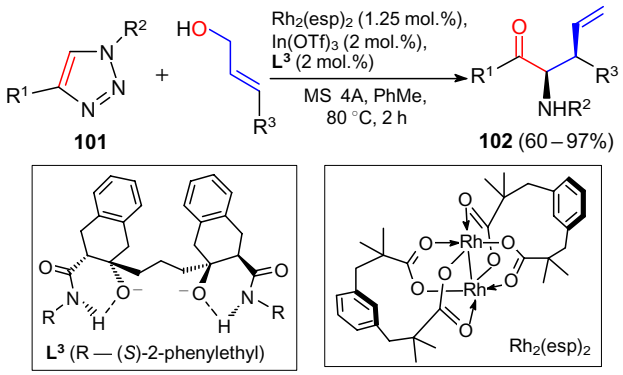
A similar approach was implemented in the synthesis of 2-substituted 2-amino ketones **98** (Scheme 58).[122] *N*-Sulfonyl-1,2,3-triazoles **99** and allylic alcohols **100** were used as the starting materials. The reaction is initiated by the insertion of α-imino carbene into the O–H bond of an alcohol to afford intermediate 2-alkenoxy enamide. This is followed by a thermal [3,3]-sigmatropic rearrangement, which yields 2-allyl-2-amino ketone **98**. With the use of enantiomerically pure allylic alcohol **100b** and triazole **99a**, the reaction proceeds in a stereoselective manner. The double bond formed after the rearrangement has exclusively a *E*-configuration. The above methodology was successfully employed in the synthesis of (−)-α-conhydrine.

The study [123] describes the first example of a tandem catalytic reaction, which includes the insertion and asymmetric Claisen rearrangement involving *N*-sulfonyl-1,2,3-triazoles **101** and allylic alcohols (Scheme 59). The authors made use of a system comprising an achiral rhodium salt and a chiral indium complex. This approach provides a convenient route to a variety of enantioenriched derivatives of β(γ)-unsaturated amino acids **102** in yields of up to 99% with excellent diastereo- and enantioselectivities (*dr* = >95 : 5, *er* = 98 : 2).[123] The Claisen rearrangement also serves as an intermediate step in other syntheses of unsaturated amino acids.[124, 125]

An effective approach was developed to convert diallyl ethers **103** into cyclopentanones **104**.[126] The reaction is promoted by a cationic Rh^I complex and the dppf ligand (1,1′-bis(diphenylphosphino)ferrocene), which catalyze the isomerization of diallyl ether into allyl vinyl ether followed by the Claisen rearrangement. The partial participation of the cationic rhodium complex in the rearrengement is supported by the fact that the replacement of the dppf ligand with (*R*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) significantly decreases the yield of compounds **105** (10% yield, 14% *ee* enantioselectivity for R1 = Ph, R2 = Me). Next, the insertion of the rhodium atom into the C–H bond of the aldehyde and the *endo*-addition of rhodium hydride to a multiple bond take place followed by the reductive elimination. As a result, substituted cyclopentanones **104** are produced in moderate yields (Scheme 60).

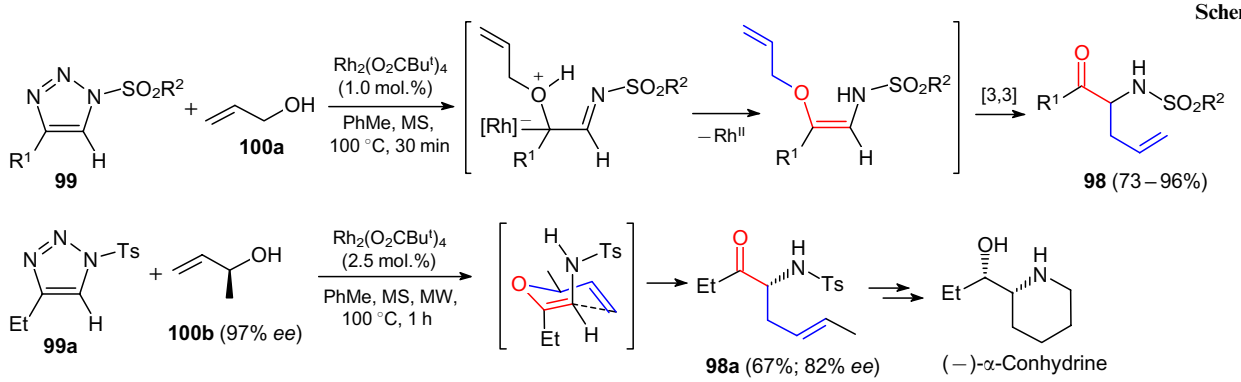
A new method for the synthesis of γ,δ-unsaturated aldehydes bearing a pyrrolidone moiety at the α-position was developed in the study.[127] This approach involves a copper-catalyzed coupling between β-iodoenamide derivatives and allylic alcohols to give β-allyloxyenamide derivatives (Scheme 61). The latter compounds undergo the Claisen rearrangement upon heating and form target products **106** as a mixture of *anti* and *syn* isomers in a ratio of 1.8 : 1 to 1 : 1.5 in a overall yield from 5 to 90% depending on the nature of substituents and reaction conditions (solvent and temperature).

Scheme 59



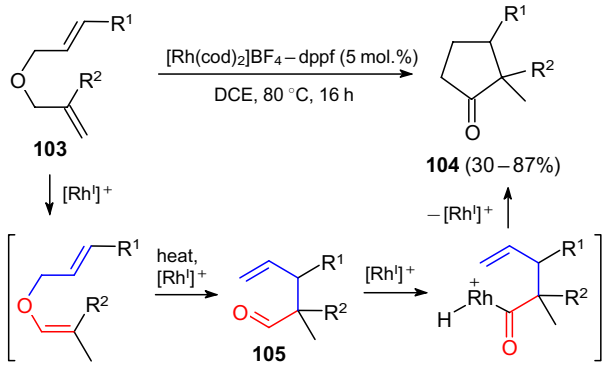
R1 = Ph, 4-MeC6H4, 4-MeOC6H4, 4-FC6H4, 4-ClC6H4, 4-BrC6H4, 4-F3CC6H4, 3-FC6H4, 3-MeOC6H4, 2-Th, 1-Naph, Bn, Pr^n, (CH2)2Ph, cyclohex-1-enyl; R2 = Ts, Ms;
R3 = CO2Me, CO2Et, CO2Pr^i, CO2Bu^t, Bz

Scheme 58



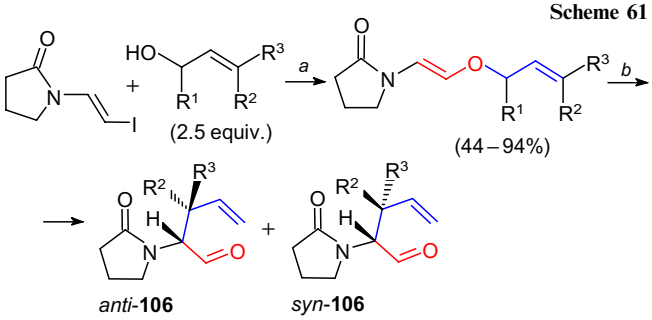
R1 = Ph, 4-MeC6H4, 4-PhC6H4, 4-MeOC6H4, 4-F3CC6H4, n-C6H13, Bu^i, OEt, 3-Th; R2 = 4-MeC6H4, 2-Naph, Me, Bu^n, Bn, (CH2)2TMS

Scheme 60



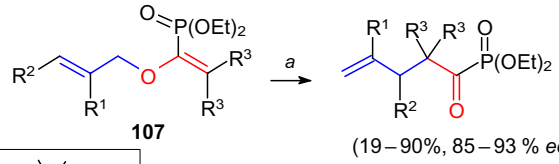
R^1 = Ph, 4-MeOC$_6$H$_4$, 4-F$_3$CC$_6$H$_4$, 4-BrC$_6$H$_4$, 3-ClC$_6$H$_4$, 2-Naph, 2-MeOC$_6$H$_4$, 2-MeC$_6$H$_4$, 2-Fu, Bu^n,
R^2 = H, Me, Ph; cod is cycloocta-1,5-diene

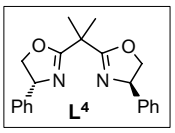
Scheme 61



(*a*) CuI (50 mol.%), DMEDA (80 mol.%), Cs_2CO_3 (4 equiv.), THF (2.0 M), 55 °C, 24 h; (*b*) solvent, *T*, 24 h;
R^1 = H; R^2 = H, Me; R^3 = Pr^n, prenyl; solvent = DCM, THF, PhH, PhMe, *o*-xylene; *T* = 40 – 153 °C

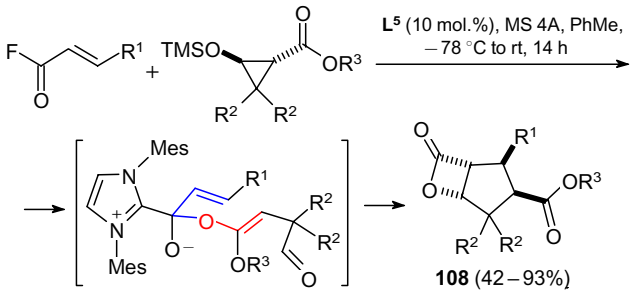
Scheme 62

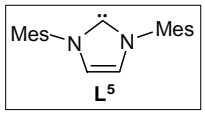




(*a*) Cu(OTf)$_2$ (5 mol.%), **L^4** (6 mol.%), DCM, 15 – 30 °C, 4 – 170 h; R^1 = H, Me, Br; R^2 = Ph, n-C$_6$H$_{13}$; R^3 = Me; R^3 – R^3 = $(CH_2)_n$ (*n* = 4, 5)

Scheme 63





R^1 = Ph, 2-MeOC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-BrC$_6$H$_4$, 4-NO$_2$C$_6$H$_4$, 2-Fu, n-C$_5$H$_{11}$;
R^2 = Me; R^2 – R^2 = $(CH_2)_n$ (*n* = 4, 5, 6);
R^3 = Et, Ph, 4-MeOC$_6$H$_4$, 2,4-(MeO)$_2$C$_6$H$_3$;
Mes is 2,4,6-trimethylphenyl (mesityl)

The copper-catalyzed enantioselective Claisen rearrangement was carried out for the easily available enol phosphonates **107** (Scheme 62).[128,129] The commercially available bis(oxazoline) ligand **L^4** was used as a chiral ligand. It was shown that the process is significantly accelerated by microwave heating. Examples of using phosphorus-containing moieties to stabilize carbanion-accelerated Claisen rearrangements were also reported in the literature.[130] This strategy provides high stereo- and regioselectivities and also leads to an decrease in the reaction time at room temperature.

Another way for implementation of catalyzed transformations, which was extensively studied in recent years, is organocatalysis, *e.g.*, using heterocyclic carbenes. It was shown[131] that *N*-heterocyclic carbenes (NHC) are commonly applied in homogeneous catalysis both in the individual state and as complexes with transition metals. Thus, the NHC-catalyzed Claisen rearrangement gives rise to highly functionalized β-lactones **108** in a stereoselective manner.[132] This reaction proceeds with high diastereoselectivity (*dr* = > 20 : 1) and affords a wide range of fused β-lactones derived from silylated cyclopropanols (Scheme 63).

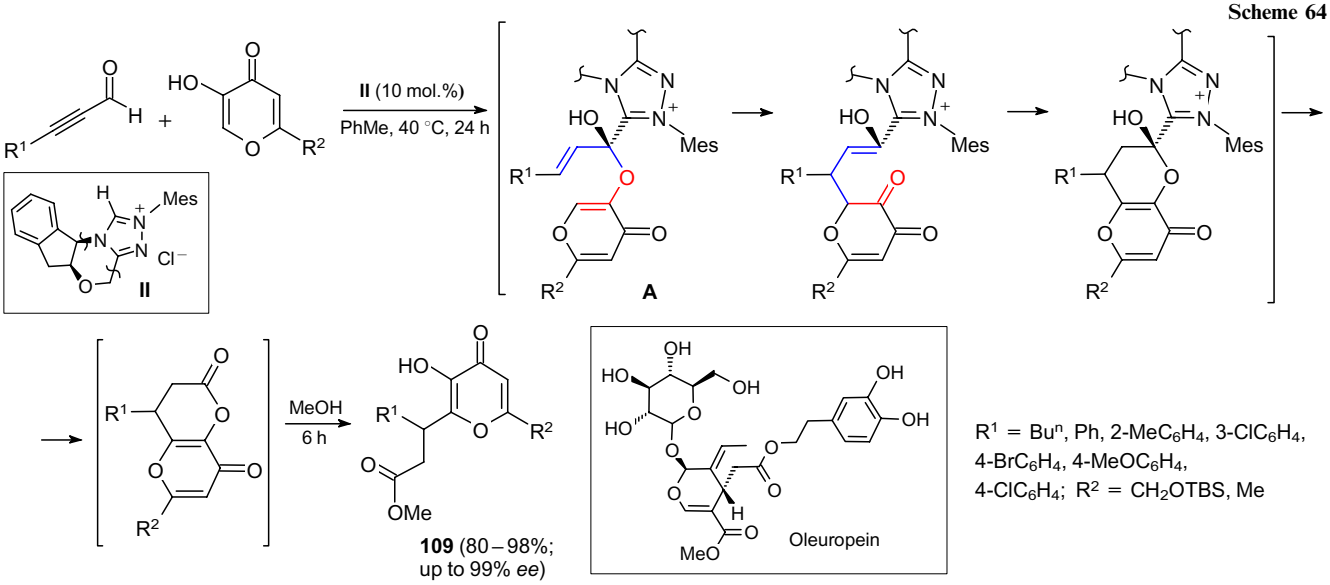
Chiral catalysts provide excellent enantioselectivities of Claisen rearrangements.[133–135] For example, the reaction of chiral *N*-heterocyclic carbene catalyst **II** with α,β-unsaturated aldehyde yields a catalytically generated α,β-unsaturated acyl azolium intermediate **A**. The latter species is involved in a highly enantioselective annulation to give dihydropyranone derivatives **109**.[136] This approach makes it possible to implement the enantioselective synthesis of natural glycosylated seco-iridoid oleuropein (Scheme 64). Chiral guanidines can also serve as chiral catalysts for the Claisen rearrangement.[137]

Another example of using the Claisen rearrangement in the synthesis of natural compounds is the preparation of mutisianthol and its epimer.[138] The multi-step protocol includes the rearrangement of allyl vinyl ether **110** giving compound **111** followed by the reaction of the latter with isopropyltriphenylphosphorane (Scheme 65). Other key steps of this transformation are palladium-catalyzed intramolecular 5-*endo*-*trig* Heck cyclization, demethylation and chemoselective reduction of a double bond.

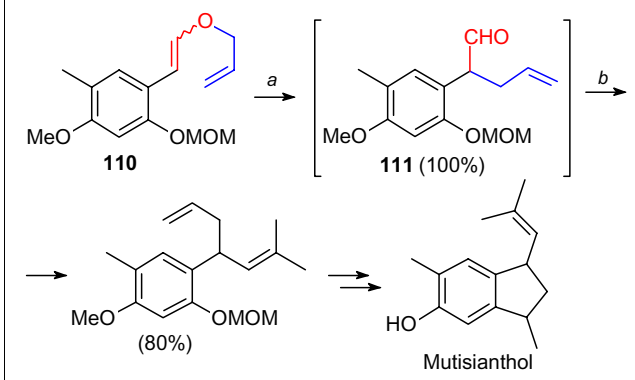
A similar rearrangement was implemented in the total synthesis of (*R*)- and (*S*)-arundic acids from aldehyde **112** (Scheme 66).[139] These compounds can be used to design anti-Alzheimer agents. The ratio of their precursors, isomers **113a**,**b**, varies from 46 : 44 to 73 : 18 and is governed by the conditions of the rearrangement of allyl vinyl ether **114** to aldehyde **115**.

Penostatins are a family of secondary metabolites isolated from the fungus *Penicillium* sp. OUPS-79, which is derived from the marine algae *Enteromorpha intestinalis*. Penostatins I and F are primarily of interest because they have the same absolute stereoconfiguration of the hydroxy group at the C(5) atom and the opposite configuration of the remaining four stereocentres. Among natural compounds of the same family such stereoisomers are quite rare, thus raising the question as to how the said configuration can appear in a living organism. It is hypothesized that penostatins I and F are generated in nature *via* a spontaneous [3,3]-sigmatropic rearrangement

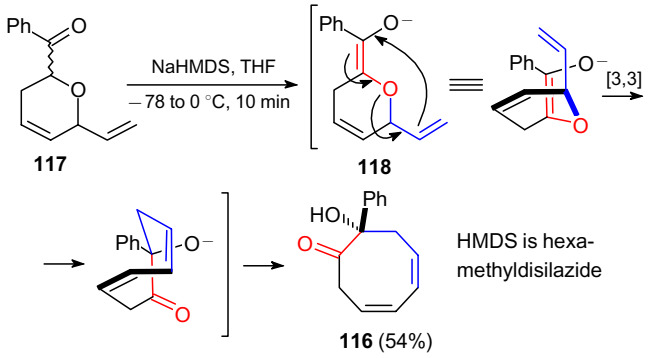
Scheme 64

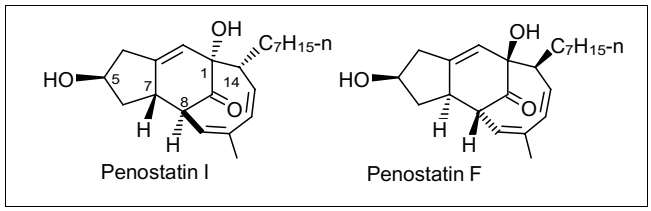


Scheme 65



Scheme 67

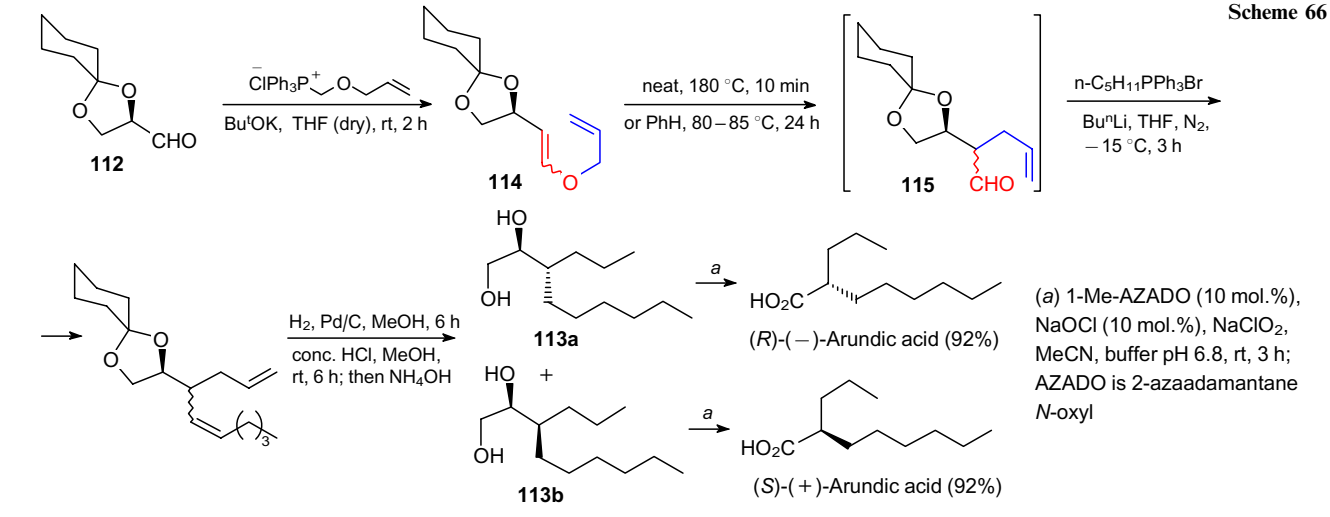




(Scheme 67).[140] To confirm this assumption, the model synthesis of cyclooctadienone **116** from 6-benzoyl-2-vinyldihydropyran (**117**) was performed. Thus, enolate **118** was subjected to the anionic oxy-Claisen rearrangement giving the target product.

An enantioselective synthetic approach to (−)-9,10-dihydroecklonialacton B containing a 14-membered ring was based on the catalytic asymmetric Claisen rearrangement of compound **119**. Using the copper-containing chiral

Scheme 66



catalyst **III**, it is possible to perform a key step with high diastereo- and enantioselectivities (Scheme 68).[141] This approach was also used to prepare a series of medium-ring compounds.[142]

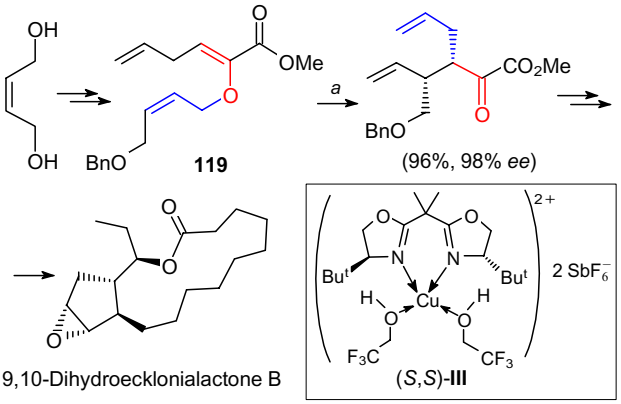
A total synthesis of enantiomerically pure lavandulol pheromones from readily available starting materials represents another example of an effective use of a [3,3]-sigmatropic rearrangment in the synthesis of natural compounds (Scheme 69).[143] This strategy implies a sequence of a proline-catalyzed asymmetric aminooxylation, the [3,3]-Claisen rearrangement of compound **114** and reduction of intermediate **115** (the overall yield of isomers was 89–96%).

Neurymenolides are α-pyrone macrolides isolated from the Fijian red algae *Neurymenia fraxinifolia*, which are active against methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium* strains. The macrocyclic core of neurymenolide A was constructed based on protected tetrahydro-2*H*-pyran-2,4,5-triol *via* the Claisen rearrangement of lactone **120** as a key step (Scheme 70).[144] The yield of rearrangement product **121** varied from 61 to 87% based on the results of a series of experiments.

The synthesis of hydroxylated vinyl-substituted nine-membered lactone **122** from tartaric acid was performed in five steps (Scheme 71).[145] The key step was the Claisen rearrangement spontaneously occurring with the C_2-symmetric ketene acetal **A**. These nine-membered lactones are potential precursors of analogues of eleutherobin and other natural compounds.

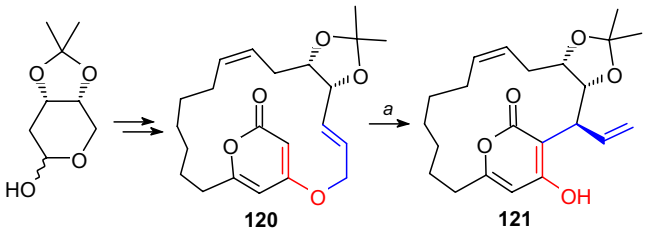
Similar reactions were used to synthesize eunicellins. A key moiety for the preparation of the resulting nine-membered lactone **123** was pepared by the sigmatropic rearrangement of the intermediate ketene acetal **A** (Scheme 72).[146] The use of selenium-based reactants provides a good scalability of the procedure while retaining high yields (up to multi-gramm amounts) of the target lactone.

Scheme 68



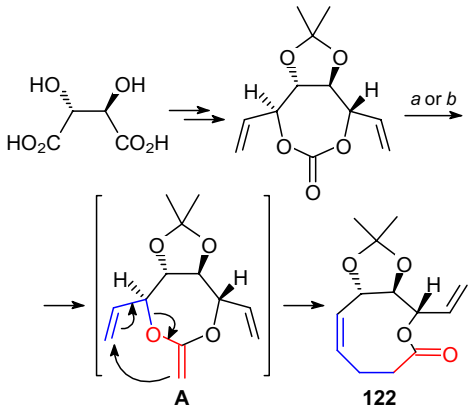
(*a*) (*S*,*S*)-**III** (0.1 equiv.), DCE, rt, 16 h

Scheme 70



(*a*) K_2CO_3, DCB, 150 °C

Scheme 71



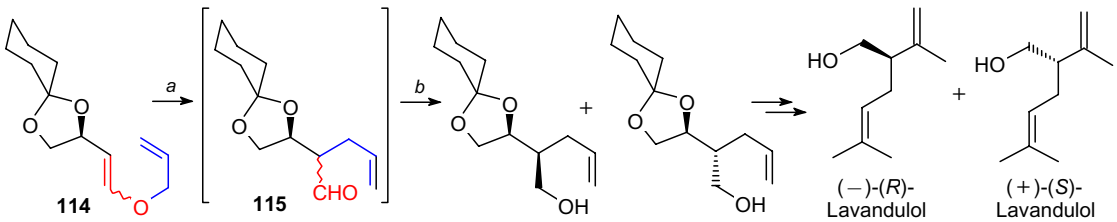
(*a*) Cp_2TiMe_2, THF, MW, 130 °C, 30 min (15–28%);
(*b*) Tebbe reagent, DMAP, MS 4 Å,THF, 0 to 25 °C,
4 h (35–57%); Cp is cyclopentadienyl

The tandem oxyanionic 5-*exo*-*dig*-cyclization–Claisen rearrangement provides a convenient route to various seven-membered carbocycles. This microwave-assisted process was used as a key step in the synthesis of several natural compounds, including frondosins A, B and C.[147] Scheme 73 illustrates the main reactions, including the [3,3]-rearrangement to afford tetracycle **124**, which was subsequently converted into frondosin C and its 8a-epimer. The sigmatropic rearrangement was also implemented to obtain spiroidral triterpenoids.[148]

The synthesis of (+)-decytospolide A from the readily available chiral reagent tri-*O*-acetyl-D-glucal involves the [3,3]-sigmatropic rearrangement as one of the key steps giving product **125** in high yield (Scheme 74).[149]

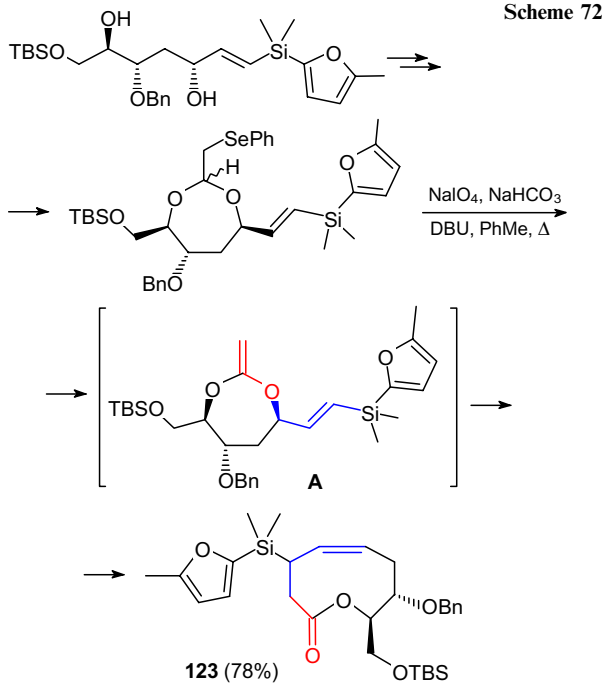
The corresponding ester was transformed to obtain functionalized dibenzo[*a*,*c*]cycloheptene **126** (Scheme 75).[150] A domino sequence included $MoCl_5$-promoted oxidative cyclization and the subsequent generation of the cationic intermediate **A**, which reacts with esters followed by the [3,3]-sigmatropic rearrangement to form compound **126** containing the metasequirin B skeleton.

Scheme 69



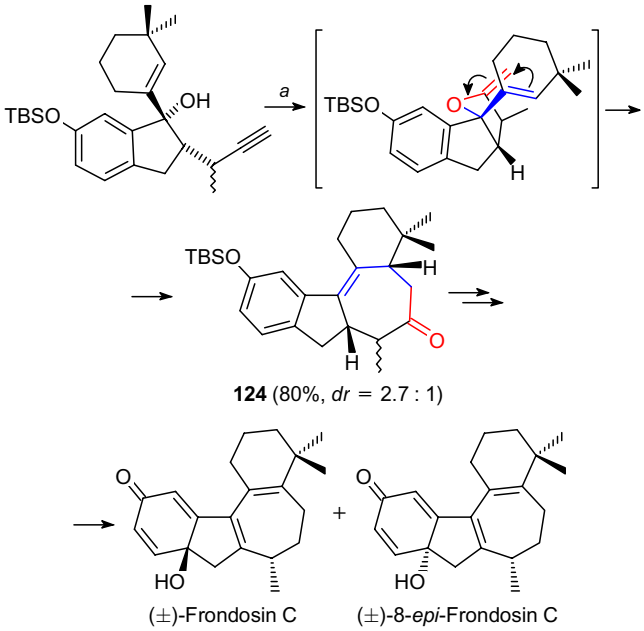
(*a*) neat, 180 °C, 10 min or PhH, 80–85 °C, 24 h;
(*b*) $NaBH_4$, MeOH (aq.), 0 °C, 45 min

Scheme 72



123 (78%)

Scheme 73



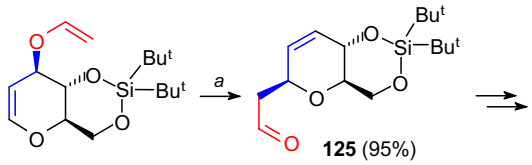
124 (80%, *dr* = 2.7 : 1)

(±)-Frondosin C (±)-8-*epi*-Frondosin C

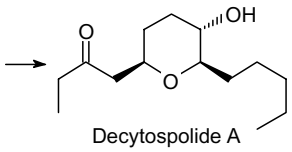
(*a*) phenetole, MeLi (10 mol.%), MW, 210 °C, 40 min

Diazocarbonyl derivatives proved to be multifunctional building blocks for the synthesis of compounds with various biological activities.[151] In particular, the synthesis of the sesquiterpenoid pericondianone A can be accomplished through the reaction of diazo ketone **127** with crotyl alcohol (Scheme 76).[152] The final major diastereomer in this reaction is determined by the configuration of the double bond of the unsaturated alcohol. For *trans*-crotyl alcohol, the rhodium-mediated insertion of a carbenoid into the O–H bond can be followed, already at room temperature, by the Claisen rearrangement to afford diastereomer (2*S*)-**128**. In this case, the diastereomeric ratio is slightly shifted towards the said product, despite the fact that the starting *trans*-crotyl alcohol contained as low as 5% of the *cis*-isomer. This can be attributed to the possible occurrence of the reaction not only *via* **TS1** transition state with a chair conformation but also *via* the transition state featuring the *twist* conformation of the allyl vinyl moiety (not shown in Scheme 76). Diastereomers **128** can not be separated by column chromatography. The [1,2]-allyl shift leads to compounds (2*S*)-**129**, which are unsuitable for the preparation of pericondianone because of the opposite stereoconfiguration of the methyl group. However, the replacement of *trans*-crotyl alcohol with its *cis* isomer gives compound

Scheme 74



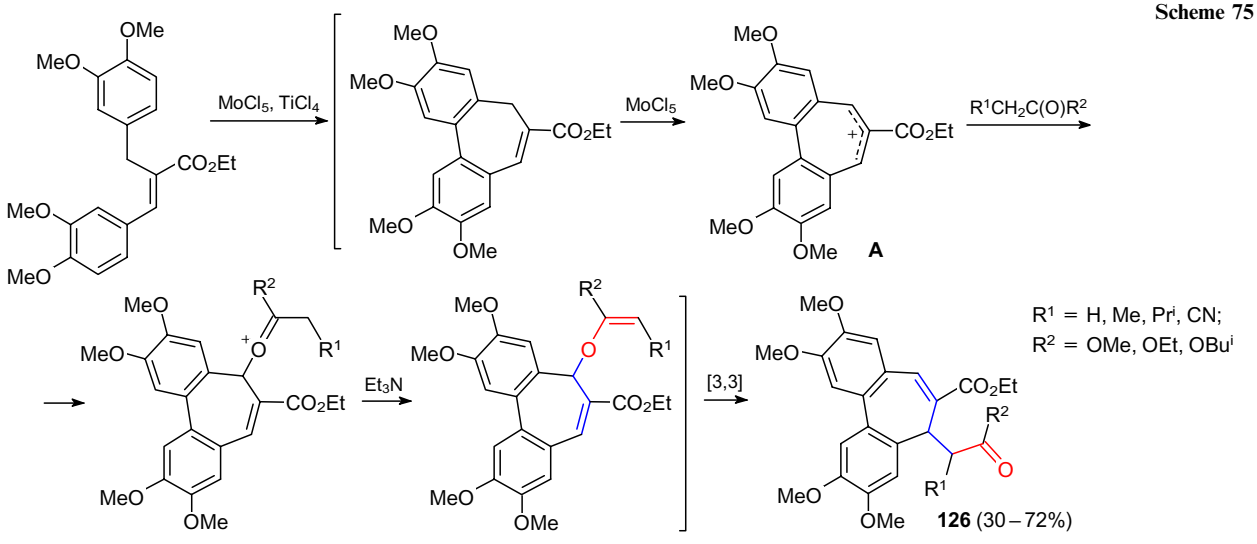
125 (95%)



Decytospolide A

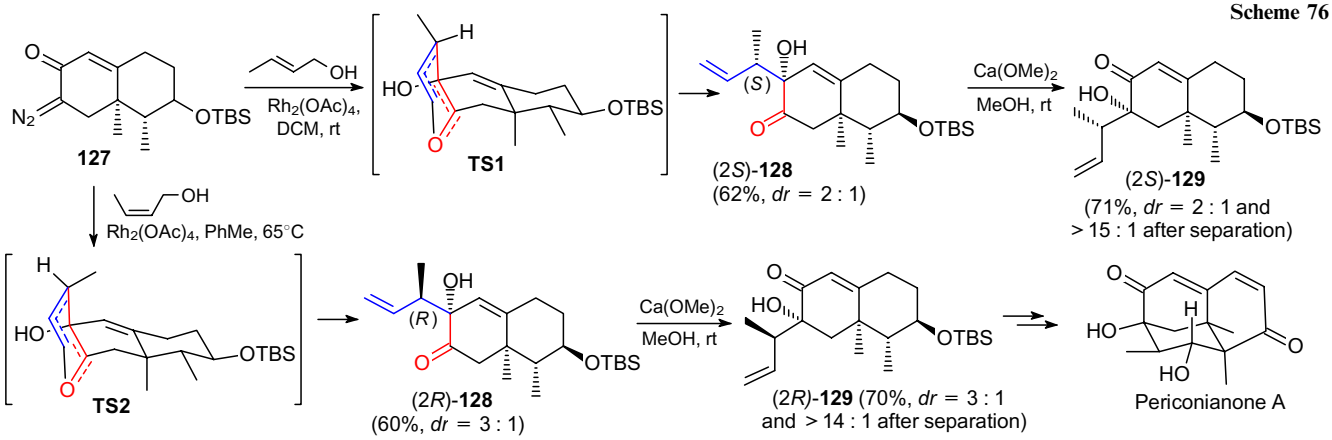
(*a*) sealed tube, PhMe, 185 °C, 6 h

Scheme 75



126 (30–72%)

Scheme 76



(2*R*)-**128** (mainly through **TS2** transition state) having the desired configuration of the methyl moiety, with the diastereomeric ratio increasing by one and a half times towards the target isomer. In this case, the reaction requires heating to 65 °C. The final products, (2*S*)-**129** and (2*R*)-**129**, can be separated by column chromatography, and diastereomer (2*R*)-**129** can be further used to obtain periconianone A.

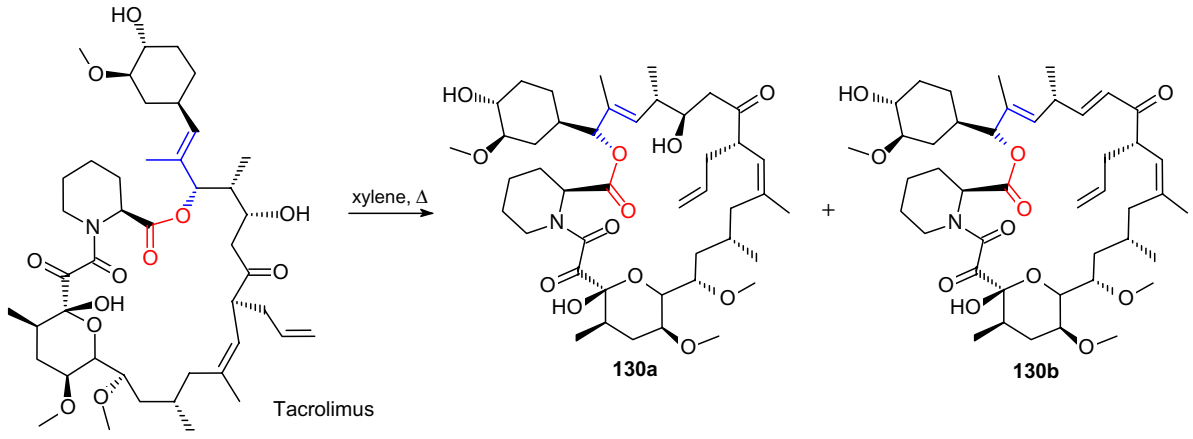
Transformations, including the thermal sigmatropic rearrangement, of the macrocyclic lactone tacrolimus, which is a well-known immunosuppressive drug produced by certain actinobacteria *Streptomyces* have been reported (Scheme 77).[153] Thus, thermolysis of tacrolimus results in the ring-expansion *via* a [3,3]-sigmatropic rearrangement of the allyl ester moiety followed by the loss of water from the β-hydroxy ketone moiety. Methods for detecting compounds **130a**,**b** and understanding of the mechanism for their formation are of interest, primarily, for the identification of the tacrolimus degradation products,including those in commercial preparations.

Substituted cyclobutene **131** can be synthesized by the microwave-driven [3,3]-sigmatropic rearrangement (Scheme 78).[154] The starting materials were polysubstituted cyclobutenes **132** bearing the (*E*,*E*)-dimethyl 2,2′-(cyclobutene-1,2-diylidene)diacetate structural motif. High reactivity of cyclobutanes **132** is due to steric strain. Their reactions with secondary amines afford cyclobutane-substituted analogues of amino acids **133** in yields of up to 95% with high diastereoselectivity (*dr* up to 99 : 1).

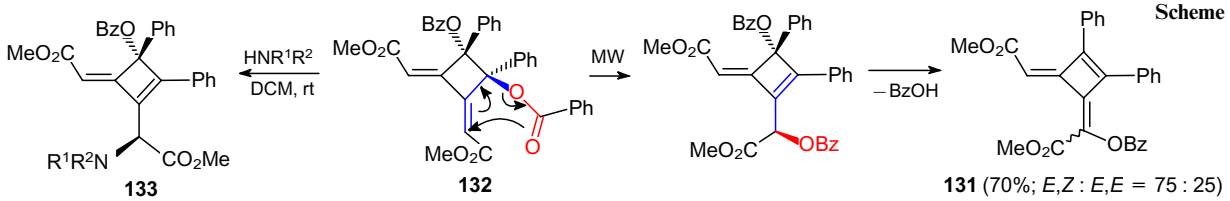
A one-pot synthesis of diaryldicarboxylic acids **134** was based on the microwave-assisted three-component reaction involving amino acid, aromatic aldehyde and primary alcohol.[155] This is a diastereoselective process, which was confirmed by X-ray diffraction analysis of the products. The resulting acids were isolated as sodium salts by the direct precipitation from the reaction mixture. Diastereospecificity of the reaction is provided by the [3,3]-sigmatropic rearrangement. Note that dicarboxylic acids **134** are readily converted into the corresponding δ-lactones (Scheme 79).

The rearrangement of allyl acetate **135** was implemented to prepare dihydroxyvitamin D_3.[156] Scheme 80 illustrates the key step of the synthesis representing the stereocon-

Scheme 77

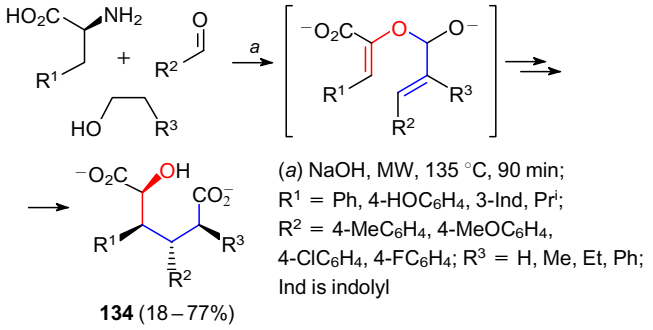


Scheme 78



R^1 = Me, All, Bn, PMB; R^2 = All, Bn, PMB; $R^1–R^2$ = $(CH_2)_4$, $(CH_2)_2O(CH_2)_2$; PMB is *p*-methoxybenzyl

Scheme 79



(*a*) NaOH, MW, 135 °C, 90 min; R^1 = Ph, 4-HOC_6H_4, 3-Ind, Pr^i; R^2 = 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-FC_6H_4; R^3 = H, Me, Et, Ph; Ind is indolyl

134 (18–77%)

trolled introduction of a hydroxy moiety at the 24 position *via* palladium-induced [3,3]-sigmatropic rearrangement. This affords a mixture of diastereomeric products **136a**,**b** (75% overall yield, 15 : 85 ratio) and **137a**,**b** (15%, 20 : 80), where only one product (**136b**) features the required configuration. Another example of a rearrangement induced by a palladium complex is the synthesis of (+)-crocacin C (see Scheme 80).[157] Roche ester (**138**), used as the starting reagent, was converted into compound **139** in several steps followed by its [3,3]-sigmatropic rearrangement.

3.1.2. Heteroaromatic version

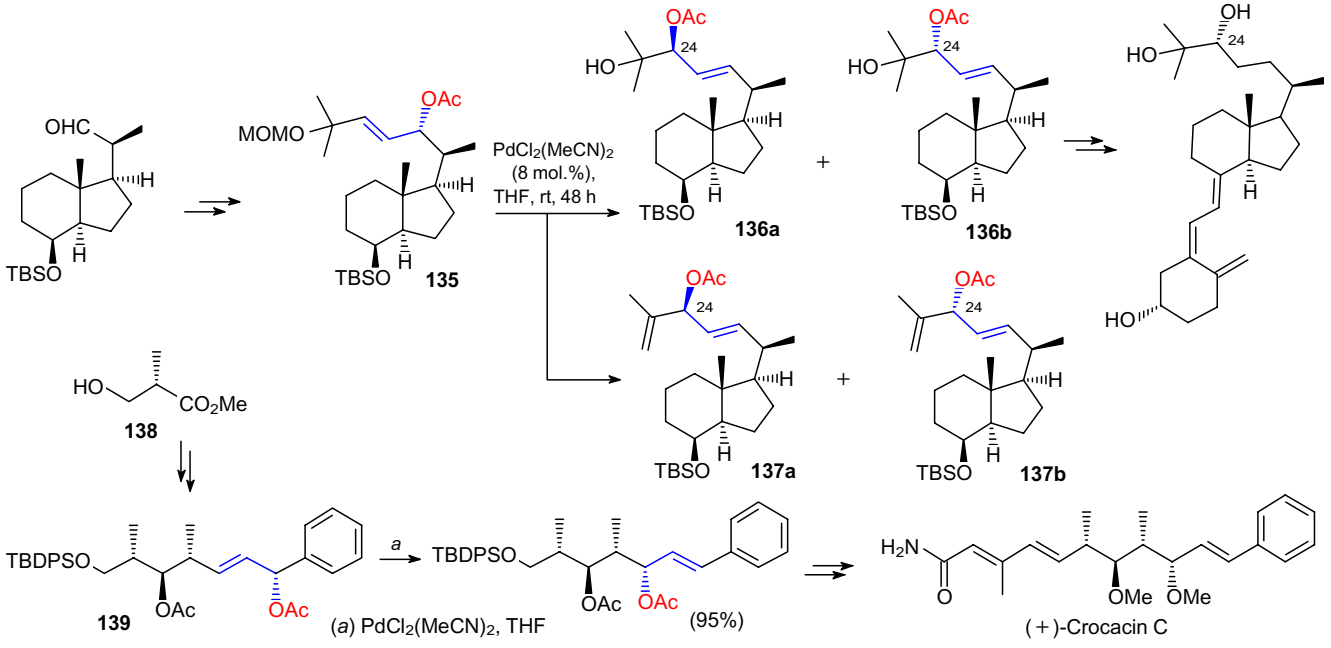
In some cases, heteroaromatic compounds bearing an allyl vinyl moiety are subjected to rearrangements. Substituted butenolides **140** and **141** can be synthesized *via* ring expansion in cyclopropenecarboxylates (Scheme 81).[158] A rhodium catalyst induces the recyclization in allyl cyclopropenecarboxylates **142** to afford 2-allyloxyfurans, which are converted to $\Delta^{\beta,\gamma}$-butenolides **140** through the Claisen rearrangement or to $\Delta^{\alpha,\beta}$-butenolides **141** *via* the subsequent Cope rearrangement.

Later, a method was developed for the highly enantio- (*er* up to 94 : 6) and diastereoselective (*dr* up to > 20 : 1) synthesis of γ-butenolides **141** containing two adjacent asymmetric centres.[159] The authors used the following transformations: palladium-catalyzed asymmetric allylation, *E*-selective cross-metathesis and [3,3]-sigmatropic Cope rearrangement. Readily available α-substituted 5*H*-furan-2-ones **143** served as starting materials in this method (Scheme 82). Contrary to the previous example, in this case, precursors **144**, intended for the Cope rearrangement, were obtained without the use of the Claisen rearrangement.

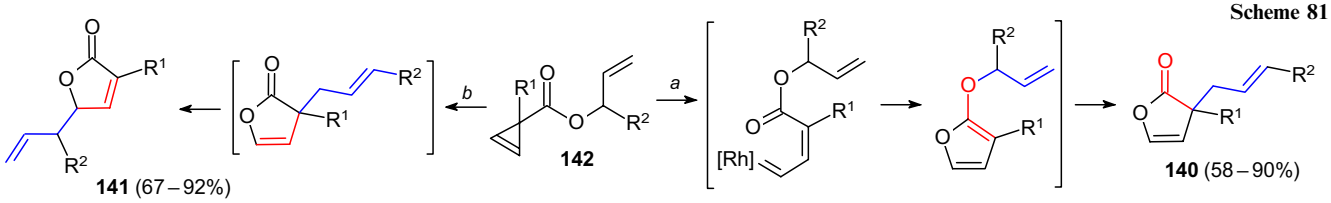
The gold-catalyzed cyclization of allyl ynoates (**145**) is successfully used for the preparation of α-allylbutenolides **140** (Scheme 83). Due to the presence of a basic moiety in the ligand, cyclization of the starting ester is followed by aromatization of intermediate **A** to give 2-alkoxyfuran **B**. The latter compound undergoes the Claisen rearrangement and a double bond migration affording the target α-allylbutenolide.[160]

5-Substituted furfuryl alcohols can give rise to substituted furans **146** *via* the formation of intermediate vinyl ether **A** (Scheme 84).[161] This transformation occurs as a tandem O–H insertion and [3,3]-sigmatropic rearrangement of rhodium carbenoids.

Scheme 80

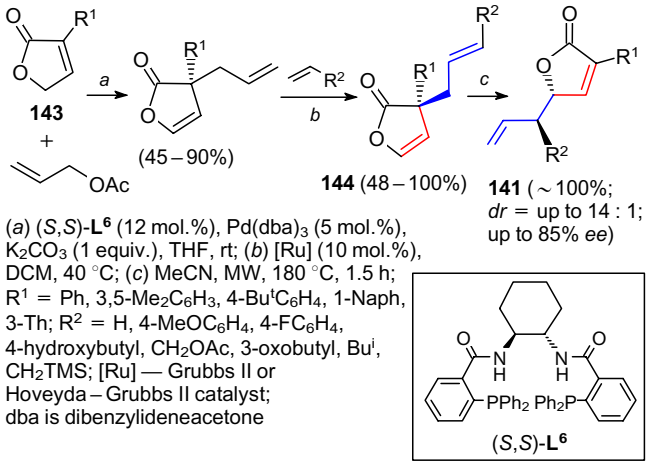


Scheme 81

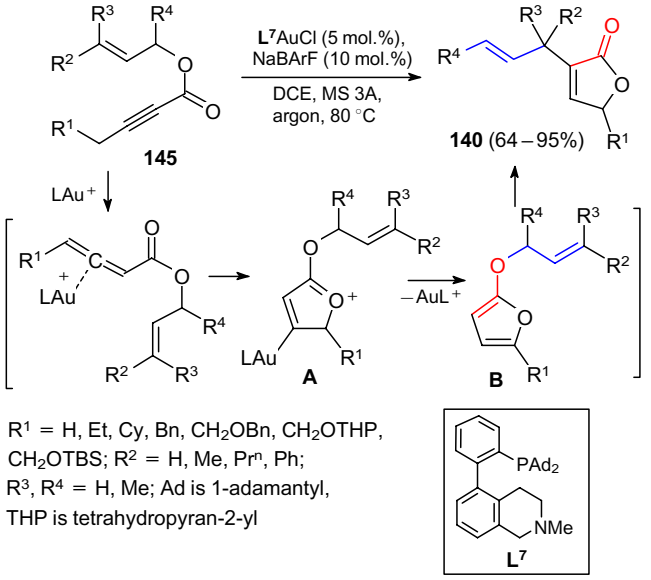


(*a*) $Rh_2(OPiv)_4$ (5–10 mol.%), PhH, 60 °C; (*b*) $Rh_2(OPiv)_4$, PhMe, 110 °C; R^1 = Ph, Me; R^2 = H, n-C_5H_{11}, 2-MeC_6H_4; Piv is pivaloyl

Scheme 82



Scheme 83

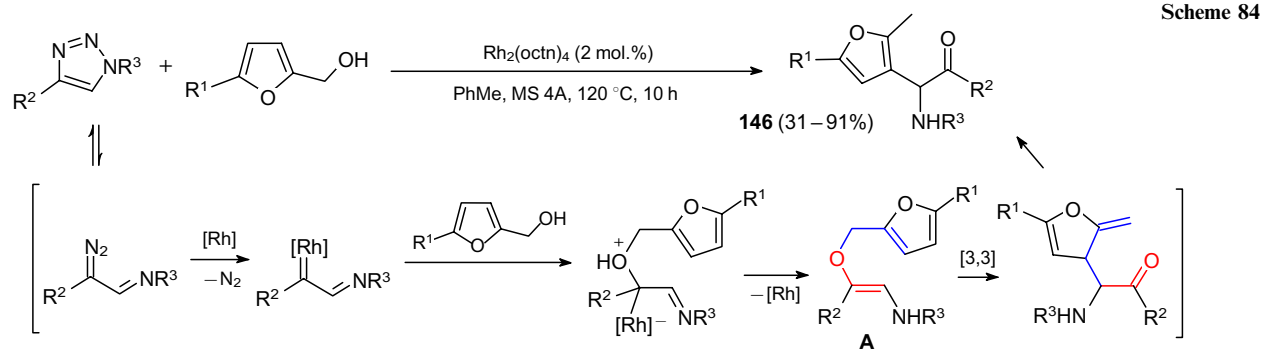


A synthetic approach to the synthesis of 2,3-disubstituted indoles **147** involves the rearrangement of the allyl vinyl moiety in the intermediate **A** (Scheme 85).[162] This approach enables the straightforward formation of a bond between the indole C(2) and pyrazole C(4) atoms. Formally, the 1,2-addition of pyrazol-5-ones to isatin derivatives promoted by acid **IV** takes place supposedly through the sequence including the addition of pyrazol-5-one, [3,3]-rearrangement, 1,3-hydride shift and tautomerization. The [3,3]-sigmatropic rearrangement of the intermediate **A** is a key step of the regiospecific 1,2-addition.

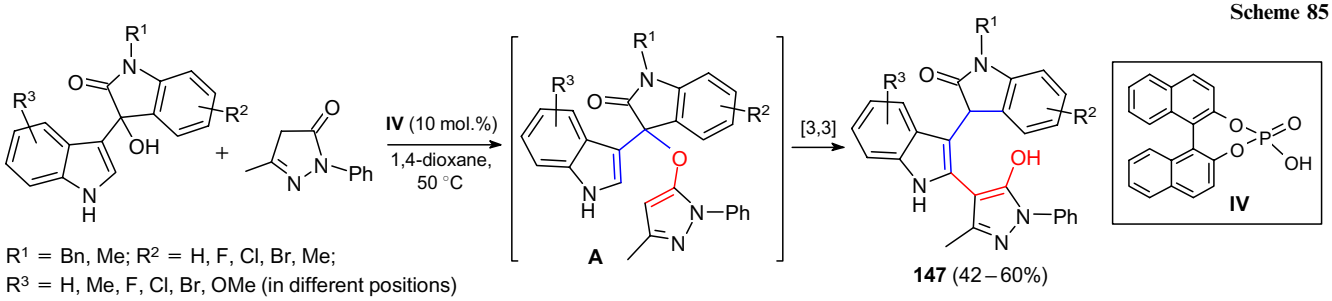
An elegant method for the synthesis of 4-benzyloxyindoles **148** from 2-benzylated oxindoles **149** is based on the Claisen rearrangement.[163] This strategy involves the *in situ* formation of isotoluene intermediates *via* the benzyl transfer to the 3 position of indole (Scheme 86). The subsequent Cope rearrangement and aromatization provide a route to the target products in yields from 51 to 92%. A similar transformation of benzofurans (*e.g.*, compound **150**) was applied to prepare a series of natural products, for example, lespedezol A_1,[164] and several herbicides.[165]

A similar strategy of the Claisen rearrangement involving allyl- and propargyl oxindoles was performed in an asymmetric manner. The use of bis(oxazoline) copper complex **V** provided a route to oxindoles **151** bearing allyl or allenyl moieties in the 3 position (Scheme 87).[166] Excellent stereoselectivities (up to 99% *ee*) were achieved also when using the $Sc(OTf)_3$ – PyBox system (see Scheme 87).[167] A similar reaction was carried out in an achiral manner for 3-oxindoles.[168] Later, this approach was extended to the synthesis of spirocyclic indole derivatives,[169, 170] and was

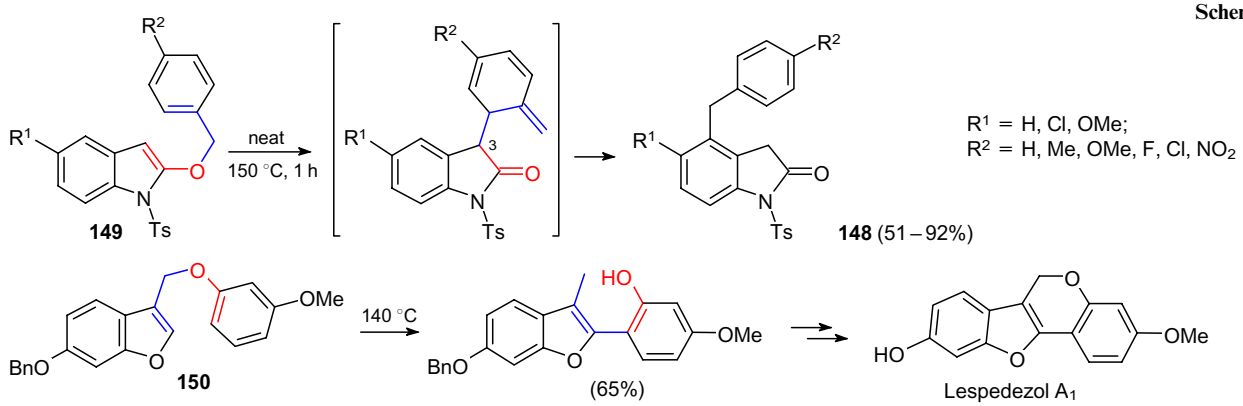
Scheme 84



Scheme 85



Scheme 86

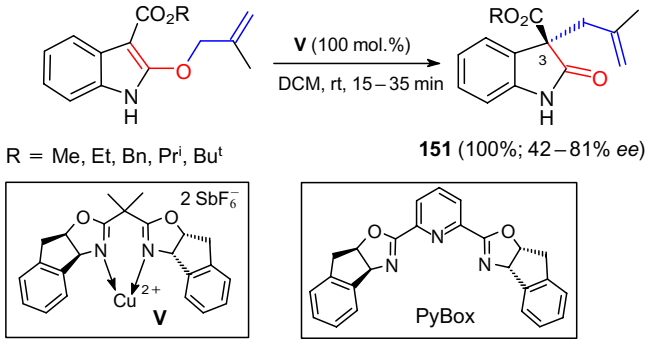


also accomplished as the Fischer–Claisen rearrangement of aryl hydrazines.[171]

An interesting transformation was reported for indoles **152** bearing an aminoacetylene moiety in the 3 position (Scheme 88).[172] A tandem reaction sequence is catalyzed by Brønsted acid, is commenced with the Claisen rearrangement and results in the stereocontrolled formation of indole-fused bridged [4.2.1]-lactones **153**.

6-Allyloxypurines readily undergo the palladium-catalyzed Claisen rearrangement to give N^1-substituted hypoxanthines **154** (Scheme 89).[173] The reaction supposedly occurs *via* a π-allyl palladium complex with the starting allyloxypurine. Complex **155** exists in equilibrium with its dissociated form, the π-allylpalladium cation and the hypoxanthine anion. The latter species, acting as a nucleophile, adds to the π-allyl ligand to afford rearrangement products **154**. Similar transformations take place under thermal conditions for allyloxypyrimidines,[174] allyloxypyrazoles,[175,176] pyrones[177] and furanones.[178]

Scheme 87

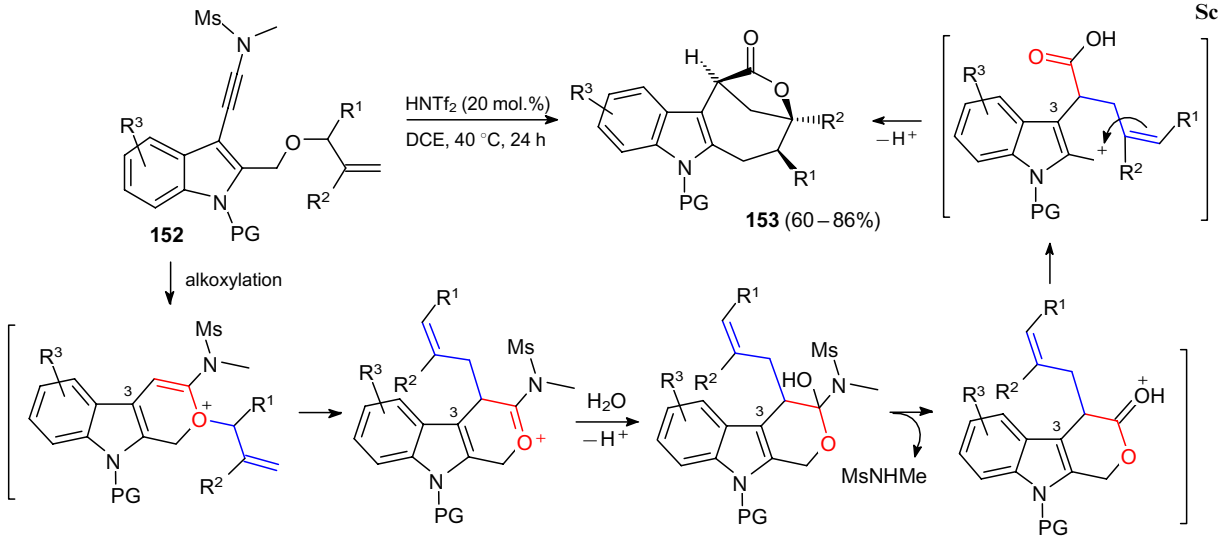


The reaction of 2*H*-chromenes **156** with arylacetylenes in the presence of catalytic amounts of boron trifluoride etherate initially gives an intermediate **A**, which subsequently undergoes a [3,3]-sigmatropic rearrangement to give chromene ketones, compounds **157** (Scheme 90).[179] This approach can be applied to transfer the $CH_2C(O)Ph$ moiety to the 4 position of the chromene system.

Allyloxyoxadiazoles **158** undergo a palladium-catalyzed [3,3]-sigmatropic rearrangement to afford compounds **159** (Scheme 91).[180] The study of the mechanism of this reaction indicates that it proceeds through the nucleophilic attack of the nitrogen atom on the palladium-coordinated unsaturated bond. This interaction generates a cationic palladium-substituted six-membered ring, which is converted into the final product *via anti*-β-Pd,O elimination. In the transition state, R^1 occupies a pseudo-equatorial position, resulting in the exclusive formation of *E*-alkene.

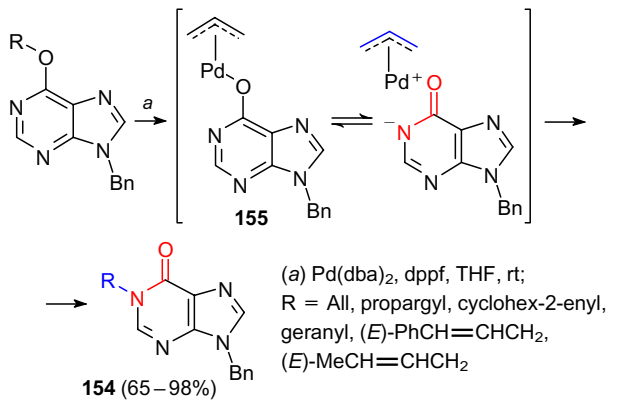
N-Allylated 2-pyridones **160** were synthesized using 2-allyloxy derivatives **161** as the starting reagents

Scheme 88

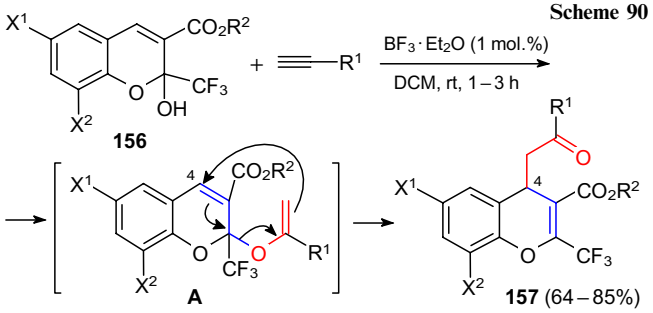


R^1 = H, Me; R^2 = H, Me, Ph, 4-MeC_6H_4, 4-ClC_6H_4; R^3 = F, Cl, Br, CF_3, Me, OMe, CN, CO_2Me (in different positions);
PG = Ts, Ms, Bs; PG is protecting group, Bs is 4-bromobenzenesulfonyl

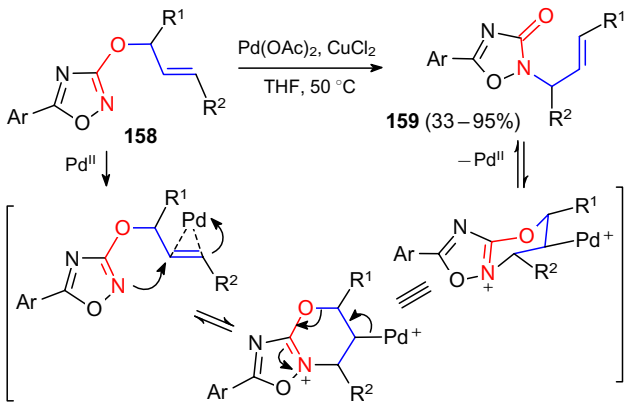
Scheme 89



Scheme 90



Scheme 91



(Scheme 92).[181] The [3,3]-sigmatropic rearrangement of (*E*)- and (*Z*)-allyloxy-substituted pyridines catalyzed by a chiral palladium catalyst affords *N*-allylpyridones in 33–96% yields with high enantioselectivity (up to 96% *ee*). A combination of a chiral palladacycle **VI** with silver(I) trifluoroacetate is used for catalysis of the mentioned rearrangement. Along with allylated 2-pyridones, the similar approach was employed to obtain chiral quinolin-2(1*H*)-ones and isoquinolin-1(2*H*)-ones.

3.2. Johnson–Claisen rearrangement

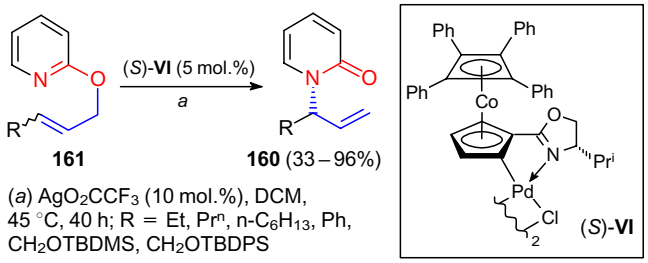
The sigmatropic Johnson–Claisen rearrangement is commonly used in the synthesis of natural compounds. To carry out the classical version of the reaction, a reaction mixture should contain at least traces of a weak acid, most often, propionic acid.

Nevertheless, examples of the use of non-classical catalytic systems in this approach are known. For example, the total synthesis of (±)-floribundane B was carried out in 2019 based on the Johnson–Claisen rearrangement of a Morita–Beylis–Hillman adduct, compound **162** (Scheme 93; the parentheses denote an unfavourable steric interaction between proximal groups).[182] Instead of propionic acid, the authors used a heterogeneous catalytic system based on a molecular iodine supported on silica gel. The absence of *E*–*Z* selectivity in this reaction is confirmed by its occurrence *via* a six-membered transition state featuring two conformations, which are equally destabilized due to the position of the methyl group. This approach also enabled the synthesis of (±)-oleocanthal, a component of olive oil.

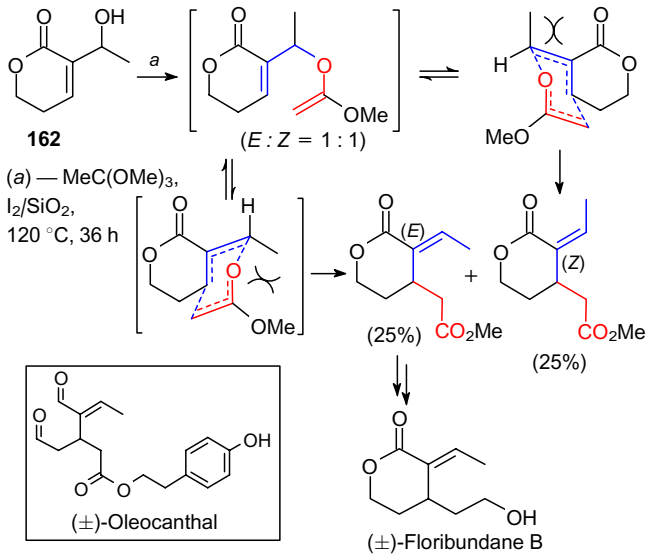
A series of bisabolane sesquiterpenes such as (±)-curcumene, (±)-curcuphenol, (±)-curcudiol and (±)-curcuhydroquinone, were obtained in a racemic form using the Johnson–Claisen rearrangement, the example of which is depicted in Scheme 94.[183,184] The advantage of this approach is the use of available starting compounds. This transformation was also implemented in the preparation of allylic terpenols in the presence of ionic liquids[185] and monoterpenols under microwave irradiation.[186]

Two types of sigmatropic rearrangements (Johnson–Claisen and Ireland–Claisen) were used in the stereoselective synthesis of derivatives of cholestenoic acids **163** based on 1,4-chirality transfer. The Johnson–Claisen rearrangement of propargylic alcohols **164** occurs stereoselectively to

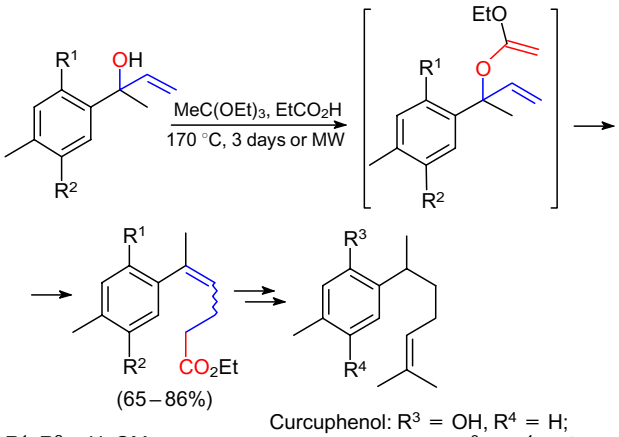
Scheme 92



Scheme 93



Scheme 94



give (25*R*)- and (25*S*)-isomeric allenes (Scheme 95), which are reduced to cholestenoic acids **163**.[187] The overall yield of the products varies from 66 to 84%, the ratio of *R*- and *S*-isomers is 27 : 1 (from (*R*)-**164**) and 1 : 8 (from (*S*)-**164**). The use of allylic alcohols instead of propargylic ones significantly lowers the stereoselectivity.

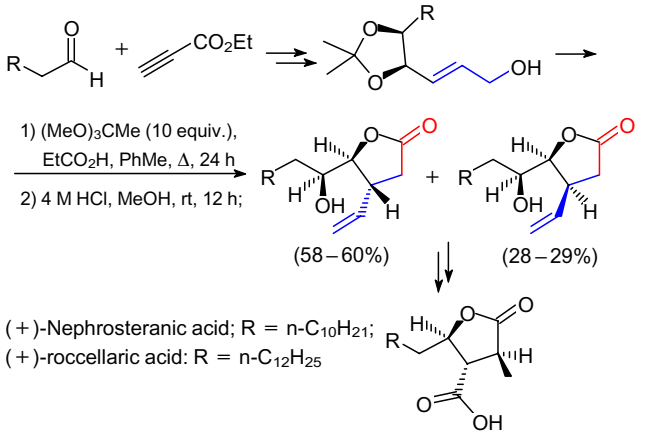
The stereoselective synthesis of (+)-nephrosteranic and (+)-roccelaric acids is based on a simple strategy, which comprises the regioselective asymmetric dihydroxylation of the β,δ-double bond in α,β,γ,δ-unsaturated ester and the Johnson–Claisen rearrangement (Scheme 96).[188] This transformation is performed in 10 steps with the overall yield of 6.8% (for nephrosteranic acid) and 7.6% (for roccelaric acid).

The diastereoselective Johnson–Claisen rearrangement was employed in the synthesis of enantiomers of arundic acid, which is a potential anti-Alzheimer agent (Scheme 97).[189] The authors studied the effect of the solvent, alkene geometry and alcohol chirality on the diastereoselectivity of the rearrangement of a tartrate-based allylic alcohol, which made it possible to quite easily implement this transformation.

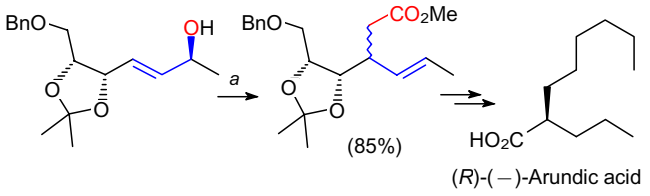
An efficient synthetic approach to obtain several natural compounds isolated from lavender, namely, (*R*)- and (*S*)-lavandulols, (+)-lavandulyl 2-methylbutanoate and (+)-lavandulyl senecioate, comprised the Johnson–Claisen rearrangement as a key step (Scheme 98).[190]

Dihydrocodeine and hydrocodone were synthesized from bromobenzene and other substituted arenes in 16 and 17 steps, respectively.[191] One of the key steps was the Johnson–Claisen rearrangement as illustrated in Scheme 99. A similar rearrangement was applied in the atom-efficient synthesis of several esters [192] and in the synthesis of (±)-homosarkomycin.[193]

Scheme 96

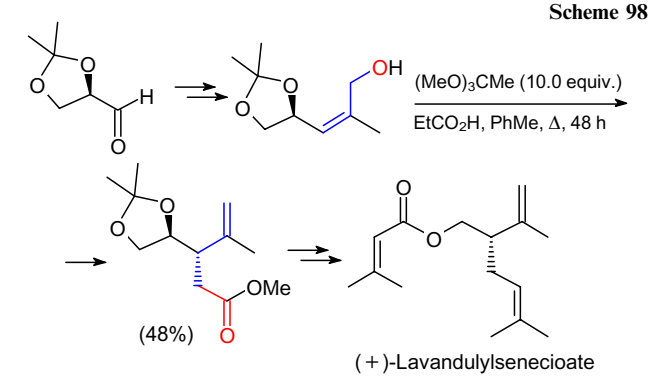


Scheme 97



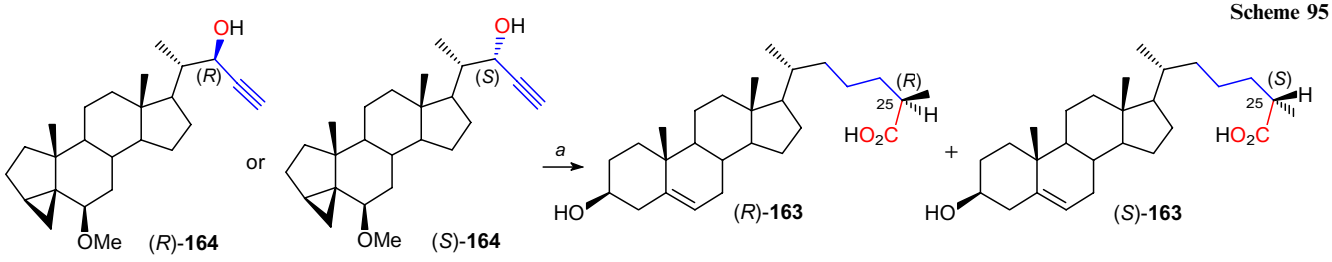
(*a*) $MeC(OMe)_3$ (10.0 equiv.), $EtCO_2H$, decalin, Δ, 1 h

Scheme 98



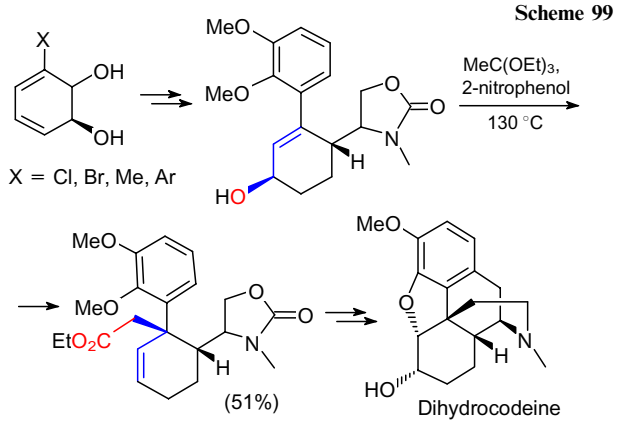
A sequence of sigmatropic rearrangements provides an opportunity for the synthesis of (−)-morphine from diol derivative **165** (Scheme 100).[194] Two one-pot consecutive Claisen rearrangements involving allylic diol **165** selectively generate two adjacent carbon centres including the sterically hindered quaternary carbon atom.The use of *o*-nitrobenzene as an acid catalyst improves the yield in the second Claisen rearrangement and, according to data of the study,[194] facilitates the formation of the quaternary stereo-

Scheme 95

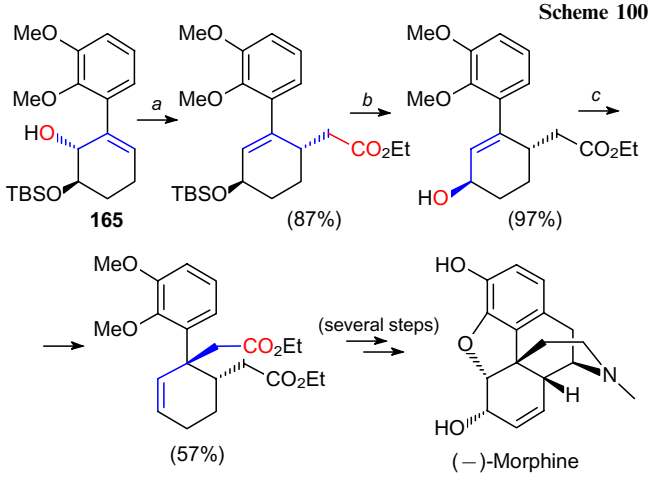


(*a*) 1) $EtC(OEt)_3$, $EtCO_2H$, Δ; 2) H_2, Pd/C; 3) TsOH; 4) LiOH

Scheme 99



Scheme 100

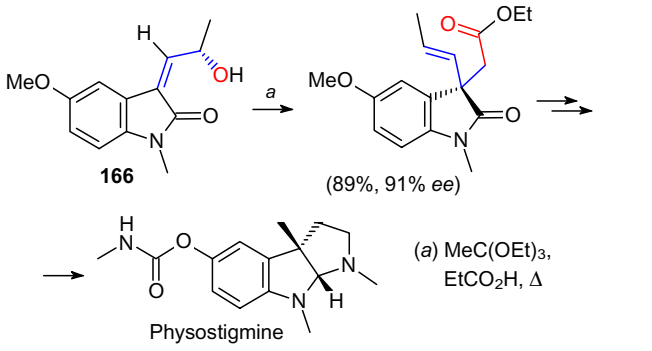


(*a*) sealed tube, $MeC(OEt)_3$, $EtCO_2H$, MS 4A, 140 °C; (*b*) TBAF, THF, rt; (*c*) $MeC(OEt)_3$, 2-nitrophenol

centre at the benzylic position. Two stereoisomeric ethyl esters formed in this reaction were successfully differentiated during the subsequent Friedel–Crafts-type cyclization. The double bond in (−)-morphine is formed in one of the final steps.

One way to create quaternary stereocentres in lactams was used in the synthesis of (−)-physostigmine (Scheme 101).[195] The synthetic approach is based on the Johnson–Claisen rearrangement of γ-hydroxy-α,β-unsaturated lactams, with geometry of an alkene determining the absolute stereochenistry of the product. The rearrangement of oxindole **166** provides the stereoselectivity of 91% *ee*.

Scheme 101

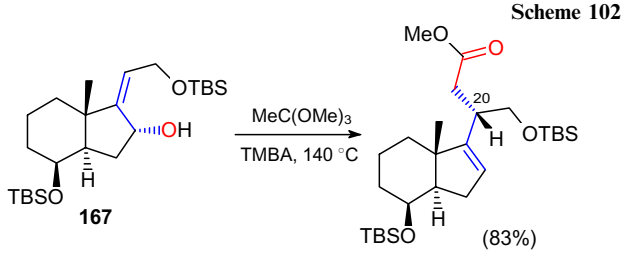


A rather flexible method was developed for the synthesis of analogues of vitamin D_3.[196] A key step is a sigmatropic rearrangement of compound **167** (Scheme 102), which allows the control of stereochemistry at the C(20) atom, providing a versatile way to introduce new side chains into the vitamin D backbone.

An effective approach to the synthesis of δ-ethoxycarbonyl-α,β-unsaturated nitriles is based on the conversion of unsaturated cyanohydrins (Scheme 103).[197] The Johnson–Claisen rearrangement afforded target products **168** in moderate yields with moderate diastereoselectivity (the ratio of the *Z*- to *E*-isomers varied from 100 : 0 to 7 : 93).

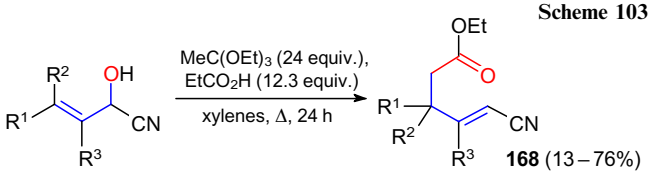
It was shown that the Johnson–Claisen rearrangement is suitable to construct functional graphene-based materials **169** (Scheme 104).[198] Hydroxy functionalities in graphene oxide were modified by the treatment with triethyl orthoacetate. This version of the Claisen rearrangement offers great opportunities for the further functionalization while retaining the unique properties of non-functionalized graphene.

Scheme 102



TMBA is trimethylbenzoic acid

Scheme 103



R^1 = Me, n-C_5H_{11}, prenyl, Ph; R^2 = H, Me; R^3 = H, Me, Br

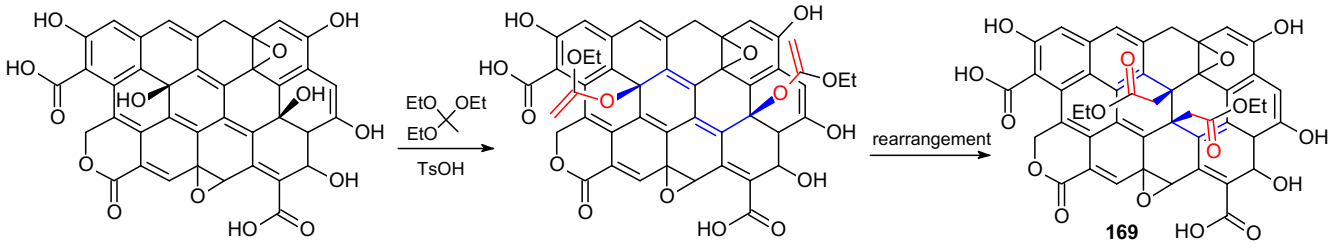
3.3. The Eschenmoser–Claisen rearrangement

This type of rearrangement is relatively rare, apparently due to the need to heat the reaction mixture (sometimes even in a sealed tube), which is not always acceptable for unstable substrates. Another possible reason is the relative inertness of the resulting *N*,*N*-dialkylamides, which can make their use challenging if further transformation of the amide group is required in the presence of other substituents sensitive to harsh conditions. For example, the inertness of the amide moiety was the reason why the authors [194] refused to use the Eschenmoser–Claisen rearrangement in the synthesis of (−)-morphine discussed in the previous Section (see Scheme 100).

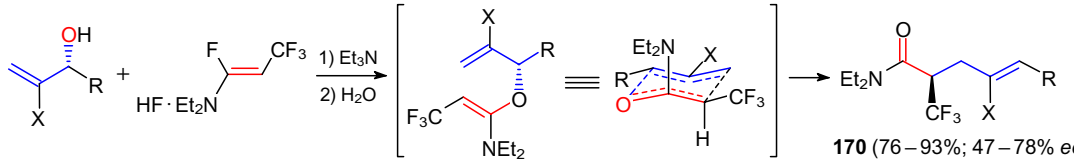
Nevertheless, the Eschenmoser–Claisen rearrangement is quite suitable for producing, *e.g.*, α-trifluoromethylated amides **170** bearing the γ-positioned double bond (Scheme 105).[199] Thus, the corresponding allylic alcohols react with 1,1,3,3,3-pentafluoropropenediethylamine in the presence of a base such as triethylamine.

The enantioselective synthesis of aplysin was accomplished using the palladium-catalyzed addition of an arylboronic acid to an allenic alcohol followed by the

Scheme 104

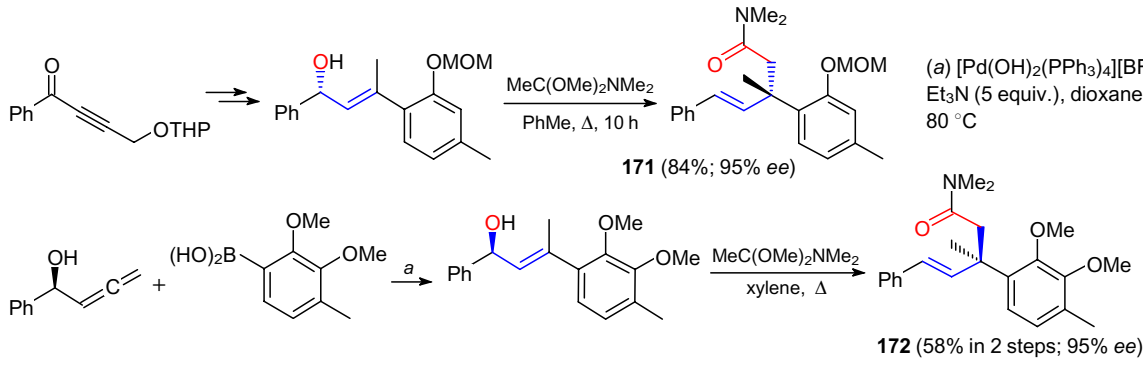


Scheme 105



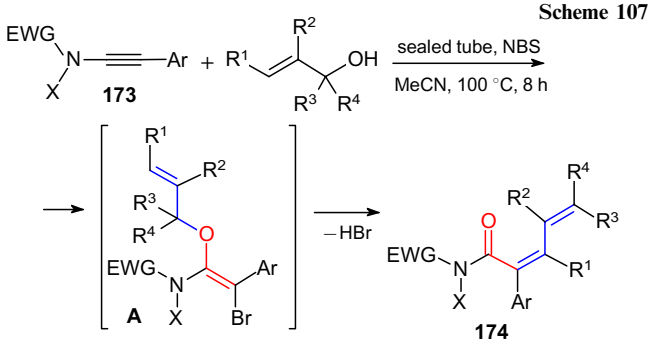
X = H, F;
R = n-C_5H_{11}, n-$C_{15}H_{31}$

Scheme 106



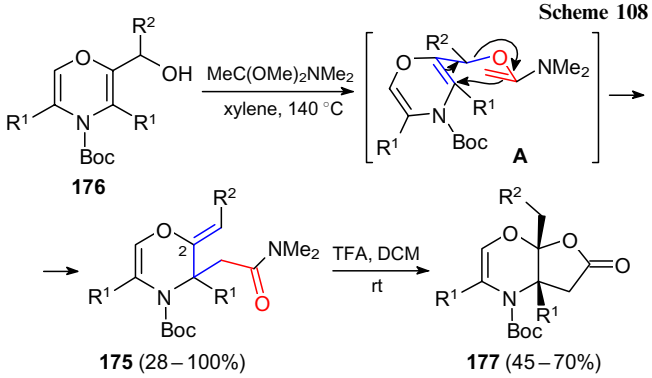
(*a*) $[Pd(OH)_2(PPh_3)_4][BF_4]_2$ (5 mol.%), Et_3N (5 equiv.), dioxane–H_2O (20 : 1), 80 °C

Scheme 107



EWG = Ts, Ms; X = Me, Bu^n, Bn, Ph;
R^1 = Ph, 4-MeC_6H_4, 4-ClC_6H_4, 4-$MeOC_6H_4$; R^2, R^3, R^4 = H, Me

Scheme 108



R^1 = Ph, 4-$MeOC_6H_4$; R^2 = H, Me, Pr^n;
Boc is *tert*-butoxycarbonyl, TFA is trifluoroacetic acid

Eschenmoser–Claisen rearrangement to give compound **171** (Scheme 106).[200] A similar approach was also used in the asymmetric synthesis of aromatic sesquiterpenes isolated from the phytopathogenic fungus *Helicobasidium mompa* (in Scheme 106, intermediate compound **172** is shown).[201]

A cascade transformation of alkynylsulfonamides **173** was implemented in the preparation of 2,4-dienamides **174** *via* the formation of intermediates **A** (Scheme 107).[202] This was carried out for more than 20 substituted alkynylsulfonamides; the yields varied from 27 to 91%. Theoretical calculations suggested a [3,3]-sigmatropic rearrangement to be the rate-limiting reaction step.

The [3,3]-sigmatropic rearrangement is useful to prepare dihydrooxazine derivatives **175**, containing an exocyclic double bond, from 1,4-dihydrooxazines **176**.[203] The multiple bond geometry is controlled by the Eschenmoser–Claisen rearrangement proceeding through the less sterically hindered transition state with the substituent R^2 being in an equatorial position (intermediate **A**), which gives exclusively isomer **175** bearing a double bond in the *Z* configuration in the 2 position of the 1,4-oxazine ring. Subsequently, derivative **175** was successfully converted to fused γ-butyrolactone **177** (Scheme 108).

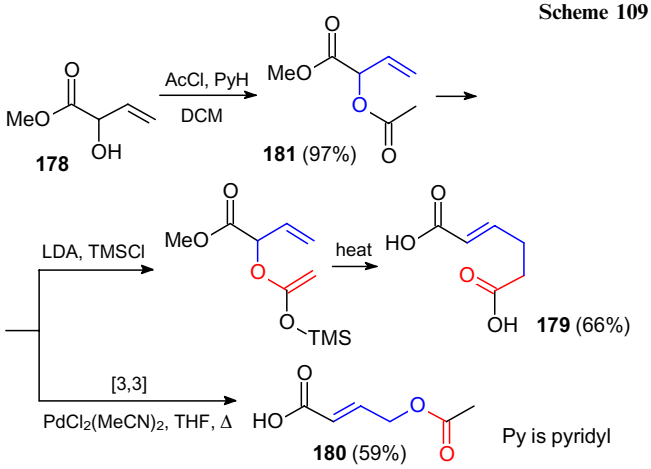
3.4. The Ireland–Claisen rearrangement

This version of the Claisen rearrangement has considerable synthetic potential and offers access to a variety of target compounds in high yields. The method is based on the formation of silyl ketene acetals from esters when treated with lithium diisopropylamide (LDA) or a similar strong base. Silyl ketene acetals *per se* are rather unstable and

rearrange spontaneously at room temperature in the absence of any additional catalyst. However, the need for organometallic bases in the step of the formation of silyl ketene acetals limits the application of this method to compounds sensitive to the reaction medium. At the same time, when an additional electron-withdrawing substituent is present in the acyl moiety, even triethylamine can be used as a base. But such an approach requires a further modification of the substrate in certain cases.

One example of the implementation of the Ireland–Claisen rearrangement in organic synthesis involves the use of methyl 2-hydroxybut-3-enoate (methyl vinyl glycolate, MVG (**178**)) (Scheme 109).

Scheme 109

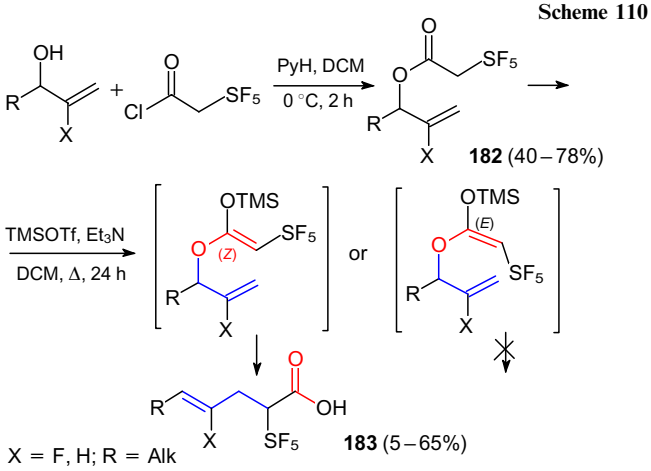


This compound arises from the zeolite-catalyzed degradation of mono- and disaccharides.‡‡ In the presence of alkali metal salts, glucose can give methyl vinyl glycolate in a yield of up to 18%; meanwhile, tetroses (particularly, erythrulose) can provide the product yield of up to 50–60%. Methyl vinyl glycolate is capable of becoming a renewable platform molecule for commercially significant catalytic transformations and can be used as the starting material in the synthesis of valuable organic compounds.[204] Several synthetic protocols were developed involving methyl vinyl glycolate, including unsaturated derivatives of adipic acid **179**, precursors of γ-butyrolactone and butane-1,4-diol (compound **180**). The common precursor of the target products in these approaches is acetylated derivative **181** (see Scheme 109).

It was shown that allylic esters **182** can be used to prepare novel pentafluorosulfanyl-substituted carboxylic acids (Scheme 110).[205] Based on compounds **182** derived from fluorinated or non-fluorinated allylic alcohols *via* esterification with (pentafluorosulfanyl)acetyl chloride, a series of γ,δ-unsaturated β-pentafluorosulfanyl carboxylic acids **183** were obtained as *trans* isomers using the Ireland–Claisen rearrangement. The formation of intermediate *E*- and *Z*-enolates was confirmed by NMR spectroscopy, which also demonstrated that only *Z*-enolates rearrange, whereas *E*-forms are stable under the reaction conditions and hydrolyze back to the starting allylic esters during deprotection. As a consequence, the incomplete conversion of the starting esters **182** into final products **183** is observed. The conversion of the resulting acids into

‡‡ See M.S.Holm, Y.J.Pagán-Torres, S.Saravanamurugan, A.Riisager, J.A.Dumesic, E.Taarning. *Green Chem.*, **14**, 702 (2012).

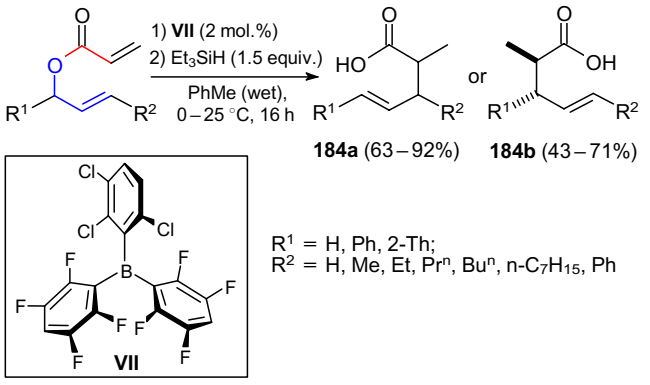
Scheme 110



the corresponding methyl esters simplified the isolation of the desired pentafluorosulfanyl-substituted derivatives. It is worth noting that the above procedure cannot be used to produce aryl-substituted rearrangement products (R = Ph). However, later the conditions of this reaction were modified, thereby providing a route both to aryl derivatives and compounds bearing trifluoromethyl and methyl moieties in place of the pentafluorosulfanyl one.[206]

Allyl acrylates were shown to undergo the Ireland–Claisen rearrangement mediated by a special boron-containing catalyst **VII**.[207] This reaction is highly diastereoselective, with the structure of the product **184a** being largely dictated by the nature of substituents in the starting compound (Scheme 111). Depending on the electronic and structural parameters, the reaction can be accompanied by a 1,3-allylic shift to afford isomeric product **184b**.

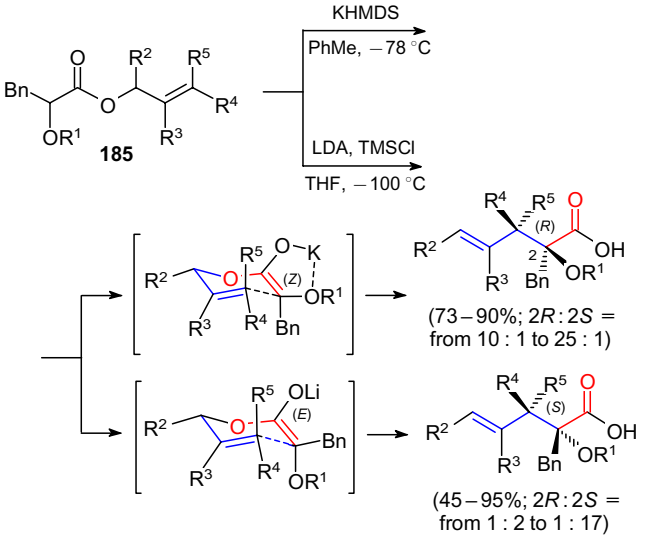
Scheme 111



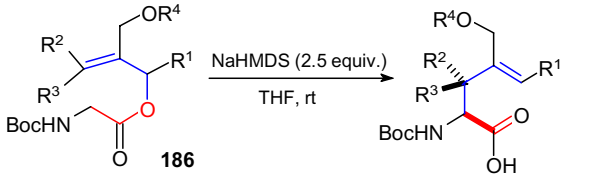
A systematic survey of the Ireland–Claisen rearrangement of α-alkoxy-substituted esters **185** showed that the use of KHMDS as a base in toluene provides excellent diastereoselectivity due to chelation control (Scheme 112).[208] A similar transformation was carried out for Boc-glycine allyl esters **186** using NaHMDS as a base.[209]

An interesting tandem reaction was reported[21] for allylic silyl glyoxylates, initiated by the addition of organozinc, -magnesium or -lithium derivatives, which induce Brook and Ireland–Claisen rearrangements. This results in rather high yields of γ,δ-unsaturated α-silyloxy acids **187a** (major isomer) and **187b** (minor isomer), which were obtained in an overall yield of 31–74% with a diastereomeric ratio for each isomer from 1 : 1 to 20 : 1 (Scheme 113).

Scheme 112



R^1 = Me, Bn; R^2 = H, Me, Bu^n; R^3 = H, Me; R^4, R^5 = H, $(CH_2)_2Ph$



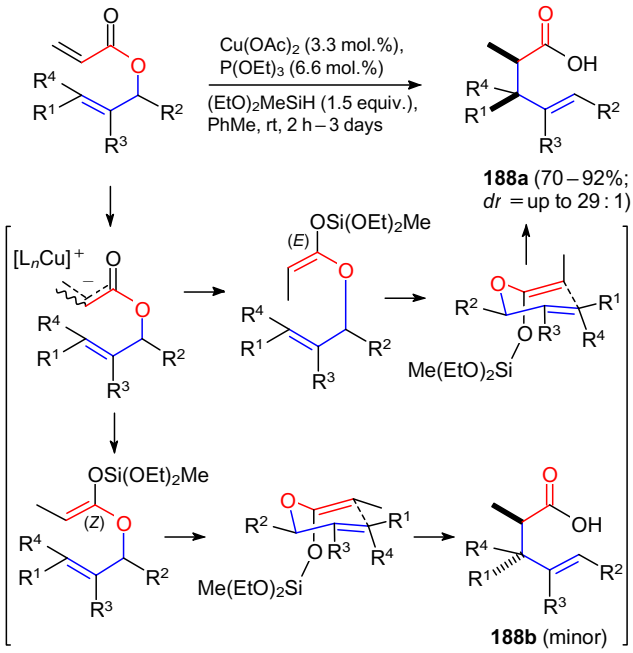
R^1 = H, Me, Et, Pr^i, Bu^t, Ph; R^2 = H, Me, Et, n-C_5H_{11}, Ph; R^3 = H, Me; R^4 = TBDPS

In 2015, a reductive Claisen rearrangement was developed based on the use of copper.[211] The transformation of unsaturated allylic esters is catalyzed by the *in situ* generated copper hydride, and methyl ethoxy silane serves as a stoichiometric reducing agent (Scheme 114). Copper hydride selectively reduces the starting unsaturated esters to give (*E*)-silyl ketene acetals, which rearrange into the target unsaturated acids **188a**,**b**. The reaction occurring *via* a chair transition state affords the target products in high yields with good diastereoselectivities.

A boron-based version of the Ireland–Claisen rearrangement allows the exclusion of strong bases. In this case, the process occurs at room temperature with high stereoselectivities for the resulting acids **189** (Scheme 115).[212] The application of the commercially available iodoborane gives rise to a wide range of substrates.

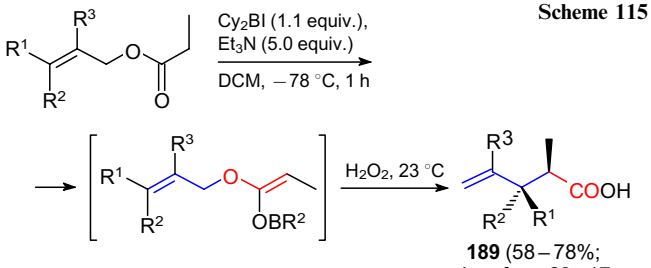
β-Amino acid esters **190** were obtained *via* a sigmatropic rearrangement of compounds **191** (Scheme 116).[213] Studies on the optimization of the reaction conditions revealed a pivotal role of enolization and the nature of the substituents at the nitrogen atom. It was suggested that when the tosyl protecting group in molecule **191** is replaced with, *e.g.*, phthaloyl or *tert*-butyloxycarbonyl, such an enamide will be more prone to decomposition and the formation of undesirable by-products. The yield of product **190** is also

Scheme 114



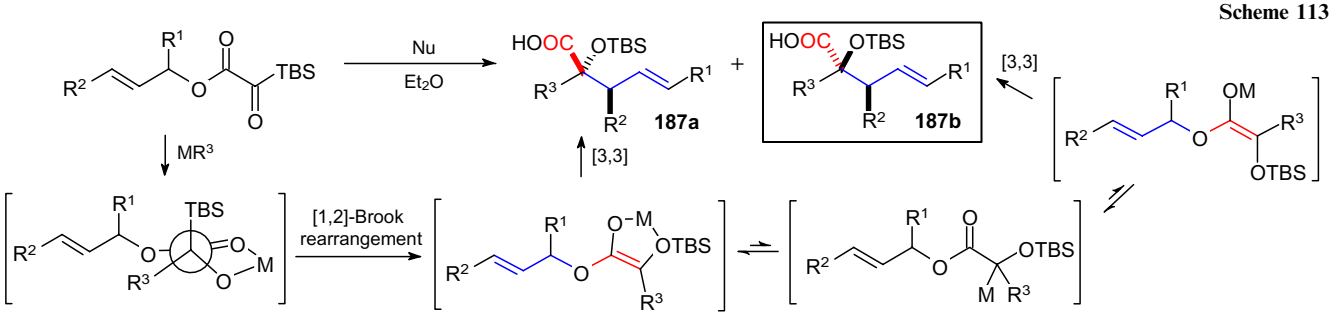
R^1 = Me, Ph, Pr^n, n-C_5H_{11}, CH_2OTBS, CH_2OAc, 3,4,5-$(MeO)_3C_6H_2$; R^2 = Me, Bu^n, Cy; R^3, R^4 = H, Me

Scheme 115



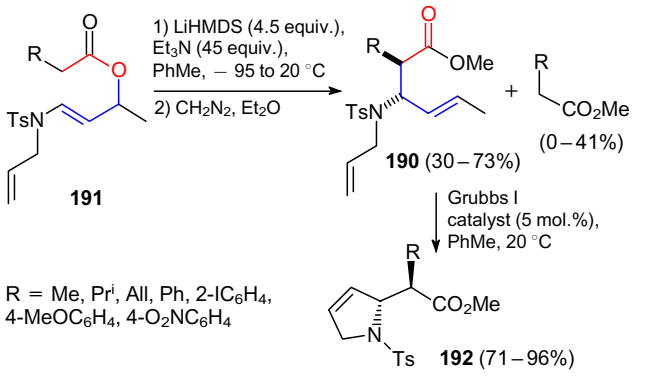
R^1 = H, Me, Pr^n, Ph; R^2 = H, prenyl; R^2–R^3 = $(CH_2)_4$

Scheme 113



R^1 = H, Me; R^2 = Me, Ph; R^3 = H, Me, CH_2Boc, All, 2-methylallyl, propargyl; Nu = MeMgBr + TMSOTf, $ZnEt_2$, AllZnBr, allenylzinc bromide, 2-methylallylzinc bromide, lithium 1-*tert*-butoxyethenolate; M = Li, ZnBr, MgBr, ZnEt; Nu is nucleophile

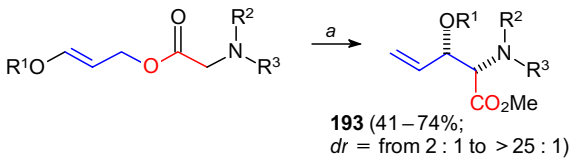
Scheme 116



affected by the nature of the substituent R. Thus, electron-donating groups capable of conjugation with the newly formed enolate stabilize it and facilitate the process. This reaction is characterized by high *anti*-selectivity (the ratio of *anti* and *syn* isomers exceeds 25 : 1), and it is also possible to transfer the stereoconfiguration of products **190** to pyrroline molecules **192** formed therefrom by cross-metathesis in the presence of Grubbs catalysts.

Amino acid derivatives **193** were produced from the appropriate allylic esters using the Ireland–Claisen rearrangement involving 3-alkoxy- and 3-aryloxy-substituted allyl glycinates (Scheme 117).[214] Such a [3,3]-sigmatropic rearrangement provides straightforward access to *syn*-β-alkoxy and *syn*-β-aryloxy derivatives of α-amino acids. Later, this strategy was applied to the total synthesis of furanomycin.[215]

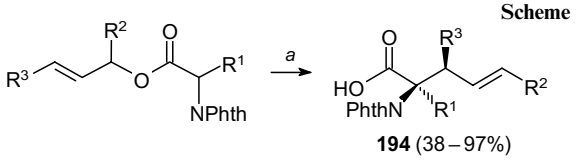
Scheme 117



(*a*) 1) LiHMDS (1.2 equiv.), TMSCl (1.3 equiv.), THF, –95 °C to rt, 70 min; 2) CH_2N_2, Et_2O, 0 °C; R^1 = Me, Pr^i; R^2 = Me, Bn, All, Boc; R^3 = Boc, Cbz, CO_2Me, Ts, Ac; Cbz is benzyloxycarbonyl

Ireland–Claisen rearrangements in the series of tetra-substituted α-phthalimido ester enolates provides an approach to α,β-substituted α-amino acids **194** containing a double bond in their structures.[216] This transformation is highly diastereoselective (*dr* = > 20 : 1) (Scheme 118), with

Scheme 118

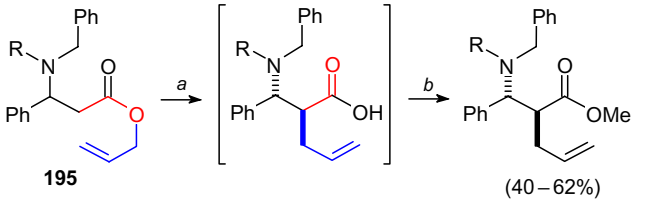


(*a*) 1) LiHMDS (2.0 equiv.), Me_2NEt (2.0 equiv.), PhMe, –78 °C; 2) TMSCl (2.0 equiv.), –78 to 20 °C; R^1 — 3,5-dimethylisoxazol-4-yl, 2-Fu, 3-Th, C_6H_4X (X = H, 4-OMe, 4-Bu^t, 4-F, 4-CF_3, 3-Cl, 4-Cl, 2-Cl, 2-OMe); R^2 = H; R^3 = 3-Py, *N*-Boc-pyrrol-2-yl, 2-thiazolyl, 3,5-dimethylisoxazol-4-yl, C_6H_4X (X = 4-OMe, 4-Br, 4-F, 4-CF_3, 4-Me, 3-Me, 2-Me)

the stereochemical outcome being retained regardless of the geometries of the enolate or allylic moiety.

Substituted allyl β-amino esters **195** undergo the stereoselective Ireland–Claisen rearrangement to afford the corresponding enantiomerically pure α-substituted β-amino esters (Scheme 119).[217] The application of this methodology was demonstrated by the asymmetric synthesis of transpentacins from sorbic acid.

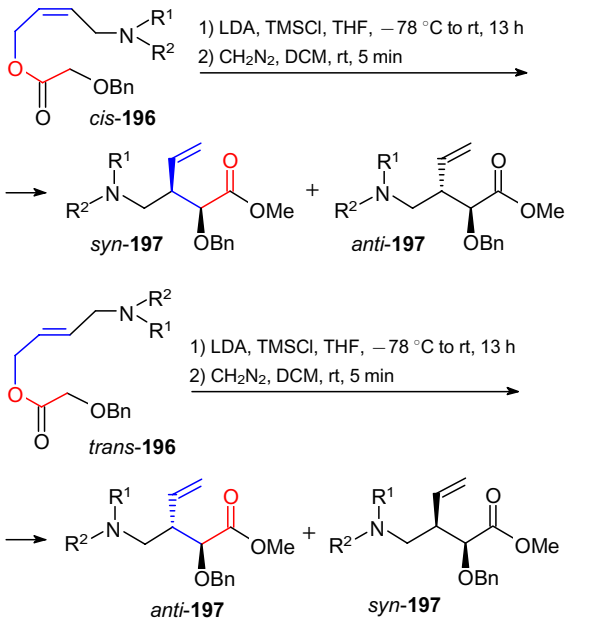
Scheme 119



R = Bn, Pr^i; (*a*) 1) TMSCl, PhMe, –78 °C, 10 min; 2) LiHMDS, –78 °C, 30 min; then Δ, 1 h; (*b*) $SOCl_2$, MeOH, 50 °C, 48 h

The Ireland–Claisen rearrangement of benzyloxyacetates **196**, bearing an allylamine moiety, gives products **197** with excellent diastereoselectivity in high yields (Scheme 120).[218] It should be emphasized that high diastereoselectivity is observed irrespective of the double bond configuration in the starting compound: in the case of *cis* configuration, the *syn* isomer is formed as the major product (*dr* = from 4 : 1 to > 95 : 5, overall yield of 57–90%), while the *trans* form furnishes mainly the *anti* isomer (*dr* = from 3 : 1 to > 95 : 5, overall yield of 54–86%).

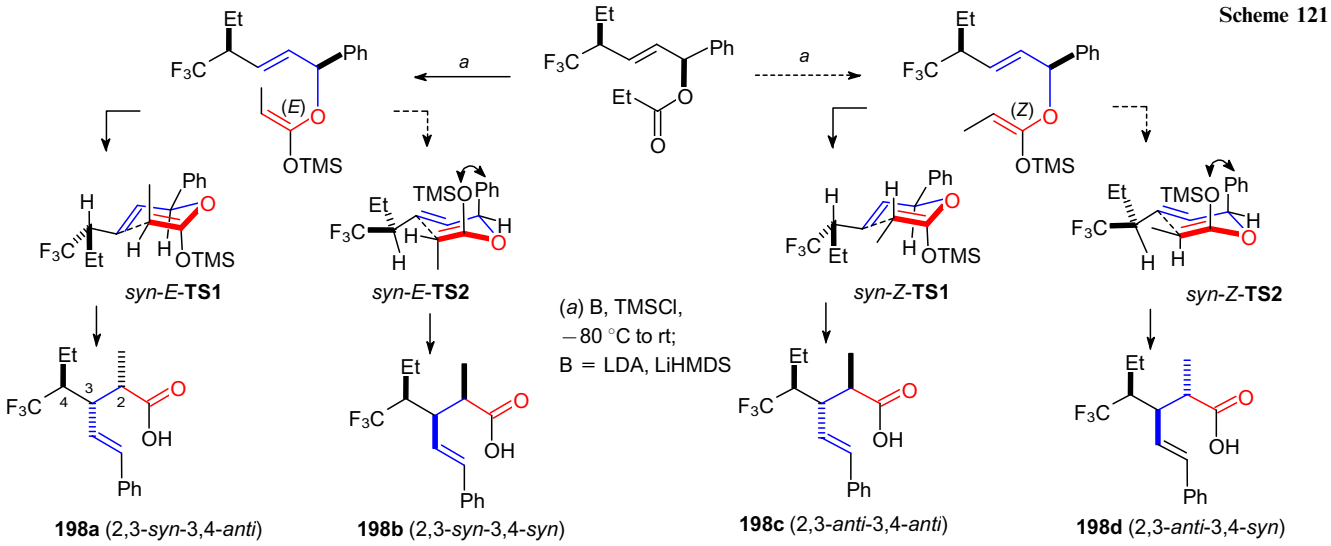
Scheme 120



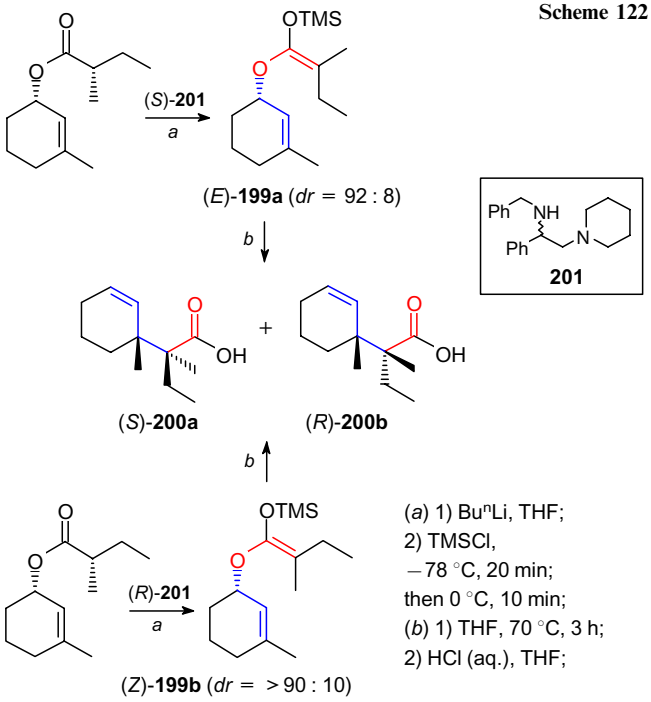
R^1 = Me, Pr^i, All, Bn, Cy, Ph, PMB, N_3; R^2 = Me, Pr^i, Bn, Cy, N_3; R^1NR^2 is pyrrolidino, piperidino

The Ireland–Claisen rearrangement was used to develop a protocol to access optically active CF_3-substituted carboxylic acids **198** from readily available mandelic acid (Scheme 121).[219] The stereoselectivity of the reaction strongly depends on the ratio of *syn* and *anti* isomers of the

Scheme 121



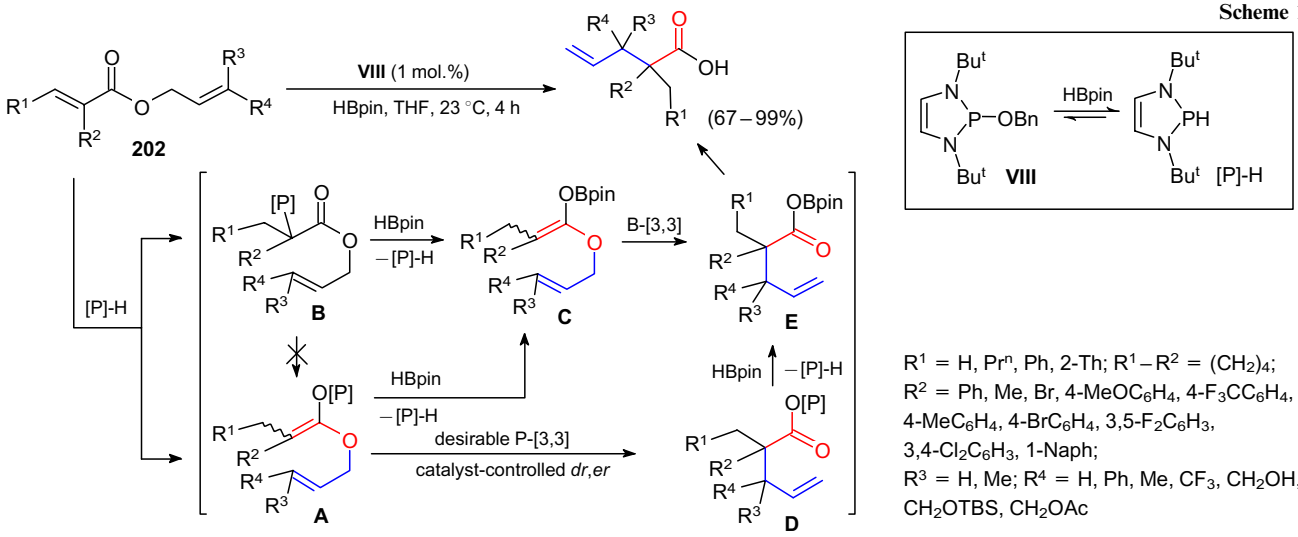
Scheme 122



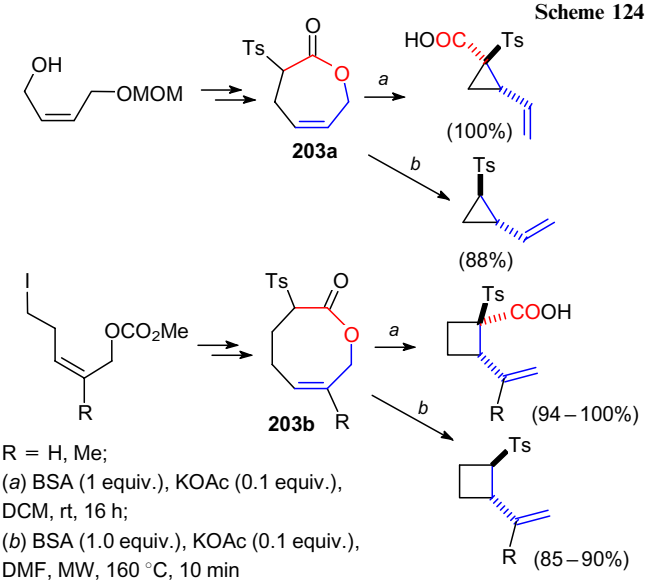
starting allylic ester, and the dominating geometry is governed by the strain experienced by a molecule in the transition state. Generally, compound **198a** is predominantly formed since there are no unfavourable interactions between phenyl and TMSO moieties in the *syn*-*E*-**TS1** transition state.The highest yield and diastereoselectivity are observed using 3 equiv. of LDA as a base and 3 equiv. of TMSCl. At a 90 : 10 initial ratio of *syn* and *anti* isomers of allylic ester, the resulting product mixture is enriched with 2,3-*syn*-3,4-*anti* diastereomer **198a** (the overall isolated yield is 68%, the ratio of the major diastereomer is 87%), while at a 3 : 97 initial ratio, 2,3-*syn*-3,4-*syn* diastereomer **198b** prevails (the overall isolated yield is 64%, the ratio of the major diastereomer is 84%). The total yield of product **198** varies from 5 to 82%, and the **198a** : **198b** : **198c** : **198d** diastereomeric ratio is from 5 : 84 : < 1 : 11 to 87 : 5 : 7 : 1.

The [3,3]-sigmatropic rearrangement of compounds **199a**,**b** is well suitable for constructing quaternary stereocentres in molecules **200a**,**b** (Scheme 122).[220] It is based on the conversion of disubstituted enolates derived from esters of cyclic alcohols in the presence of base **201**. The process shows moderate diastereoselectivity; *E* isomer **199a** produces a mixture of *R*-(**200a**) and *S*-(**200b**) products in 70 : 30 ratio in 85% yield, whereas *Z* isomer **199b** provides 76%

Scheme 123

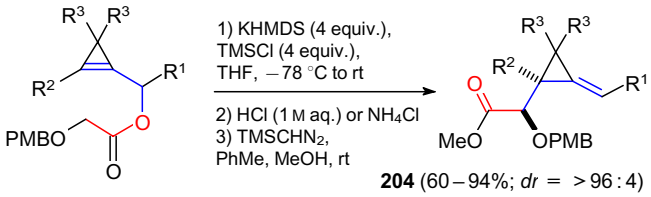


Scheme 124



R = H, Me;
(*a*) BSA (1 equiv.), KOAc (0.1 equiv.), DCM, rt, 16 h;
(*b*) BSA (1.0 equiv.), KOAc (0.1 equiv.), DMF, MW, 160 °C, 10 min

Scheme 125



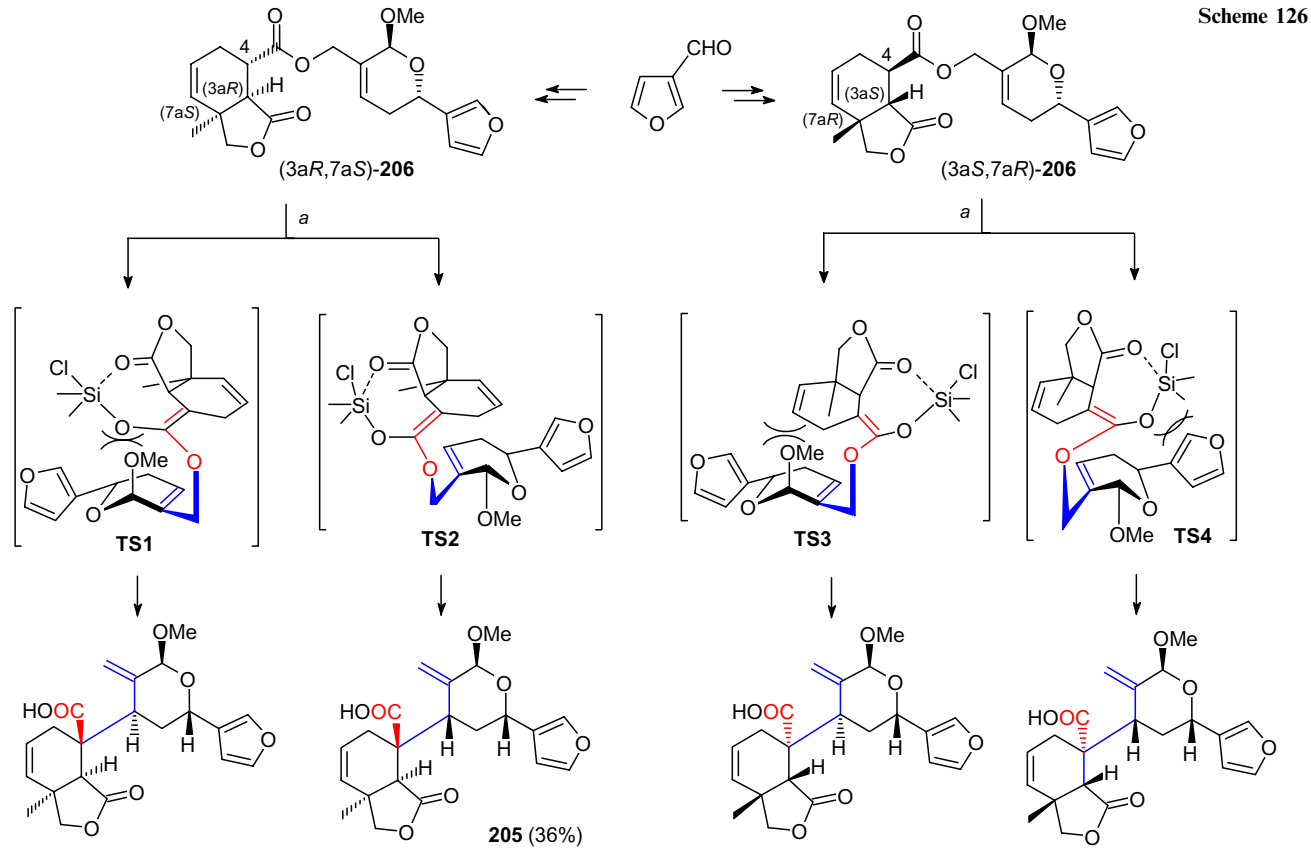
204 (60–94%; *dr* = >96 : 4)

R^1 = $(CH_2)_2Ph$, CH_2OBn, $(CH_2)_2OTIPS$, Ph, 4-$F_3CC_6H_4$, 4-$MeOC_6H_4$, 3-Py, 3-Th, *N*-methylpyrazol-4-yl; R^2, R^3 = H, Me

yield and *dr* = 40 : 60. The formation of two adjacent quanternary sterogenic centres is attributed to a chair-like transition state.

1,3,2-Diazaphospholenes (DAP) are a novel class of potent catalysts for the Claisen rearrangement (Scheme 123). Reed *et al.*[221] suggested using such catalysts for the very mild reductive Claisen rearrangement and opposed this approach to the classical Ireland–Claisen rearrangement. The latter protocol requires low temperatures and an equimolar amount of a strong base, thus precluding the use of base-sensitive compounds. Theoretical studies suggest that the nature of intermediates and the mechanism of the catalytic action to a large extent depend both on the substrate nature and diazaphospholene structure. The initial reaction of the activated form of the catalyst **VIII** (hereinafter designated as [P]-H) with compound **202** can afford intermediate **A** or **B**. It was experimentally shown that intermediate **B** cannot be converted into alkyl ketene acetal **A**, but it can produce boron enolate **C** through the loss of the [P]-H molecule and the reaction with pinacolborane (HBpin). Further, the enolate **C** undergoes the [3,3]-sigmatropic rearrangement (conditionally designated in the Scheme as B-[3,3]) to afford compound **E**. In this case, the diastereomeric ratio of compound **E** upon completion of the reaction is determined by the *E* and *Z* isomer ratio for intermediate **C** and preferred geometry of the transition state (chair- or boat-like; this mainly depends on the nature of substituents in the starting molecule). There are more possible pathways for subsequent transformations of intermediate **A**. First of them is the reaction

Scheme 126



(*a*) 1) LiHMDS, PhMe; 2) Me_2SiCl_2, Et_3N, −78 to 80 °C

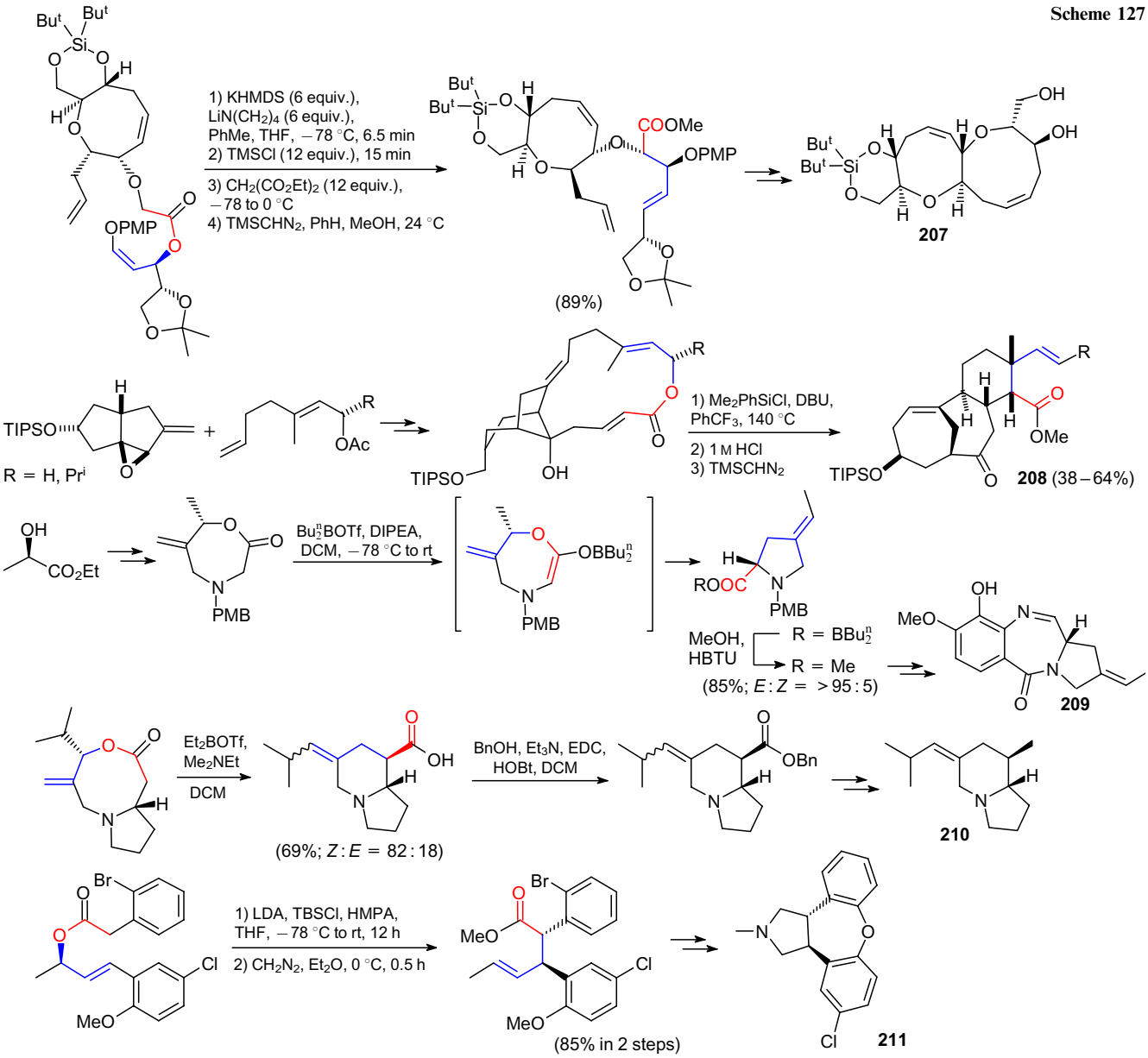
with HBpin and a shift towards the pathway B-[3,3]. However, the direct rearrangement of alkyl ketene acetal **A** to compound **D** (pathway P-[3,3]) followed by the [P]-H molecule elimination to give intermediate **E** would be more beneficial as it would provide the highest level of stereocontrol. The search for the optimal chiral diazaphospholene to improve stereo- and enantioselectivity of the reaction is currently underway but it can already be noted that this method tolerates a wide range of functionalities in the substrate and is carried out at room temperature.

Unsaturated seven-membered lactone **203a** bearing an arylsulfonyl (or arylsulfoximinyl) substituent undergoes stereoselective transannular Claisen rearrangement to afford substituted vinylcyclopropanes (Scheme 124).[222] A similar transformation involving eight-membered lactones **203b** produces substituted vinylcyclobutanes.[223]

Ernouf *et al.*[224] pioneered the study of the Ireland–Claisen rearrangement of glycolates and glycinates derived from substituted secondary cyclopropenyl carbinols. This reaction provides an efficient and stereoselective access to densely functionalized alkylidene cyclopropanes **204** bearing an α-hydroxy or α-amino acid functionality (Scheme 125). These compounds are valuable precursors of substituted cyclopropanes formed *via* diastereoselective hydrogenation of an exocyclic double bond. A similar one-pot transformation involving the formation of difluorocyclopropene followed by the Ireland–Claisen rearrangement was employed in the synthesis of difluoro-substituted analogues.[225]

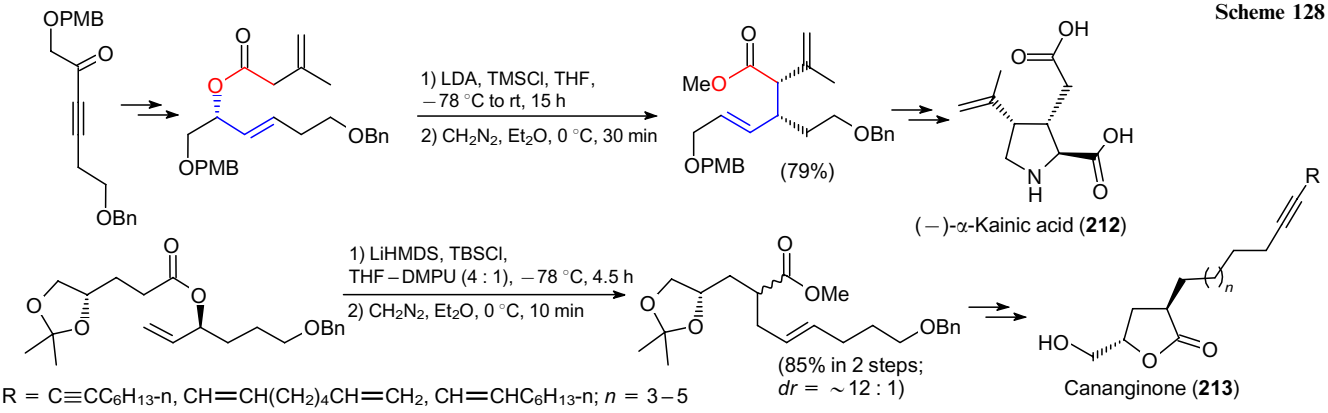
Clutiolide is a secolabdane diterpene isolated from the shrub *Clutia abyssinica*. The Ireland–Claisen rearrangement provided the basis for the stereoselective synthesis of a precursor of clutiolide **205** (Scheme 126).[226] The selectivity of the reaction is controlled by chelation of the dimethylsilyl group with the carbonyl oxygen of the lactone moiety. In this situation, four transition states (**TS1**–**TS4**)

Scheme 127

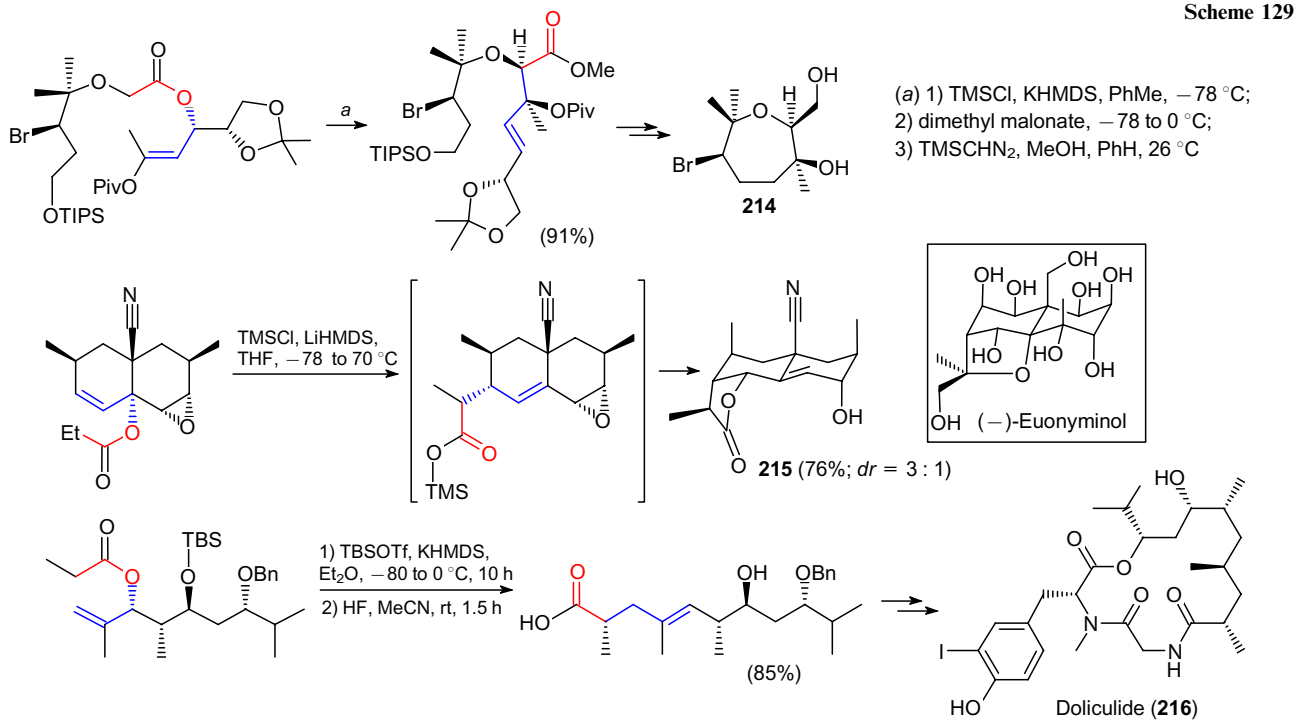


PMP is 4-methoxyphenyl, DBU is 1,8-diazabicyclo[5.4.0]undec-7-ene, HBTU is 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethylurea, DIPEA is diisopropylethylamine, EDC is 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, HOBT is 1-hydroxybenzotriazole, HMPA is hexamethylphosphoramide

Scheme 128



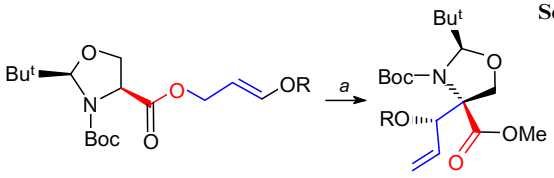
Scheme 129



are possible for two diastereomers of compound **206** but only one of them (**TS2**) provides the lowest steric strains and prevails. The latter fact was confirmed experimentally. Thus, the desired diastereomer **205** was isolated from the reaction mixture in 36% yield along with a minor unidentified diastereomer (4% yield). The geometry of compound **205** was established by 2D NOESY spectroscopy of its iodolactonization product (not shown in Scheme 126). The authors assume that using the individual (3a*R*,4*S*,7a*S*) isomer of compound **206** can lead to an increase in the yield of desired product **205** to 70%.

In recent years, the Ireland–Claisen rearrangement was extensively applied as a reliable synthetic tool to the synthesis of complex natural and biologically active compounds, which can easily be optimized for a certain purpose. Based thereon, for example, the following polycyclic compounds were obtained: bicycle **207**, which is a fragment of E and F rings of ciguatoxin 3C isolated from dinoflagellate *Gambierdiscus toxicus*;[227] the (iso)cyclocitrinol core (**208**);[228] limazepine E (**209**) and barmumycin, which are superpotent naturally occurring antitumour agents;[229,230] the putative structure of 8-deoxypumiliotoxin

Scheme 130



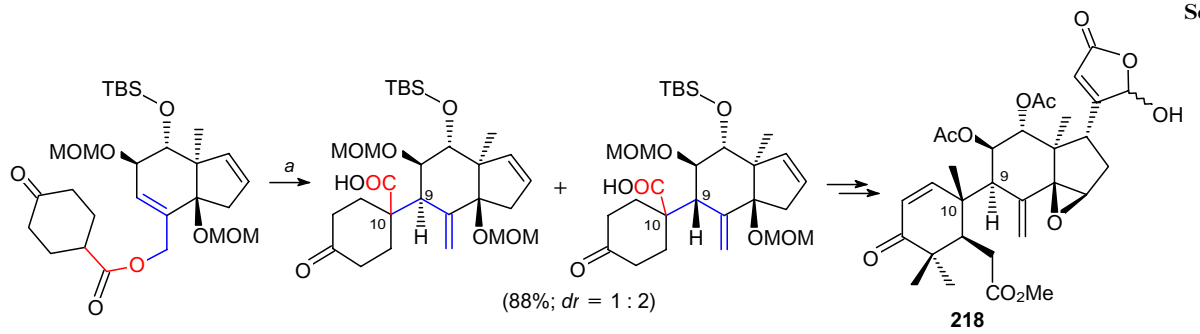
a — 1) TMSCl (3 equiv.), LiHMDS (3 equiv.), THF, −78 to 23 °C, 16 h
2) CH_2N_2, Et_2O; R = Me, Et, Pr^i, Bu^i, All, propargyl, Cy, Bn, Ph

193H (**210**);[231] (±)-asenapine (**211**), an active ingredient of the drug Saphris (Sycrest),[232] which is used for the treatment of bipolar disorders (Scheme 127).

The Ireland–Claisen rearrangement was also successfully implemented to prepare natural heterocyclic compounds based on a five-membered ring, namely, (−)-α-kainic acid (**212**)[233] and the γ-butyrolactone derivative, cananginone (**213**) (Scheme 128).[234]

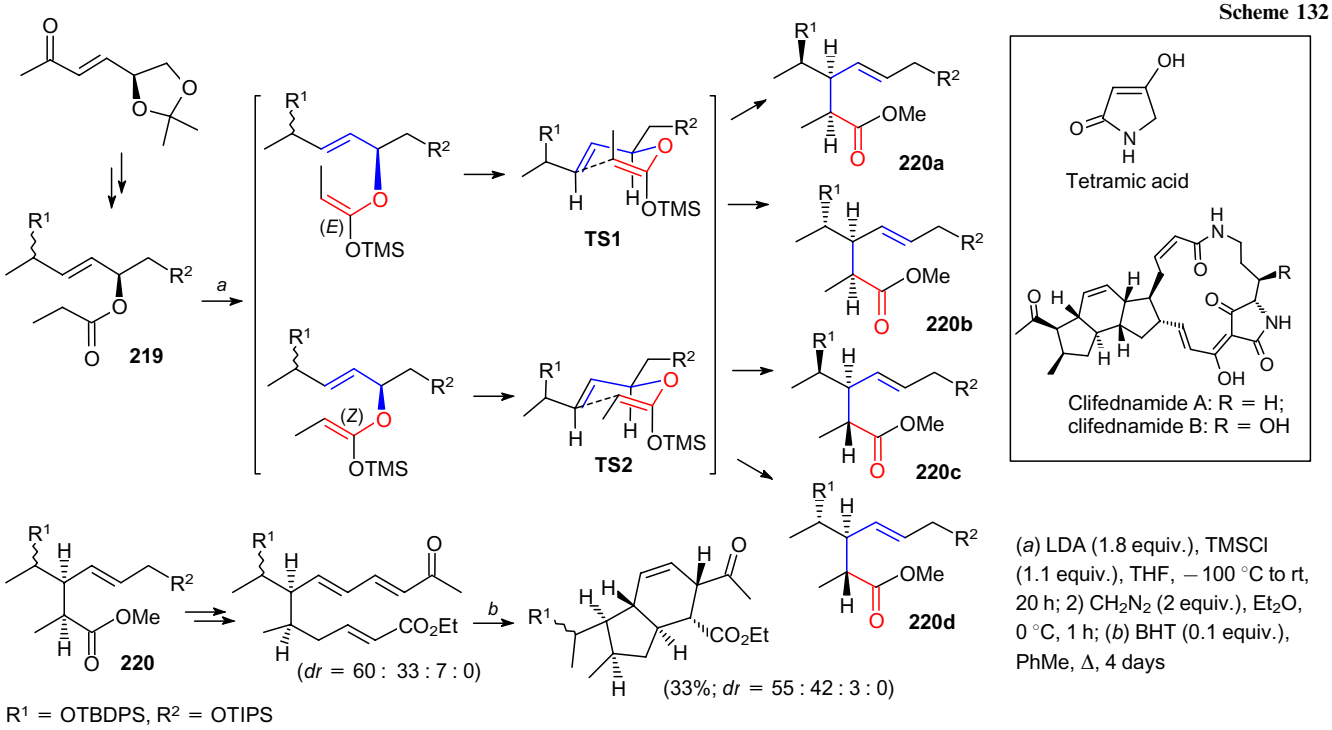
Other examples of great synthetic potential of the Ireland–Claisen rearrangement for the construction of complex compounds are reactions as depicted in

Scheme 131



(*a*) LiHMDS, TMSCl–Et_3N [1 : 1 (vol.)], PhH, −78 to 65 °C, 6 h; then 65 °C, 60 h

Scheme 132



(*a*) LDA (1.8 equiv.), TMSCl (1.1 equiv.), THF, −100 °C to rt, 20 h; 2) CH_2N_2 (2 equiv.), Et_2O, 0 °C, 1 h; (*b*) BHT (0.1 equiv.), PhMe, Δ, 4 days

R^1 = OTBDPS, R^2 = OTIPS

Scheme 129. They include the synthesis of moiety **214** of armatol A, naturally occurring polycyclic ether of the triterpene series isolated from the red alga *Chondria armata*,[235] compound **215** having the euonyminol scaffold[236] and marine cyclodepsipeptide doliculide (**216**).[237]

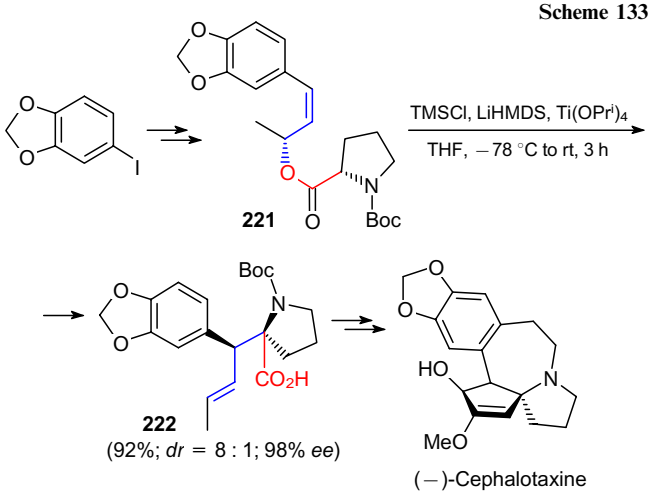
Using the Ireland–Claisen rearrangement, one can obtain precursors of the immunosuppressant mycestericin G, compound **217** (Scheme 130).[238] This transformation was also employed to prepare other biologically relevant β,β′-dihydroxy amino acids. The rearrangement is characterized by high stereoselectivity and provides a high level of remote stereocontrol.

A possible access to the 21-hydroxytoonacilide core scaffold **218** using the Ireland–Claisen rearrangement was explored (Scheme 131).[239] Detailed model studies showed that this rearrangement can be used to construct the central C(9)–C(10) bond, thereby facilitating the formation of the B-seco limonoid scaffold. However, the application of the developed strategy failed in more complex and sterically crowded systems.

Clifednamide is a member of the class of macrocyclic tetramic acid lactams. A fragment of this compound was synthesized by the Ireland–Claisen rearrangement and the intramolecular Diels–Alder reaction. First, precursor **219** was prepared starting from di-*O*-isopropylidene-D-mannitol followed by a diastereoselective sigmatropic rearrangement (Scheme 132). The treatment with LDA affords mainly *E*-enolate of compound **219**, resulting in the predominant formation of the transition state **TS1.** This gives rise to a 97 : 3 ratio of diastereomers formed *via* transition states **TS1** and **TS2**. The ratio of individual diastereomers **220a** : **220b** : **220c** : **220d** was 50 : 47 : 2 : 1 (52% overall yield). The subsequent Diels–Alder reaction of compound **220** gives the target ethyl hexahydro-1*H*-indenecarboxylate with high diastereoselectivity.[240]

A total synthesis of (−)-cephalotaxine was accomplished using the Claisen rearrangement of corresponding esters **221**. During this synthesis, a variety of issues have to be addressed, related to the low selectivity of the rearrangement for (*Z*)-allylic esters and the formation of large amounts of the undesirable *threo*-form in the case of (*E*)-allylic esters. The solution was to use (*Z*)-allylic esters without pendant substituents in the aromatic moiety, which relieved the steric strain in the transition state and improved the diastereomeric ratio to 6 : 1 in favour of the desired *erythro* isomer of product **222** [the presence of $Ti(OPr^i)_4$ in

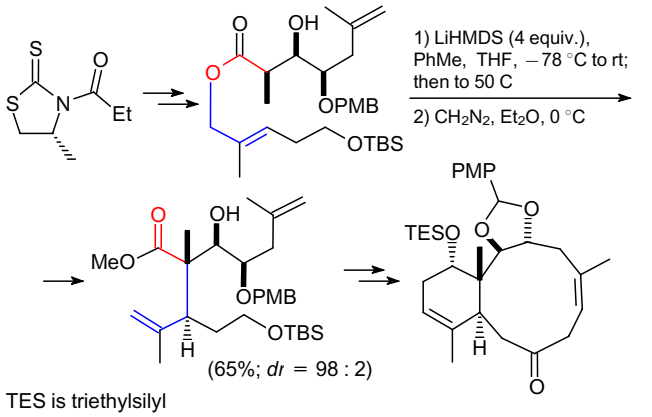
Scheme 133



the reaction mixture increases this ratio to 8 : 1] with an enantiomeric excess of 98%. These results show that the *ortho* substituent on the aromatic ring has a decisive influence on the stereochemical outcome of the rearrangement (Scheme 133).[241]

The dianionic Ireland–Claisen rearrangement enabled the construction of the briarane–brianthein A core.[242] Two consecutive ring-closing metathesis reactions helped to assemble a *trans*-fused system consisting of six- and ten-membered carbon rings (Scheme 134).[243]

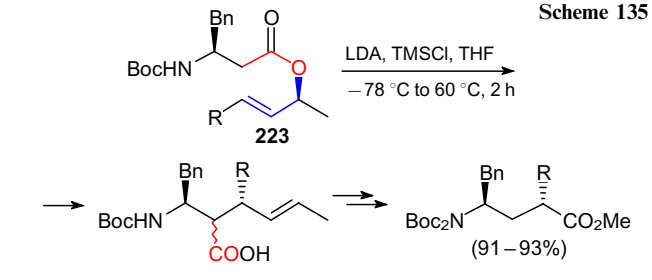
Scheme 134



TES is triethylsilyl

The Ireland–Claisen rearrangement is a key step in the synthesis of tubuphenylalanine, a major building block for the highly potent anticancer agents tubulysins.[244] The successive implementation of this rearrangement involving substituted β-amino acid allylic esters **223**, decarboxylation and oxidative cleavage of the double bond allows for the highly stereoselective introduction of substituents at the α-position of the newly formed γ-amino acids (Scheme 135).[244]

Scheme 135



R = Me, Et, CH_2OTBS

3.5. Aza-Claisen rearrangement

The aza-Claisen rearrangement did not attract the attention of researchers for a long time because this reaction with allyl vinyl amines required significant heating, resulting either in the formation of undesirable by-products or the decomposition of the starting compounds. However, the development of metal complex catalysis made it possible to reduce the temperature of the process down to room temperature (and below), and the use of charged intermediates in the process significantly reduced the reaction time. This version of the rearrangement is referred to as a charge-accelerated aza-Claisen rearrangement. The methods most frequently used to generate charged intermediates to be rearranged include the protonation, quaternization of the nitrogen atom or coordination to Lewis acids.

These changes in the reaction conditions made it possible to readily adapt this method to prepare various nitrogen-containing molecules and effectively apply it to the synthesis of natural compounds. In 2017, the data on the use of the aza-Claisen rearrangement for ring expansion under various conditions were summarized in the study,[245] and a review[246] published in 2009 described known examples of this rearrangement.

Using diallylanisidine as the starting material, Mandal *et al.*[247] developed an effective approach to produce benzo[*b*]azepines **224**. The double Claisen rearrangement, ring-closing metathesis and subsequent cross-metathesis can be accomplished in a one-pot fashion (Scheme 136). A similar reaction sequence was implemented for the synthesis of seven–nine-membered nitrogen heterocycles (see Scheme 136). The reaction of arynes, generated *in situ* under the action of cesium fluoride, with secondary allylamines affords *ortho*-allyl-substituted *N*-arylanilines, which react with the second equivalent of the aryne. The newly formed diallyldiarylammonium salts undergo aza-Claisen rearrangement to give compounds **225.** The metathesis reactions of the latter compounds produce azepines, azocines and azonines.[248] Similar annulated nitrogen-containing heterocycles are available from naphthalene,[249] pyrimidine,[250] coumarin and quinoline[251] derivatives.

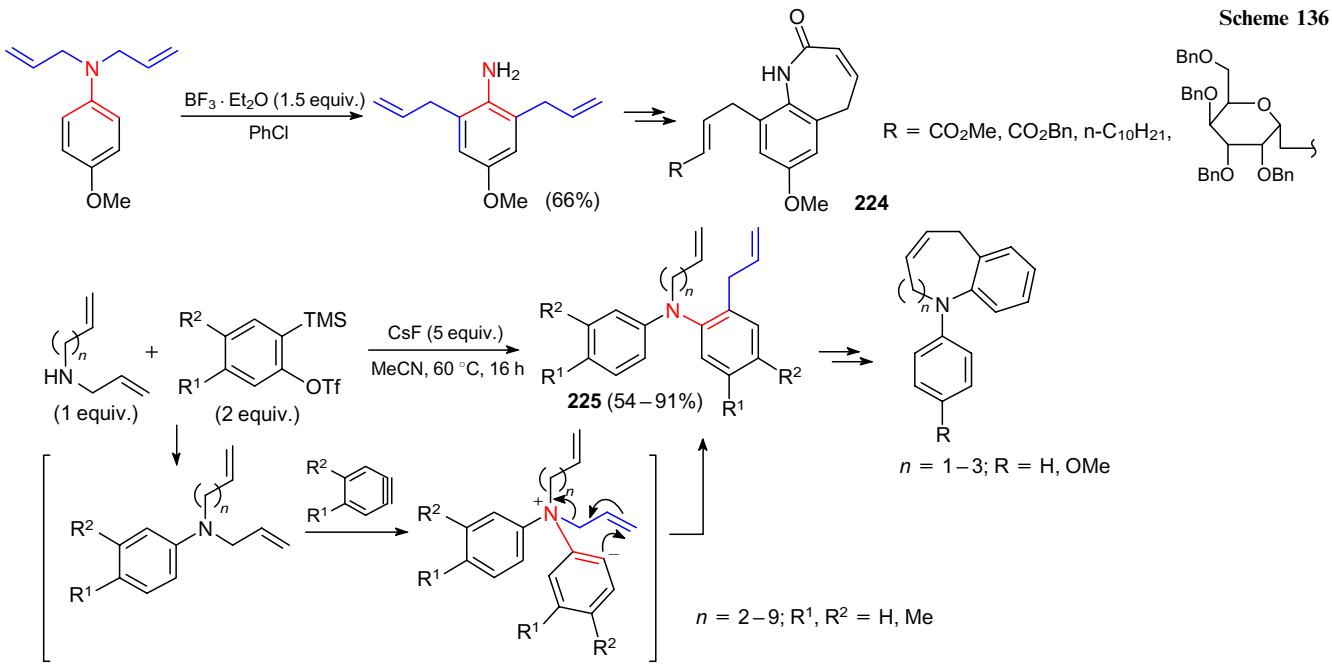
N-Allyl-*N*-methylanilines **226** react with methyl diazoacetate or diazoacetone in the presence of Y, Sc or Sm triflates to furnish the corresponding methyl *N*-(2-allylaryl)-*N*-methylglycinates **227** or 2-allyl-*N*-methyl-*N*-(2-oxopropyl)anilines *via* the aza-Claisen rearrangement (Scheme 137).[252]

The cyclization of diallylanilines **228**, bearing an *ortho*-ethynyl substituent in the aromatic ring, is catalyzed by ruthenium complexes (Scheme 138).[253] The transformation occurs through the aza-Claisen rearrangement and is accompanied by an allyl group migration to give substituted indoles **229**. The authors confirmed the mechanism involving the vinylidene intermediate.

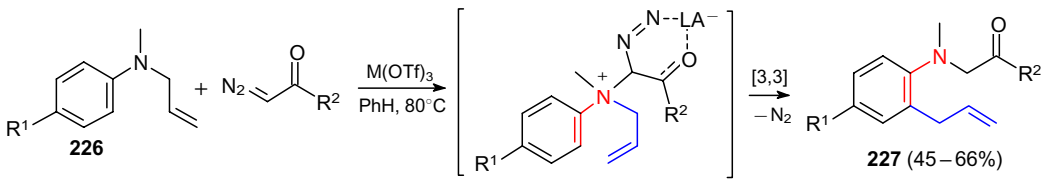
In 2013, the first example of an enantioselective indole aza-Claisen rearrangement was reported.[254] The reaction is catalyzed by chiral Brønsted acid **IX** (Scheme 139). This approach affords 3-amino-2-allyl-substituted indoles **230** in 81–93% yields with enantioselectivity from 22 to 96%.

A novel version of the Claisen rearrangement involving the Breslow intermediate was described by Alwarsh *et al.*[255] This method is of considerable interest for medicinal chem-

Scheme 136



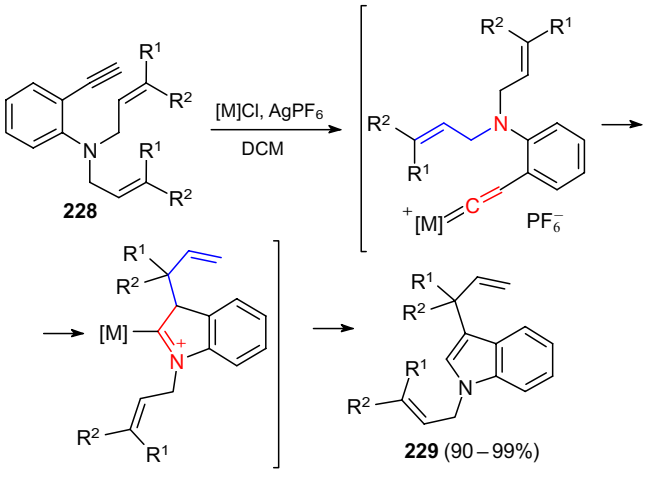
Scheme 137



R1 = H, Me, OMe, F;
R2 = Me, OMe;
M = Y, Sc, Sm;
LA is Lewis acid

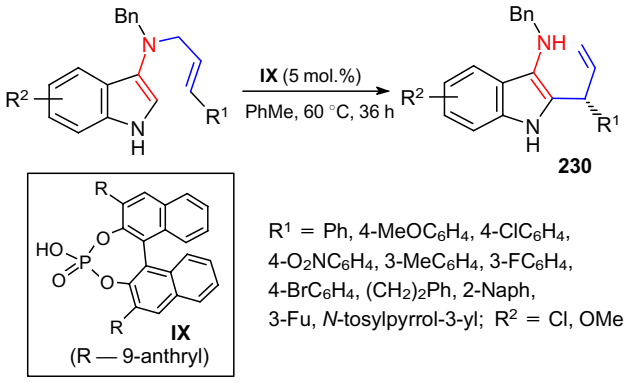
istry since the benzothiazole motif is found in a number of pharmaceutical drugs. Applying the reaction sequence proposed by the authors, one can prepare tertiary benzothiazole-substituted alcohols without the need for low temperatures and organometallic reagents. It is also worth mentioning that the reaction with electron-deficient aldehydes under the said conditions is more rapid than that with electron-rich ones (Scheme 140).[255] This is also true for the condensation of an aldehyde with a benzothiazolium salt as well as for the subsequent Claisen rearrangement.

Scheme 138



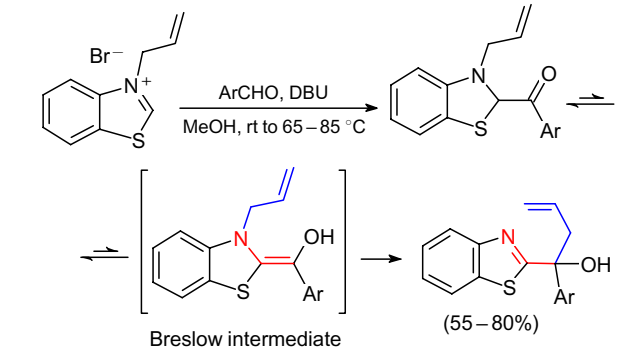
[M] = Cp(PPh3)2Ru, Cp(dppe)Ru; R1, R2 = H, Me;
dppe is 1,2-bis(diphenylphosphino)ethane

Scheme 139



R1 = Ph, 4-MeOC6H4, 4-ClC6H4, 4-O2NC6H4, 3-MeC6H4, 3-FC6H4, 4-BrC6H4, (CH2)2Ph, 2-Naph, 3-Fu, *N*-tosylpyrrol-3-yl; R2 = Cl, OMe

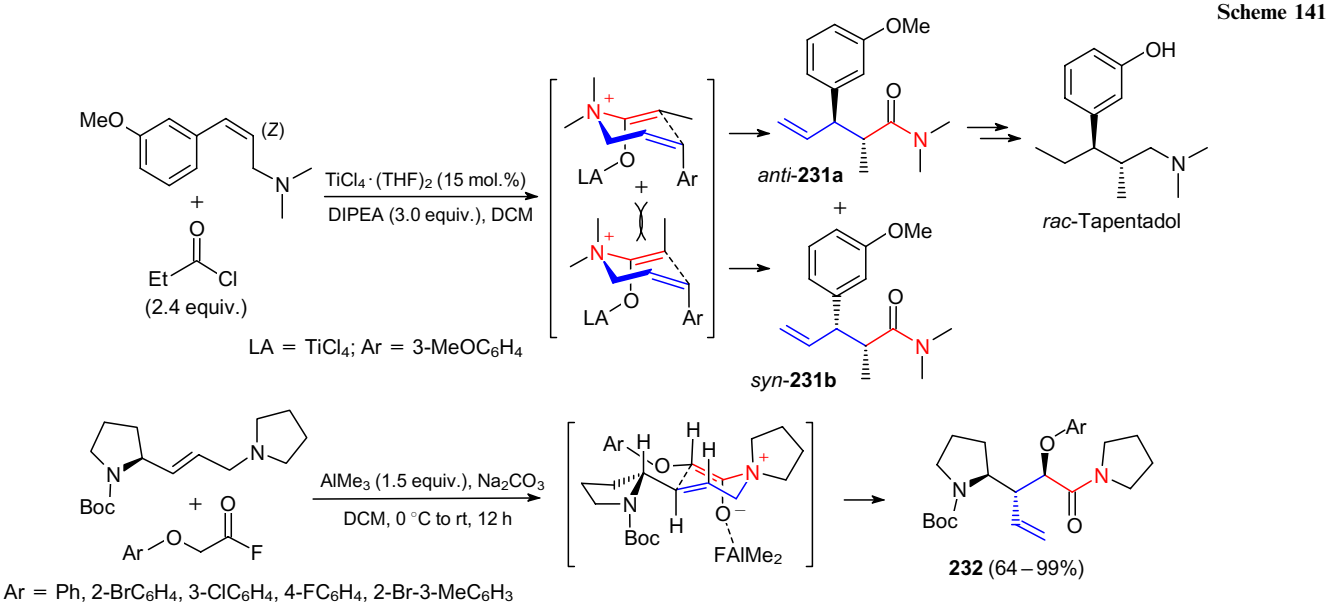
Scheme 140



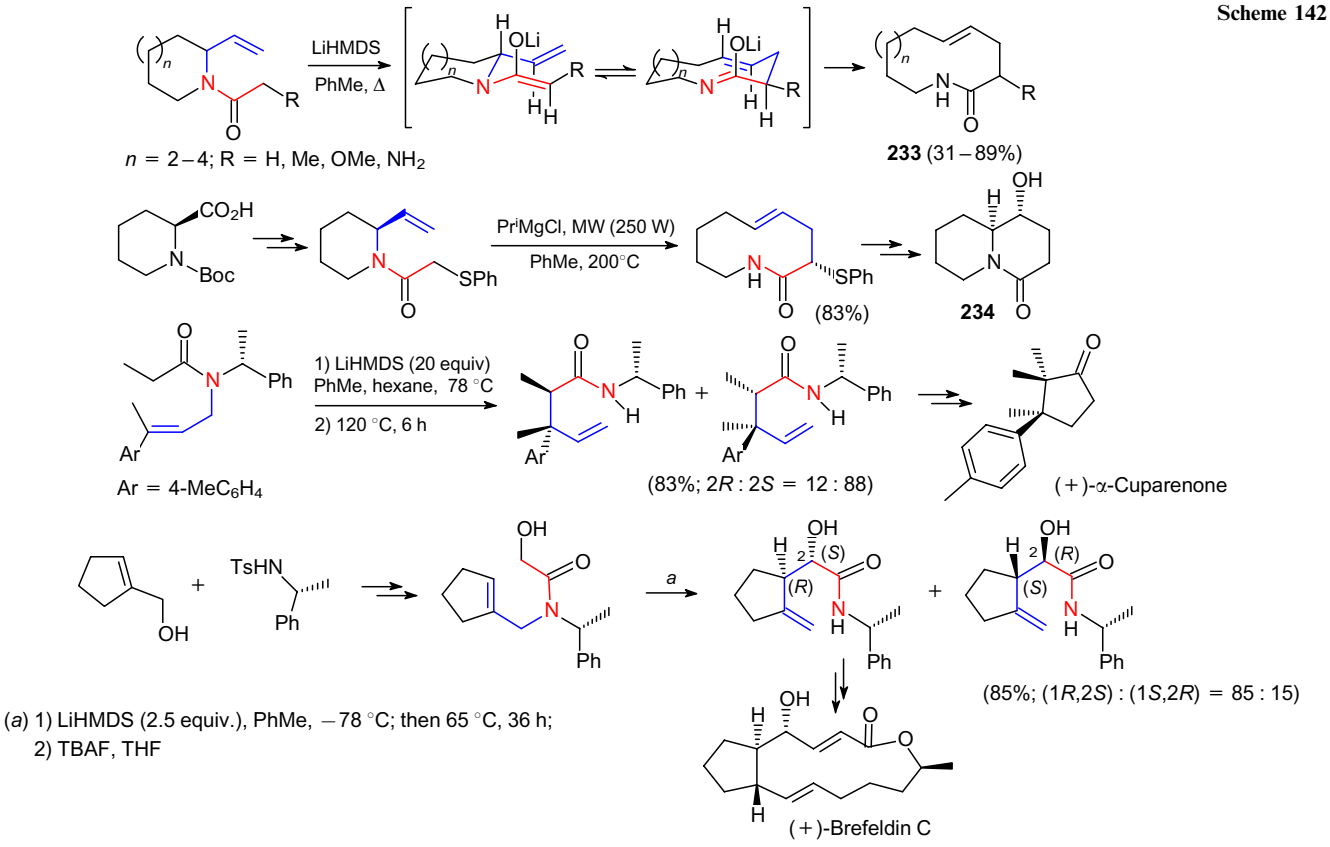
Ar = Ph, 2-BrC6H4, 2-MeOC6H4, 2-HOC6H4, 2,4-Cl2C6H3, 1-Naph, 2-Py, 2-Fu

The aza-Claisen rearrangement was employed in the synthesis of racemic tapentadol with analgesic properties. A key step of this synthesis was a $TiCl_4$-catalyzed reaction giving rise to two vicinal tertiary carbon stereocentres. The subsequent amide reduction and alkene hydrogenation produced tapentadol and its stereoisomers. The low yield of the reaction product in the case of the *Z*-alkene (13%, 5.1 : 1 *anti*-**231a** : *syn*-**231b** ratio) was attributed to the higher energy of the transition state due to the pseudoaxial position of the *m*-methoxyphenyl substituent or the possible reaction pathway *via* the boat-like conformation. The product yield for the starting *E*-alkene was significantly higher (76%); however, in this case, the *syn* diastereomer **231b** was the major product (1 : 11 *anti* : *syn* ratio) unsuitable for the synthesis of tapentadol (Scheme 141).[256] A similar strategy was used in the aza-Claisen rearrangement of optically active *N*-allylpyrrolidines. These compounds react with α-phenoxyacetyl fluorides with high diastereoselectivity to generate a new C—C bond (see Scheme 141). Resulting γ,δ-unsaturated amides **232** served as precursors for the synthesis of pyrrolizidine alkaloids.[257]

Scheme 141



Scheme 142



Systematic studies of the amide enolate-induced aza-Claisen rearrangement provided a convenient route to 11–13-membered lactams **233** (Scheme 142).[258] A key feature of this method is the introduction of electron-donating substituents at the α-position of amide substrates to facilitate the rearrangement.[259–262] A similar approach was employed in the synthesis of (+)-1-hydroxyquinolizidinone (**234**)[263] and also certain natural compounds such as (+)-α-cuparenone[264] and (+)-brefeldin C.[265]

A tandem Reformatsky-aza-Claisen rearrangement in the synthesis of compound **235** containg the tabernaemontanine scaffold became the basis for the preparation of alkaloids of this family from carboline **236** (Scheme 143).[266]

Carba analogues of physostigmine **237** were obtained by the reaction between substituted *N*-methylanilines and six–seven-membered carbocycles. The aza-Claisen rearrangement occurs in the presence of boron trifluoride etherate to afford products in moderate yields. A possibility to use compounds **237** in the Suzuki reaction was investigated (Scheme 144).[267]

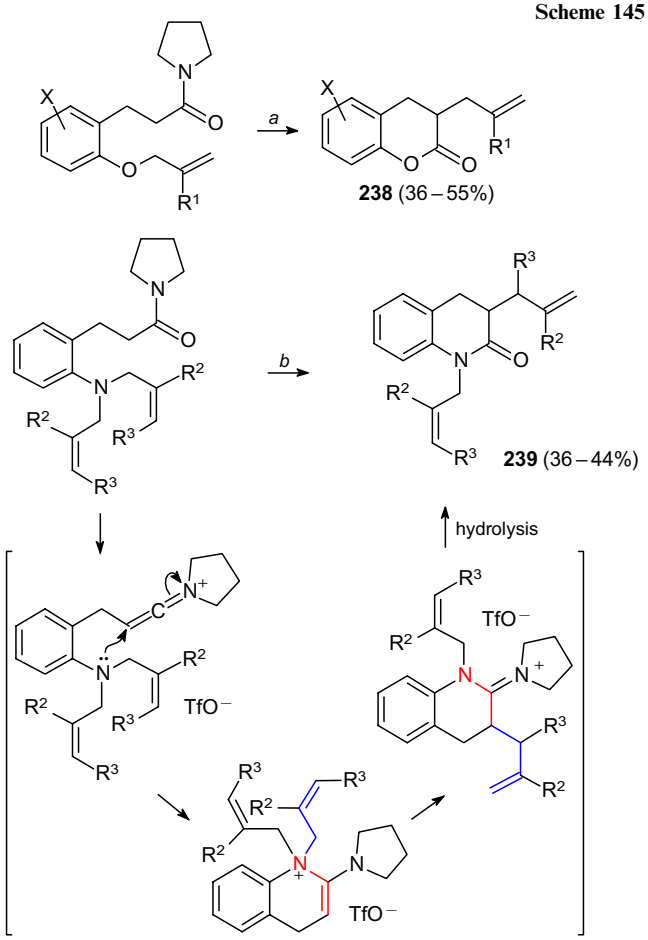
The electrophilic Claisen rearrangement was extended to the preparation of conformationally hindered amides bearing an aromatic ring.[268] The developed protocol is applicable to the synthesis of 3-allylhydrocoumarins **238** (valuable components in inorganic synthesis), with compounds bearing an allyloxy moiety in the aromatic ring serving as the starting materials. When attempting to carry out the aza-Claisen rearrangement under the same conditions, two reaction pathways are possible. The tosyl migration is observed for sterically unhindered *N*-allyl derivatives, whereas for compounds containing bulky substituents at the aniline nitrogen atom, the Claisen rearrangement occurs to give a variety of quinolines **239** and isoquinolines (Scheme 145). A similar procedure described above was used to produce substituted γ-butyrolactones (see Scheme 40).

Allenic esters **240** react with N-allylated pyrrolidines in the presence of Lewis acids to give allyl(vinyl)ammonium intermediates prone to the Claisen rearrangement. The microwave-assisted protocol improves the yields of products **241** (Scheme 146).[269]

The copper-catalyzed three-component reaction of alkynes, tosyl azide and tertiary allyl amines allows for a one-pot synthesis of α-allylated amidines (39–99% yield, diastereomeric ratio **242a** : **242b** > 99 : 1). The high diastereoselectivity is achieved through the predominant interaction of allyl amine with the ketene iminium intermediate on the side opposite to the substituent R. In reactions of alkynes with sterically less demanding substituents (*e.g.*, alkyls) participate in the reaction the diastereoselectivity decreases, thus supporting this hypothesis (Scheme 147).[270] A similar transformation was also accomplished in an intramolecular fashion for compounds **243**.[271]

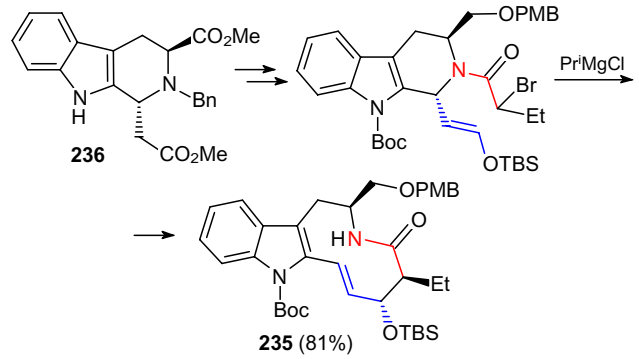
The gold-catalyzed amination of allyl-substituted *N*-tosylcarbamates furnishes substituted *N*-tosylated allyl-

Scheme 145

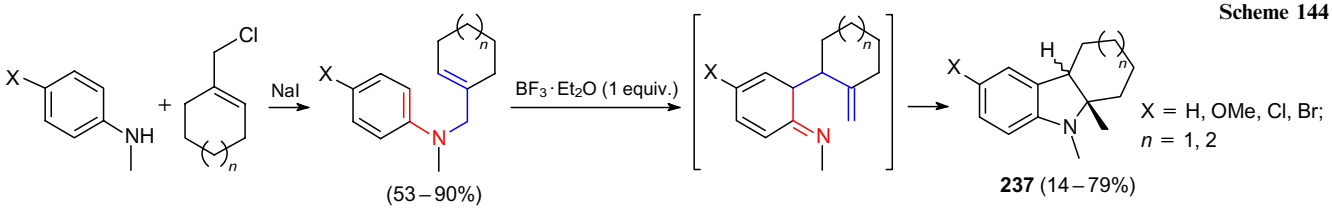


(*a*) 1) Tf_2O (1.05 equiv.), *s*-collidine (1.2 equiv.), DCM, MW, 120 °C; 2) 1 M AcOH, 24 h; (*b*) 1) sealed tube, Tf_2O (1.05 equiv.), *s*-collidine (1.2 equiv.), DCM, MW, 120 °C; 2) sealed tube, 1 M AcOH, 80 °C, 24 h; X = H, 3-Me, 4-OMe; R^1 = H, Me, CH_2Cl, CH_2OAc, CO_2Et, Br; R^2, R^3 = H, Me

Scheme 143

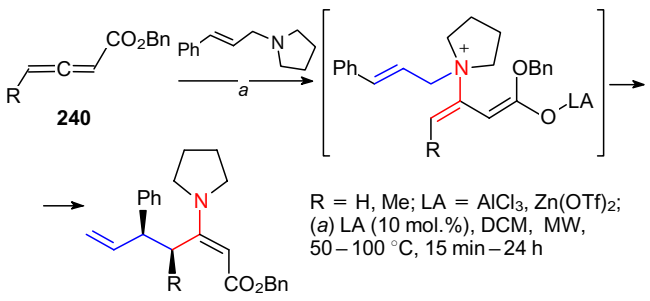


Scheme 144



X = H, OMe, Cl, Br; *n* = 1, 2

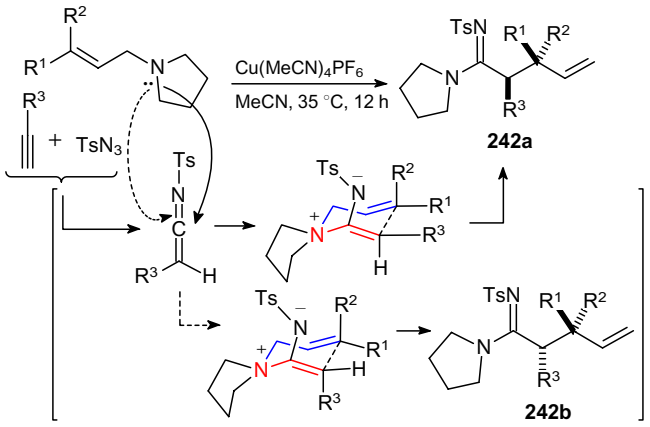
Scheme 146



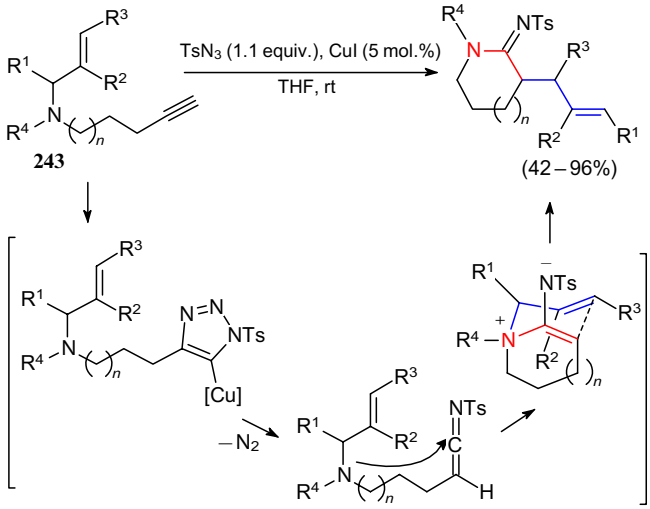
R = H, Me; LA = $AlCl_3$, $Zn(OTf)_2$;
(*a*) LA (10 mol.%), DCM, MW,
50 – 100 °C, 15 min – 24 h

241 (59 – 99%; *syn* : *anti* = from 67 : 33 to 76 : 24)

Scheme 147



R^1 = Me, Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, 4-$O_2NC_6H_4$, 2-Fu; R^2 = H, Me; R^3 = XC_6H_4 (X = H, 4-Me, 4-OMe, 2-OMe, 4-Bu^t, 4-F, 4-Cl, 4-Br, 2-Br, 4-CF_3, 4-NO_2, 4-CO_2Me, 3,4-Cl_2), 3-Py, Bu^n, $(CH_2)_2OAc$, $(CH_2)_2OBoc$, $(CH_2)_4OBoc$



n = 0, 1; R^1, R^2 = H, Ph; R^3 = H, CO_2Et, Ph; R^4 = Ph, PMB, 4-ClC_6H_4, 4-$F_3CC_6H_4$, 4-$O_2NC_6H_4$, n-C_6H_{13}, All, Bn, CH_2CO_2Et

amines **244** in yields of up to 82% with high regio- and stereoselectivity (Scheme 148).[272] This tandem reaction proceeds through the aza-Claisen rearrangement *via* the formation of a six-membered cyclic intermediate. The Grob-type fragmentation followed by decarboxylation yield the final products. This reaction can be carried out in a one-pot fashion.

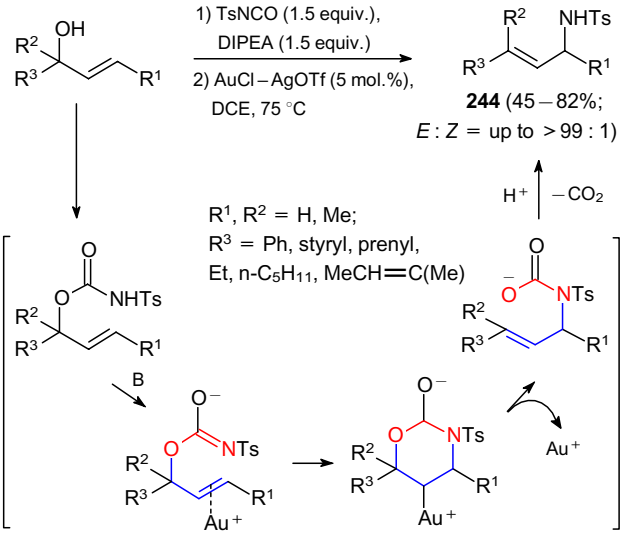
A sigmatropic rearrangement of a structurally similar motif was used as a key step in constructing iminosugars from compounds **245** derived from allyl imidate **246** (Scheme 149).[273] The copper-catalyzed ketenimine-mediated multicoponent reaction afforded the desired *N*-allyl *N*-sulfonyl amide functionality necessary for the implementation of this process. Similar rearrangements of heteroaromatic compounds were outlined above (see Section 3.1.2).

In the presence of platinum chloride, 1,8-enynes **247** are converted into fused tetrahydropyridines **248**.[274] The reaction proceeds as a [3,3]-sigmatropic rearrangement of intermediate **249** generated by the reaction of an acetylene moiety with platinum chloride (Scheme 150).

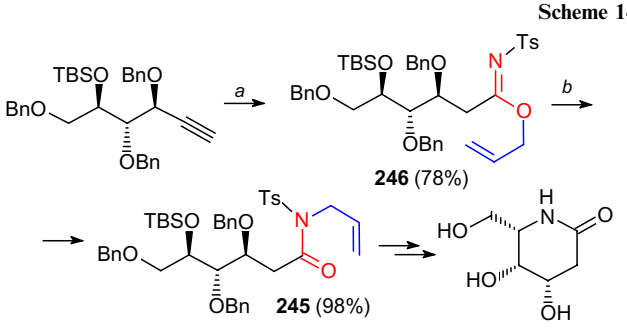
The gold chloride-catalyzed rearrangement of *N*-allylheterocycles **250** gives annulated indoles **251** in high yields (Scheme 151).[275] This cyclization is accompanied by an [3,3]-allylic migration.

A sequence involving the reaction of α-amino acids with 2-alkynylbenzaldehydes is suitable for the preparation of polyfused isoquinolines.[276] The subsequent allylation of the nitrogen atom yields compounds **252**, which can undergo the aza-Claisen rearrangement in the presence of a gold-containing catalyst to afford polyfused systems **253** (Scheme 152). The selectivity of the reaction is controlled by the bulkiness of the substituent R^4: the benzene ring provides the exclusive formation of the *cis* diastereomer, whereas less bulky alkyl groups afford a mixture of diastereomers. In terms of the reaction mechanism, this pattern is

Scheme 148



Scheme 149

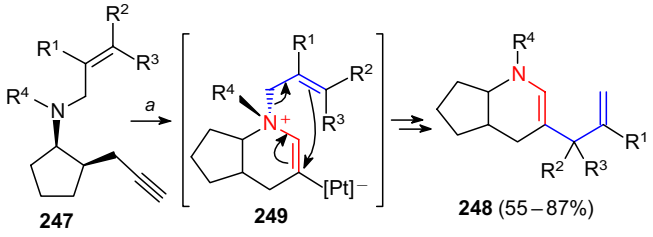


(*a*) AllOH, TsN_3, CuI, Et_3N, $CHCl_3$, rt,12 h;
(*b*) $PdCl_2(MeCN)_2$, DCE, rt, 2 h

attributable to spatial interactions between the substituents R^4 and phenyl moieties in the gold-containing catalyst.

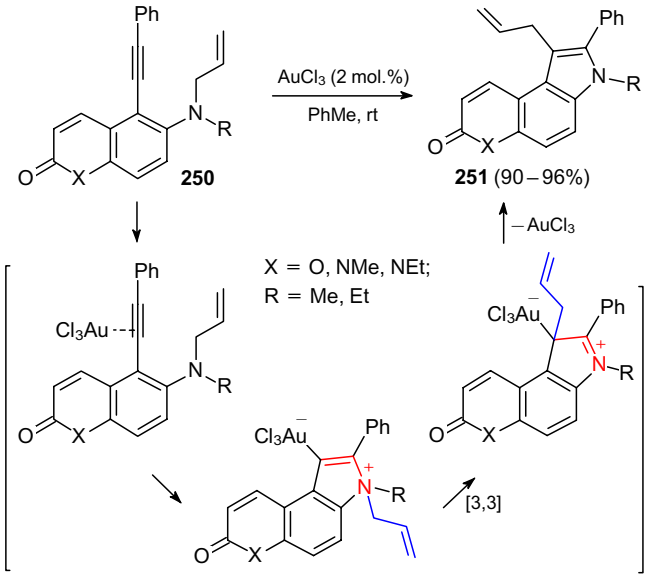
The reaction between carbodiimides and azanorbornene can be used to produce bicyclic guanidines **254** (Scheme 153).[277] The conditions for the generation of carbodiimides significantly affect the yield of the products and are largely determined by the nature of the substituents R^1 and R^2 in the starting (thio)urea. The difference in the yield of the final product depends on the procedure in use and can vary from 4 to 11% for the same substituents R^1 and R^2. The reaction proceeds *via* the 1,3-diaza-Claisen rearrangement of intermediate **A**. A similar transformation

Scheme 150

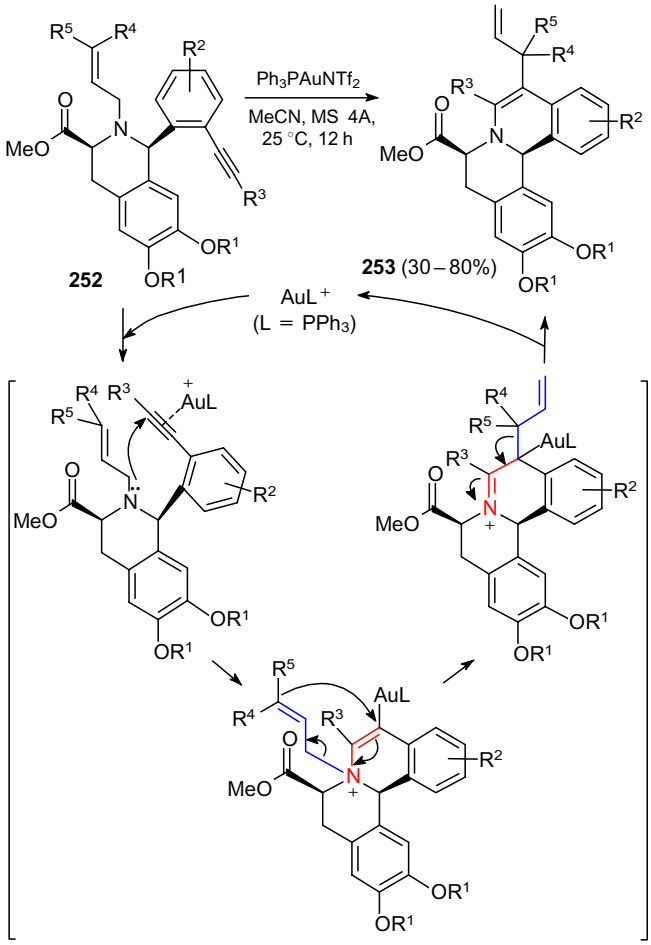


(*a*) $PtCl_2$ (7 mol.%), PhMe, MS 4A, 85 °C, 1–8 h;
R^1, R^2, R^3 = H, Me; R^4 = All, Bn, 2-$MeOC_6H_4$, 3-$MeOC_6H_4$, 4-$MeOC_6H_4$, 4-MeC_6H_4

Scheme 151



Scheme 152

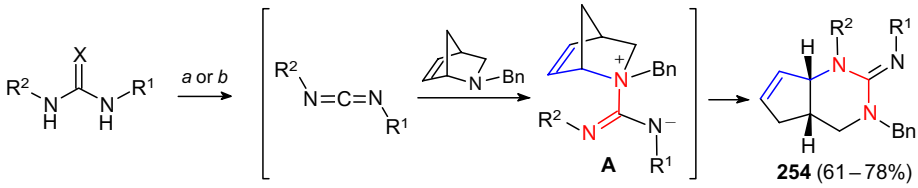


R^1 = Me, All; R^1–R^1 = $(CH_2)_2$; R^2 = F, OMe; R^3 = Pr^n, Ph, 4-BrC_6H_4, 4-$F_3CC_6H_4$, 4-MeC_6H_4, 3-$MeOC_6H_4$; R^4 = H, Me, Ph, 2-methylpent-2-en-5-yl; R^5 = H, Me

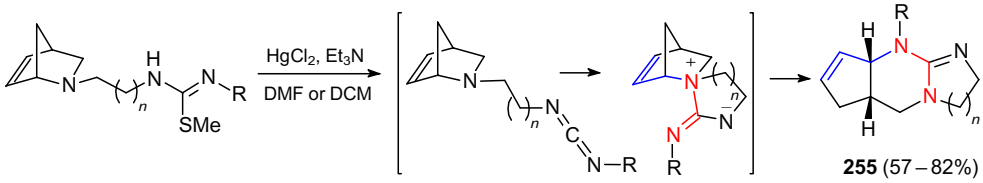
was involved in the intramolecular version. Thus, tricyclic guanidines **255** were obtained by the treatment of isothiouronium salts with mercury chloride.[278]

The aza-Claisen rearrangement catalyzed by zinc chloride provides the isomerization of *N*-allylindolines **256** into 7-allylindolines **257** (Scheme 154).[279] The process is influenced by the stereoelectronic effects of substituents in the starting *N*-allylindolines. In the case of electron-donating substituents, the rearrangement occurs at lower temperatures.

Scheme 153

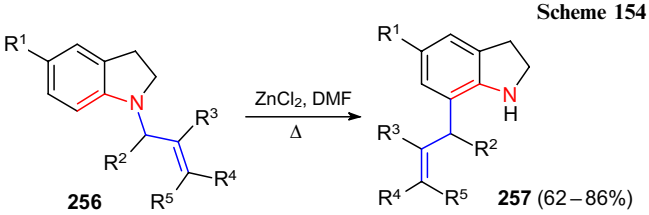


(*a*) EDC,DIPEA, $CHCl_3$, rt;
(*b*) $COCl_2$, THF, 0 °C to rt, 6 h;
X = O, S; R^1 = Ts, Tf, Ns;
R^2 = Pr^i, n-C_6H_{13}, Bn, Bz



n = 1–3; R = Pbf, Ts;
Ns is 4-nitrobenzenesulfonyl,
Pbf is 2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-sulfonyl

Scheme 154



R^1 = Me, OMe, NO_2, CO_2Et; R^2, R^3, R^4, R^5 = H, Me

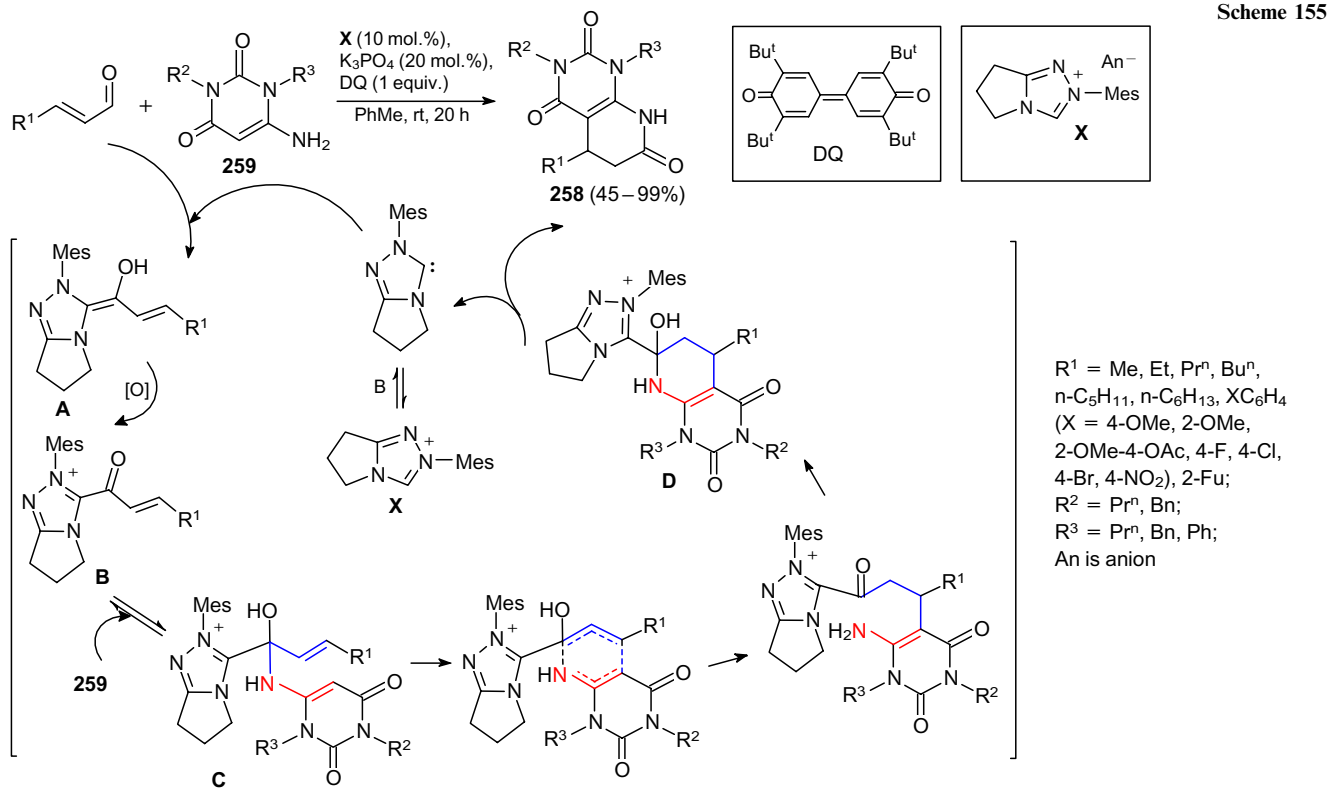
Fused uracils **258** are available from the reaction of α,β-unsaturated aldehydes with cyclic amidines **259** using 3,3′,5,5′-tetra-*tert*-butyl-4,4′-biphenylquinone (DQ) as an oxidant.[280] The reaction involved the aza-Claisen rearrangement catalyzed by N-heterocyclic carbenes, *e.g.*, generated from the salt **X**. Being treated with NHC, the starting aldehyde is converted into the Breslow intermediate **A**, which is further oxidized to acyl azolium salt **B**. The addition of cyclic enamine **259** to this salt gives hemiaminal **C**, which undergoes the aza-Claisen rearrangement. This process is followed by the intramolecular lactamization to give intermediate **D** and turnover of the catalyst to afford target fused uracils **258** (Scheme 155).

3.6. Thio(seleno)-Claisen rearrangement

Over the past decade, few examples of the use of the thio(seleno) Claisen rearrangement were described compared to the classical oxygen version, although they are characterized by general patterns. In both cases, the formation of the new [3,3]-bond occurs prior to the cleavage of the [1,1]-bond, and the transition state is predominantly highly symmetric, with little or no charge separation. The following reactions provide good examples of the great synthetic potential of heteroatom rearrangements.

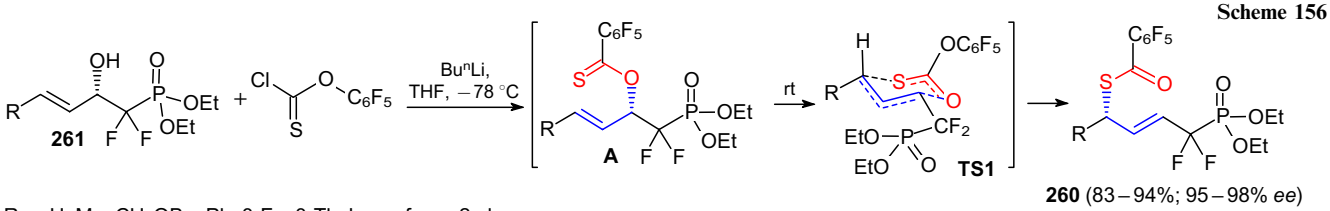
For example, the use of a combination of enzyme systems and [3,3]-sigmatropic rearrangements allowed the development of unique efficient synthetic approaches to the target compounds. Thus, a highly selective method for the preparation of fluorinated phosphonates **260**, precursors of various biologically active compounds, was described in 2015.[281] The starting alcohols **261** are derived from appropriate β-keto-α,α-difluorophosphonates in the presence of clostridial alcohol dehydrogenase (CaADH). According to the outcome of the reaction, the enantiomeric excess of the (*S*)-isomer of alcohol **261** is 93–99%. Then, alcohols **261** are reacted with pentafluorophenyl-substituted thionochloroformate at −78 °C. The newly formed thionocarbonates **A** undergo spontaneous rearrangement at room temperature with a quantitative conversion into final products **260** (isolated yields are 83–94%) (Scheme 156).

Scheme 155



R^1 = Me, Et, Pr^n, Bu^n, $n\text{-}C_5H_{11}$, $n\text{-}C_6H_{13}$, XC_6H_4 (X = 4-OMe, 2-OMe, 2-OMe-4-OAc, 4-F, 4-Cl, 4-Br, 4-NO_2), 2-Fu;
R^2 = Pr^n, Bn;
R^3 = Pr^n, Bn, Ph;
An is anion

Scheme 156



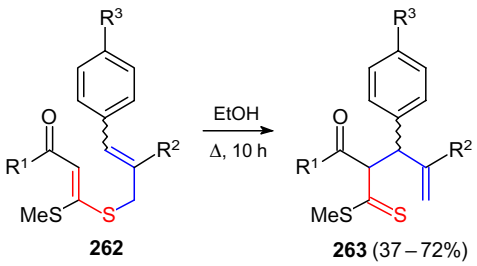
R = H, Me, CH_2OBn, Ph, 3-Fu, 3-Th, benzofuran-2-yl

A distinguishing feature of this approach is a high rate of the rearrangement. Thus, under the said conditions the half-time of the reaction ($t_{1/2}$) is 3 min, thereby making this reaction one of the fastest neutral (*i.e.* involving no charged intermediates) Claisen-type rearrangements. For comparison, $t_{1/2}$ for allyl cyclopentenyl ether is 45 min at room temperature,[282] a half of the substrate undergoes the Overman rearrangement in the same time,[283] while $t_{1/2}$ for lithium enolates of allyl esters varies within 10–60 min at room temperature[284] (more detailed data concerning the conversion times for fluorinated phosphonates and the specific reaction rates are available in Supporting information for original publications).

It is also worth noting that fluorine atoms have a critical impact on the reaction rate: when replacing the pentafluorophenyl moiety by a non-fluorinated substituent, the half-time of the reaction increases to 20 h. Based on the stereochemistry of the starting compounds and resulting products, one might assume the reaction to proceed through the formation of the transition state **TS1** as the least strained and corresponding to the configuration of the alkene moiety in the product. Changing the solvent (from THF to acetonitrile) leads to even greater acceleration of the reaction ($t_{1/2}$ = 1.7 min at room temperature), which suggests the partially dissociative nature of the transition state. Quantum chemical calculations[285] for non-fluorinated allyl-substituted thionocarbonates also indicate that the reaction proceeds through a concerted rather than biradical mechanism.

Thioallyl compounds **262** undergo rearrangements upon heating in ethanol (Scheme 157).[286] The resulting products **263** were used in the synthesis of thiopyrans. The advantages of this method are the ease of implementation, the availability of the starting compounds and no need for expensive catalysts.

Scheme 157

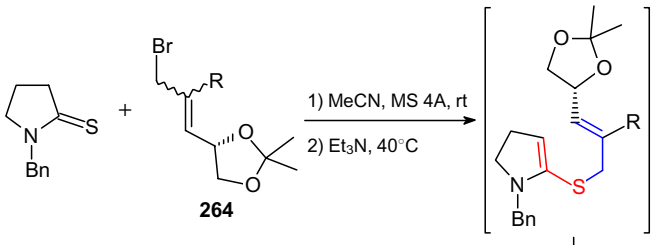


262 **263** (37–72%)

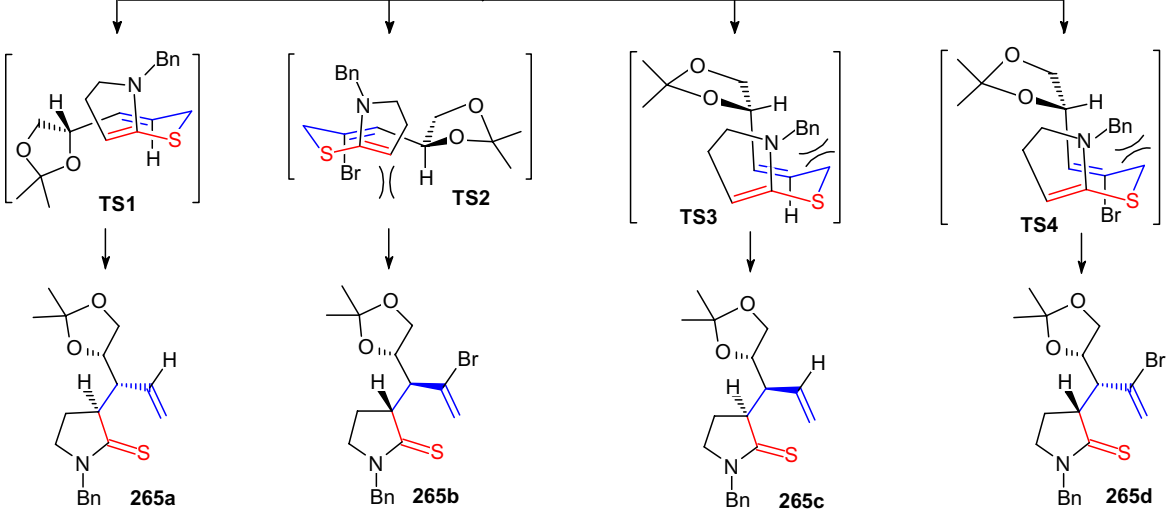
R^1 = Ph, 4-$MeOC_6H_4$, 2-ClC_6H_4, 4-$F_3CC_6H_4$, 2-Th;
R^2 = CO_2Me, CO_2Et; R^3 = H, F, OMe

The products of the reaction of *N*-benzylpyrrolidine-2-thione with D-mannitol-derived chiral allyl bromides **264** undergo the thio-Claisen rearrangement (Scheme 158).[287] Derivatives **265a–d** are inermediates in the synthesis of sarain alkaloids. An interesting feature of this transformation is the possibility of influencing the stereoconfiguration of the final products by the installation of a bromine atom at the unsaturated bond. Quantum chemical calculations and a series of experiments show that the existing C–C bond in the transition state is antiperiplanar with respect to the newly formed bond. This observation can be attributed to the Cieplak effect.[287] Scheme 158 illustrates the major transition states for all substituent patterns and multiple bond configurations. In the absence of any significant sterical hindrances, the transition state **TS1** prevails. The states **TS2** and **TS3** predominate in the case of steric interactions between molecular moities. Minor product

Scheme 158



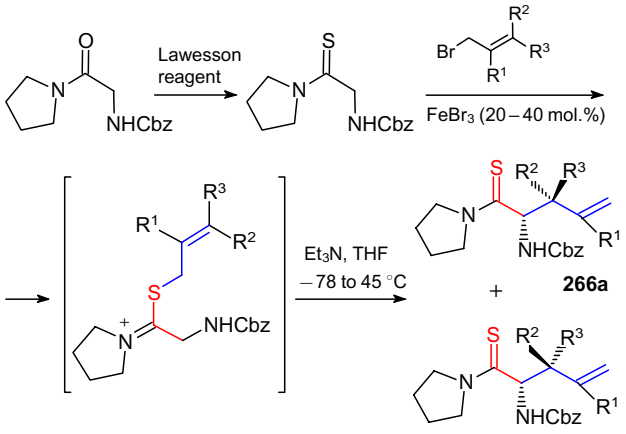
R	Configuration	*dr* (**265a** : **265b** : : **265c** : **265d**)	Yield (%)			
			265a	**265b**	**265c**	**265d**
H	*E*	69 : 28 : 3 : 0	38	10	1	0
Br	*Z*	7 : 28 : 5 : 0	2	52	2	0
H	*Z*	25 : 25 : 50 : 0	10	11	18	0
Br	*E*	5 : 17 : 61 : 17	1	6	39	9



265d is formed only in the presence of the bromine atom in the vinylic position of the multiple bond.

Based on the thio-Claisen rearrangement, an improved method was developed for the synthesis of β-functionalized γ,δ-unsaturated amino acids, which are non-protein amino acids useful in chemistry and biology.[288] The $FeBr_3$-catalyzed allylation of thioamide, 2-benzyloxycarbonylamino-1-(pyrrolidin-1-yl)ethanethione, and the subsequent treatment with base afforded target products **266a**,**b** in moderate yields (42–82%) with high stereoselectivity (the ratio of the *anti* and *syn* isomers exceeded 49 : 1) (Scheme 159).[289]

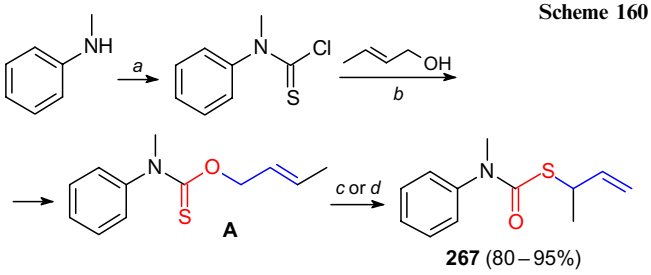
Scheme 159



R^1 = H, Me, CO_2Et; R^2 = H, Me; R^3 = H, Me, CO_2Et, CO_2Me, Ph

S-Allyl thiocarbamate **267** was synthesized *via* a sigmatropic rearrangement of intermediate **A**, derived from methylaniline in two steps (Scheme 160).[290]

Scheme 160

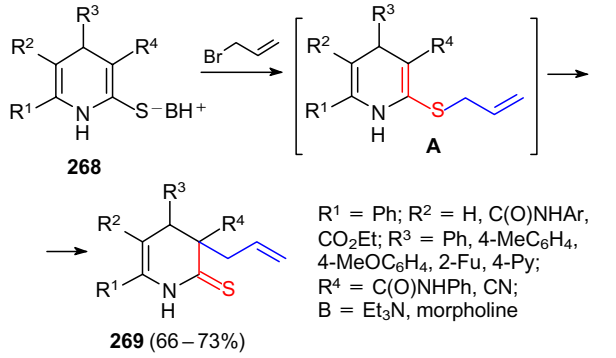


(*a*) $CSCl_2$, Et_3N, THF, 0 °C to rt; (*b*) NaH, NaI, THF, 0 °C; (*c*) K_2CO_3, PhMe, 72 h; (*d*) MW, 135 °C, 45 min

The reaction of allylic alcohols with thiocarbonyl diimidazole gives unstable *O*-allyl imidazolyl thione ester undergoing a spontaneous rearrangement into the corresponding *S*-allyl imidazolyl thiol ester in high yields.[290] The replacement of imidazole with *N*-alkylanilines in the presence of a nucleophilic catalyst (HOBt or ethyl 2-(hydroxyimino)-2-cyanoacetate (ECHIA)) afforded *S*-allyl-*N*-aryl thiocarbamates (yields of up to 97% in two steps). Later, it was demonstrated that this protocol can be employed to obtain dihydrothiophenes bearing quaternary stereocentres.[291, 292]

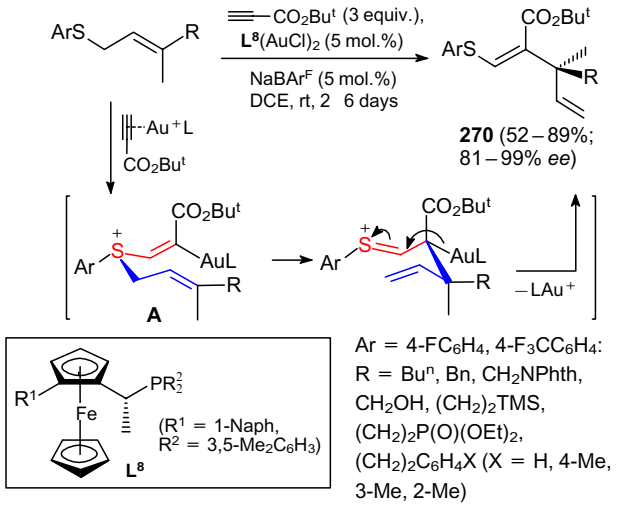
The literature shows [293–296] that dihydropyridinium salt **268** reacts with allyl bromide, and the resulting intermediate **A** undergoes a rapid sigmatropic rearrangement into compound **269** (Scheme 161). Various derivatives of tetrahydropyridine,[293] nicotinamide,[294] functionalized hydrogenated quinolines [295] and dihydronicotinic acid were produced [296] using similar reactions.

Scheme 161



The reaction of propiolates with allyl sulfides catalyzed by a chiral gold(I) complex with ligand $\mathbf{L^8}$ allows the stereoselective synthesis of sulfur-containing compounds **270** bearing quaternary stereocentres. The rearrangement of allyl vinyl sulfonium intermediate **A** is a key step in the reaction mechanism, providing high enantioselectivity due to the simultaneous formation of C–S and C–C bonds (Scheme 162).[297]

Scheme 162

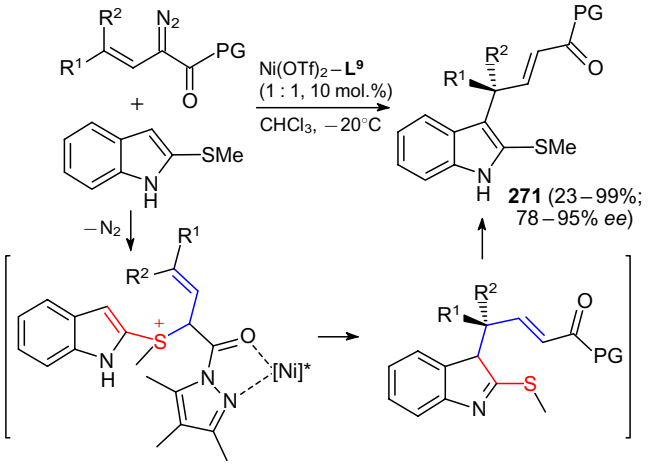


An enantioselective version of the nickel-catalyzed thio-Claisen rearrangement afforded a variety of 3-substituted indoles **271** in yields of up to 99% and with selectivities of up to 95% *ee*.[298] This high enantioselectivity is achieved due to the interaction of a protective group with a chiral nickel(II) complex. A similar reaction of diazaalkanes with indole derivatives **272** is catalyzed with rhodium acetate (Scheme 163).[299] The above approach was used in the synthesis of a series of indole alkaloids.

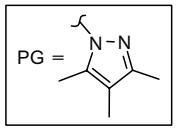
In the presence of scandium compounds, allenyl imidates **273** react with allyl sulfides to give products **274** (Scheme 164).[300] The reaction involves a sigmatropic rearrangement of a thioallylic intermediate generated after the Michael addition of allyl sulfide to the double bond of the carbonyl-activated allenic system.

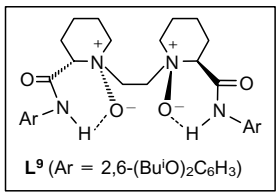
The seleno-Claisen rearrangement is also known. The deprotonation of α-monosubstituted selenoamides with

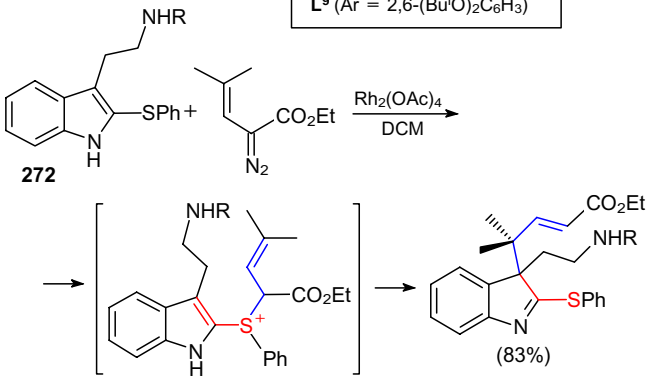
Scheme 163



R^1 = XC_6H_4 (X = H, 2-F, 2-Cl, 2-Me, 3-F, 3-Cl, 3-Me, 4-F, 4-Cl, 4-Br), 2-Fu, 3-Th, 2-Naph, Bn; R^2 = H, Me

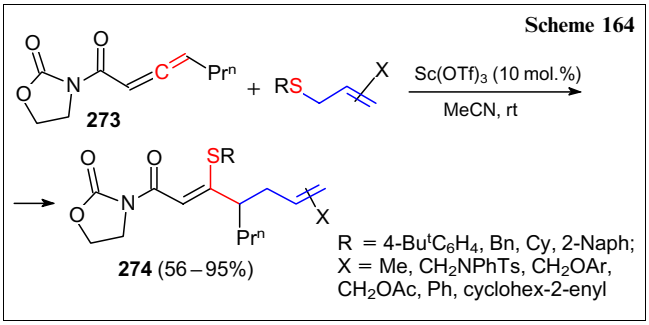






R = Boc, CHO

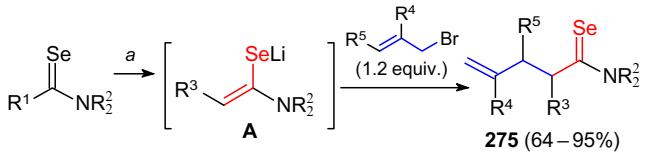
Scheme 164



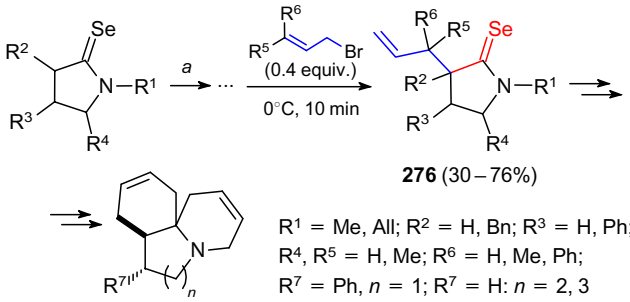
R = 4-Bu^{t}C$_6$H$_4$, Bn, Cy, 2-Naph; X = Me, CH_2NPhTs, CH_2OAr, CH_2OAc, Ph, cyclohex-2-enyl

LDA and subsequent allylation furnish γ,δ-unsaturated selenoamides **275** in yields of up to 95%.[301] Presumably, in the initial step, the allylation occurs at the selenium atom of lithium eneselenolates to give allyl vinyl selenides **A** followed by their rearrangement (Scheme 165). The highly diastereoselective α-allylation was accomplished using selenolactams. Products **276** thus obtained can be efficiently converted into polycyclic amines.[302]

Scheme 165



R^1 = Et, CH_2All; R^2 = All; R^2–R^2 = $(CH_2)_4$;
R^3 = Me, All; R^4 = H, Br; R^5 = H, Me



R^1 = Me, All; R^2 = H, Bn; R^3 = H, Ph;
R^4, R^5 = H, Me; R^6 = H, Me, Ph;
R^7 = Ph, n = 1; R^7 = H: n = 2, 3

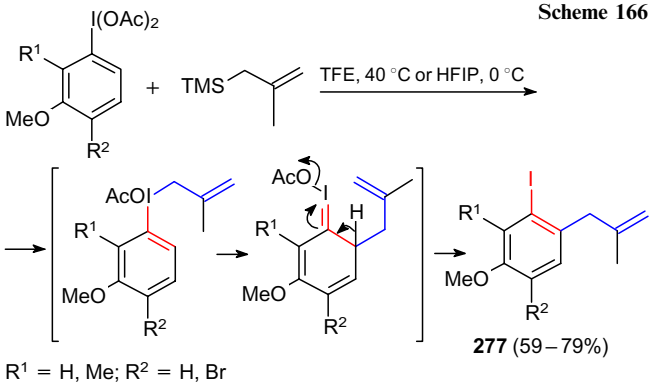
(*a*) LDA (1.2 equiv.), THF, 0 °C, 10 min

3.7. Iodonio-Claisen rearrangement

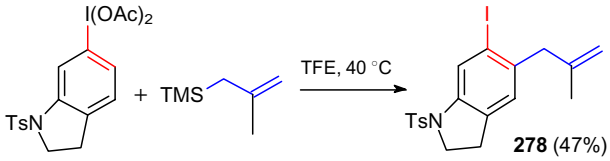
One of the newest and a few (according to the number of publications) modifications of the Claisen rearrangement is the iodonio version involving the reactions of λ^3-iodanes and is so far only applied to aromatic compounds.

The reductive iodonio-Claisen rearrangement (RICR) involving λ^3-iodanes and allylsilanes can be carried out in fluoroalcohols such as 1,1,1,3,3,3-hexafluoroisopropyl (HFIP) and 2,2,2-trifluoroethyl (TFE) alcohols.[303] It was shown that RICR proceeds more efficiently in fluoroalcohols compared to boron trifluoride etherate. For example,

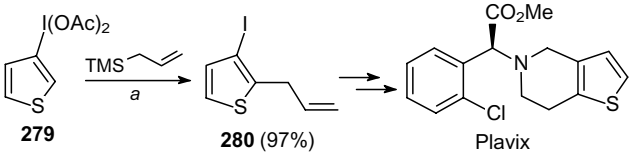
Scheme 166



R^1 = H, Me; R^2 = H, Br

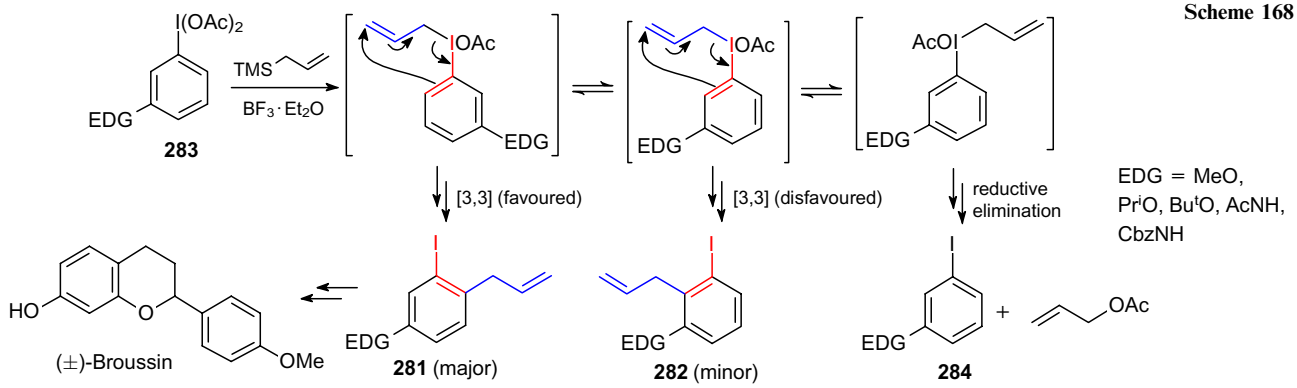


Scheme 167



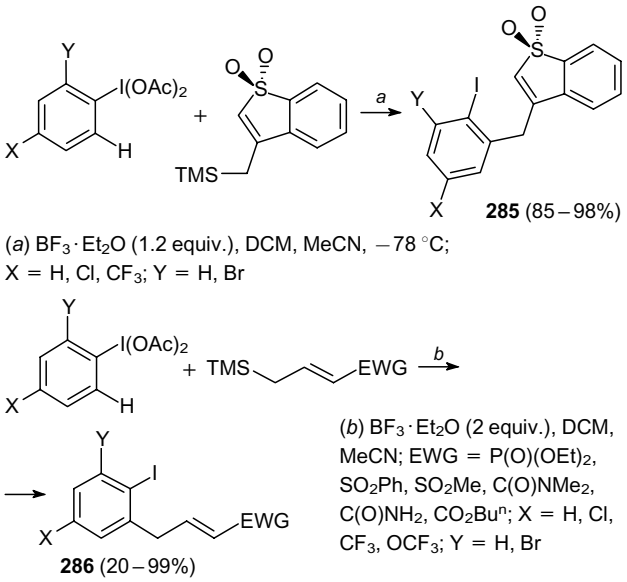
(*a*) $BF_3 \cdot Et_2O$, DCM, –50 °C, 1 h

Scheme 168

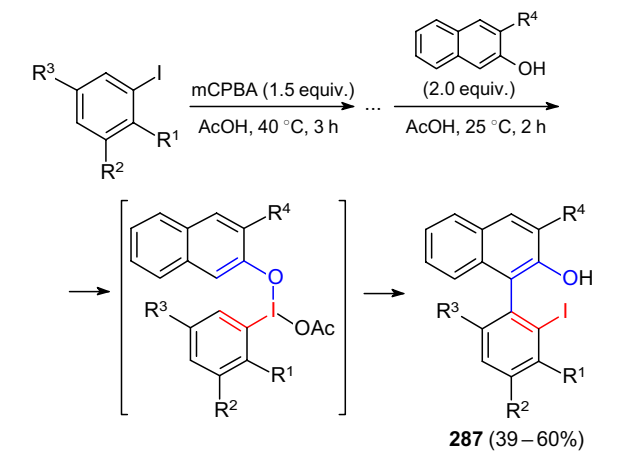


these conditions can provide access to *o*-allyliodoarenes **277** and **278**, which are versatile synthetic intermediates that are easily transformed into heterocyclic compounds (Scheme 166).[303]

Scheme 169



Scheme 170



Iodothiophene diacetate **279** reacts with allyltrimethylsilane in the presence of boron trifluoride etherate to afford 2-allyl-3-iodothiophene (**280**) *via* the reductive iodonio-Claisen rearrangement. This strategy was successfully applied to the synthesis of Plavix©, the blood clot inhibitor lowering the risk of heart attack and stroke (Scheme 167).[304]

It was demonstrated that allylated iodoarenes **281** and **282** can be prepared from compound **283** using the reductive iodonio-Claisen rearrangement (Scheme 168).[305] In the course of the survey, the [3,3]-sigmatropic rearrangement was shown to dominate over the reductive elimination, resulting in the formation of iodoarene **284**, in the presence of electron-donating groups in the *meta* position to the iodine-containing functionality. The overall yield of the reaction products was 62–93%, and the **281**:**282**:**284** ratio varied from 1.33:0:1 to 33:6.6:1. This method is useful to prepare the chromanol (±)-broussin showing antimycotic activity.[305]

Subsequently, the synthetic approach using the iodonio-Claisen rearrangement was extended to benzothiophene derivatives **285** (see Ref. 306) and compounds **286** bearing electron-withdrawing groups at the multiple bond (Scheme 169).[307]

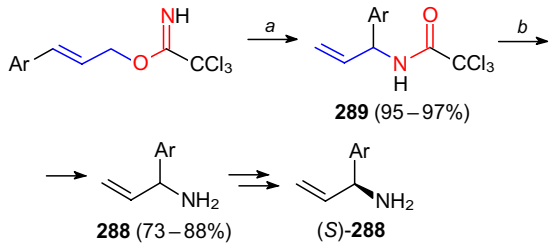
The reaction of aryliodanes with phenols occurs through the ligand exchange on the hypervalent iodine atom followed by the [3,3]-sigmatropic rearrangement and yields 2-hydroxy-2′-iodobiaryls **287** with complete regioselectivity (Scheme 170).[308] These products contain the iodine atom and a hydroxy group in close proximity and can be useful in the synthesis of fused furans and [5]helicene.

4. Rearrangements of trichloroacetimidates (the Overman rearrangement)

The Overman rearrangement involves trichloroacetimidates, which are readily available by the reaction of highly reactive trichloroacetonitrile with alcohols in the presence of bases. This process can be carried out under rather mild conditions and allows for the introduction of an allylic amine functionality into various compounds. In 2017, a review[309] was published on the Overman rearrangement covering the studies reported up to that time. Nevertheless, certain important examples of the Overman rearrangement deserve to be mentioned in the present review as well.

Thus, (*S*)-1-aryl allylamines (*S*)-**288** were successfully synthesized using an enzymatic resolution.[310] First, the Overman rearrangement was carried out to produce allyl-substituted trichloroacetamides **289**, which were subjected

Scheme 171



(*a*) K_2CO_3, xylene, Δ, 20 h; (*b*) 5 M NaOH, EtOH, rt, 20 h;
Ar = Ph, 2-MeC_6H_4, 4-MeC_6H_4, 3,5-$Me_2C_6H_3$, 2,4,6-$Me_3C_6H_2$, 1-Naph, 4-methylnaphthalen-1-yl

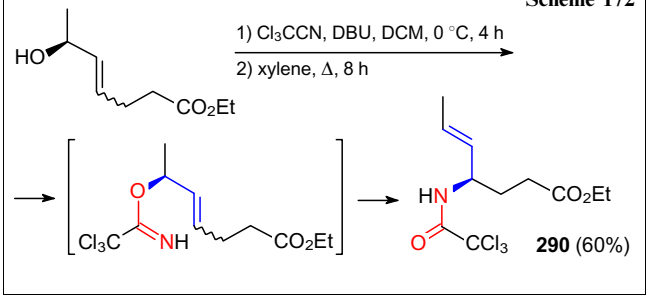
to alkaline hydrolysis to yield a racemic mixture of amines **288** (Scheme 171). This mixture was treated with lipase B isolated from the fungus *Candida antarctica*, which selectively acylates the *R*-isomer without affecting the *S*-isomer. A series of 1-aryl allylamines (*S*)-**288** were obtained with enantioselectivity ranging from 63.5 to 99.9% *ee*.

Also, the use of the Overman rearrangement allows for the construction of the δ-unsaturated γ-amino acid backbone.[311] Precursor **290** was obtained in one synthetic step with high stereoselectivity (>94% *ee*) (Scheme 172) and was subsequently used in the synthesis of fluorescent amino acids to be employed in bioimaging.

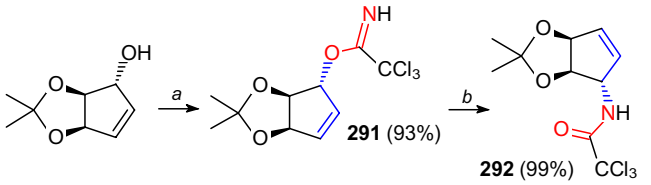
It was demonstrated that chiral polyfunctionalized cyclopentenes can be prepared *via* the rearrangement of imidate **291** (Scheme 173).[312] Starting from D-mannose, the reaction included the Wittig olefination and ring-closing metathesis as key steps followed by the [3,3]-sigmatropic Overman rearrangement to yield resulting amide **292**.

An enantioselective approach to the natural (−)-stemoamide found in the root extracts of *Stemona tuberosa* comprises Johnson–Claisen and Overman rearrangements

Scheme 172



Scheme 173

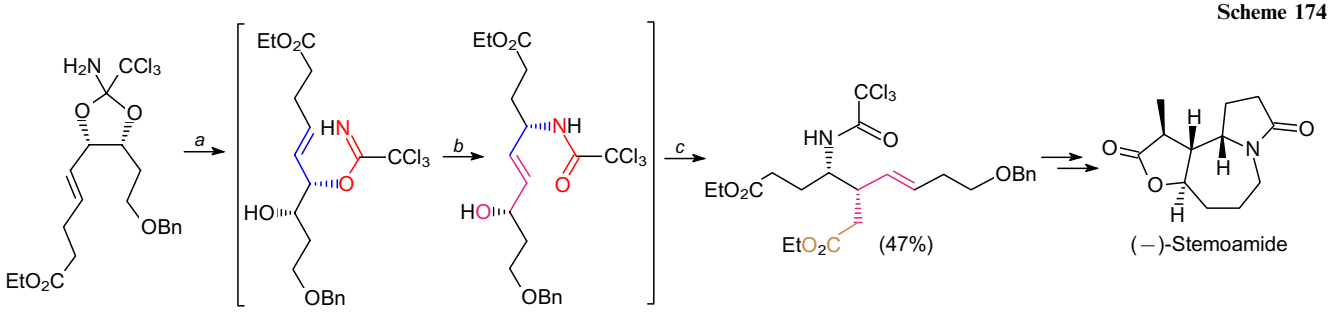


(*a*) Cl_3CCN, DBU, DCM, rt, 10 min; (*b*) xylene, Δ, 16 h

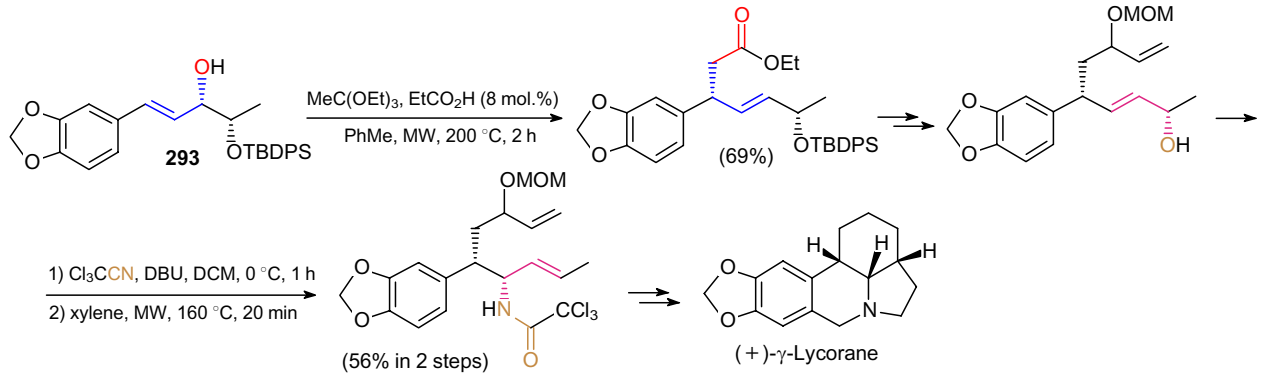
(Scheme 174).[313] This approach made use of enantiopure allyl-1,2-diol obtained from natural dimethyl tartrate. The chirality transfer *via* two consecutive [3,3]-sigmatropic rearrangements occurred with high diastereoselectivity in a one-pot fashion. Similar rearrangements were implemented in the synthesis of (+)-γ-lycorane using protected diol **293**.[314]

At present, glycine transporter 1 (GlyT1) inhibitors are considered as potential candidates for the development of drugs for schizophrenia and acute manic episodes. The GlyT1 inhibitor, compound **294**, can be obtained using a method based on the Overman rearrangement as a key step (Scheme 175). Parent alcohol **295** is first converted to imidate **A**,which transforms into compound **296a** on heating. In this case, isomeric by-product **296b** can be formed

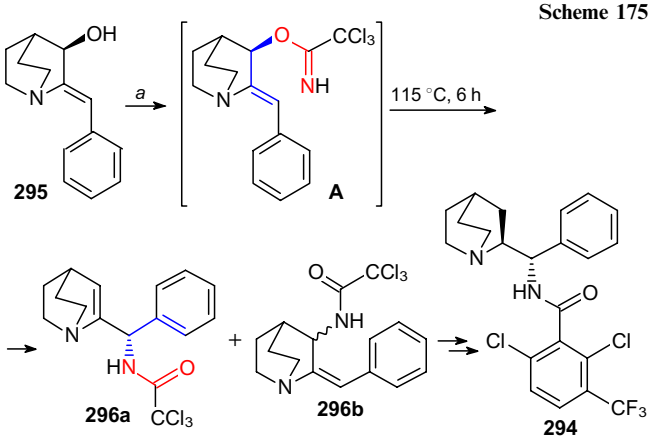
Scheme 174



(*a*) BHT, Bu^{t}Ph, 160 °C; (*b*) Overman rearrangement; (*c*) Claisen rearrangement: $MeC(OEt)_3$, BHT, 140 °C;
BHT is 4-methyl-2,6-di-*tert*-butylphenol



Scheme 175



(*a*) Cl_3CCN (0.98 equiv.), tert-$C_5H_{11}ONa$ (0.1 equiv.), xylene, 0 °C, 1 h

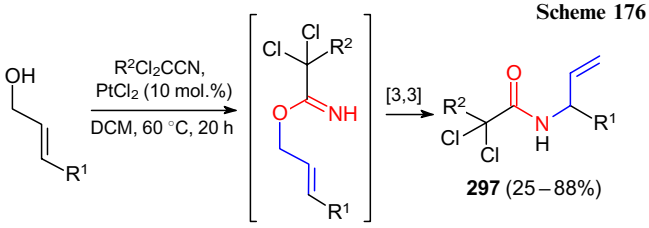
through a [1,3]-sigmatropic rearrangement. However, by varying the amount of trichloroacetonitrile, the probability of formation of compound **296b** can be minimized (the lowest yield of the impurity obtained by the authors was 0.9%). An additional advantage of this approach is the scalability to multigram amounts. In six replicates of the synthesis, the yield of compound **296a** fluctuated within 71–76%, its enantiomeric excess exceeded 97.5% in all cases, and in total, more than 150 kg of the product were obtained.[315]

A straightforward synthesis of halogenated allyl amides **297** was accomplished from allylic alcohols (Scheme 176)[316] and halonitriles using the platinum chloride catalyst. In this case, both the nucleophilic addition and the subsequent [3,3]-sigmatropic rearrangement were catalyzed by the same platinum complex.

The palladium-catalyzed rearrangement of allylic acetimidates **298** can occur with different stereoselectivities (Scheme 177).[317] When studying the mechanism of this reaction and also the ratio of products **299**, it was demonstrated that dimeric chiral cobalt oxazoline palladacycle **XI** is the catalyst of choice for the enantioselective Overman rearrangement.

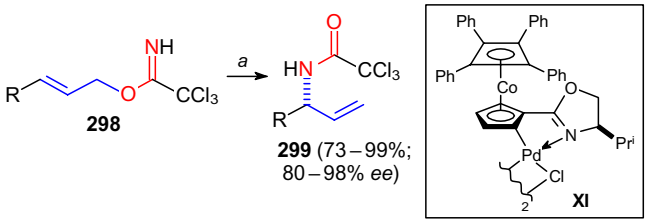
The enantioselective method for the synthesis of (2S,3S)-3-hydroxy-L-arginine (**300**) from commercially available butane-1,4-diol included ten steps and afforded the product in 10.9% overall yield and 98% *ee* (Scheme 178).[318] The success of this method was due to a diastereoselective Pd-catalyzed rearrangement of an allyl-type trichloroacetimidate. Another interesting example of using the Overman

Scheme 176



R^1 = Alk, All, Ph, 2-BrC_6H_4, 4-BrC_6H_4; R^2 = Cl, H

Scheme 177



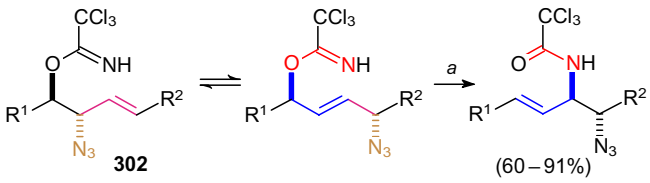
(*a*) **XI**, DCM (5 mol.%), 40 °C;
R = Cy, CH_2OH, $(CH_2)_3N(Boc)_2$, CH_2OTBS, $(CH_2)_9NBn_2$

rearrangement is the synthesis of isofagomine and azasugars *via* the generation of intermediate products **301** (78–88% yield, α : β epimeric ratio varied from 1 : 1 to 8.5 : 1.5).[319]

A method for the simultaneous construction of two C–N bonds was proposed based on a sequence of the initial reversible rearrangement of azides **302** and the irreversible Overman rearrangement (Scheme 179).[320] The reacion occurs in a stereocontrolled fashion in two steps; readily available alkenyl epoxides are employed as the starting materials undergoing an oxirane ring opening with sodium azide.

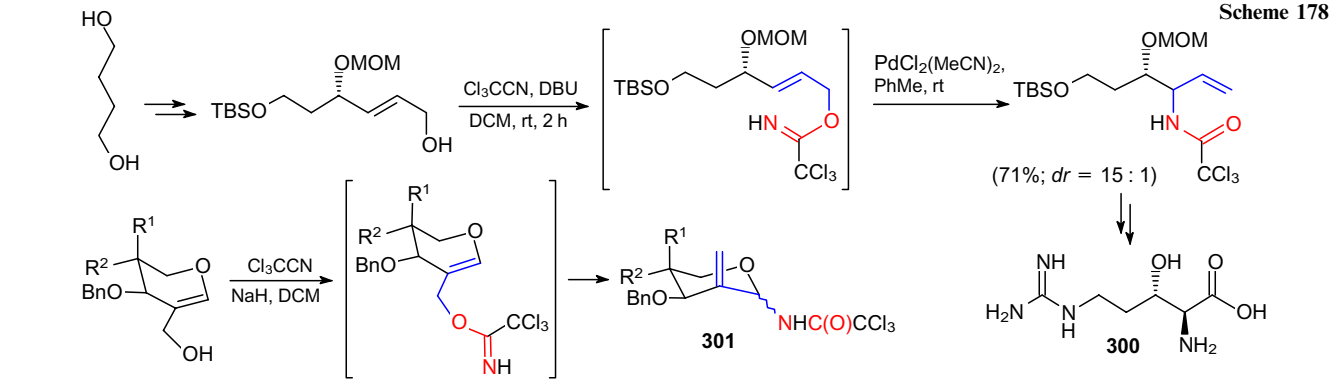
For certain trichloroacetimidates, competitive [3,5]- and [3,3]-sigmatropic rearrangements are possible affording,

Scheme 179



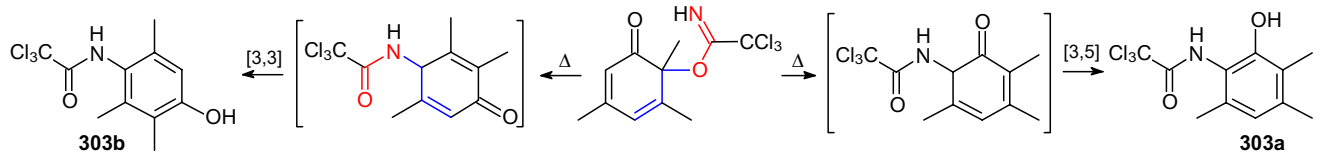
(*a*) K_2CO_3, DCB, MW, 180 °C, 15 min;
R^1 = Me, OTBDPS, Bu^n; R^2 = OTBDPS, Bu^n

Scheme 178



R^1 = OBn, R^2 = H; R^1 = H, R^2 = OBn

Scheme 180

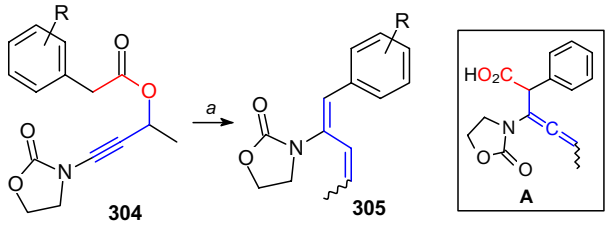


e.g., compounds **303a**,**b**, respectively (Scheme 180).[321] Thus, the [3,5]-rearrangement is more favourable in deuterated benzene at 60 °C.

5. Rearrangements of compounds containing a triple bond

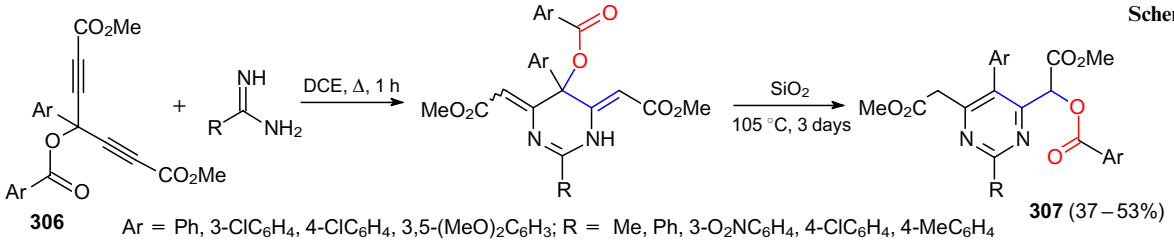
A triple bond is an important moiety capable of undergoing sigmatropic rearrangements. Such reactions have been partly addressed in several reviews, where the rearrangements of compounds containing a triple bond were considered among other synthetic approaches. These include, for example, a review article[322] on the formal insertion of activated alkynes into the carbon–heteroatom bond, a study[323] on transformation of allenamides derived from alkynes, a review[324] on rearrangements of propargyl esters in the synthesis of various biologically active substances and a summarizing review[325] on transformations of *S*-propargyl xanthates. The said rearrangements are frequently mediated by transition metals compounds such as gold, rhodium, palladium, platinum, silver, copper derivatives, *etc*. The transition metals serve as triple bond activators and reduce the activation energy of the reaction.

Scheme 181



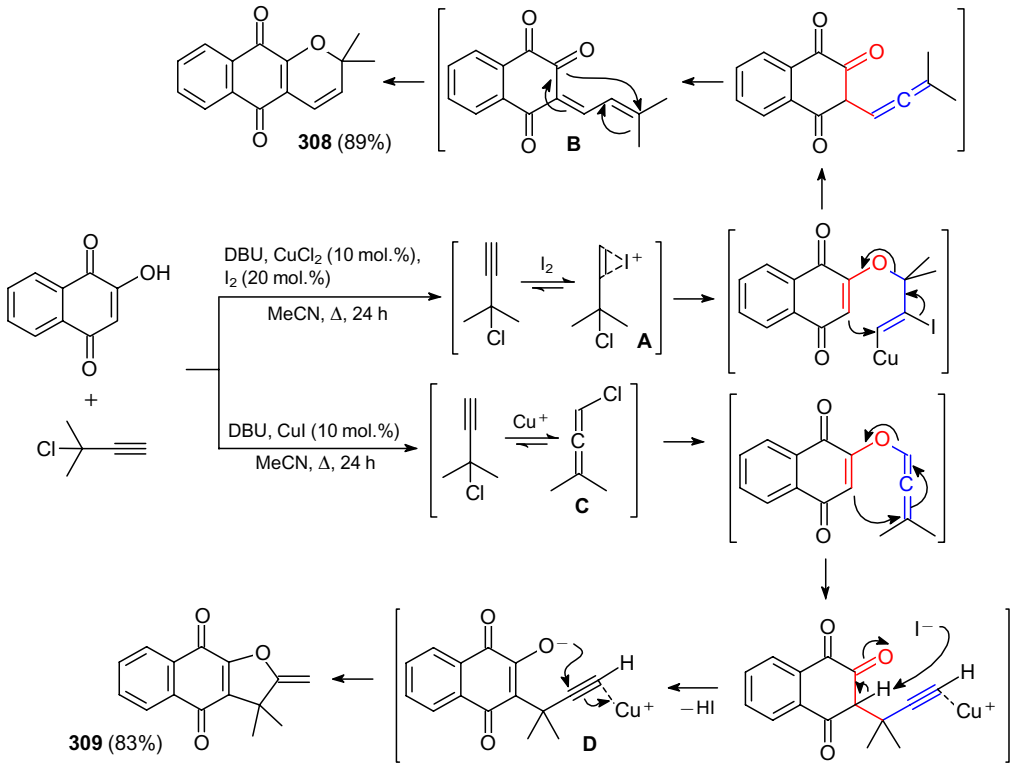
(*a*) LiHMDS (1.8 equiv.), TMSCl (1.8 equiv.), THF, −95 °C to rt, 24 h; R = Me, OMe, Cl, F, NO_2, NMe_2 (in different positions)

Scheme 182

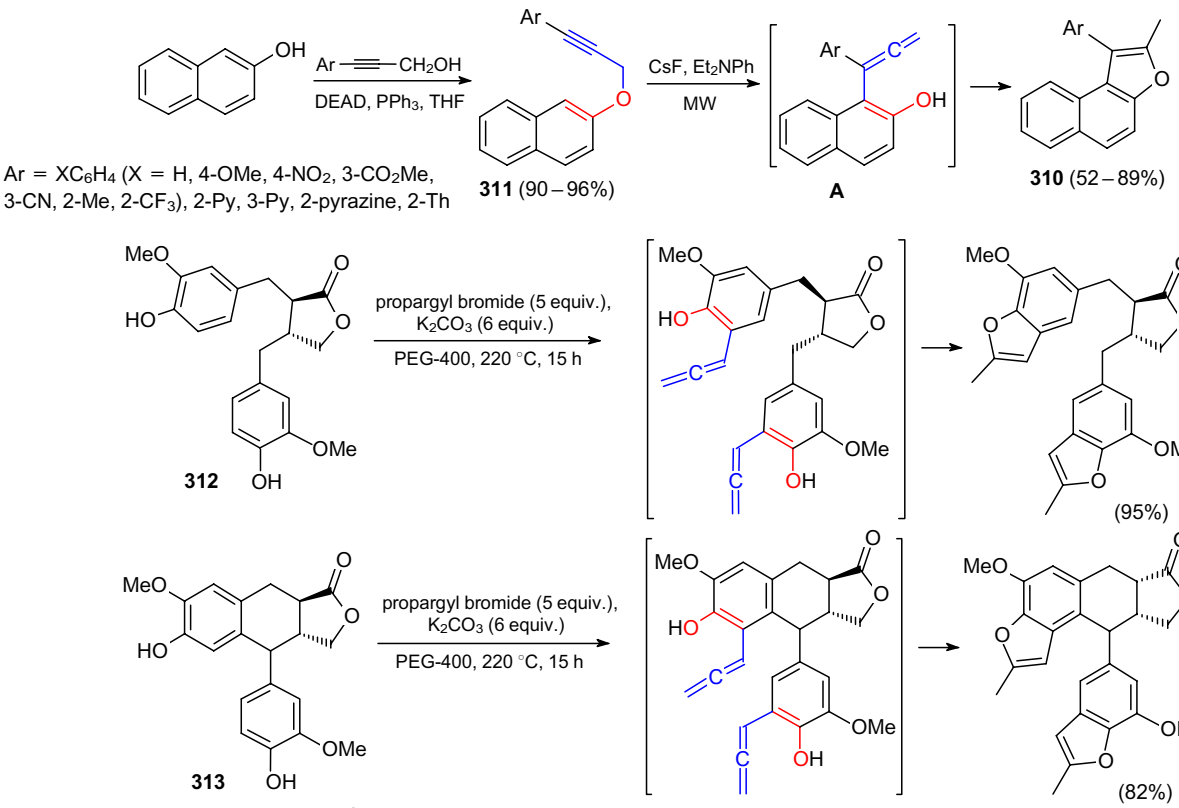


Ar = Ph, 3-ClC_6H_4, 4-ClC_6H_4, 3,5-$(MeO)_2C_6H_3$; R = Me, Ph, 3-$O_2NC_6H_4$, 4-ClC_6H_4, 4-MeC_6H_4

Scheme 183



Scheme 184



DAED is diethyl azodicarboxylate, PEG is polyethylene glycol

The rearrangement of propargyl esters **304** can be used in the synthesis of substituted 2-amidodienes **305** (Scheme 181).[326] The expected products of the [3,3]-sigmatropic rearrangement, *i.e.*, allenamide carboxylic acid derivatives **A**, were not detected, and the decarboxylation gave 2-amidodienes in yields of up to 73% with high levels of *Z*–*E*-selectivity (the isomer ratio varied from 2 : 1 to > 95 : 5).

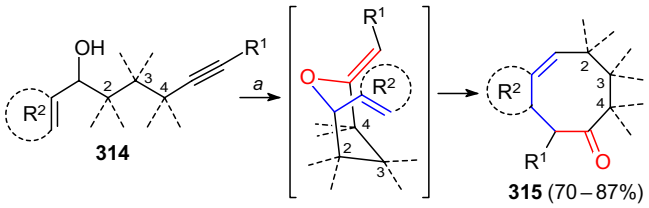
Propargyl esters **306** can serve as multifunctional building blocks capable of participating in domino reactions.[327] By way of example, the synthesis of polysubstituted pyrimidines **307** is outlined in Scheme 182.[328] The double Michael reaction gives a six-membered heterocycle and the subsequent hydride shift and [3,3]-sihmatropic rearrangement lead to the aromatization of the product.

α-Xiloidone (**308**) is a chromene structurally related to the lapachone series. The synthesis of this compound as well as of its five-membered isomer **309** was carried out using the propargyl Claisen rearrangement (Scheme 183).[329] The selectivity of the reaction changes depending on the presence of molecular iodine in the reaction medium. The authors assumed that the addition of iodine shifts the equilibrium towards the formation of the iodonium salt **A**, which ultimately leads to the intermediate **B** and its heterocyclization to product **308**. In the absence of iodine, intermediate **C** is generated and then transforms into the cuprous ion-stabilized propargyl derivative **D**. The heterocyclization of the latter species affords compound **309**.

The Claisen rearrangement provided the basis for an effective approach to prepare naphtho[1,2-*b*]- and naphtho[2,1-*b*]furans **310**. The reaction of propargylic alcohols with α- or β-naphthol under Mitsunobu conditions yields the corresponding naphthyl 2-propynyl esters **311** (Scheme 184 illustrates an example for β-naphthol).[330] The subsequent microwave-assisted Claisen rearrangement furnishes naphthofurans **311** *via* the formation of intermediate allenes **A**. The use of diphenyl diselenide in this reaction provides an access to the corresponding aldehydes.[331] A similar approach was employed to produce matairesinol (**312**) and α-conidendrin (**313**) containing the benzofuran skeleton from natural lignans.[332]

A structural unit of *gem*-disubstituted cyclooctanoids, found in several biologically active compounds, can be constructed using the Claisen rearrangement. Thus, substituted 1-alkenyl-5-hexyn-1-ols **314** were converted into cyclooct-4-enones **315** through the oxyanionic 6-*exo*-*dig* cyclization followed by a [3,3]-sigmatropic rearrangement (Scheme 185).[333]

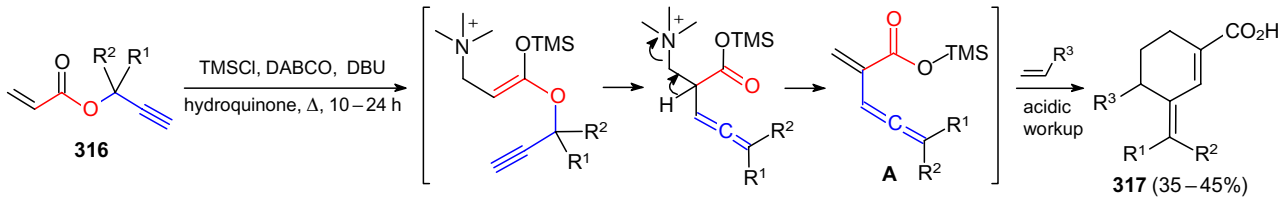
Scheme 185



(*a*) LiHMDS (10 mol.%), PhOEt, MW, 210 °C, 1 h; dimethyl group at either C(2), C(3) or C(4); R^1 = H, Ph, 2,5-$(MeO)_2C_6H_3$; R^2 is cyclohex-1-enyl, 6,6-dimethylcyclohex-1-enyl, cyclopent-1-enyl, isopropenyl, vinyl

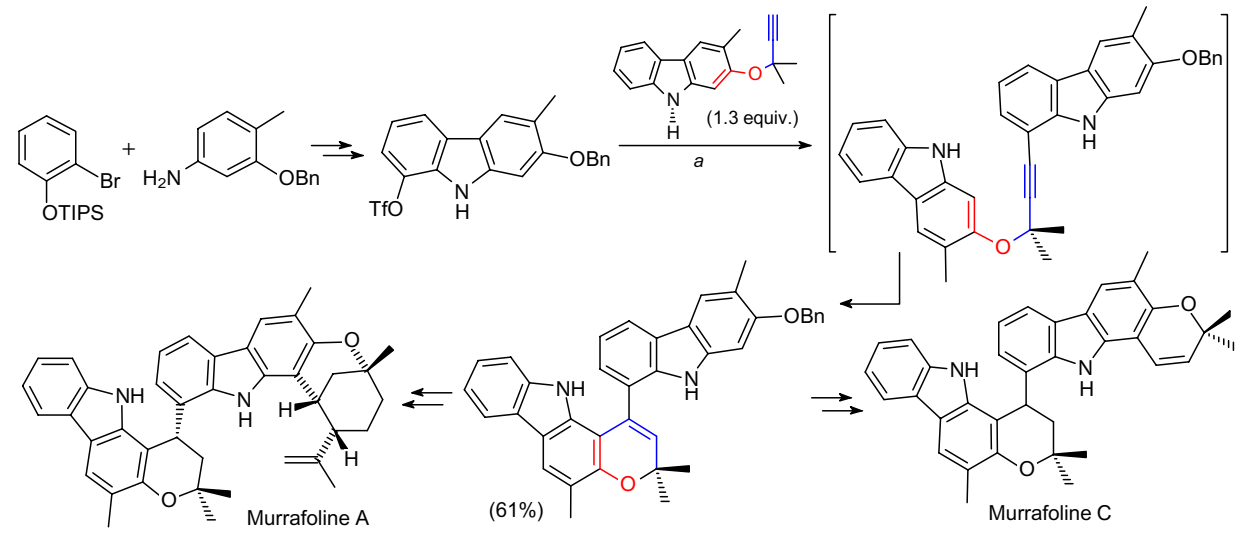
Propargyl acrylates **316** tend to undergo a DABCO-catalyzed Ireland–Claisen rearrangement (Scheme 186).[334] The intermediate allenes **A** are highly unstable and prone to polymerization, so they were *in situ* introduced into the

Scheme 186



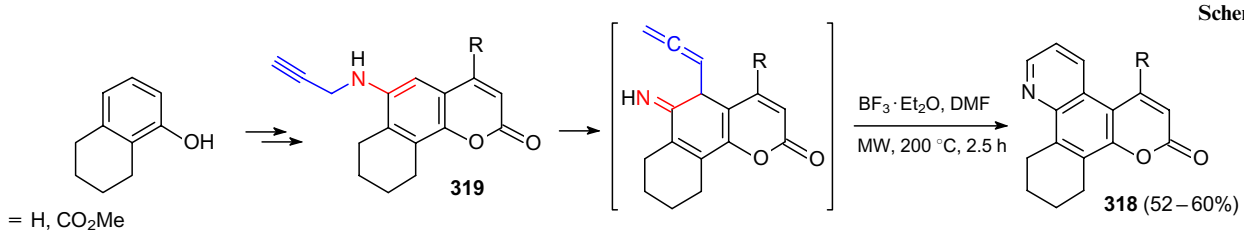
R^1 = Me, Pr^i, Pr^n; R^2 = H, Me; R^3 = CO_2Et, CO_2Me, CHO, CN

Scheme 187



(*a*) 1) $[Pd(PPh_3)_4]$ (10 mol.%), CuI (0.5 mol.%), piperidine, rt, 20 h; 2) xylene, Δ, 1.5 h

Scheme 188



R = H, CO_2Me

Diels – Alder reaction, thus providing the regioselective synthesis of cyclic α,β-unsaturated carboxylic acids **317**.

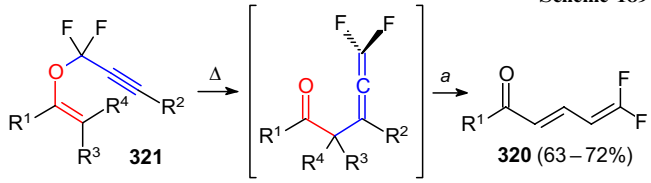
The biscarbazole alkaloids murrafolines were produced *via* a domino sequence involving the Sonogashira coupling, the Claisen rearrangement and electrocyclization. These structurally complex alkaloids were synthesized in a one-pot fashion in several steps (Scheme 187).[335]

Symeonidis *et al.*[336] developed a synthetic route to [5,6]-fused pyridocoumarins **318**. The aza-Claisen rearrangement of 6-propargylaminocoumarins **319** was followed by a microwave-assisted cyclization in the presence of boron trifluoride etherate (Scheme 188).

The Claisen rearrangement was employed to prepare difluorodienones **320** from difluoropropargyl vinyl ethers **321** (Scheme 189).[337]

The Claisen rearrangement was used to synthesize cyclobutenes bearing an exocyclic double bond. Under conditions of a thermal aza-version of this rearrangement, 3-aza-1,5-enynes **322** transform into allene imines, which are then cyclized to give cyclobutenes **323** (Scheme 190).[338]

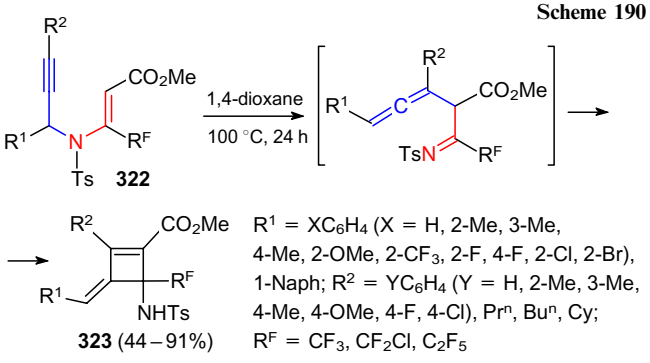
Scheme 189



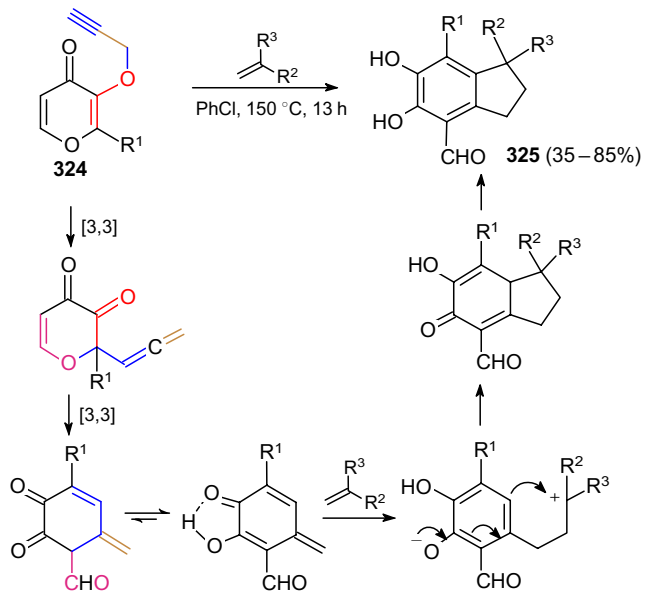
R^1 = Ph, 4-$MeOC_6H_4$; R^2, R^3, R^4 = H, Alk;
(*a*) DTBMP (20 mol.%), PhMe, 80 °C, 2 h (for R^2 = R^3 = R^4 = H);
DTBMP is 2,6-di-*tert*-butyl-4-methylpyridine

A cascade Claisen rearrangement of maltol propargyl ether **324** was used to prepare polysubstituted salicylaldehydes **325**. This reaction features a high atom economy (100%) and can be implemented on a multigram scale. Products **325** gave rise to a variety of natural molecules (hemigossypol, gossypol) and their analogues (Scheme 191).[339]

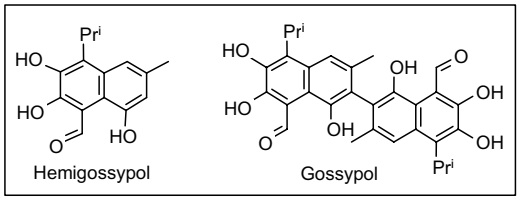
Scheme 190



Scheme 191



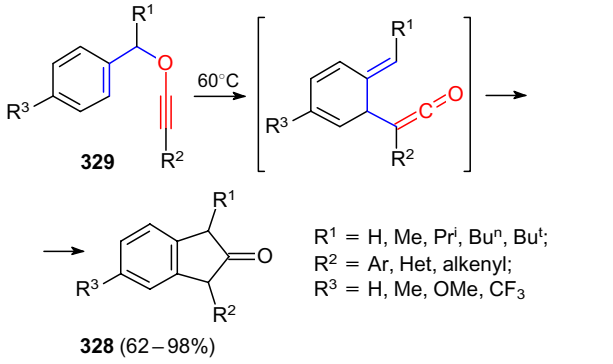
R1 = Me, Et, Pri ; R2 = H, Me, Ph;
R3 = H, Me, Bn, XC6H4 (X = 4-Me, 4-But, 4-OMe, 4-F, 4-Cl, 4-Br, 4-NO2, 4-CF3, 3-Br, 2-Br, 2-Cl), 2,6-dimethylhepta-1,5-dienyl, 2,2-diphenylethenyl, 4-bromophenylethynyl



The addition of triisopropylsilyl trifluoromethanesulfonate to macrocyclic furan derivative **326** initiates the Ireland – Claisen rearrangement, which afford a corresponding allenic derivative. The conversion of the latter compound followed by heating into an azide triggers a cascade reaction including the cycloaddition, loss of a nitrogen molecule and diyl-furan transannular [4 + 3]-cycloaddition of azatrimethylene methane (ATMM) (Scheme 192). The major product (**327**) of this reaction comprises a pentacyclic core common to naturally occurring compounds such as guanacastepenes D, H and radianspenes J – L.[340]

A method for the synthesis of indan-2-ones **328** was developed based on the rearrangement of alkynyl ethers **329** (Scheme 193).[341] Substituted benzyl alkynyl ethers, derived from the corresponding alkoxy ketones, undergo a [3,3]-sigmatropic rearrangement and an intramolecular 5-*exo*-*dig* cyclization to afford substituted indan-2-ones **328**. This transformation gives products predominantly with 1,3-*cis* configuration.[342]

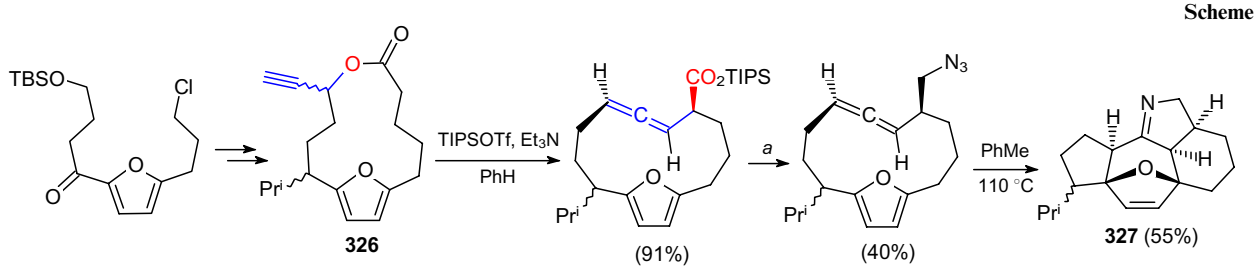
Scheme 193



Alexander *et al.* reported[343] that the formation of compounds **330** from allyl esters of *N*-allyl-*N*-propargylamides **331** is accompanied by two palladium-catalyzed rearrangements, namely, π-allylic and sigmatropic. This sequence is an auto-tandem catalytic process, *i.e.* the same catalyst is involved in two transformations that have fundamentally different mechanisms. The former rearrangement is responsible for the formation of an allene intermediate **A** and follows a dissociative π-allylic mechanism (Scheme 194). The latter rearrangement involves the formation of a transition state, which is typical both of sigmatropic and π-allylic processes. The transformation is accompanied by electron density donation from the palladium catalytic centre to the antibonding σ*-orbital of the C – N bond. Several other mechanisms are also possible for the second transformation; however, the palladium-catalyzed [3,3]-sigmatropic rearrangement is the most rapid reaction. The proposed mechanisms are consistent with experimental data and quantum chemical calculations.[343]

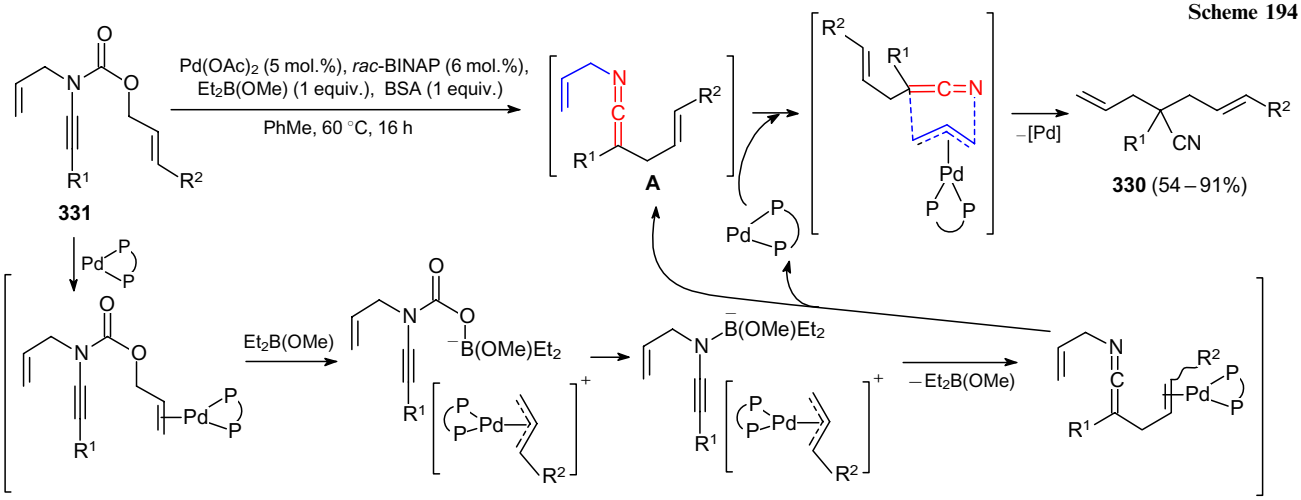
The synthesis of β-lactone **332** from allyldichlorovinyl ether **333** was reported to proceed through a low-temper-

Scheme 192



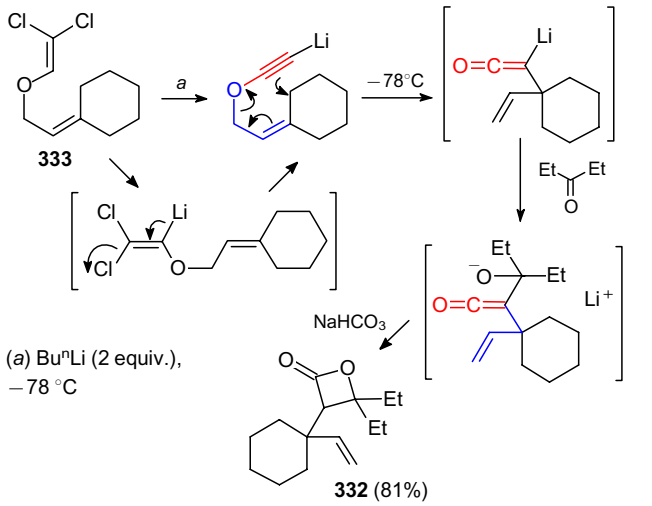
(*a*) 1) $LiAlH_4$, Et_2O, 0 °C; 2) CBr_4, Ph_3P, DMF, 0 °C; 3) NaN_3, DMF, 35 °C

Scheme 194



R^1 = Bu^n, n-C_6H_{13}, CMe_2OTMS, $(CH_2)_2Ph$, XC_6H_4 (X = H, 4-Me, 4-Bu^t, 4-F, 2-F, 4-CF_3, 4-CN, 4-NO_2), 2-Naph, 1-Naph; R^2 = H, Ph; P⌒P = *rac*-BINAP; BSA is *N*,*O*-bis(trimethylsilyl)acetamide

Scheme 195



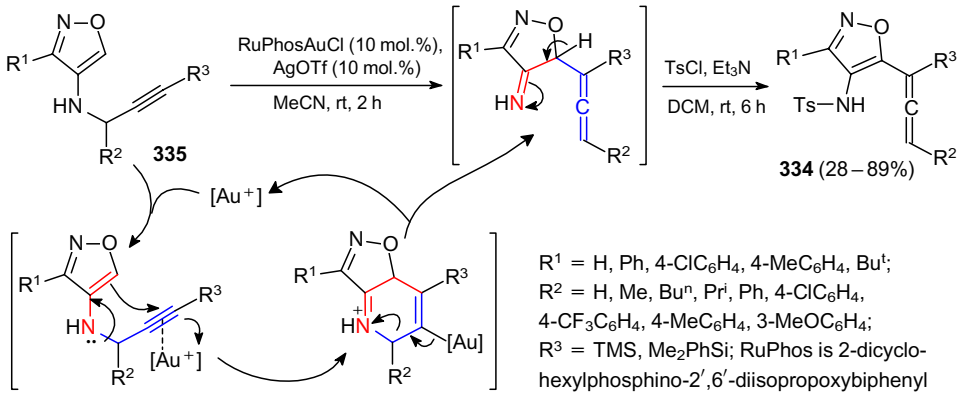
ature sigmatropic rearrangement (Scheme 195).[344] A similar method can be applied to prepare γ- and δ-lactones.

Allenyl-substituted isoxazoles **334** became available *via* the metal-catalyzed aza-Claisen rearrangement, which made use of 4-propargylaminoisoxazoles **335** as the starting materials (Scheme 196).[345] The presence of TMS or $SiMe_2Ph$ moieties as the substituent R^3, as well as a sterically crowded gold-containing catalyst, is essential for the reaction to proceed successfully.

Isatin derivatives, produced by the Morita–Baylis–Hillman reaction, can be reacted with (*R*)-but-3-yn-2-ol to afford chiral allenes. The rearrangement of the intermediates **A** gives products **336** with high diastereoselectivity (Scheme 197). In all cases, the major diastereomer is an allene with (1*R*,2*R*,5*R*)-configuration.[346] One more use of adducts from the Morita–Baylis–Hillman reaction was demonstrated. Yttrium triflate-catalyzed hydroalkoxylation of aminoacetylenes followed by the Claisen rearrangement affords a variety of γ,δ-unsaturated amides **337** in moderate to high yields. The first step comprises a nucleophilic attack of a chiral alcohol on the yttrium-activated triple bond to generate vinyl-yttrium intermediate **B**. The latter species undergoes a [1,3]-hydride shift to give the intermediate **C**, which rearranges into final products. When enantiopure reagents are used, this method shows high diastereoselectivity with the predominant formation of *Z*-alkenes.[347] A similar transformation can also be accomplished in an intramolecular fashion, thus paving the way for the synthesis of eight-membered fused lactams **338**.[348] Replacing a linker (benzene ring) between ynamide and the alcoholic moiety with an aliphatic chain makes it possible to prepare 8–19-membered lactams in yields from 58 to 99%.

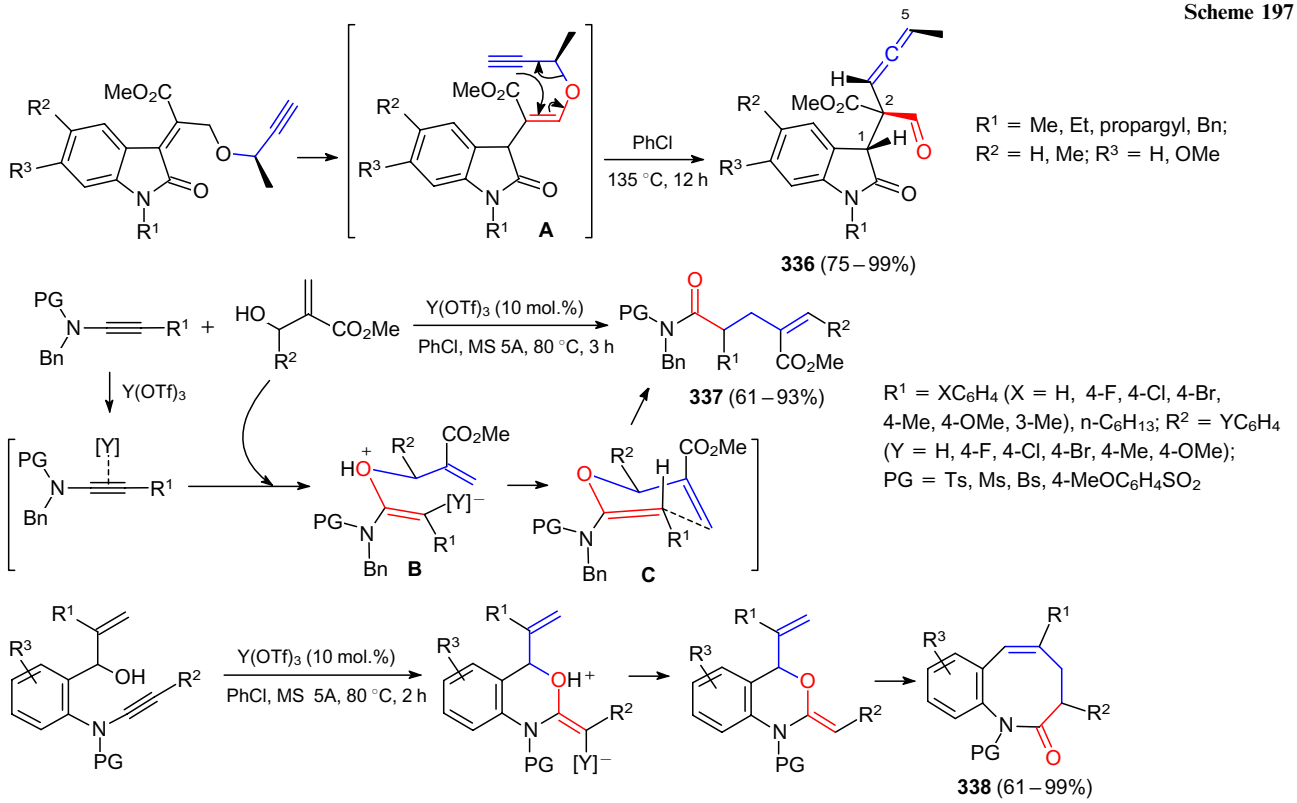
Moreover, [3,3]-sigmatropic rearrangements are implemented in the design of tetracene rings. Thus, 1,4-diols **339**, resulting from the double addition of lithium acetylides to

Scheme 196



R^1 = H, Ph, 4-ClC_6H_4, 4-MeC_6H_4, Bu^t;
R^2 = H, Me, Bu^n, Pr^i, Ph, 4-ClC_6H_4, 4-$CF_3C_6H_4$, 4-MeC_6H_4, 3-$MeOC_6H_4$;
R^3 = TMS, Me_2PhSi; RuPhos is 2-dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl

Scheme 197

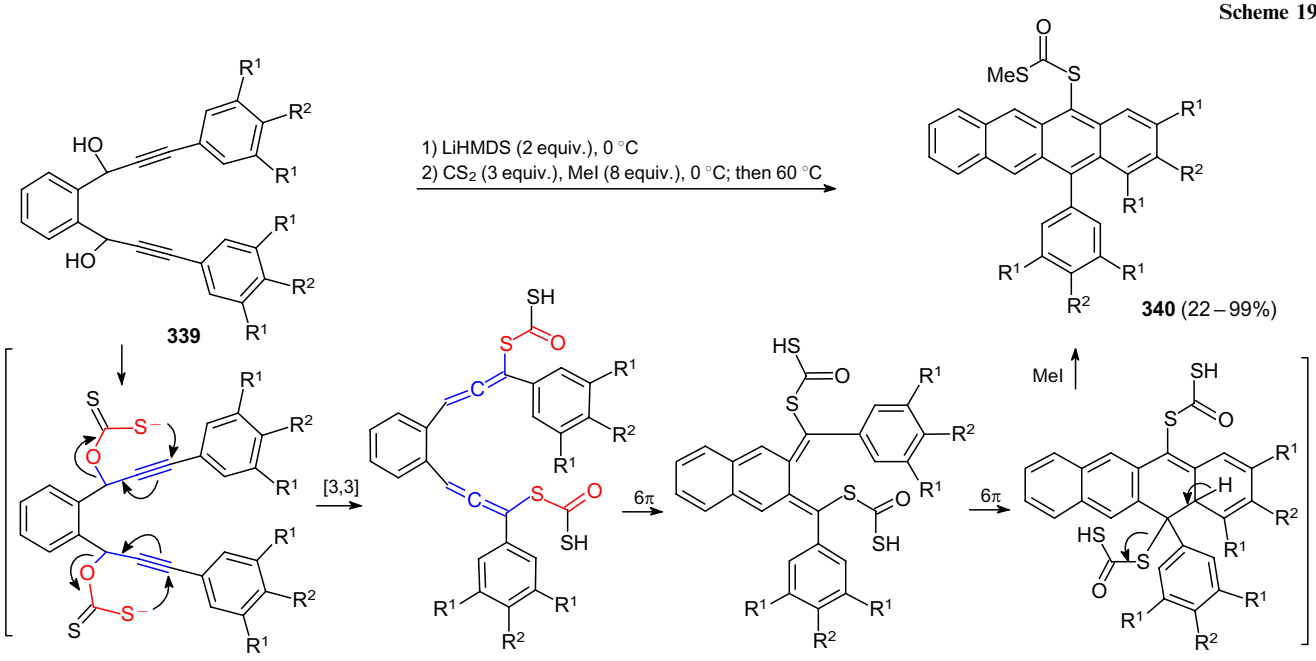


R1 = H, CO_2Me, CO_2Et, Ph; R2 = H, Me, styryl, XC_6H_4 (X = H, 4-F, 4-Cl, 4-Me, 3-Me); R3 = Me, OMe, Cl, Br;
PG = Ts, Bs, 4-$MeOC_6H_4SO_2$, $PhSO_2$

phthalic aldehyde, react with carbon disulfide and iodomethane to afford tetracenes **340** (Scheme 198).[349,350] The formation of acene occurs *via* a [3,3]-sigmatropic rearrangement of xanthate anions followed by 6π-electrocyclization. The reaction cascade can result in the elimination by the E_2 mechanism or the anionic Chugaev elimination. The mechanism of this transformation was confirmed by quantum chemical calculations.

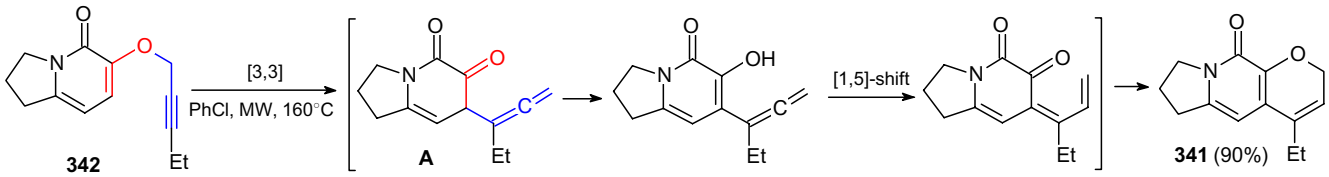
Heterocycle **341**, which is an intermediate in the synthesis of a camptothecin analogue, was obtained using a sigmatropic rearrangement (Scheme 199).[351] Under microwave irradiation, the starting compound **342** undergoes the Claisen rearrangement to give an allenic intermediate **A**.

Scheme 198

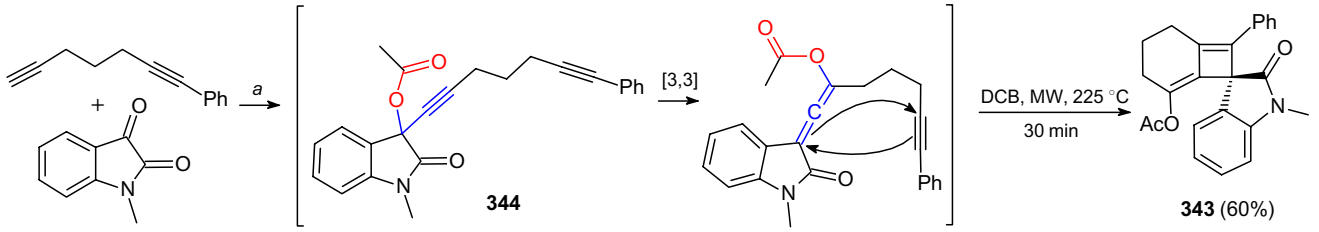


R1 = H, OMe, CF_3; R2 = H, Me, OMe, CF_3, Bu^t

Scheme 199



Scheme 200



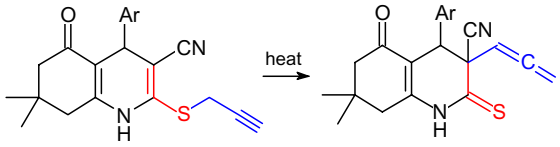
(*a*) 1) Bu^{n}Li, THF, −78 °C (66% yield); 2) Ac_2O, DMAP, Et_3N (98% yield)

The latter product is converted into the final product in high yield *via* a [1,5]-hydride shift and electrocyclization.

C_3-Carbocyclic spirooxindoles **343** can be synthesized through an intramolecular [2 + 2]-cycloaddition to an adduct of *N*-methylisatin and dialkyne (Scheme 200).[352] The reaction is selective — in all cases, the distal double bond of an allene is affected. The starting intermediate for the cycloaddition arises from the sigmatropic rearrangement of derivative **344**. Most frequently, [3,3]-sigmatropic rearrangements involving propargyl moieties require transition metal catalysis to activate the triple bond; however, the above reaction represents a rare example of a thermal [3,3]-rearrangement with the paticipation of the propargyl moiety.

The synthesis of allene-substituted polyhydroquinolines **345** was performed using a sigmatropic rearrangement (Scheme 201).[353, 354] This process features high yields of the products reaching 90%.

Scheme 201

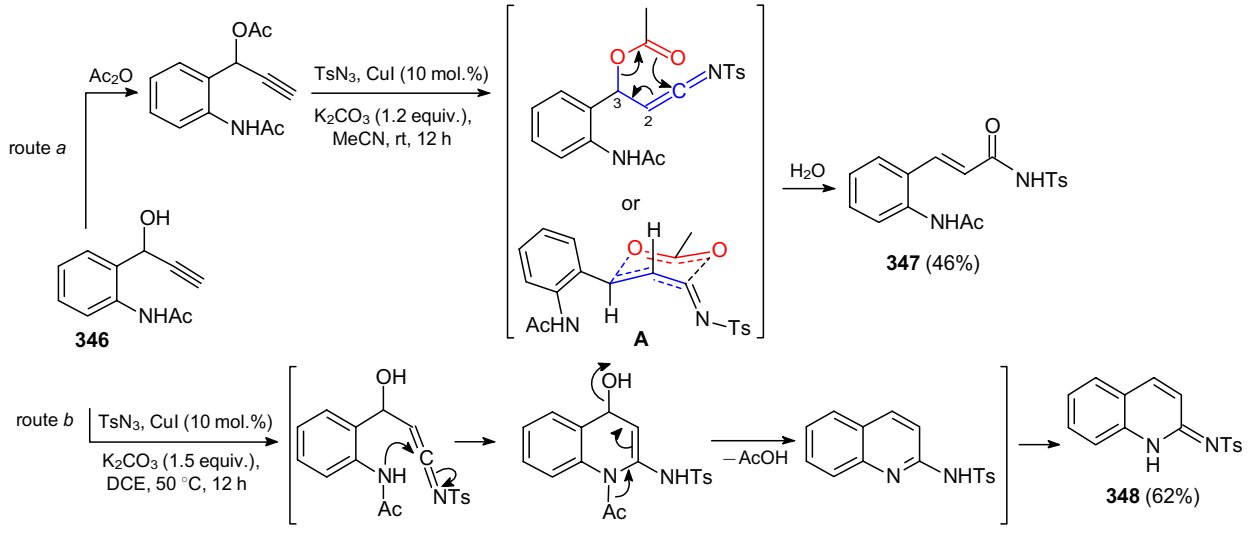


Ar = Ph, 2-$O_2NC_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4

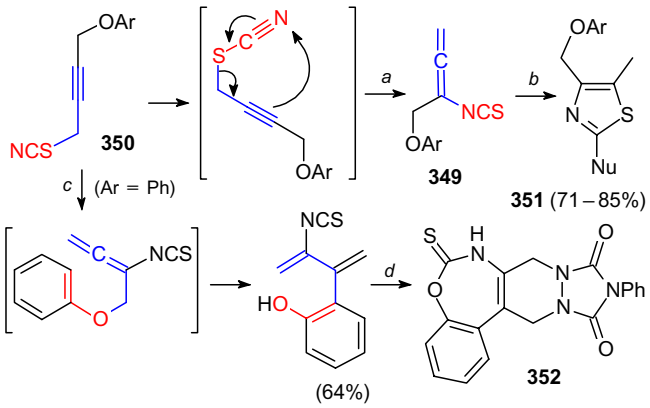
The reactions involving propargyl derivative **346** can proceed *via* two possible routes (Scheme 202).[355] The route *a* leads to amides **347** through the formation of the six-membered transition state comprising acetyl and ketene imine moieties of intermediate **A**. Hydrogen atoms at the C(2) and C(3) atoms in this intermediate presumably occupy axial positions, thus facilitating the formation of solely *E*-alkenes. The route *b* leads to iminoquinolines **348**, since the formation of a four-membered ring bearing a hydroxy group is unfavourable because of a large steric strain.Therefore, the route involves the nucleophilic attack on the central carbon atom of the allene system followed by elimination.

Allenyl isothiocyanates **349** can be derived from propargyl thiocyanates **350** using the solution spray flash vacuum pyrolysis (SS-FVP) (Scheme 203).[356] In this case,

Scheme 202



Scheme 203

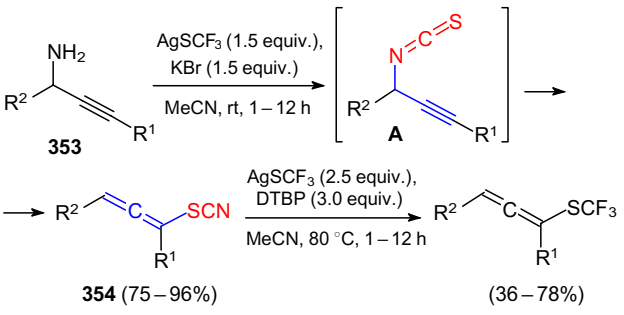


(*a*) SS-FVP, PhMe, 400 °C; (*b*) NuH, PhMe; (*c*) SS-FVP, PhMe, 600 °C; (*d*) PTAD, $CDCl_3$; Ar = Ph, 4-MeC_6H_4; Nu = OMe, NHPh; PTAD is 4-phenyl-1,2,4-triazoline-3,5-dione

products **349** can be further transformed into thiazoles **351** or polyfused compounds **352**. At 400 °C, propargyl thiocyanates **350** undergo a single sigmatropic rearrangement to give compounds **349**, while at higher temperatures (600 °C) already these compounds undergo the sigmatropic rearrangement involving multiple bonds of the benzene ring. However, care must be taken when distilling the starting propargyl thiocyanate: there is evidence that an undesirable side reaction is possible during the distillation to give products, which can undergo exothermic polymerization leading to an explosion.[357]

Later, a safer synthetic route was developed for allenyl thiocyanates using the reaction of propargylamines **353** with silver trifluoromethylthiolate (Scheme 204).[358] First, $AgSCF_3$ reacts with KBr to give potassium trifluoromethylthiolate, which decomposes to potassium fluoride and thiocarbonyl fluoride (not shown in Scheme 204) reacting with propargylamines. Intermediate isothiocyanate **A** *in situ* undergoes a [3,3]-sigmatropic rearrangement. Allenyl thiocyanates **354** bearing electron-donating substituents can further react with $AgSCF_3$ in the presence of di-*tert*-butyl peroxide (DTBP) to furnish allenyl trifluoromethyl sulfides in moderate yields.

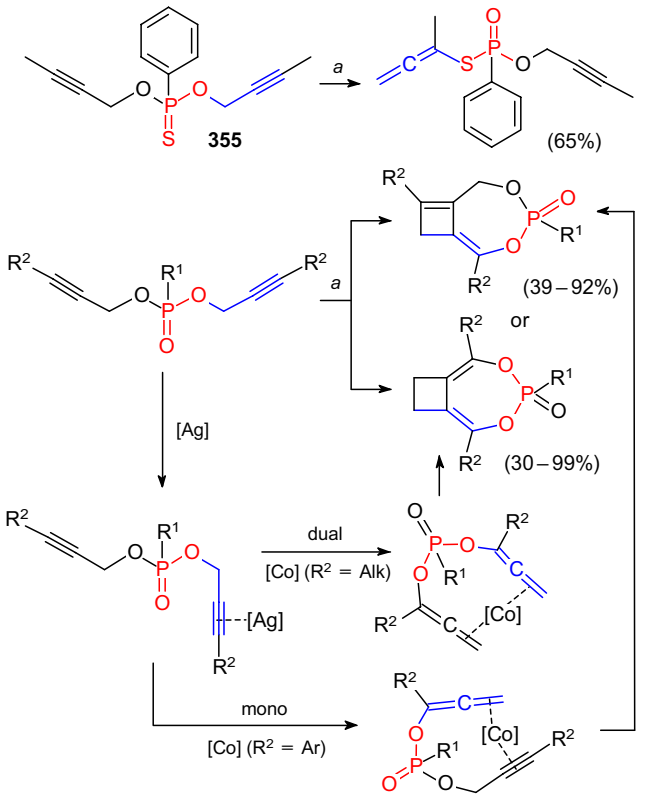
Scheme 204



R^1 = Bu^n, Bu^t, CH_2OBn; R^2 = Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$

Variants of multiheteroatomic rearrangements involving several atoms other than carbon were reported. Such rearrangement can be exemplified by the transformation of compound **355** (Scheme 205).[359] In the initial version, the formation of an allene product was observed from an

Scheme 205

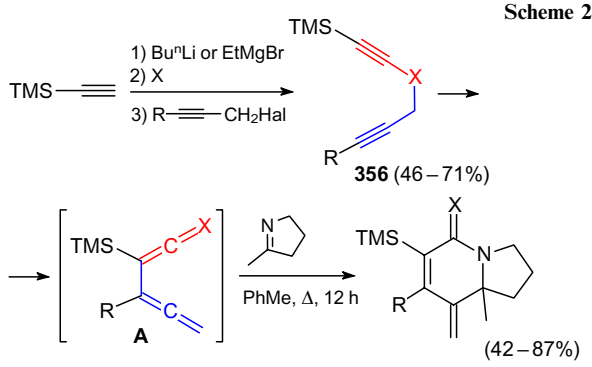


(*a*) $AgBF_4$ (5 mol.%), $Co(OAc)_2$ (5 mol.%), PhMe, 100 °C, 16 h; R^1 = Et, Bn, OPh; R^2 = Ph, 4-MeC_6H_4, 4-FC_6H_4, 4-$MeO_2CC_6H_4$, 3-$MeOC_6H_4$, 3,5-$Me_2C_6H_3$, H, Me, Et, Pr^n, Bu^n, n-C_5H_{11}, CH_2Bn, CH_2OMe, CH_2OPh, CH_2OBn, cyclo-C_3H_5

oxygen analogue. However, the reaction usually does not terminate at this stage, but either another sigmatropic rearrangement occurs (for R = Alk) followed by the tail-to-tail [2+2]-cycloaddition or the [2+2]-cycloaddition occurs immediately through the interaction between the allene and alkyne moieties (for R = Ar).

Sulfur- and selenium-containing compounds undergo sigmatropic rearrangements. This transformation is used to construct the phenanthroindolizidine core (a fragment of this synthesis is outlined in Scheme 206).[360] Compounds **356**, derived from trimethylsilylacetylene, chalcogen and propargyl halide, produce *in situ* α-allenylchalcogenoketenes **A** by a thermal [3,3]-sigmatropic rearrangement followed by the Diels–Alder reaction with cyclic imines, *e.g.*, 2-methyl-1-pyrroline.

Scheme 206



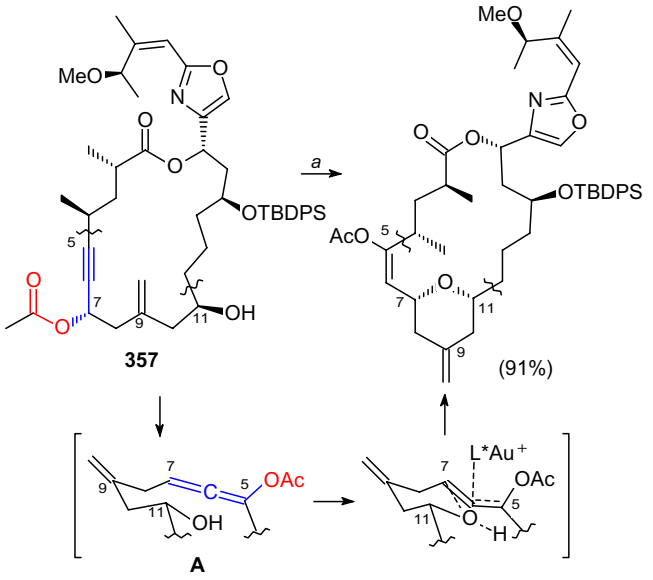
R = Ph, 3,4-$(MeO)_2C_6H_3$; X = S, Se; Hal = Cl, Br

In many studies describing [3,3]-sigmatopic rearrangements involving a triple bond, the authors employed transition metal catalysis, most often using gold derivatives. Propargyl esters are generally used as substrates, whereas the rearrangement *per se* proceeds *via* the formation of an allenic intermediate, which is then used to prepare structurally complex compounds. Thus, a gold-catalyzed [3,3]-sigmatopic rearrangement of compound **357** was implemented in the synthesis of enigmazole A, a macrolide isolated from sea sponges (Scheme 207).[361] Enigmazole A is considered as one of the most promising candidates for anticancer drug development. The efficiency of this transformation is achieved by a gold-catalyzed reaction cascade. One step is a [3,3]-sigmatropic rearrangement of the propargyl acetate moiety along the periphery of a macrocyclic scaffold followed by a transannular hydroalkoxylation of an intermediate allenyl acetate **A**. This transformation requires the use of a chiral gold-containing catalyst to provide asymmetric induction.

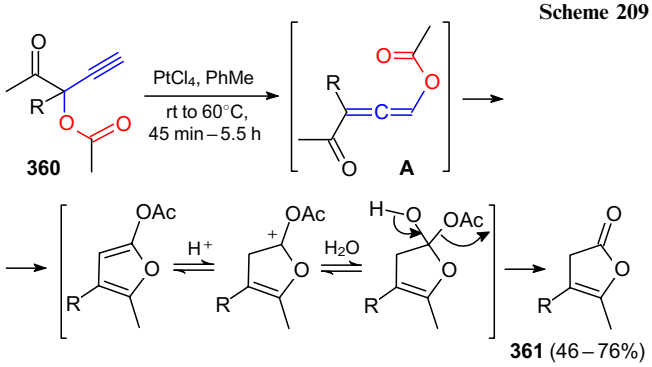
The [3,3]-sigmatropic rearrangement of propargyl esters **358** enabled the construction of substituted variable-sized carbocycles **359** (Scheme 208).[362] This sequence is initiated by the reaction of compounds **358** with gold chloride in the presence of silver perchlorate. This approach allows access to regioisomers, which are unavailable *via* traditional methods for the synthesis of unsaturated carbocycles. Where necessary, this protocol can be extended to the production of exocyclic enones.

The platinum(IV)-catalyzed cascade reaction of propargyl esters **360** afforded lactones **361**.[363] The process occurs *via* the formation of an allenic intermediate **A** (Scheme 209).

Scheme 207



Scheme 209

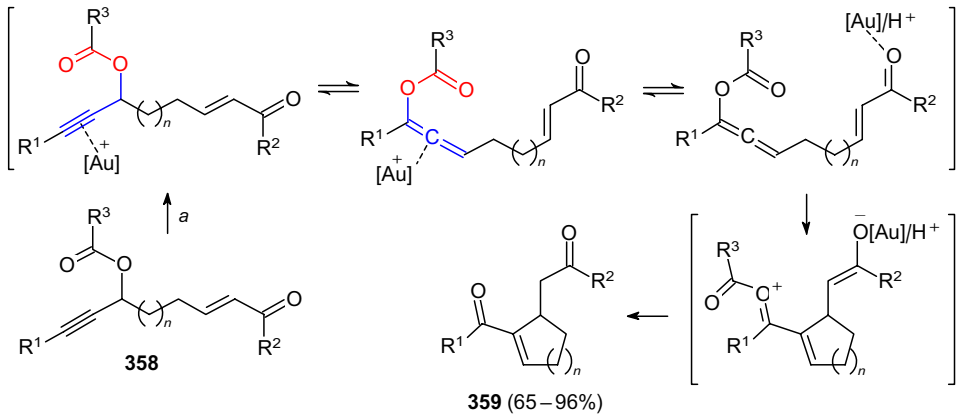


1,4-Oxazine derivatives **362** were obtained from esters **363** using silver triflimide as the catalyst.[364] The reaction proceeds through the rearrangement yielding an allene intermediate **A** and an acyl shift (Scheme 210).

Rearrangements mediated by a gold-containing catalyst **XIII** can be used to prepare substituted α-enones **364** (Scheme 211).[365] The selective alkylation of intermediate enones with alcohols proceeds *via* the gold-initiated formation of nucleophilic allenoates **A** through a [3,3]-sigmatropic rearrangement of propargylic carboxylates **365**. A series of α-alkylated enones was obtained in high yields using 2 mol% of the gold complex [JohnPhosAu(MeCN)]SbF_6 (**XIII**).

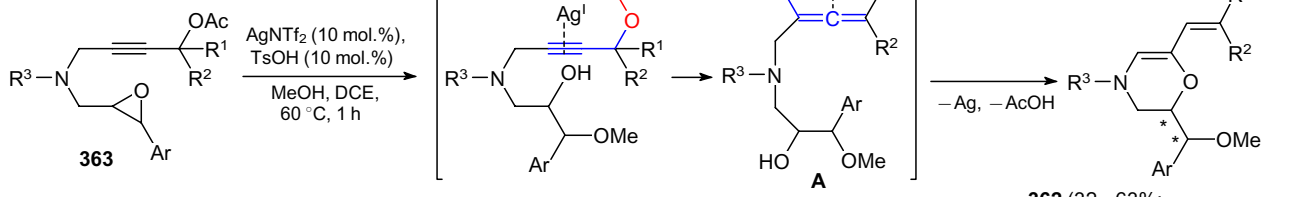
The alkene formation involved a sigmatropic rearrangement of the appropriate alkyne.[366] The reaction was catalyzed by gold compounds through the metal-activation of the carbon–carbon triple bond. The intermediate allenol

Scheme 208



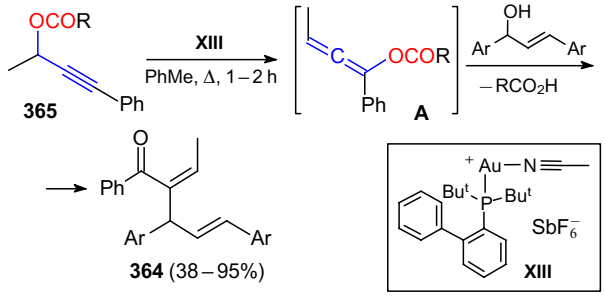
a — AuCl (10 mol.%), $AgClO_4$ (20 mol.%), $MeNO_2$, rt, 15 min – 1 h;
n = 1, 2; R^1 = Ph, Me, Bu^n; R^2 = Me, Ph, 4-MeC_6H_4; R^3 = Bu^t, Piv

Scheme 210



R^1, R^2 = Me, Et, Pr^i, Bu^t; R^3 = Ts, Bs, 2-MeC_6H_4

Scheme 211



R = Me, Bu^t; Ar = 4-MeC_6H_4, 2-MeC_6H_4, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4

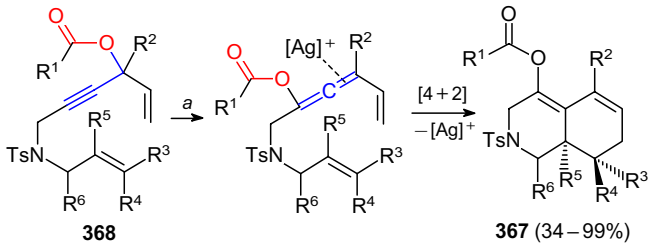
ester **A** *in situ* reacted with *p*-quinone methide **366** (in this step, gold also served as a catalyst but acted as a Lewis acid) (Scheme 212). The reaction of the methide with the allene followed the mechanism of 1,6-conjugate addition and afforded exclusively compounds with a unsaturated bond with a *Z*-configuration.

Partially hydrogenated isoquinolines **367** were synthesized *via* a rearrangement of esters **368** (Scheme 213).[367] The domino reaction occurs under silver catalysis and involves a [3,3]-sigmatropic rearrangement and the intramolecular Diels–Alder reaction.

Examples of using rearrangements of propargyl ethers were also reported in the literature. Thus, the rearrangement of propargyl vinyl ether **369**, mediated by tosyl amide and gold catalysts, occurs *via* the formation of 2,4-dienal and affords substituted dihydropyridines **370** (Scheme 214).[368] This transformation involves the gold-catalyzed [3,3]-sigmatropic rearrangement, isomerization, amine condensation and 6π-aza-electrocyclization.

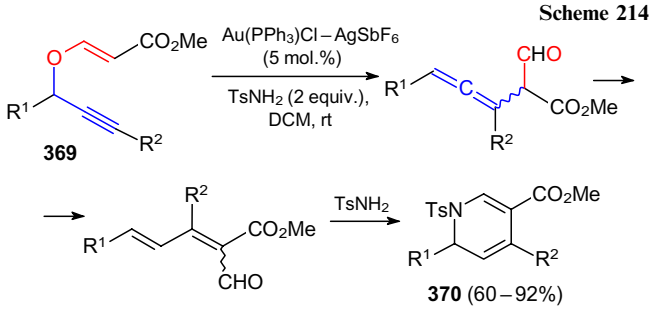
Cyclopentadienes **371** fused to various carbocycles and nitrogen-containing rings became available through a tandem reaction based on the gold(I)-catalyzed Claisen rearrangement and Nazarov cyclization (Scheme 215).[369] This

Scheme 213



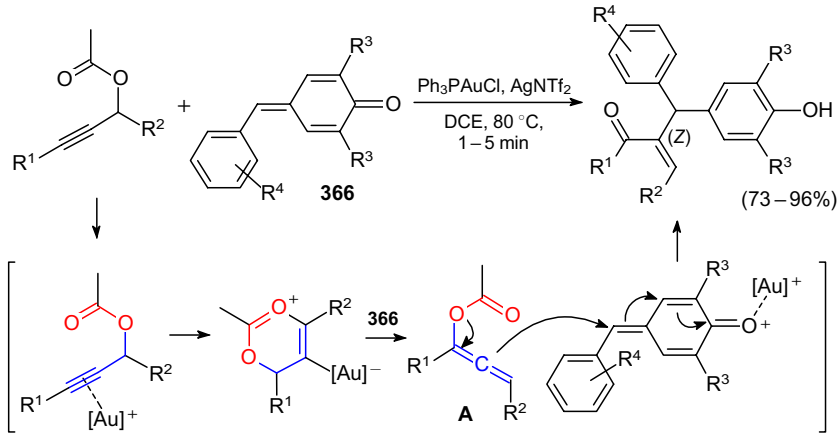
(*a*) $AgSbF_6$ (5 mol.%), JohnPhos (5 mol.%), PhMe, MS 4A, 80 °C, 2–72 h; R^1 = Me, Ph, 4-$MeOC_6H_4$, 4-$O_2NC_6H_4$; R^2 = Et, Bn; R^3 = Me, Et, CH_2OBn, Ph, 4-$F_3CC_6H_4$; R^3–R^4 = $(CH_2)_2$; R^5 = H, Me; R^6 = H; R^6–R^3 = $(CH_2)_3$

Scheme 214



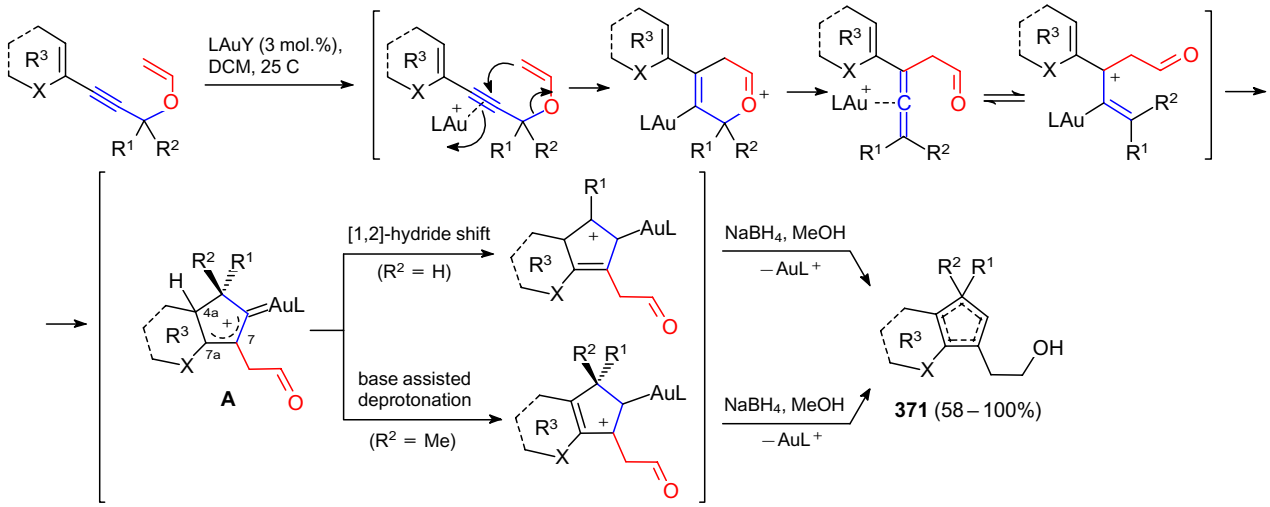
R^1 = Ph, 2-MeC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4, n-C_6H_{13}; R^2 = H, n-C_5H_{11}

Scheme 212

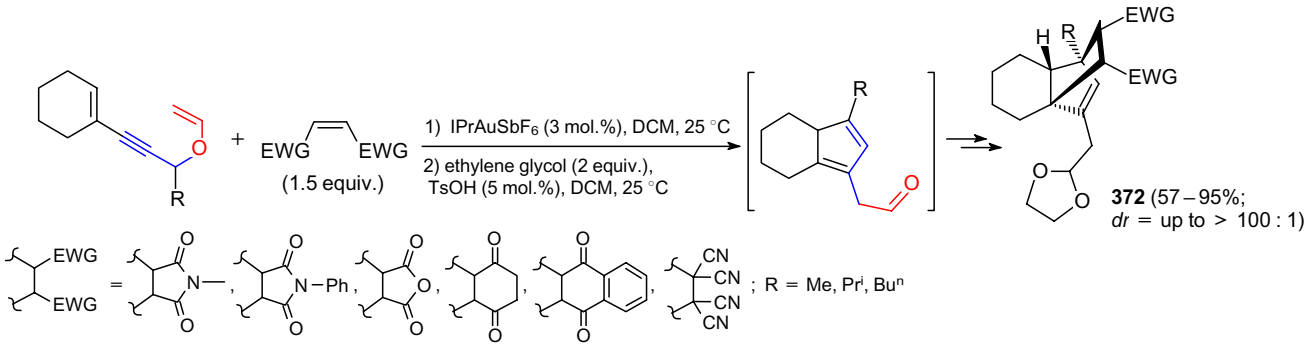


R^1 = Ph, n-C_5H_{11}, 4-$Bu^tC_6H_4$; R^2 = Me, Pr^i, Ph, 1-Naph; R^3 = Me, Bu^t; R^4 = H, Me, OMe, Cl, 1-Naph, CO_2Me (in different positions)

Scheme 215



X = CH_2, NR (R = Ts, Me); R^1 = Me, Bu^n, Ph; R^2 = H, Me; R^3 = *N*-tosyl-1,2,3,4-tetrahydropyridin-6-yl, *N*-tosyl-2,3,4,5-tetrahydroazepin-7-yl, Cy, cyclo-C_7H_{13}, Ph; L = Bu^t_3P, IPr; Y = NTf_2, OTf, SbF_6

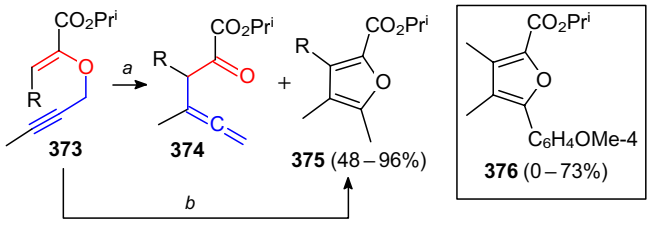


reaction is highly regioselective, with the positions of double bonds in the five-membered ring of the product being dependent on the substituent on the propargyl moiety of the substrate. Thus, if intermediate **A** bears a substituent R^2 other than the hydrogen atom, the proton is abstracted from the C(4a) atom. In this case, the first multiple bond arises between the C(7a) and C(4a) atoms. If R^2 = H, intermediate **A** undergoes a [1,2]-hydride shift, and the first multiple bond is formed between the C(7) and C(7a) atoms. This reaction is also useful in the synthesis of indenes,[370] and the addition of the Diels–Alder reaction to this sequence provides an access to polycyclic derivatives **372** with various skeletons (see Scheme 215).[371]

Under acidic conditions, 2-alkoxycarbonyl-substituted propargyl vinyl ethers **373** form the products of rearrangement (γ-allenyl esters **374**) and(or) cyclization (substituted furans **375**) (Scheme 216).[372] Their ratio depends on the nature of the substituent and varies in the range of 1–43% (for **374**) and 15–99% (for **375**). In this case, when R is the *p*-methoxyphenyl moiety, regioisomeric product **376** is formed in significant amounts, whereas only furans **375** are obtained in moderate to high yields under the action of a gold- and silver-containing catalytic system.

Alkynylcyclopropyl allyl ethers **377** were converted to tetrasubstituted methylenecyclobutanones **378** using the reaction as depicted in Scheme 217.[373] A ring expansion in ethers **377** occurs through a [3,3]-sigmatropic rearrangement followed by a [1,2]-allyl shift in the presence of catalytic amounts of water and a gold catalyst, which activates the triple bond. Water facilitates the [1,2]-allyl

Scheme 216

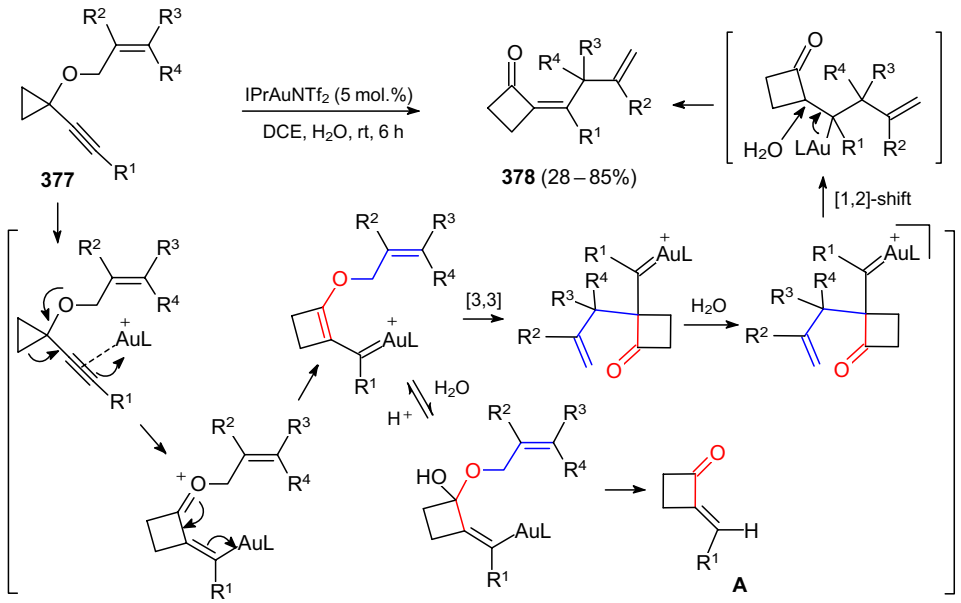


(*a*) HOTf, HFIP, rt, 45 min (44–99%); (*b*) Ph_3PAuCl (0.05 equiv.), $AgSbF_6$ (0.05 equiv.), DCM (dry), rt, 20–150 min;
R = Me, Bn, Ph, 4-$MeOC_6H_4$, 4-$O_2NC_6H_4$, vinyl

shift and stabilizes the carbenium ion in the step of the catalyst regeneration. During the reaction, the by-product **A** can be formed *via* deallylation and protodeauration reactions. The participation of water in this process was confirmed by experiments with the addition of an isotopic label ($H_2{}^{18}O$ and D_2O) to the reaction mixture. The reaction yields vary from 28 to 85%. Similar strategies were employed in the synthesis of polysubstituted furans.[374]

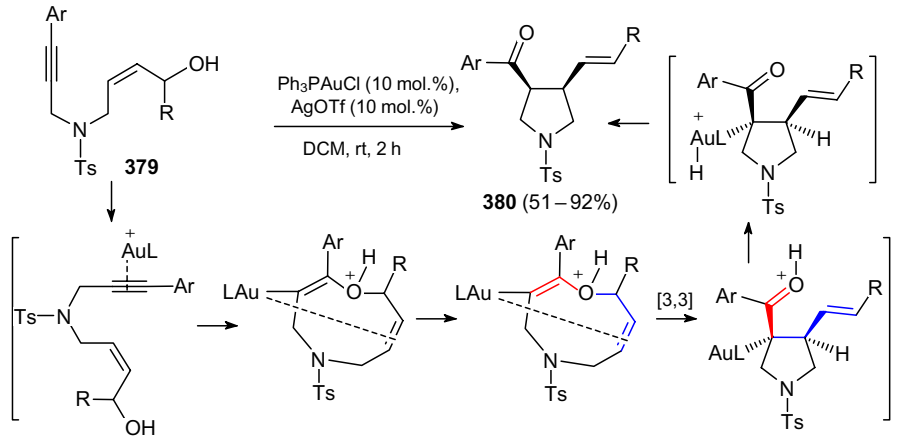
The rearrangements of substituted propargyl tosylamines **379** were implemented to prepare substituted pyrrolidines **380** using a gold catalyst (Scheme 218).[375, 376] During this reaction, the hydroxyl group attacks the gold-activated triple bond to create a configuration favourable for the Claisen rearrangement. After a hydride shift and subsequent protodeauration, *cis*-3-acyl-4-alkenylpyrrolidines are formed in yields of up to 92%.

Scheme 217



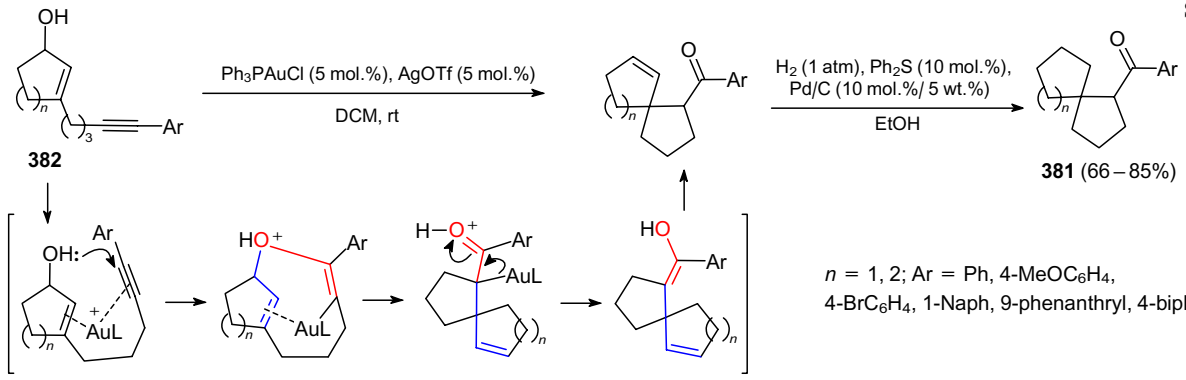
R^1 = Ph, 4-MeC_6H_4, 4-EtC_6H_4, 4-$AllC_6H_4$, 2-MeC_6H_4, 3-Th, $(CH_2)_3Ph$; R^2, R^3 = H, Me; R^4 = H, Me, Ph

Scheme 218



R = H, Me, Bn;
Ar = 4-XC_6H_4 (X = H, Me, OMe, Br, NO_2, Ph), 1-Naph

Scheme 219

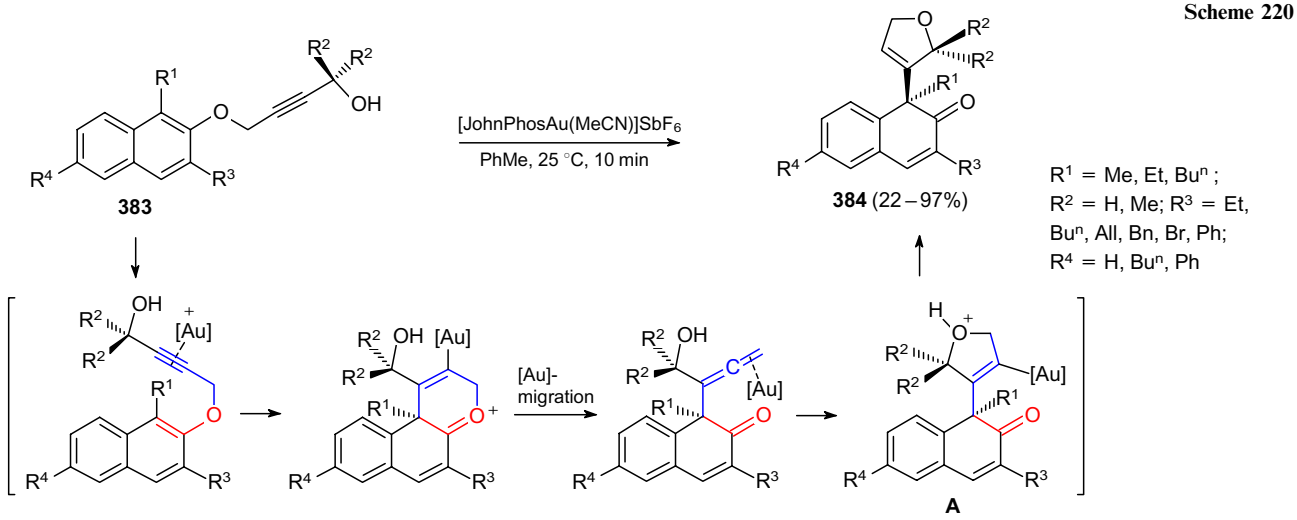


n = 1, 2; Ar = Ph, 4-$MeOC_6H_4$, 4-BrC_6H_4, 1-Naph, 9-phenanthryl, 4-biphenyl

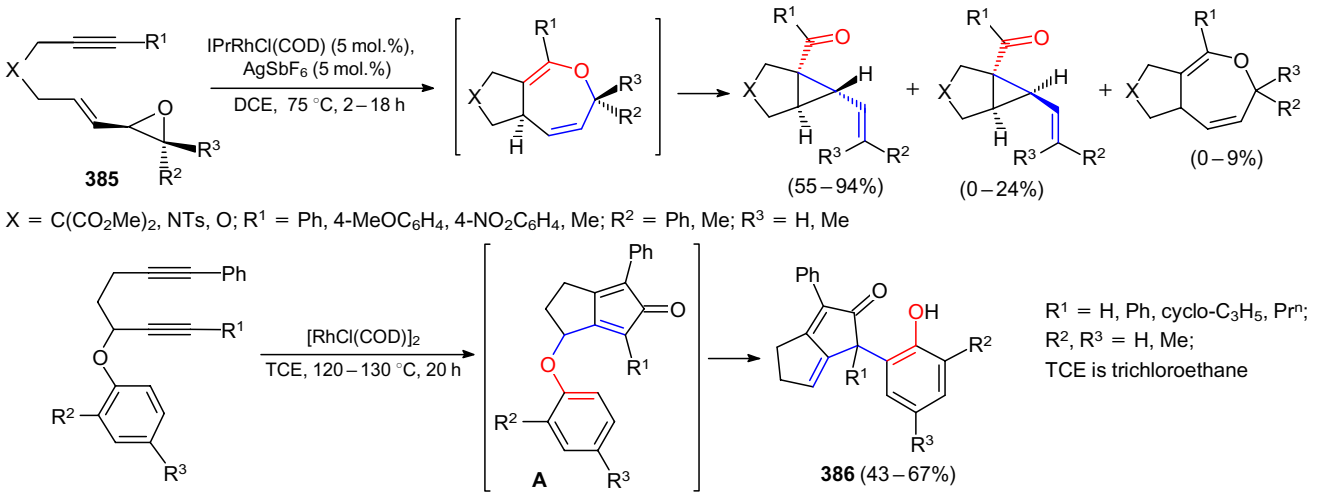
Spirocyclic ketones **381** can be synthesized using gold-catalyzed rearrangements of compounds **382** (Scheme 219).[377] The process involves an attack of the hydroxyl group on the triple bond of gold-activated alkynes followed by a [3,3]-sigmatropic rearrangement.

The reaction of naphthylpropynol **383** with a gold catalyst occurs with the loss of aromaticity of the system, resulting in functionalization of the starting compound at the 1 position of the naphthalene ring and the formation of dihydrofurans **384** (Scheme 220).[378] The dearomatization of the naphthalene ring becomes possible due to the propargyl-vinyl Claisen rearrangement occurring through the formation of a six-membered intermediate. Next, the six-membered ring decomposes, and the gold catalyst migrates to the terminus of the allene system and occupies an *anti* position with respect to the hydroxyl moiety. This allows the attack of the hydroxyl group on the terminal allene atom to generate an oxonium intermediate **A**. The latter eliminates the catalyst and the proton to give final product **384**. The stepwise course of the rearrangement provides the possibil-

Scheme 220



Scheme 221



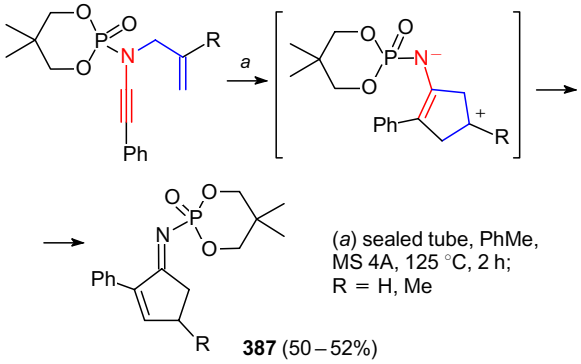
ity for the development of an enantioselective version of this reaction, which is supported by experiments using chiral gold catalysts.

A diastereoselective tandem transformation of vinyloxiranes **385** bearing an acetylenic moiety makes it possible to prepare fused systems containing a five-membered ring. The reaction is catalyzed with rhodium compounds, and a key step is the Claisen rearrangement (Scheme 221).[379] Another tandem strategy is based on the Rh-catalyzed [2+2+1]-cycloaddition of diynes and the Claisen rearrangement (*via* the formation of the intermediate **A**) to afford unusual fused carbocycles **386**.[380]

In 2012, the carbocyclization cascade of allyl ketenimines induced by the thermal aza-Claisen rearrangement of *N*-phosphoryl-*N*-allyl ynamides was described. This transformation furnished cyclization products **387** in moderate yields (Scheme 222).[381]

Later, the palladium-catalyzed and thermal aza-Claisen rearrangements were implemented in the synthesis of α,β-unsaturated cyclopentenimines **388**. The nature of an electron-withdrawing substituent at the nitrogen atom is critical for the success of this tandem process. The reaction with *N*-sulfonyl ynamides requires the use of a palladium catalyst (Scheme 223).[382] A similar approach was previously employed in the synthesis of azepin-2-ones **389**, with the

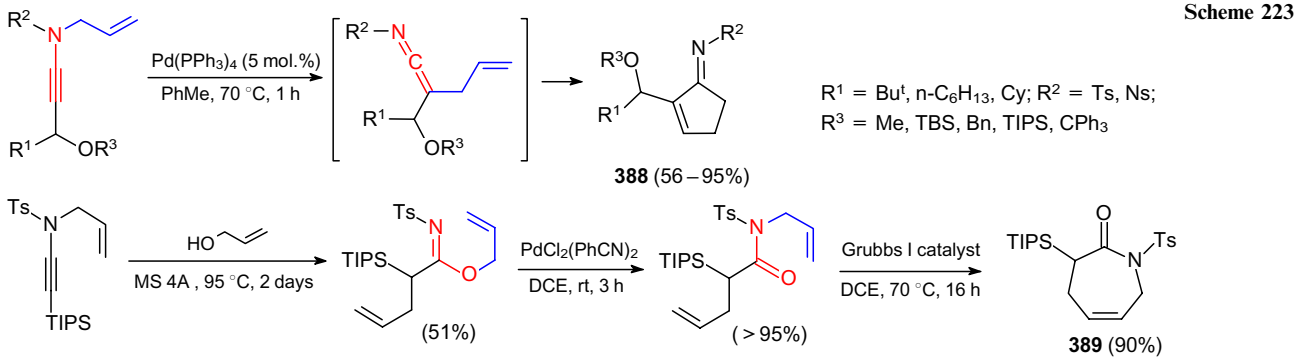
Scheme 222



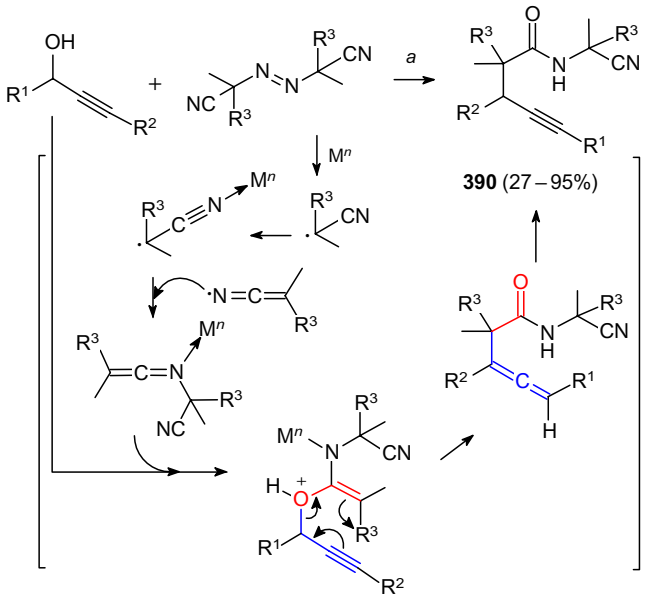
rearrangement being followed by the metathesis reaction for the purpose of cyclization.[383]

The reaction of propargylic alcohols with azobis(isobutyronitrile) (AIBN) and its derivatives provides an opportunity to produce various alkyne-containing amides **390**. The process is based on a tandem of the radical–radical cross coupling, the nucleophilic addition and the Claisen rearrangement using copper catalysts (to yield acetylenic amides) or silver catalysts (to afford allenic amides). In this

Scheme 223



Scheme 224



(*a*) $Cu(MeCN)_4BF_4$ (5 mol.%), $4\text{-}O_2NC_6H_4B(OH)_2$ (10 mol.%), DME, 100 °C, 12 h; R^1 = 4-$MeOC_6H_4$, 2-$MeOC_6H_4$, 3-$MeOC_6H_4$, 2-Th; R^2 = Bu^t, n-C_6H_{13}, Cy, n-Oct, Bn, TMS, XC_6H_4 (X = H, Me, Et, Bu^t, OMe, F, Cl, Br, CF_3), 2-Th; R^4 = Me, Et; DME is 1,2-dimethoxyethane

case, the coordination effect of metals not only affects the course of the Claisen rearrangement, but also contributes to the selective radical-radical cross-coupling (Scheme 224).[384]

Efficient methods to prepare functionalized pyrroles were developed based on the aza-Claisen rearrangement. For example, in the presence of copper catalysts, allenes and propargylamines undergo the tandem reaction to give pentasubstituted pyrroles **391** in yields of up to 84% (Scheme 225).[385] The reaction sequence comprises the aza-Michael addition to afford the intermediate **A**. The protonation and isomerization of the latter lead to the enamine ester **B**, which undergoes the aza-Claisen rearrangement to afford the allenic derivative **C**. The isomerization of compound **C** into intermediate **D** is followed by cyclization to yield the final products **391**. Possible products of 5-*exo-dig* and 6-*endo-dig* cyclizations (**E**, **F**) were not detected in the reaction mixture, although the reasons for such selectivity are not entirely clear. A similar transformation can be accomplished using a gold catalyst in the synthesis of pyrroles **392**.[386] In this case, the solvent plays an important role, since in the absence of HFIP, the reaction affords dihydropyridines **G** as the major products. Boc-protected propargyl glycinates can also undergo the Claisen rearrangement providing an efficient and stereoselective synthesis of densely functionalized allenamides **393**. Such compounds are subjected to a silver-catalyzed cyclization to 3-pyrrolines **394**, which are useful precursors to substituted pyrrolidines.[387]

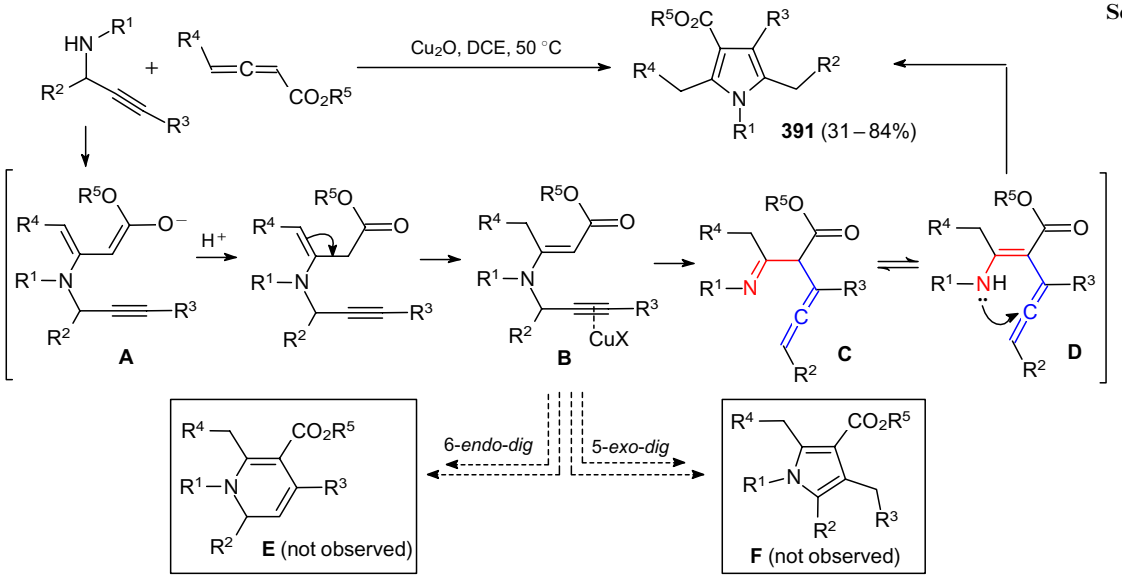
A catalytic enantioselective rearrangement of propargyl vinyl esters derived from indoles (the Saucy–Marbet–Claisen rearrangement) was first described in 2012.[388] Palladium complexes with (*R*)-BINAP (Scheme 226) or (*R*)-4-*tert*-butyl-2-[2-(diphenylphosphino)phenyl]-2-oxazoline ligands were used as catalysts. This protocol enabled the synthesis of allenyl oxindoles **395** containing a quaternary carbon centre with high enantioselectivity (up to 98% *ee*). In the future, compounds **395** can be utilized to prepare spirocyclic oxindoles.

A wide range of allenyl-substituted β-ketoesters **396** can be synthesized using a chiral nickel complex. This reaction not only provides a high yield of the product (up to 96%) but is also characterized by high diastereselectivity (*dr* up to 99 : 1) and excellent enantioselectivity (up to 99% *ee*).[389] The same catalytic system was implemented in the rearrangement of phosphonate derivatives, thus providing an access both to chiral allenes **397** and propargyl derivatives **398** due to kinetic resolution (Scheme 227).[390]

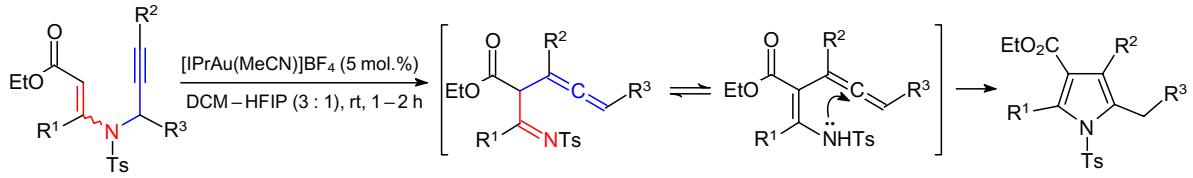
Copper triflate proved to be a very efficient catalyst for the [3 + 2]-annulation of propargyl acetates with *N*-alkylanilines to afford 2,3-disubstituted indoles **399** (Scheme 228).[391] The reaction proceeds in the presence of trimethylsilyl chloride, which facilitates an attack of the nitrogen atom on the carbon atom adjacent to the acetoxy moiety, and the additional introduction of a Cu catalyst promotes the Claisen rearrangement *via* activation of the triple bond. An alternative approach to the synthesis of indoles **400** involves a rearrangement of propargylammonium salts derived *in situ* from arynes and tertiary propargylamines.[392]

Propargylhydrazones **401** are suitable for the production of various heterocyclic systems. Thus, starting from these compounds, pyrazoles **402** were obtained using platinum compounds as catalysts and toluene as the solvent (Scheme 229).[393] The cascade reaction is based on the [3,3]-sigmatropic rearrangement initiated by platinum(IV) chloride and occurs *via* the formation of the six-membered transition state. Next, the cyclization of the newly formed *N*-propargylhydrazones **A** and elimination of the platium catalyst take place to give the resulting pyrazoles. When replacing the catalyst with silver triflate and the solvent with ethyl acetate, 1,6-dihydropyridazines **403** are produced instead of pyrazoles **402**.[394] The mechanism of the initial steps is similar to that for the process of the formation of

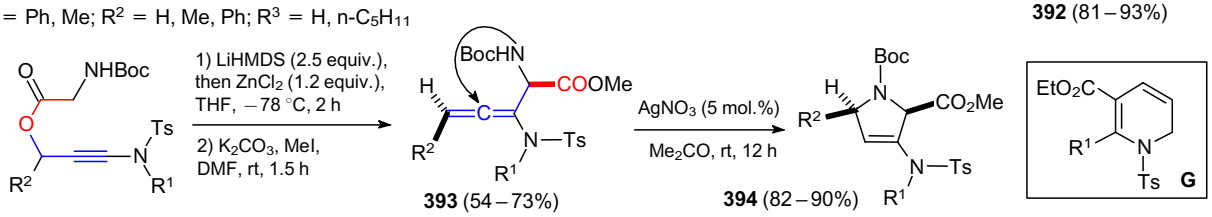
Scheme 225



R^1 = Ph, Bn, 4-MeOC$_6$H$_4$CH$_2$, 2-ClC$_6$H$_4$(CH$_2$)$_2$, 4-MeC$_6$H$_4$(CH$_2$)$_2$, 3-Ind(CH$_2$)$_2$; R^2 = Ph, 4-MeOC$_6$H$_4$, 4-EtC$_6$H$_4$, 3,4-Cl$_2$C$_6$H$_3$;
R^3 = Ph, 4-EtC$_6$H$_4$; R^4 = H, Et, Bn, 4-ClC$_6$H$_4$; R^5 = Et, Pr^i, Bu^n, Bn

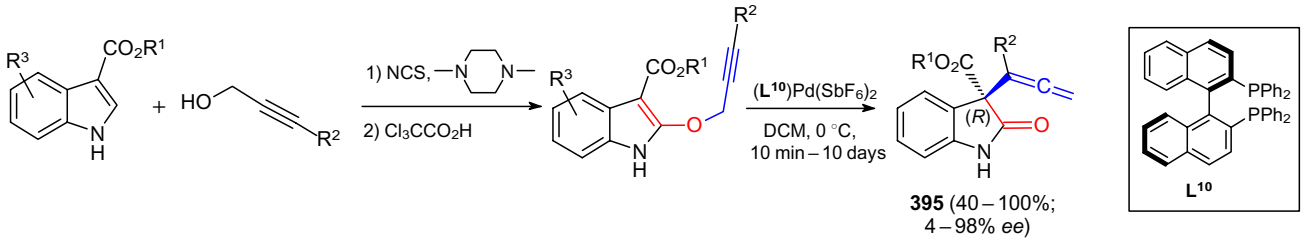


R^1 = Ph, Me; R^2 = H, Me, Ph; R^3 = H, n-C$_5$H$_{11}$



R^1 = Bn, 4-MeOC$_6$H$_2$CH$_2$, 2-ClC$_6$H$_4$CH$_2$, cyclo-C$_3$H$_5$CH$_2$; R^2 = H, Me, CH$_2$OBn, Pr^i, but-3-enyl, (CH$_2$)$_4$OTBDPS

Scheme 226



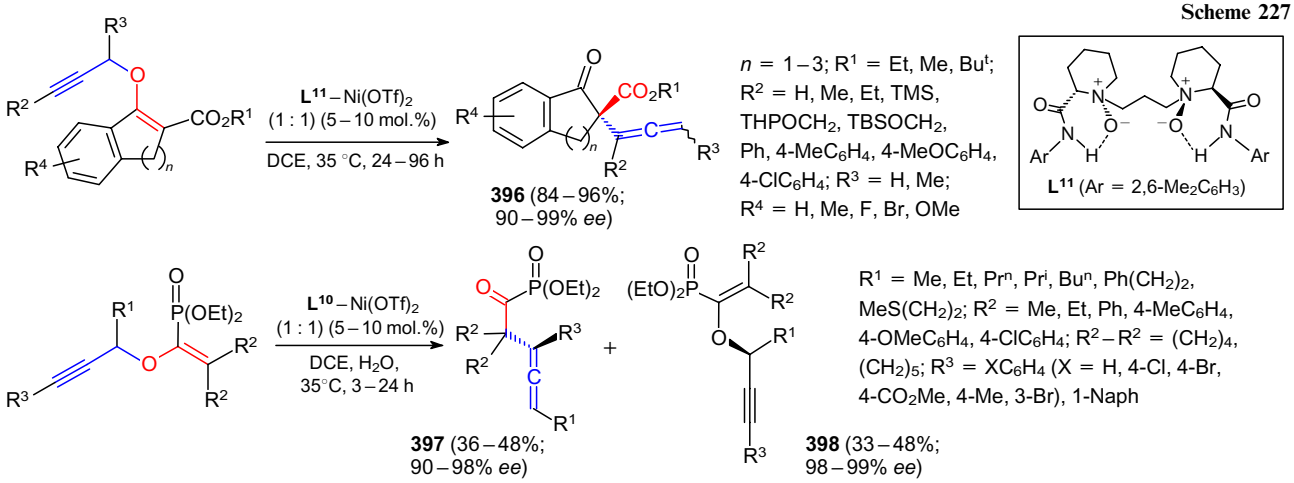
R^1 = Me, Et; R^2 = H, Me, Bu^t, TMS, TES, TBS, 2-MeC$_6$H$_4$, 2-MeOC$_6$H$_4$, 1-Naph; R^3 = H, 5-OMe, 7-OMe, 5-Br, 7-Me;
NCS is -chlorosuccinimide, TES is triethylsilyl

pyrazoles; however, being treated with silver triflate, intermediate allenes **B** undergo a [1,3]-hydride shift followed by the 6π-aza-electrocyclization to furnish products **403**.

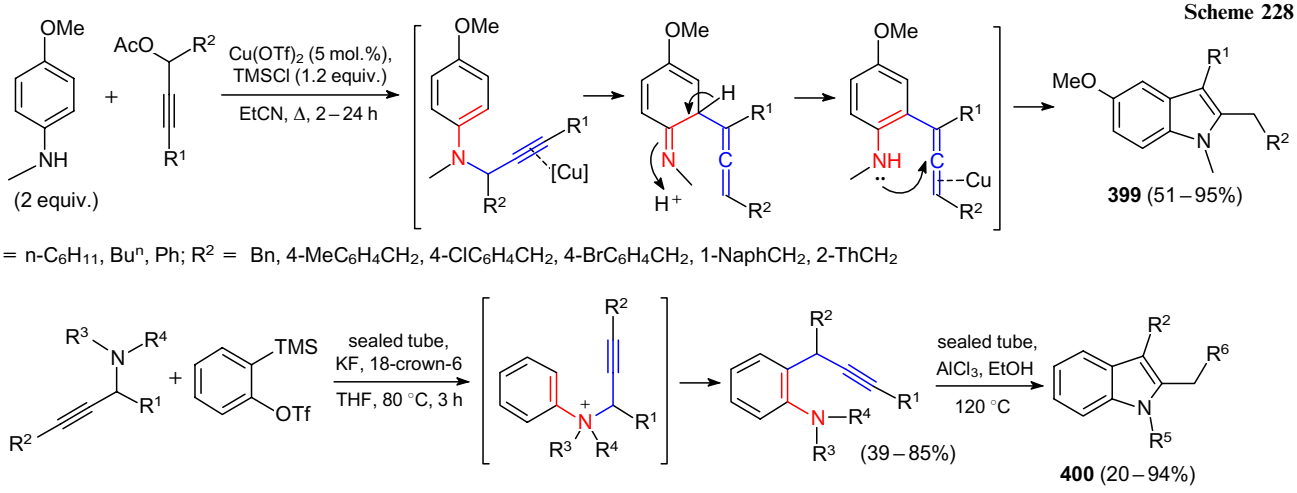
Similar rearrangement products were obtained later by Verlee *et al.*;[395] however, in this case gold(III) chloride was used in place of platinum chloride, and ethyl acetate was used as the reaction medium (Scheme 230). This process occurs *via* the consecutive formation of hydrazone, 5-*endo-dig* cyclization and the aza-Claisen rearrangement to produce polysubstituted pyrazoles **404**. The reaction with alkynyl aldehydes gives rise to the pyrazole ring containing a hydrogen atom at the 3 position (R^4 = H), and the allyl migration not only to the 4 position but also to the C(3) atom is possible. In this case, isomeric pyrazoles **404a**,**b** are produced in an overall yield of 22–79% with a ratio from 40 : 60 to 100 : 0. For R^4 = Me (*i.e.* when using alkynyl ketones), such a process was not observed.

Propargyl ethers and alcohols are also employed to produce furans (**405**, **406**)[396, 397] and dihydrofurans (**407**)[398] (Scheme 231). Thus, polysubstituted furans can be synthesized *via* a rearrangement of propargyl vinyl ethers bearing a free hydroxyl moiety. In the presence of catalytic

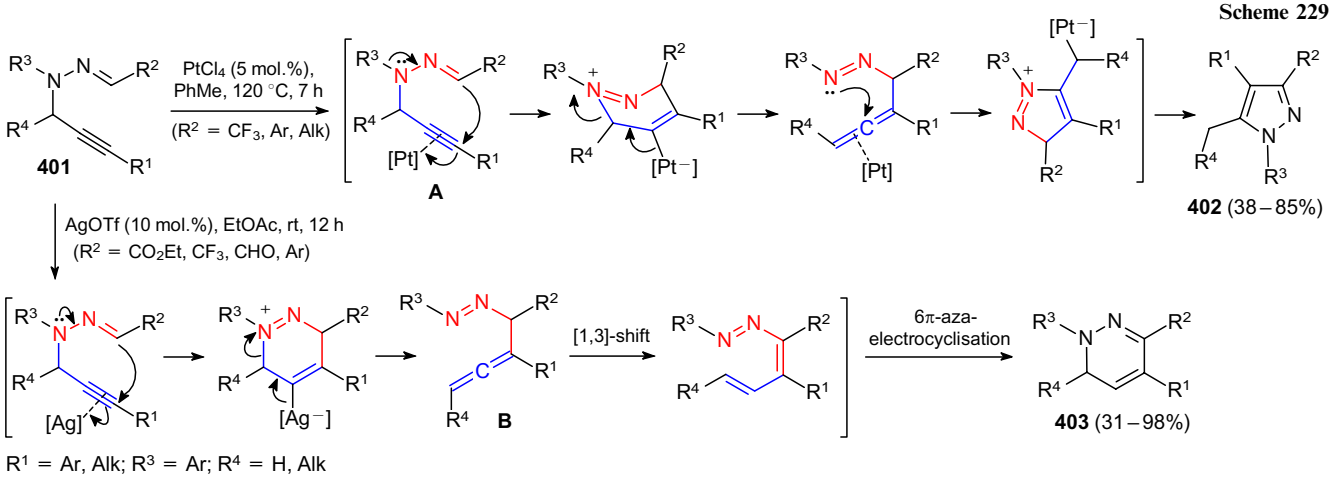
Scheme 227



Scheme 228

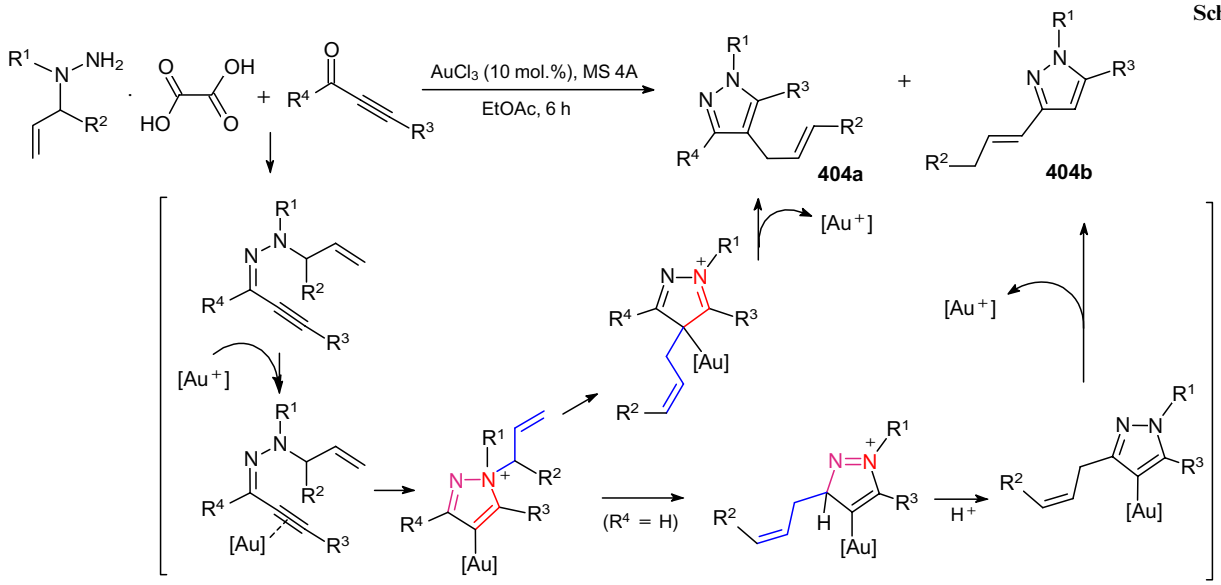


Scheme 229



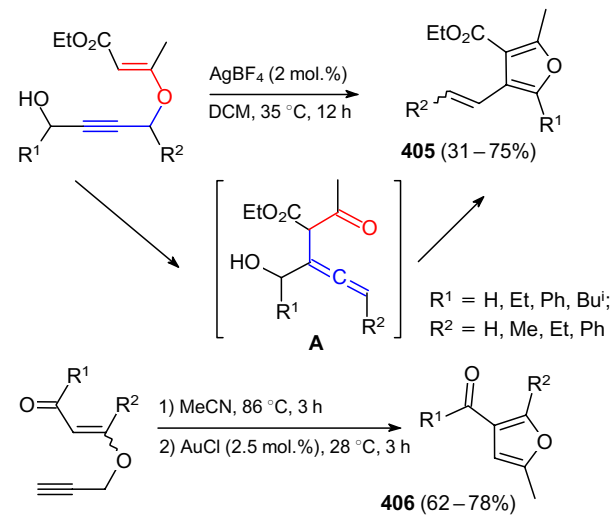
amounts of $AgBF_4$ or gold(I) chloride, the formal [3,3]-sigmatropic rearrangement occurs to give allenyl ketones **A**. The latter undergo cyclocondensation followed by the isomerization of the double bond to directly afford five-membered heterocyclic products **405** and **406**. Dihydrofurans **407** are formed using platinum chloride and carbon monoxide.

Scheme 230

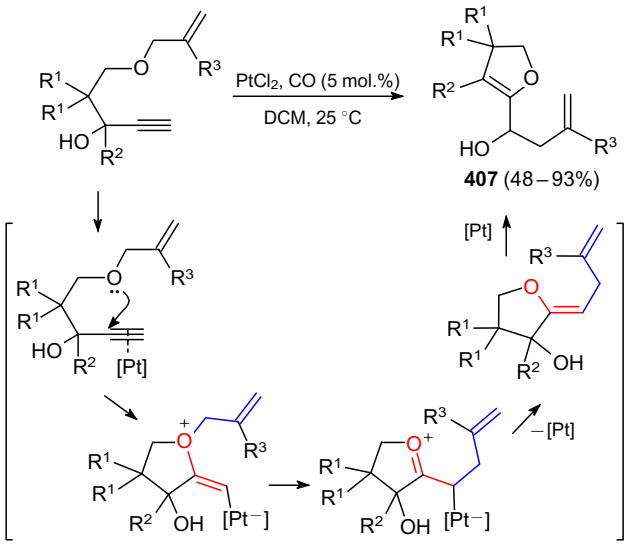


R^1 = All, Bn, Ph; R^2, R^4 = H, Me; R^3 = TMS, n-C_5H_{11}

Scheme 231



R^1 = Ph, 4-MeC_6H_4, 4-FC_6H_4, 4-BrC_6H_4;
R^2 = Ph, 4-MeC_6H_4, 4-Bu^tC_6H_4, 4-MeOC_6H_4, 2-Th



R^1 = Me, Et; R^2 = Me, Ph; R^3 = H, Me, Ph

6. Sigmatropic rearrangements involving allenes

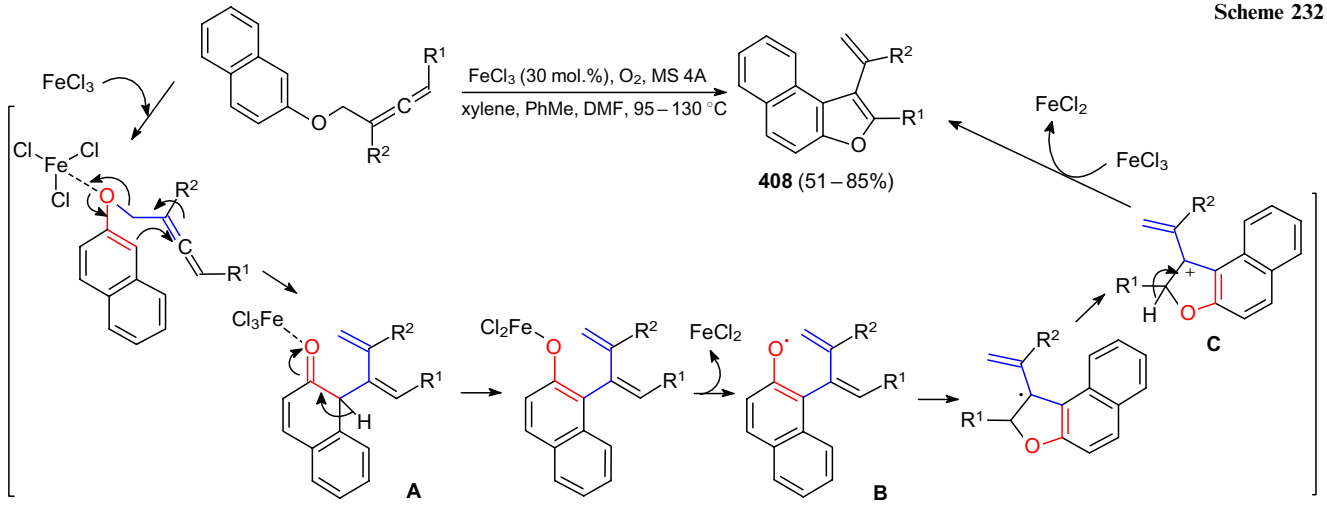
Zhang *et al.*[399] described the $FeCl_3$-catalyzed allene-Claisen rearrangement yielding naphtho[2,1-*b*]-furans **408** (Scheme 232). The authors suggest that $FeCl_3$ is coordinated by the oxygen atom and promotes the process. The product **A** of the Claisen rearrangement loses a hydrogen chloride molecule *via* keto-enol tautomerization and then decomposes to give a radical intermediate **B** and a $FeCl_2$ molecule. This is followed by radical intramolecular cyclization and further oxidation of the radical intermediate by iron(III) chloride. The resulting cationic intermediate **C** eliminates another hydrogen chloride molecule and converts into the final product **408**. Experimental results indicate that the presence of iron(III) chloride is the factor responsible for high regio- and chemoselectivity of this transformation.

The allene-Claisen rearrangement was employed in the stereocontrolled synthesis of polysubstituted 1,3-dienes. This method enables the highly stereoselective production of (1*E*,3*Z*)-1,3-dienes **409** (the ratio of 3*Z*:3*E* = 91:9), which are essential components of the respiratory toxin bongkrekic acid (Scheme 233).[400] In such a way, *anti*-allenyl alcohols **410a** can be transformed into (1*E*,3*Z*)-1,3-dienes **411a** with high selectivity, whereas *syn* isomers **410b** give predominantly (1*E*,3*E*)-1,3-dienes **411b**. Matsumoto *et al.*[400] also reported the route to similar products using the Ireland–Claisen rearrangement instead of the Eschenmoser–Claisen version.

In 2016, the first example of the asymmetric Claisen rearrangement involving allenyl vinyl ethers was described, making it possible to prepare optically active β-keto esters **412** bearing a stereocentre and a branched buta-1,3-dienyl substituent. The process features high yields of the product (65–90%) and excellent enantioselectivity (up to 98–99% *ee*) (Scheme 234).[401]

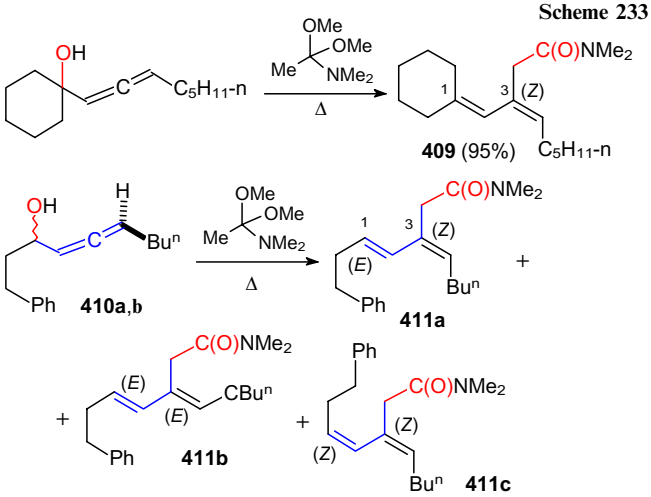
A series of 2-allenyl-2-aryl-3,3-difluoroindolines **413** were synthesized from *N*-allenyl-2-aryl indoles using Selectfluor as the reagent and iron triflate as the catalyst. The plausible mechanism for this process involves fluorination of the starting *N*-allenylindole at the 3 position with the subsequent proton abstraction by sodium hydrocarbonate.

Scheme 232



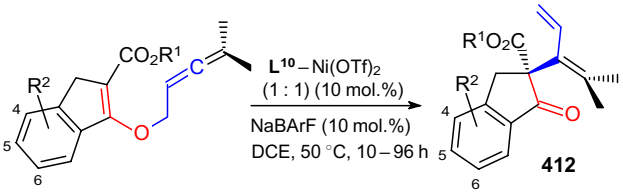
R^1 = Bu^n, Bu^t, cyclo-C_3H_5, Cy, Ph, 2-Th, XC_6H_4 (X = H, 4-F, 2-Cl, 4-Cl, 2-Br, 4-Br, 4-CF_3, 4-Me, 4-CO_2Me, 2-OMe, 3-OMe, 4-OMe);
R^2 = Et, Pr^i, Br, SCN, SCF_3, Ph, 4-ClC_6H_4, 4-$MeOC_6H_4$

Scheme 233



Substrate	*syn* : *anti*	Yield (%)	**411a** : **411b** : **411c**
410a	96 : 4	60	10 : 76 : 14
410b	20 : 80	81	80 : 15 : 5

Scheme 234



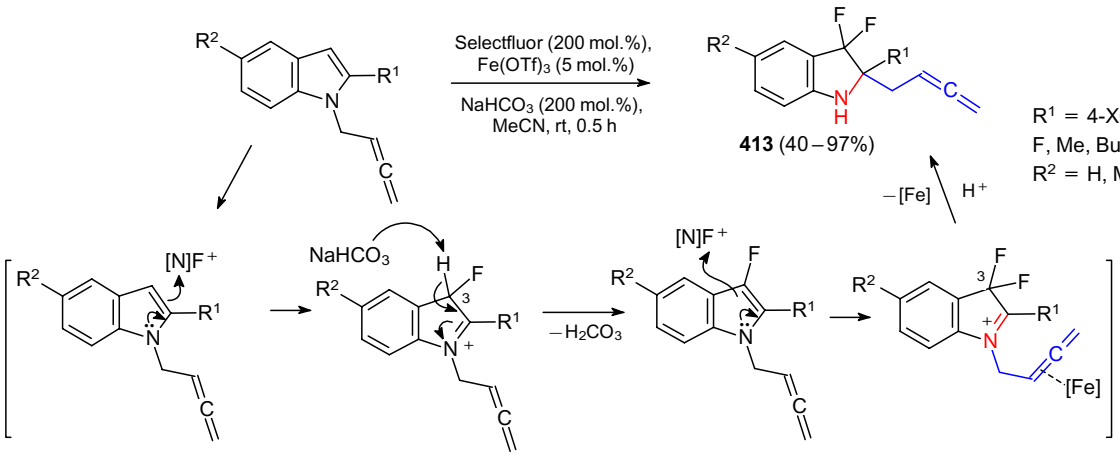
R^1 = Me, Et, Bu^t; R^2 = H, 5-F, 5-Cl, 4-Br, 5-Br, 6-Me, 5-OMe, 6-OMe, 6-Cl

This assumption relies on the fact that the reaction does not occur in the absence of $NaHCO_3$. This step is followed by one more fluorination at the 3 position of the indole ring and the formal aza-Claisen rearrangement (Scheme 235).[402]

7. Rearrangements of unsaturated sulfoxides and sulfonates

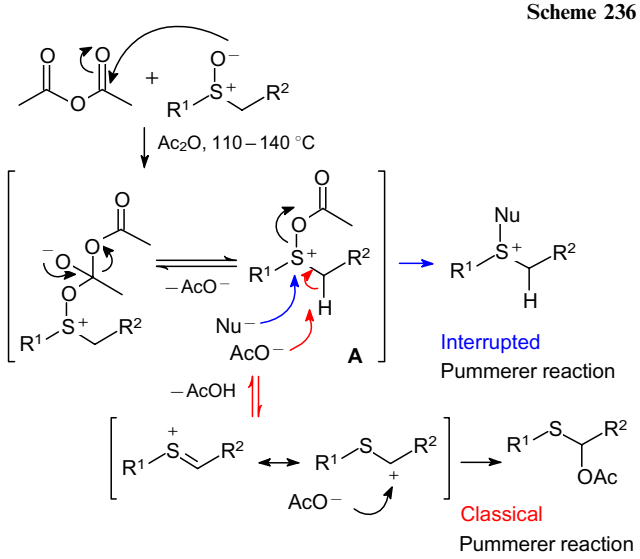
Rearrangements of sulfoxides are often closely related to the Pummerer reaction, particularly to the interrupted version of this reaction. Under certain conditions, the

Scheme 235



R^1 = 4-XC_6H_4 (X = H, Cl, F, Me, Bu^t), 2-Naph;
R^2 = H, Me, OMe, F, NO_2, CN

Scheme 236



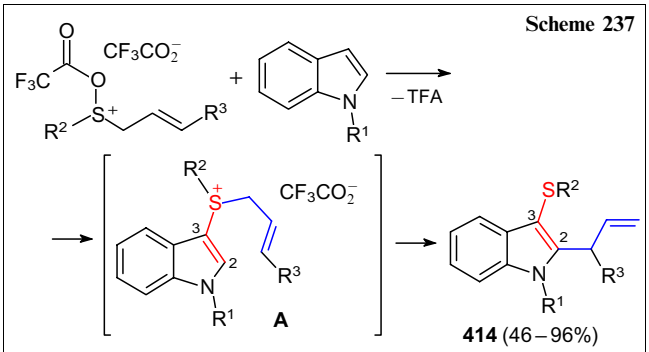
process stops at the formation of the intermediate **A** containing the three-coordinate sulfur atom (Scheme 236), allowing the attack of strong nucleophiles on this position. This area of synthetic chemistry has been extensively developed in recent years.

These transformations have already been considered in several reviews, for example, on cascade reactions involving interrupted Pummerer reaction–[3,3]-sigmatropic rearrangement sequences,[403] the use of sulfoxides and iodanes in reductive arylation,[404] rearrangements of sulfonium salts[405] and sulfoxides[406] and transformations of benzothiophene *S*-oxides.[407]

In 2018, the interrupted Pummerer reaction–[3,3]-sigmatropic rearrangement cascade was employed to perform the vicinal functionalization of indoles under mild conditions.[408] The resulting compounds **414** are substituted at the 2 and 3 positions on the indole ring (Scheme 237). The first step of this transformation is the electrophilic substitution at the 3 position of indole involving activated allyl sulfoxides as electrophiles. The intermediate allyl heteroaryl sulfonium salts **A** undergo a [3,3]-sigmatropic rearrangement to form final products.

The heating of unsaturated sulfoxides **415** in toluene affords dihydrobenzothiophenes **416** and benzothiophenes **417** (Scheme 238).[409] The sequence of [2,3]- and [3,3]-sigmatropic rearrangements is followed by the addition of the thiol group at the double bond of the enone moiety. The

Scheme 237



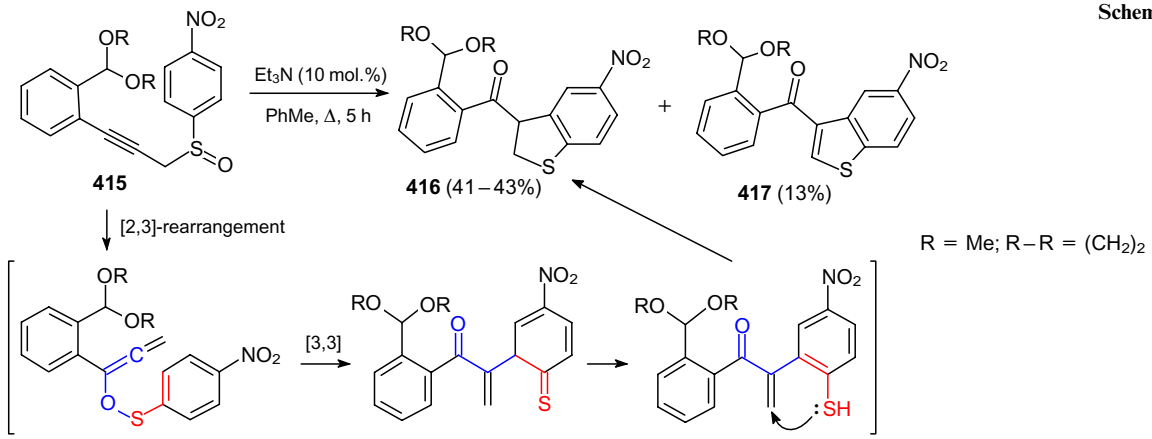
formation of products **417** was attributed to the oxidation of starting dihydrobenzothiophenes **416** with atmospheric oxygen.

2-Substituted benzothiophenes **418**–**420** were synthesized *via* an interrupted Pummerer/[3,3]-sigmatropic rearrangement/1,2-migration cascade (Scheme 239).[410] The reaction was performed with readily accessible benzothiophene S-oxides, phenols and allyl- or propargylsilanes. The interrupted Pummerer reaction of benzothiophene S-oxides affords sulfonium salts **A** followed by their [3,3]-sigmatropic rearrangement. The subsequently generated benzothiophenium salts **B** undergo a 1,2-migration to give benzothiophenes **418** functionalized at the 2 position. The possibility of preparing 3-arylated benzofuran products **421** *via* a Pummerer rearrangement–[3,3]-sigmatropic rearrangement cascade was also reported. The reaction was accomplished in the absence of transition metal compounds.[411]

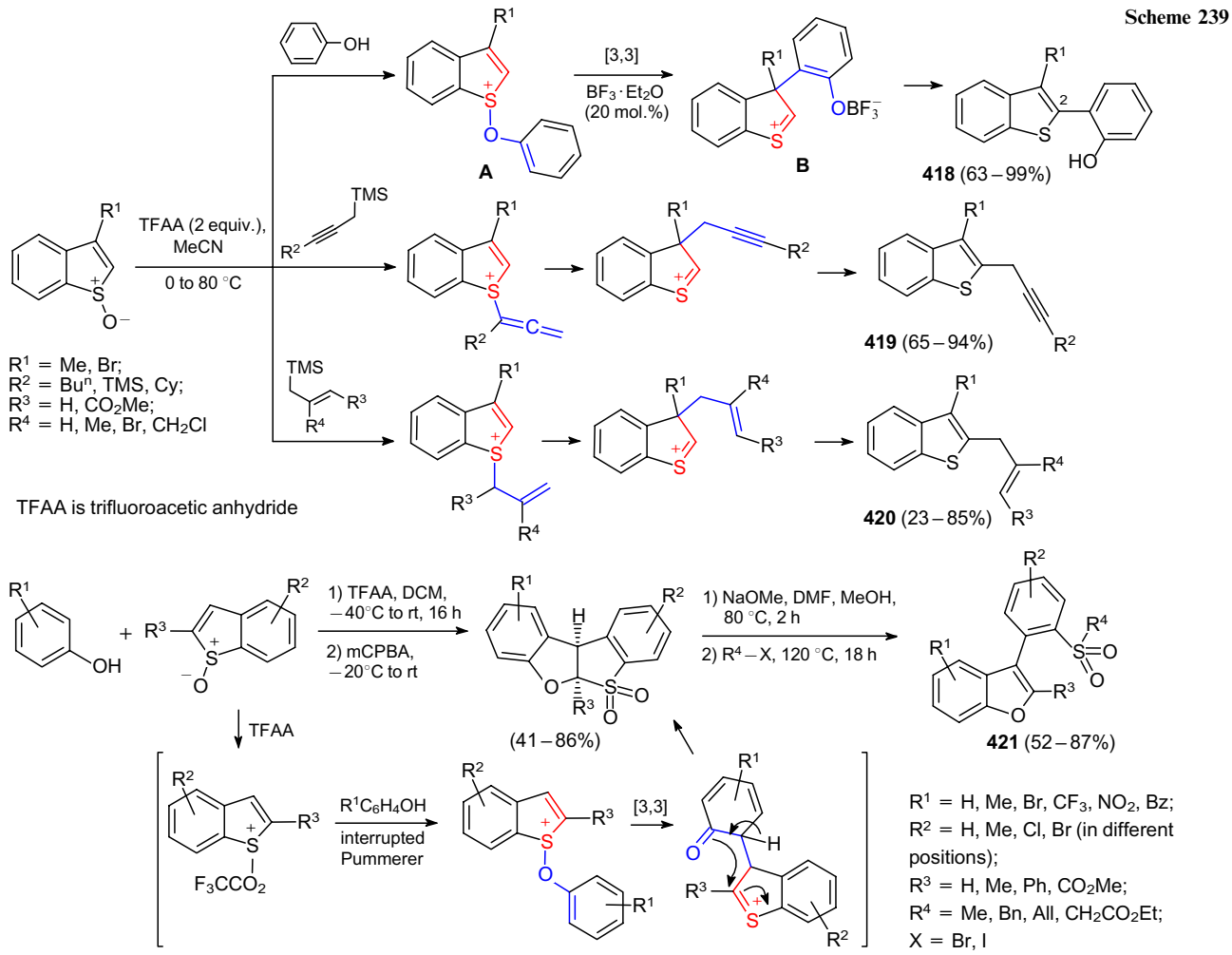
Substituted and fused dihydrobenzothiophenes **422** can be synthesized by the reactions of appropriate arenes with allyl sulfoxides (Scheme 240).[412] The transformation occurs in the absence of transition metal compounds and involves an interrupted Pummerer reaction, [3,3]-sigmatropic rearrangement and cyclization. Compounds **422** containing a hydrogen atom as the substituent R undergo subsequent aromatization in the presence of 2,3-dichloro-5,6-dicyano-1,4-benzothiophene (DDQ).

The asymmetric arylation of ynamides and thioalkynes with chiral sulfoxides allows the 1,4-chirality transfer from sulfur to a carbon atom *via* a [3,3]-sigmatropic rearrangement. This method can be applied to prepare compounds **423** and **424** with a specified configuration of the stereocentre in an atom-economical manner (Scheme 241).[413] Quantum chemical calculations demonstrated that the selec-

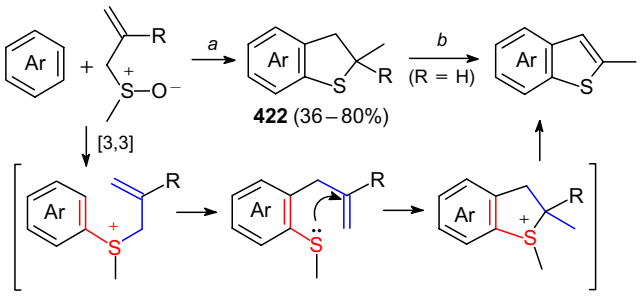
Scheme 238



Scheme 239

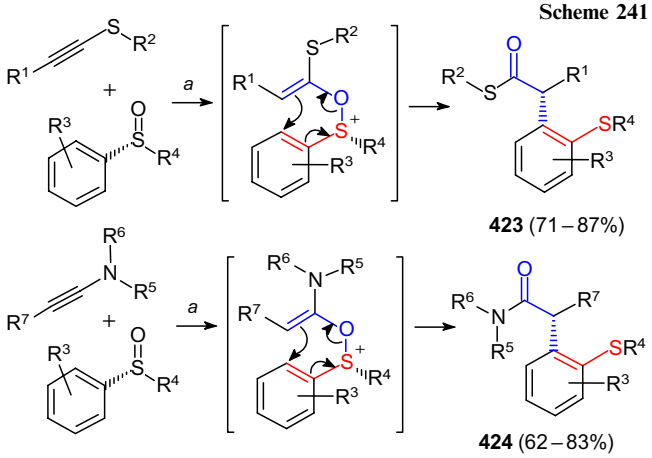


Scheme 240



(*a*) 1) Tf_2O, DCE, MW, –30 to 90 °C; 2) Et_3N, 0 to 50 °C; (*b*) DDQ, PhMe, 80 °C; R = H, Me, Et; Ar is fused aryl, substituted fused aryl

Scheme 241



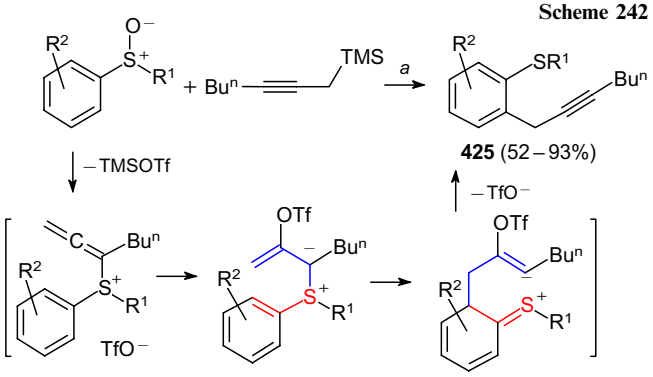
(*a*) Tf_2NH (50 mol.%), DCM, 0 °C, 3 h; R^1 = Pr^i, Bu^t, cyclo-C_5H_9, Cy; R^2 = Me, Ph; R^3 = H, Me, Br (in different positions); R^4 = Me, Cy; R^5 = Ts; R^6 = Me; R^5–R^6 = C(O)O(CH$_2$)$_2$; R^7 = Pr^i, n-C_6H_{13}, cyclo-C_5H_9, Cy, Ph(CH$_2$)$_3$

tivity of the process is determined by spatial interactions between functional groups in the transition state. The enantiomeric ratio of the arylation products reached 99.5 : 0.5.

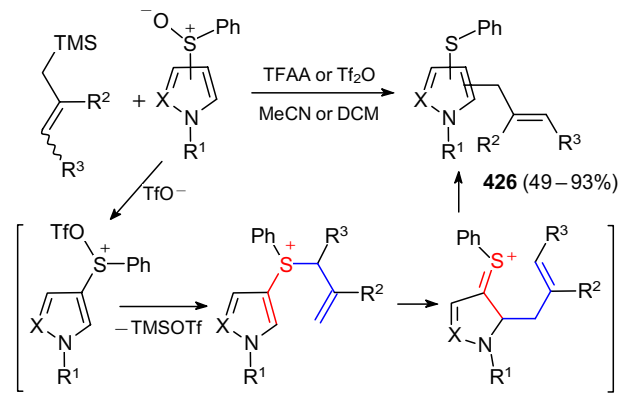
The reaction of activated aryl sulfoxide with propargylsilanes affords *ortho*-propargylated aryl sulfides **425**.[414] This is a quite versatile and regiospecific approach to the synthesis of such compounds in high yields. The utilization of allylsilanes in this reaction provides a route to *ortho*-allylated derivatives, in particular, five-membered heterocycles, compounds **426** (Scheme 242).[415]

Fluorinated benzofurans were synthesized using the reaction of fluorinated phenols **427** with unsaturated sulfoxides. The interrupted Pummerer reaction of ketene dithioacetal monoxides with polyfluorophenols followed by a [3,3]-sigmatropic rearrangement of sulfoxide inter-

Scheme 242



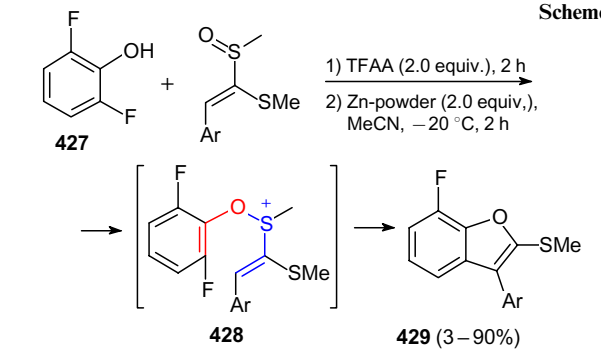
(*a*) Tf_2O, 2,6-lutidine, MeCN, 60–80 °C; R^1 = Me, Et, $(CH_2)_2OBz$, $(CH_2)_2OBn$, $(CH_2)_2C_8F_{17}$, CF_3, CH_2CO_2Me; R^2 = Cl, OMe, CF_3, Me, F, Br, CN, NHTs, ÇO$_2$, CO_2Et, CO_2H, $C(O)NEt_2$ (in different positions)



R^1 = H, Ts, Me, All, Bn; R^2 = H, Br, CH_2Cl; R^3 = H, Me, Bu^n; X = CH, N

mediate **428**, the reductive removal of fluoride from the dearomatized intermediate and acid-promoted cyclization–aromatization afforded benzofurans **429** (Scheme 243).[416] Later, this method was extended to a wide range of sulfoxides and polyphenols and made it possible to obtain indoles and benzothiophenes along with benzofurans.[417]

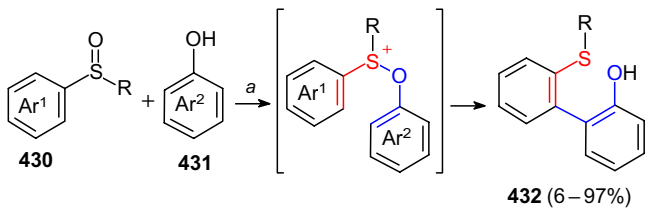
Scheme 243



Ar = 4-XC_6H_4 (X = CF_3, Br, CO_2Me, CN, NO_2, OMe)

The reaction of aryl sulfoxides **430** with phenols **431** produced substituted biaryls **432** (Scheme 244).[418] Trifluoroacetic anhydride-activated aryl sulfoxides react with phenols *via* an interrupted Pummerer reaction followed by a [3,3]-sigmatropic rearrangement. The C–C bond formation occurs exclusively at the *ortho* positions of both substrates. Later, this reaction was used as a basis for the synthesis of

Scheme 244

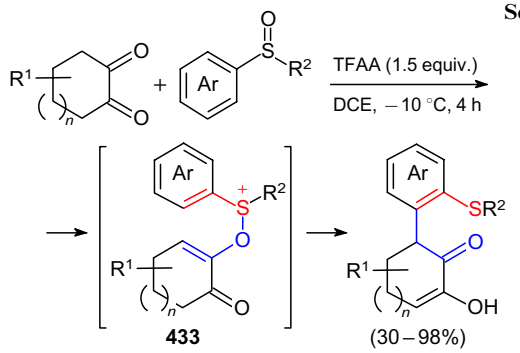


(*a*) TFAA (1.5 equiv.), DCM (0.1 M), 25 °C, 1 h; R = Me; Ar^1 = 2-Naph, 2-Ind, 3-Th, pyrrol-3-yl, benzofuran-2-yl; Ar^2 = Ph, 2-IC_6H_4, 3-BrC_6H_4, 3-$O_2NC_6H_4$, 3-NCC_6H_4

sterically encumbered oligoarenes *via* the iterative assembly from phenols and sulfoxides.[419] It was shown that N-protected anilides can be utilized in place of phenols **431**.[420]

A method was proposed for the metal-free CH-functionalization of cyclic 1,2-diketones with aryl sulfoxides. This regioselective arylation involves the generation of intermediates **433** and the O–S bond formation followed by a [3,3]-sigmatropic rearrangement (Scheme 245).[421] This method can also be applied to the synthesis of polysubstituted cyclic 1,2-diketones with predictable structures by means of iterative arylations.

Scheme 245



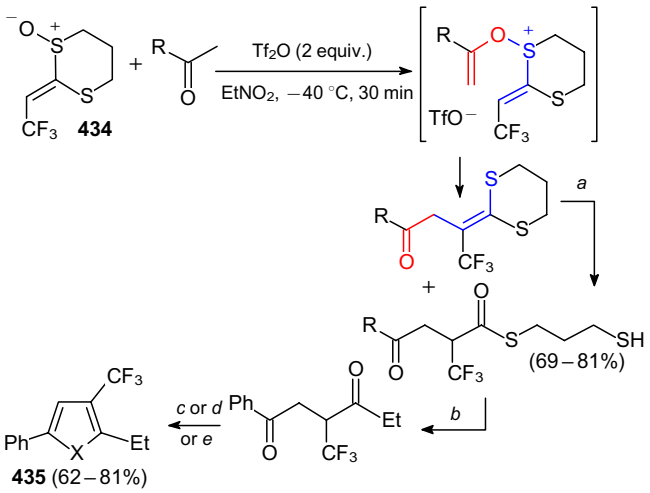
Ar = 2-$R^2SC_6H_4$, 2-R^2S-thiophen-3-yl, 2-R^2S-5-MeC_6H_3, 2-R^2S-benzofuran-3-yl; R^1 = Me, Br; R^2 = 4-BrC_6H_4, 2-MeC_6H_4, 4-$MeOC_6H_4$, 2-Th, Pr^n, Cy, Bn; *n* = 0, 1

The synthesis of polysubstituted heterocycles from sulfoxides **434** containing a trifluoromethyl group at the double bond (Scheme 246) was reported in the study.[422] The key step in this synthesis is the reaction with ketones. These products serve as building blocks for the construction of 3-trifluoromethyl-substituted heteroarenes **435**.

Rearrangements involving sulfoxides **436** are also applicable to the preparation of indoles *via* a modified Fischer indole synthesis (Scheme 247).[423] The cascade transformations are triggered by the interrupted Pummerer reaction.

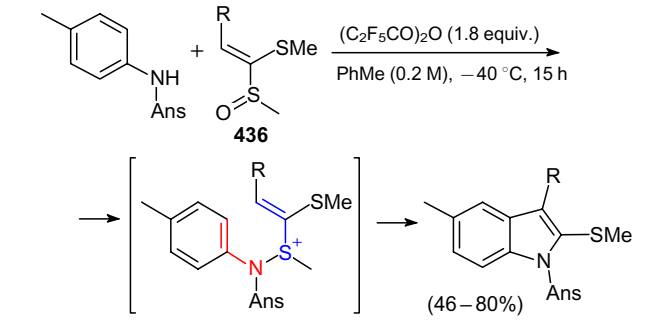
An electrophilic rearrangement can be used to accomplish the α-arylation of substituted nitriles **437** (Scheme 248).[424] The transformation consists of the following two sequential steps: the Tf_2O-initiated electrophilic assembly and the DABCO-triggered rearrangement. Later, it was demonstrated that these reactions can be applied to aryl fluoroalkyl sulfoxides (instead of reagent **438**)[425] and α,β-unsaturated nitriles (instead of reagent **437**).[426] The latter process is a hybrid version of a [3,3]-sigmatropic rearrangement and the Morita–Baylis–Hillman reaction. In some cases, the [3,3]-rearrangement can compete with the

Scheme 246



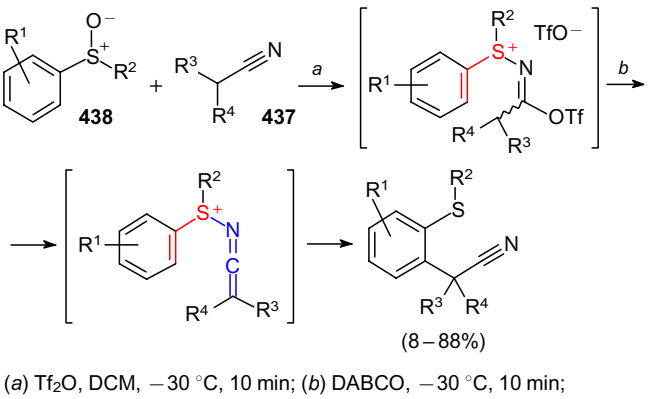
R = 4-YC$_6$H$_4$ (Y = H, Me, OMe, Ph, Cl, Br, CO$_2$Me), Bu^n; X = O, S, NBu^n; (*a*) HCl, MeOH, H$_2$O, Δ, 2 h; (*b*) 1) MeI (2 equiv.), DIPEA (2 equiv.), Me$_2$CO, 25 °C, 8 h; 2) PdCl$_2$(PPh$_3$)$_2$ (10 mol.%), EtZnI (2 equiv.), PhMe, Δ; (*c*) TsOH·H$_2$O (1.1 equiv.), PhMe, Δ, 10 h; (*d*) Lawesson's reagent (2.4 equiv.), DCE, 25 °C, 8 h; (*e*) Bu^{n}NH$_2$ (2 equiv.), Ti(OPr^i)$_4$ (1.5 equiv.), PhMe, Δ,10 h

Scheme 247



R = Ph, 4-Bu^{t}C$_6$H$_4$, 4-BrC$_6$H$_4$, 4-F$_3$CC$_6$H$_4$, 4-NCC$_6$H$_4$, 3-MeOC$_6$H$_4$, 4-O$_2$NC$_6$H$_4$; Asn is 4-methoxybenzenesulfonyl

Scheme 248

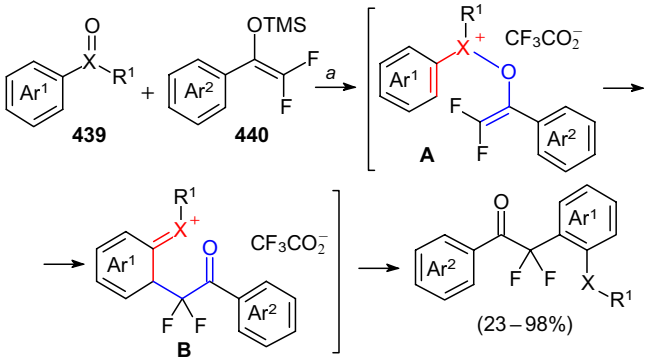


(*a*) Tf$_2$O, DCM, −30 °C, 10 min; (*b*) DABCO, −30 °C, 10 min; R^1 = Cl, Br, Me, Ac, CN; R^2 = Me, Bu^n, All, Bn, Cy, Pr^i; R^3 = H, Me; R^4 = (CH$_2$)$_3$Br, (CH$_2$)$_3$Cl, CH$_2$OEt, 4-bromobut-3-ynyl

[5,5]-rearrangement.[427] The authors succeeded in extending these reactions to some iodonium compounds.[428–430]

The reaction of aryl sulfoxides or aryl selenoxides **439** with difluoroenoxysilanes **440** provides an access to difluoromethyl-containing compounds (Scheme 249; the

Scheme 249



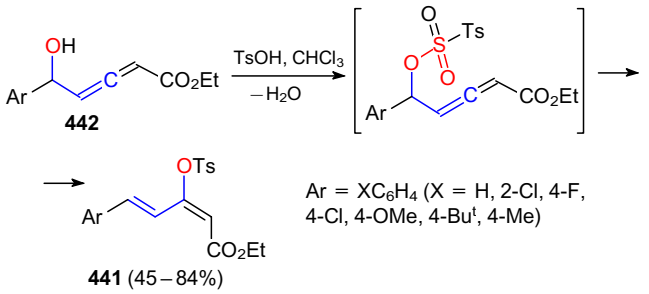
(*a*) TFAA (1.5 equiv.), DCM, −10 °C, 12 h; X = S, Se; R^1 = Ph, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$, Bn, cyclo-C$_3$H$_5$; Ar^1 = Ph, 4-MeC$_6$H$_4$, 4-ClC$_6$H$_4$, 3-MeOC$_6$H$_4$, 3-Th, 3-Py; Ar^2 = Ph, 4-MeC$_6$H$_4$, 4-FC$_6$H$_4$

group Ar^1 for the substrate is highlighted).[431] Sulf(selen)oxide is activated by trifluoroacetic anhydride. The resulting sulfonium intermediate is subjected to nucleophilic attack by an enolate oxygen atom to form intermediate **A**. The latter undergoes a sigmatropic rearrangement followed by the restoration of the aromatic system in intermediate **B** to give the final product.

1,3-Dien-2-ol sulfonates **441** were synthesized by a rearrangement of tosylates of allenic alcohols **442** (Scheme 250).[432] Products **441** are building blocks for the stereopredictable formation of polysubstituted dienes.

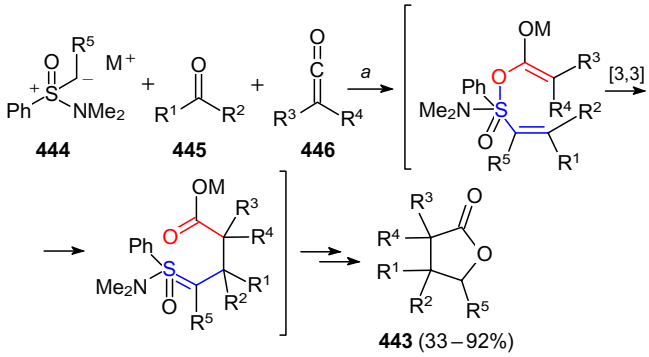
A method was proposed for the synthesis of polysubstituted γ-lactones **443** by means of reactions of sulfonium ylides **444**, aldehydes **445** and ketenes **446** (Scheme 251).[433] The results of this study provide evidence that the reaction

Scheme 250



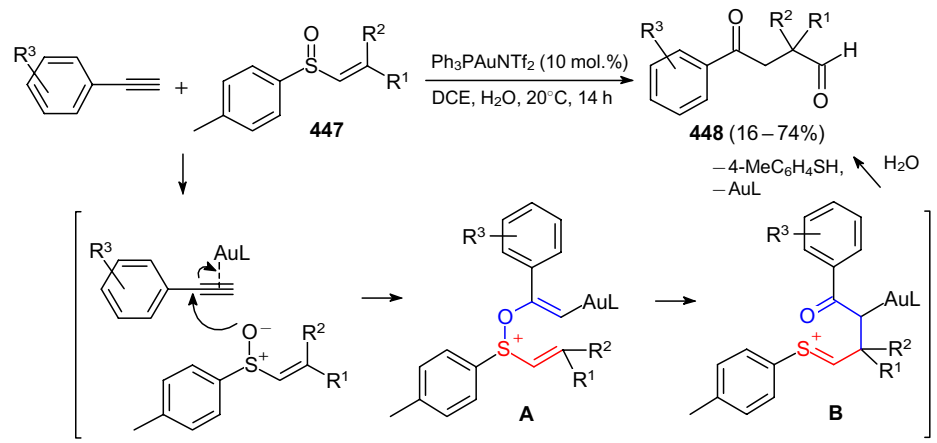
Ar = XC$_6$H$_4$ (X = H, 2-Cl, 4-F, 4-Cl, 4-OMe, 4-Bu^t, 4-Me)

Scheme 251



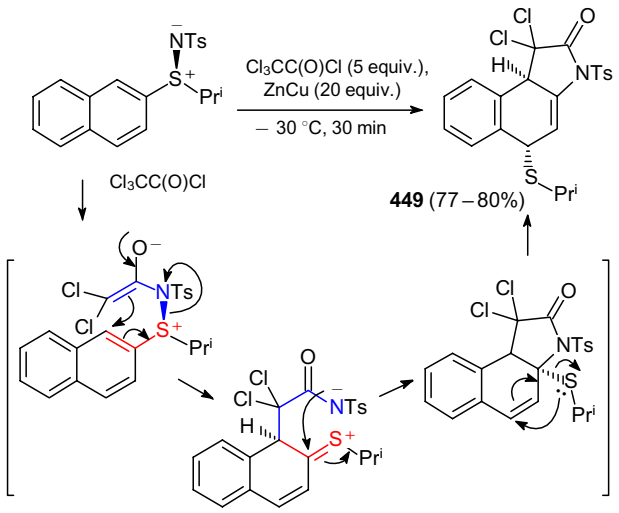
(*a*) THF, −78 °C to rt, 19–20 h; R^1 = Me, Bu^n, Pr^i, Ph, 4-O$_2$NC$_6$H$_4$, 2-O$_2$NC$_6$H$_4$, 2-ClC$_6$H$_4$, (CH$_2$)$_2$Ph, 3-Fu, 3-Th; R^2 = H, Me; R^3 = Ph, Me; R^4 = Me, Et, Bu^i, Ph; R^5 = H, Me, Ph; M = Na, MgCl, Cu

Scheme 252



R^1 = Me, Et, Pr^n, $n\text{-}C_6H_{13}$, $(CH_2)_4OTs$, $(CH_2)_4I$, Cy, Ph, 3-Th;
R^2 = H, Pr^n;
R^3 = 4-OMe, 4-OH, 4-OTBS, 3,4-$(MeO)_2$;
L = Ph_3P

Scheme 253



proceeds *via* a [3,3]-sigmatropic rearrangement. The target products were obtained in yields of up to 92% with high diastereoselectivity up to *dr* = 92 : 8.

The reaction of sulfoxides **447** with phenylacetylenes catalyzed by gold complexes affords 1,4-dicarbonyl compounds **448** (Scheme 252).[434] The gold activation of the alkyne triple bond allowed the initial addition of sulfoxide at the triple bond. This step is followed by the [3,3]-sigmatropic rearrangement of intermediate **A** to intermediate **B**. The hydrolysis of the latter intermediate accompanied by the elimination of the gold-containing catalyst gives final product **448**. The reaction using enantiomerically pure sulfoxides occurs in an enantioselective manner.

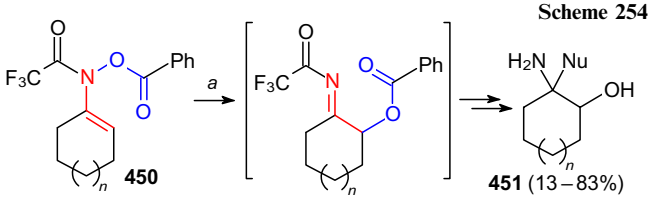
The enantioselective synthesis of dihydro-1*H*-benzindoles **449** was based on the α-lactamization of naphthyl sulfilimines in the presence of ZnCu under mild conditions. These products are generated *via* a [3,3]-sigmatropic rearrangement of azasulfonium enolate followed by an allylic rearrangement that transfers chirality (Scheme 253).[435]

8. Rearrangements of N—O compounds

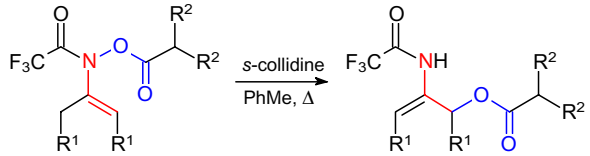
Rearrangements of compounds containing several heteroatoms often occur quite readily. This is due to the presence of a weak N—O bond in the initial system; meanwhile the cleavage of weaker bonds and the formation of stronger bonds (as mentioned in the Introduction) are the driving force of the rearrangement. Many transformations considered in this Section can be accomplished either at room temperature or upon slight heating. Nevertheless, in some cases the reflux of the reaction mixture or microwave irradiation is required for the initiation of the rearrangement. Certainly, rearrangements of compounds containing several heteroatoms, being a synthetically important area of chemistry, have drawn the attention of researchers, which is evidenced by a chapter in the book [436] on molecular rearrangements in organic synthesis. Examples of such reactions are considered below.

The [3,3]-sigmatropic rearrangement of *N*-acyloxyenamides **450** was implemented in the synthesis of β-aryl-substituted β-amino alcohols **451** (Scheme 254).[437] This transformation occurs in the presence of triarylaluminium as the Lewis acid. The substrate scope for this reaction was extended in the study,[438] in which products **452** were prepared in the presence of *sym*-collidine as the base.

Scheme 254



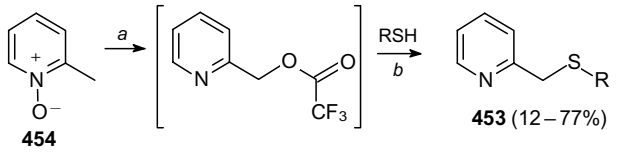
(*a*) Ar_3Al or (Het)$AlMe_2$; THF, Δ, 3h; Ar = Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-FC_6H_4, 2-$MeOC_6H_4$; Het = 2-Th, 2-Fu, 2-benzofuryl, 2-benzothienyl; Nu = Ar or Het; *n* = 0–2



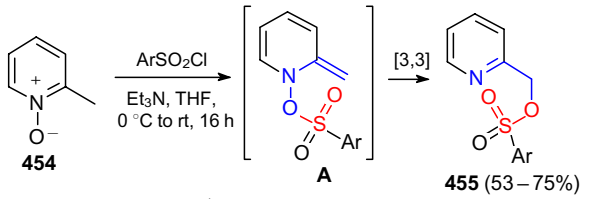
R^1 = Pr^n; R^1–R^1 = $(CH_2)_n$ (*n* = 2–5, 9);
R^2 = H, Me, Ph; R^2–R^2 = $(CH_2)_m$ (*m* = 2, 4, 5)

A method for the synthesis of pyridine thioesters **453** involved a rearrangement of 2-methylpyridine N-oxide (**454**).[439] This process was performed in trifluoroacetic anhydride. The resulting trifluoroacetates readily undergo nucleophilic substitution with arenethiols (Scheme 255). The rearrangement of intermediate sulfonates **A** can be used for the direct modification of the methyl group at the α-position of the pyridine ring and the formation of a C—O

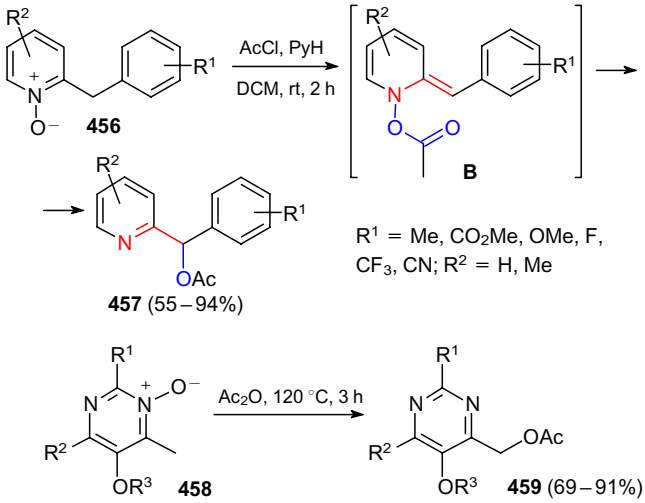
Scheme 255



(*a*) TFAA, AcOEt, Δ; (*b*) TBAB, PhMe, Δ;
R = XC_6H_4 (X = 4-Me, 3-Me, 4-OMe, 4-Cl, 2-Br, 4-NO_2), 2-Py



Ar = Ph, 4-MeC_6H_4, 4-$Bu^tC_6H_4$, 3-FC_6H_4, 4-$MeOC_6H_4$



R^1 = Me, CO_2Me, OMe, F, CF_3, CN; R^2 = H, Me

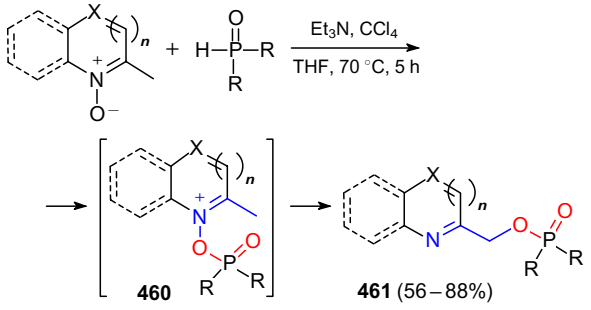
R^1 = Ph, PhHC=CH, 2-ThHC=CH, 2-Th, cyclo-C_3H_5;
R^2 = Bu^t, cyclo-C_3H_5, 1-Ad, 2-Th; R^3 = Me, TMS

bond in N-oxide **454**, giving rise to 2-pyridylmethyl arylsulfonates **455**.[440] Substituted N-oxides **456** are transformed into derivatives **457** *via* a rearrangement of intermediate **B**.[441] A similar transformation was applied to pyrimidine N-oxides **458**, which were rearranged to functionalized pyrimidines **459**.[442]

A multiheteroatom N,O,P-sigmatropic rearrangement of phosphonates **460**, accompanied by the transfer of the phosphate function to the methyl group in the α-position of the heterocycle, afforded products **461** (Scheme 256).[443]

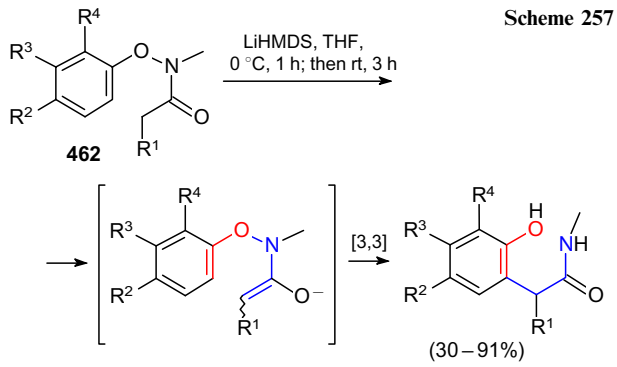
The lithium hexamethyldisilazide-catalyzed rearrangement of *N*-acyl-*O*-arylhydroxylamines **462** in THF resulted

Scheme 256



R = MeO, EtO, Pr^iO, Bu^iO, BnO; X = C, S; *n* = 0, 1

Scheme 257

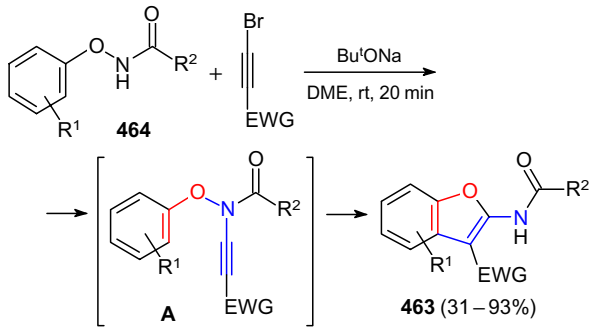


R^1 = H, Me, Ph, Bn; R^2 = H, Me, Ph, OMe, F, CN; R^3, R^4 = H, Me

in the formation of polysubstituted phenols as the final products (Scheme 257).[444]

It was demonstrated that substituted benzofurans **463** can be synthesized *via* a rearrangement of intermediate **A** (Scheme 258).[445] The ethynylation of hydroxylamine derivatives **464** with activated bromoacetylenes occurs in the presence of sodium *tert*-butoxide. The subsequent sigmatropic rearrangement and heterocyclization produce compound **463**. This method was applied to synthesize benzoxazoles. [445]

Scheme 258



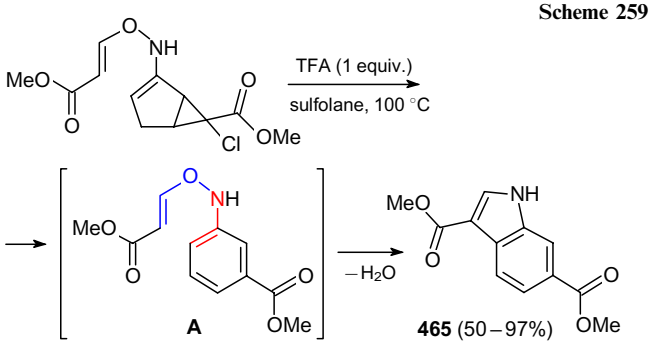
R^1 = Me, Et, Pr^i, NO_2, F, Cl, Br; R^2 = Me, C(O)Et, $C(O)Pr^i$;
EWG = CO_2Et, Bz, Ts

Indoles **465** were synthesized using a rearrangement of bicyclic hydroxylamine derivatives.[446] This cascade reaction allows also the synthesis of substituted indazoles, benzofurans and benzothiophenes from readily accessible bicyclo[3.1.0]hexan-2-ones. Mechanistic studies demonstrated that the 3,3-sigmatropic rearrangement of intermediate **A** is preceded by the electrocyclic opening of the bicyclic system and aromatization (Scheme 259).

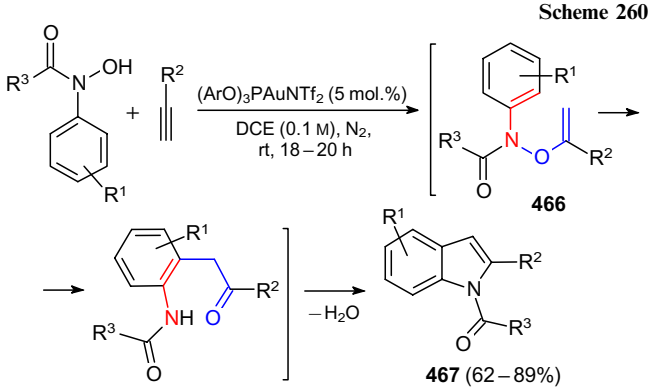
The transformation of the N,O-vinyl moiety of compound **466** can be used to prepare N-protected indoles **467** (Scheme 260).[447] The vinylation of hydroxylamine derivatives giving intermediates **466** was performed using the gold-catalyzed addition to terminal acetylenes. The subsequent rearrangement and heterocyclization afford target indoles in high yields.

The gold-catalyzed addition of hydroxybenzotriazole derivatives to alkynes at room temperature produces vinyl ethers **468** in high yields with excellent regioselectivity. The heating of the latter compounds causes a 3,3-sigmatropic rearrangement giving functionalized benzotriazoles **469** (Scheme 261).[448]

Scheme 259

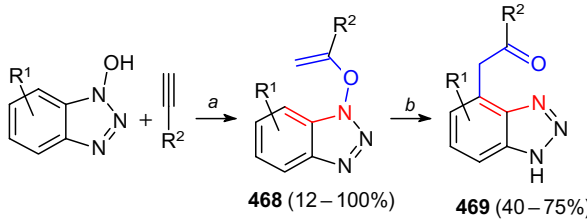


Scheme 260



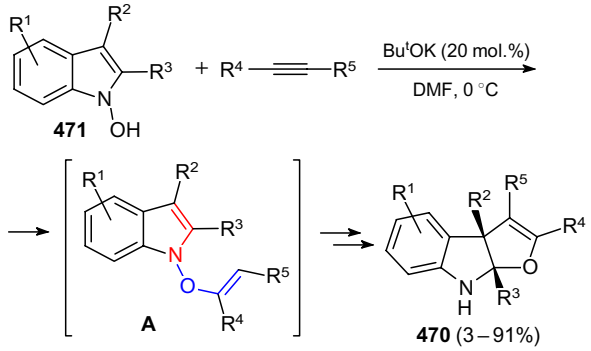
Ar = 2,4-Bu$^t_2$C$_6$H$_4$; R^1 = Me, MeO, F;
R^2 = Alk, cycloalkyl, haloalkyl; R^3 = Bu^{t}O, MeO, Me

Scheme 261



(*a*) Ph_3PAuCl (5 mol.%), AgOTf (5 mol.%), DCE, rt, 5–10 h;
(*b*) dioxane, 100°C;
R^1 = H, Me, CF_3; R^2 = Ph, n-C_6H_{13}, 4-FC_6H_4, butan-2-ol-2-yl

Scheme 262

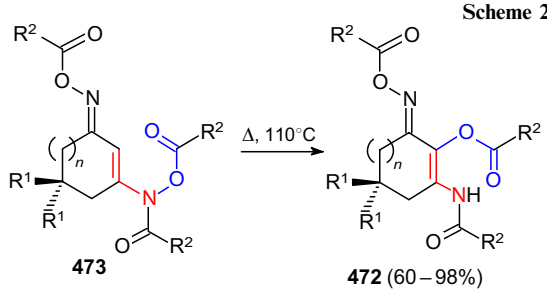


R^1 = F, Me, OMe, SO_2Me; R^2 = Me, CO_2Me; R^3 = H, Me;
R^4 = Me, Ph, CO_2Et, Py, CF_3; R^5 = CO_2Et, CN

Furoindolines **470** were synthesized based on N-oxides **471**, which reacted with various activated acetylenes (Scheme 262).[449] Intermediates **A** thus formed underwent a spontaneous [3,3]-sigmatropic rearrangement followed by cyclization to give hemiaminal products as *cis*-diastereomers.

Polysubstituted cyclohexenes and cyclopentenes **472** were synthesized by means of the rearrangement of compounds **473**, prepared by acylation of 1,3-diketone-based dioximes (Scheme 263).[450] Rearrangement products **472** were generated in high yields upon heating of the reaction mixture to 110 °C.

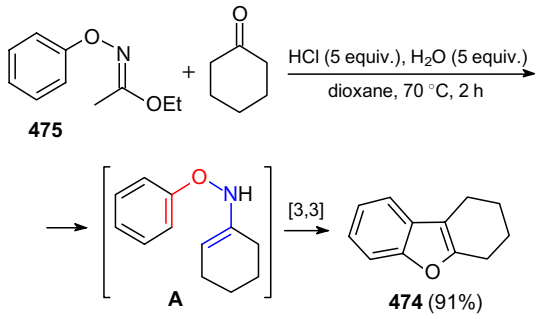
Scheme 263



R^1 = H, Me; R^2 = Me, Ph; *n* = 0,1

Tetrahydrobenzofuran **474** was synthesized from *O*-phenyl ketoxime **475** *via* a rearrangement of intermediate **A** under acidic conditions (Scheme 264).[451]

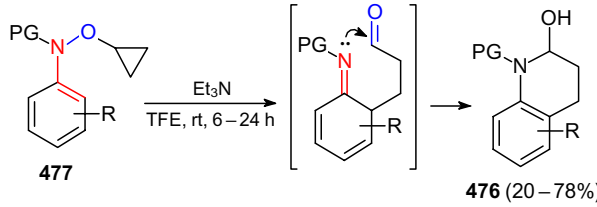
Scheme 264



The synthesis of benzotetrahydropyridines **476** was accomplished *via* a [3,3]-sigmatropic rearrangement at room temperature in trifluoroethanol using *O*-cyclopropyl hydroxylamines **477** as the starting compounds (Scheme 265).[452]

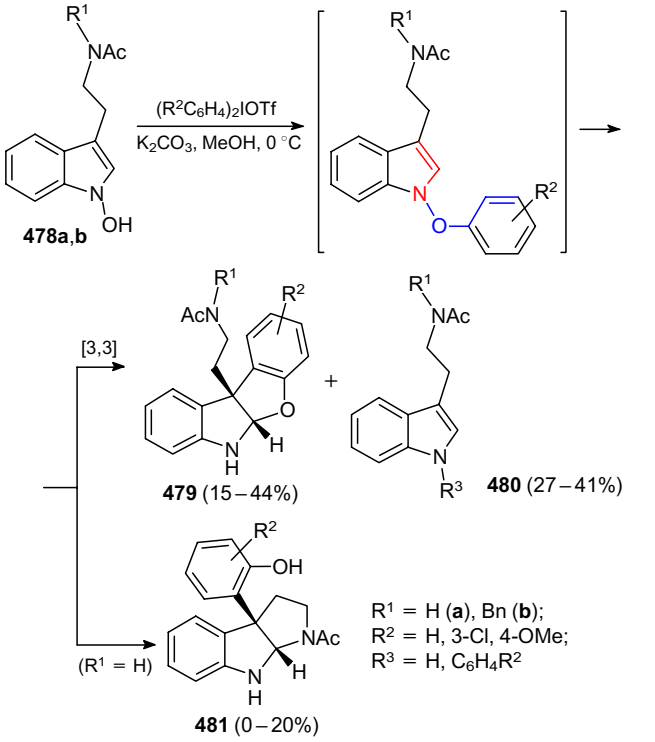
N-Hydroxyindoles **478a**,**b** can undergo O-arylation with biaryliodonium salts in the absence of transition metal catalysts. The subsequent spontaneous [3,3]-sigmatropic

Scheme 265



PG = Boc, CO_2Me, Cbz; R = H, 3-Me, 4-Me, 4-Cl, 4-Br,
4-CF_3, 4-CN, 4-CO_2Me (position in the substrate is indicated)

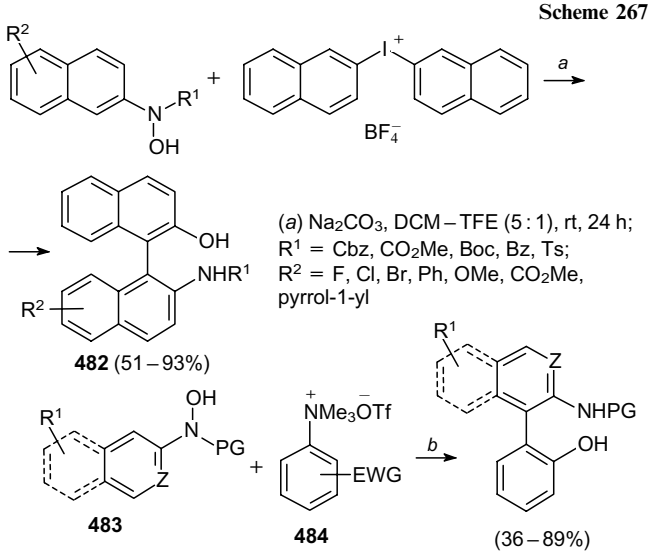
Scheme 266



rearrangement allows the synthesis of benzofuroindolines **479** in a mixture with products **480**, generated through arylation at the indole nitrogen atom (Scheme 266).[453] The reaction of compound **478a** bearing $R^1 = H$ also affords hydrogenated pyrroloindoles **481**.

2-Amino-2′-hydroxy-1,1′-binaphthyl (NOBIN) and its derivatives **482** were synthesized by arylation of 2-naphthylhydroxylamines with di(2-naphthyl)iodonium tetrafluoroborate in the presence of a base (sodium carbonate) (Scheme 267).[454] Similar products were prepared from hydroxylamine derivatives **483** by the reactions with anilinium triflates **484** containing electron-withdrawing substitu-

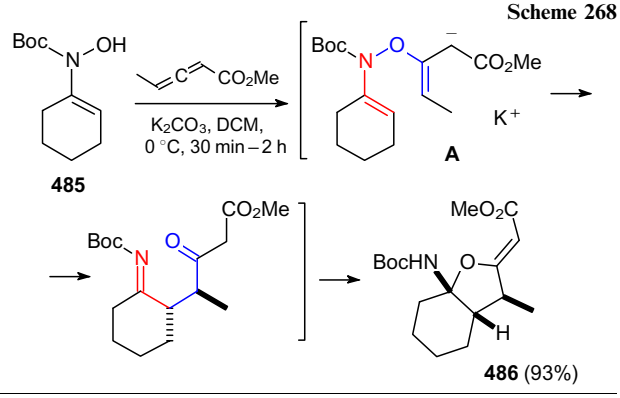
Scheme 267



ents on the benzene ring.[455] The arylation can also be performed using substituted fluoropyridines or fluorobenzenes.[456] In all cases, the process occurs through a [3,3]-sigmatropic rearrangement.

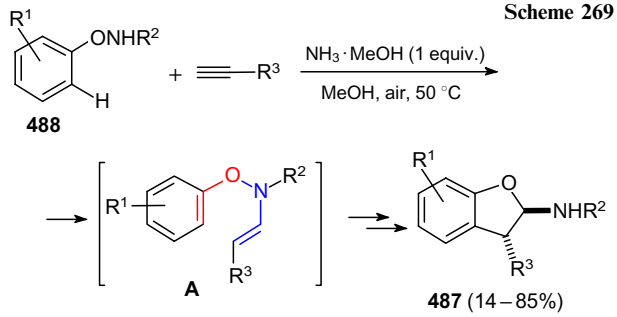
A new diastereoselective route to 2-aminotetrahydrofurans was developed based on hydroxylamine **485** (Scheme 268).[457] This compound reacts with substituted allene to form intermediate **A**, which undergoes a spontaneous [3,3]-sigmatropic rearrangement, resulting in the C–C bond formation, followed by the cyclization with the C–O bond formation. This synthesis produced hydrogenated aminobenzofuran **486**.

Scheme 268



2-Amino-2,3-dihydrobenzofurans **487** are generated in the reaction of *N*-phenoxyamides **488** with terminal alkynes (Scheme 269).[458] The cascade transformation involves the rearrangement of intermediate **A**.

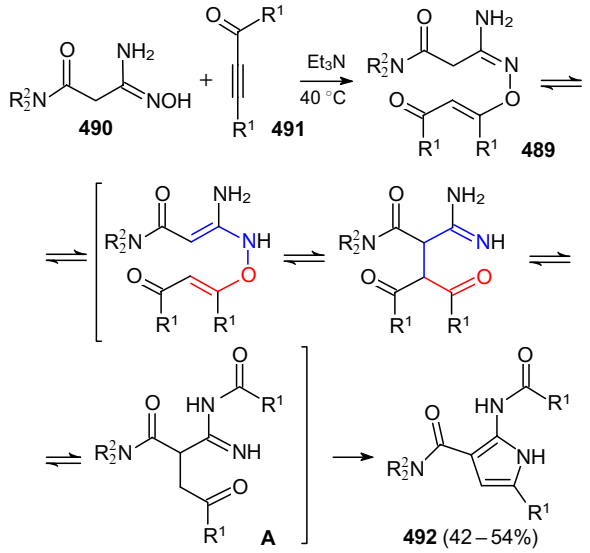
Scheme 269



Some methods of synthesis of substituted pyrroles based on [3,3]-sigmatropic rearrangements can also be included in this Subsection. Thus, the rearrangement of compounds **489** derived from hydroxylamines **490** and alkynes **491**, affords intermediate imines **A**, which cyclize to trisubstituted pyrroles **492** (Scheme 270).[459]

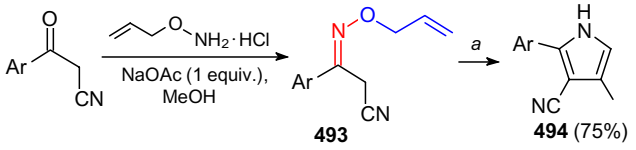
Pyrroles can also be produced by a rearrangement of *O*-allyl oximes **493** through the formation of a series of intermediates.[460] The reaction starts with the iridium-catalyzed isomerization to form the corresponding *O*-vinyl oximes, which undergo a facile [3,3]-rearrangement to 1,4-imino aldehydes that cyclize to afford pyrroles **494**. The product yields vary from 40 to 76% (Scheme 271). A year after this publication, a procedure was reported for the preparation of polysubstituted pyrroles **494** based on [3,3]- and [1,3]-sigmatropic rearrangements.[461] The mentioned

Scheme 270



R^1 = Me, Ph; R^2_2N = $N(CH_2)_4$, $N(CH_2CH_2)_2O$

Scheme 271

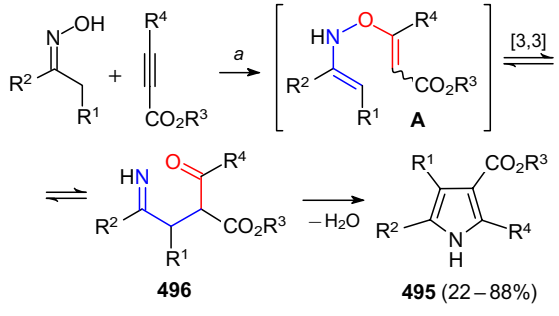


(*a*) $[(COD)IrCl]_2$ (5 mol.%), AgOTf (10 mol.%), $NaBH_4$ (10 mol.%), THF, 25 °C

study also describes conditions, under which a particular type of rearrangement ([3,3] or [1,3]) becomes preferable.

The regioselective synthesis of pyrroles **495** was accomplished *via* a gold-catalyzed rearrangement of intermediates **A** to compounds **496** followed by cyclization (Scheme 272).[462] The notable feature of this method is the gold activation of several steps.

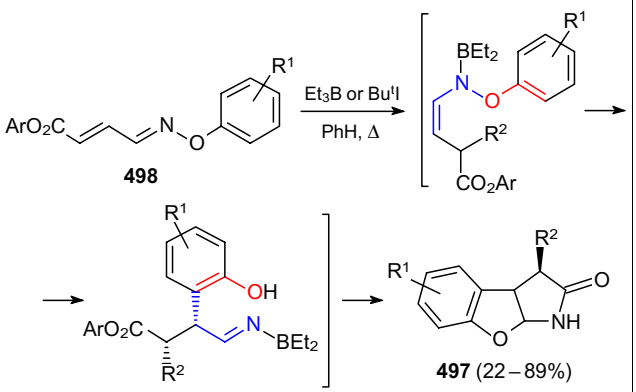
Scheme 272



(*a*) Ph_3PAuCl (10 mol.%), AgOTf (10 mol.%), PhMe, 100 °C, 18 h; R^1 = H, Ph, n-C_6H_{13}, Cl; R^2 = Et, Pr^n, Ph, 4-$O_2NC_6H_4$, 3-$O_2NC_6H_4$, 4-$MeOC_6H_4$, 4-FC_6H_4; R^3 = Me, Et; R^4 = H, CO_2Me

Polyfused heterocycles **497** can be synthesized from unsaturated oxime **498** using domino radical reactions (Scheme 273).[463,464] These reactions involve the sequential radical addition, [3,3]-sigmatropic rearrangement, cyclization and lactamization.

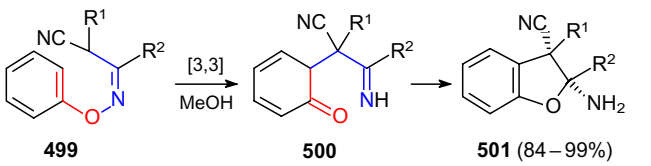
Scheme 273



R^1 = CF_3, Me, Br; R^2 = Et, Bu^t

Rearrangements of oximes **499** to imines **500** provided the basis for the construction of the skeleton of dihydrobenzofurans **501** containing a quaternary carbon atom (Scheme 274).[465] It is worth noting that all steps of the reaction occur at room temperature giving target products in high yields.

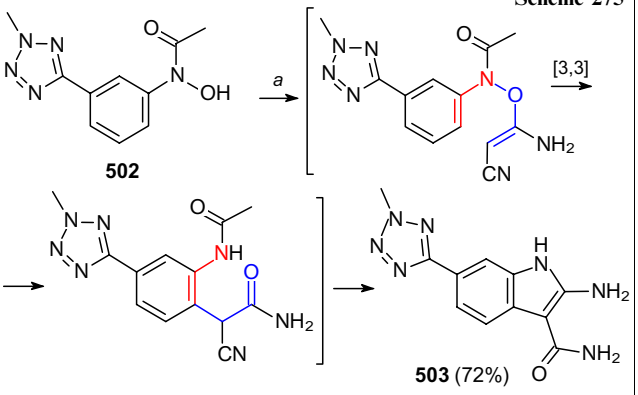
Scheme 274



R^1 = Me, Et; R^2 = Et, Pr^i; R^1–R^2 = $(CH_2)_n$ (n = 4–6, 10)

The [3,3]-sigmatropic rearrangement was implemented in the synthesis of UM171, a potent agonist for the expansion and regeneration of haematopoietic stem cells.[466] This rearrangement is a key step in the transformation of tetrazolyl-substituted hydroxamic acid **502** into indole **503** (Scheme 275).

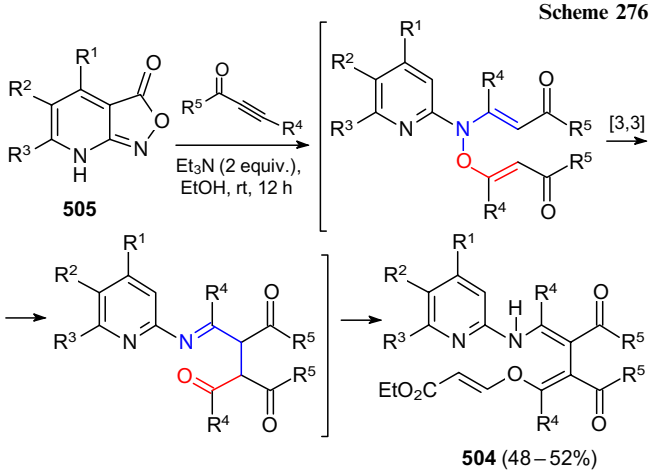
Scheme 275



(*a*) $CH_2(CN)_2$, Et_3N; then NaOMe, MeOH

The mechanisms for the formation of Paal–Knorr intermediates **504** in the Trofimov pyrrole synthesis (Scheme 276) were investigated in the study.[467] These intermediates were obtained *via* a circuitous route by reacting isoxazolopyridinones **505** with ethyl propiolate. Quantum chemical calculations of the [3,3]-sigmatropic rearrange-

Scheme 276

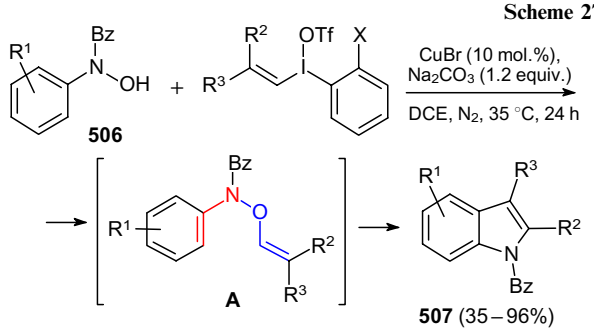


R^1, R^4 = H, Me; R^2 = H, R^3 = Me; R^2–R^3 = benzo; R^5 = OEt, Me

ment revealed that this reaction proceeds *via* a chair-like transition state and is exothermic.

The copper-catalyzed O-vinylation of arylhydroxylamine **506** involving vinyliodonium salts as intermediates **A** generates *O*-vinyl-*N*-arylhydroxylamines. These intermediates undergo a rapid [3,3]-sigmatropic rearrangement and subsequent cyclization–aromatization to form substituted indoles **507** (Scheme 277).[468]

Scheme 277

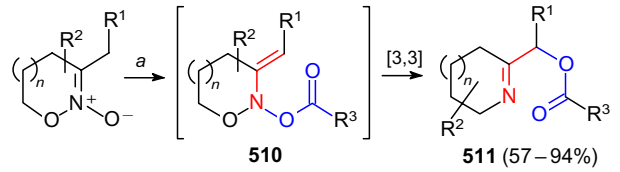


X = Me, OMe; R^1 = F, Cl, Br, Me, Ph, benzo; R^2 = H, Ph;
R^3 = Me, Ph, 4-MeC_6H_4, 4-ClC_6H_4, 2-Naph, Cy, $Cl(CH_2)_3$

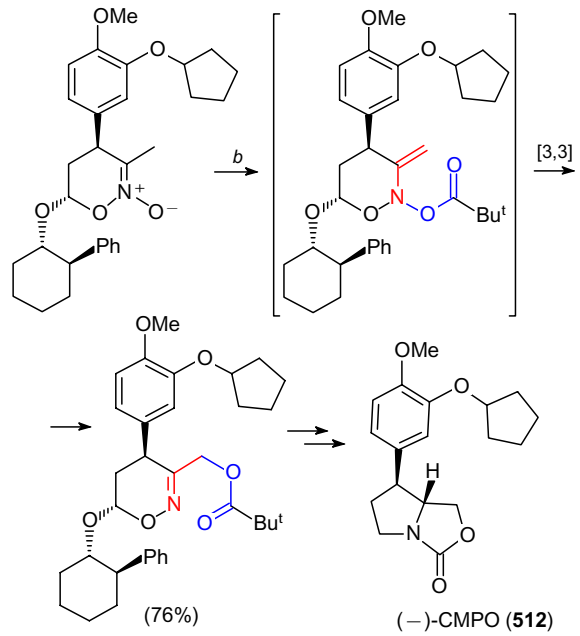
Various annulated indolines were synthesized in moderate yields with high diastereoselectivity from alkynyl oximes **508** and diaryliodonium salts (Scheme 278).[469] The reaction initially proceeds through the selective N-arylation to afford nitrones, which undergo a regioselective intramolecular [3 + 2]-cycloaddition followed by a [3,3]-sigmatropic rearrangement giving indolines **509**.

Rearrangements of acylated nitronates **510** can be used to prepare compounds **511** (Scheme 279).[470] This reaction was implemented in the synthesis of clausenamide. A similar mechanism was suggested for the construction of the PDE4 inhibitor, compound (−)-CMPO (**512**).[471]

Scheme 279



(*a*) $R^3C(O)Cl$, Et_3N, MeCN, 0 °C, 1–24 h; *n* = 0, 1;
R^1 = Me, H; R^2 = Ph, Me, 4-$MeOC_6H_4$, 2-ClC_6H_4, *etc.*; R^3 = Bu^t, Ph

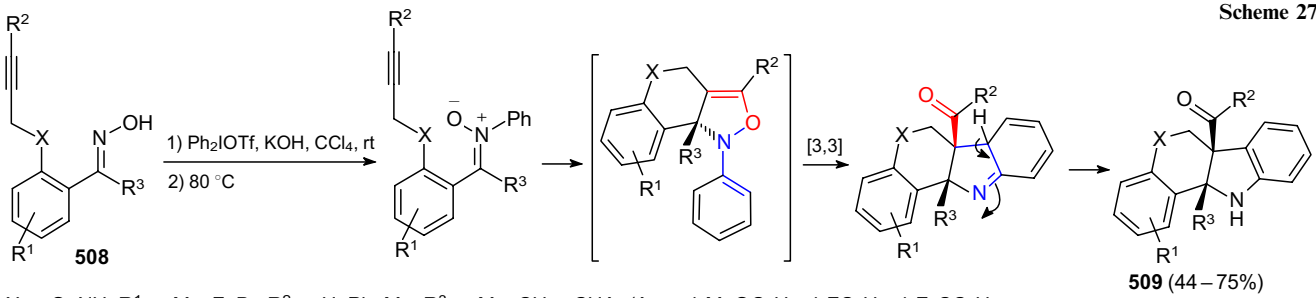


(*b*) PivCl, Et_3N, MeCN, −40 to −25 °C, 18 h

Fused pyrroles **513** were synthesized by the gold catalyst-triggered cascade condensation (Scheme 280).[472] The domino transformation involves the cyclization, subsequent sigmatropic rearrangement, tautomerization and heterocyclization.

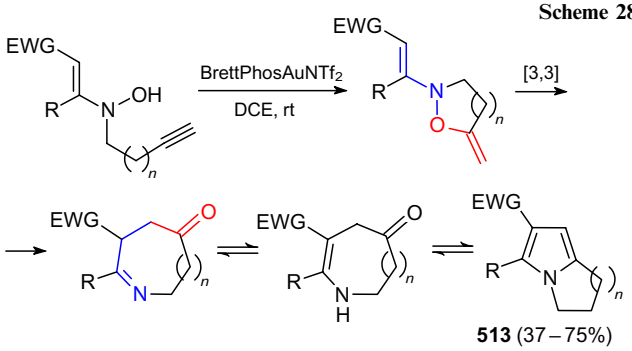
Rearrangements of nitrones are applicable to the construction of polycyclic compounds.[473] Alkyne **514** reacts with nitrone **515** in the presence of quinine as the catalyst to

Scheme 278



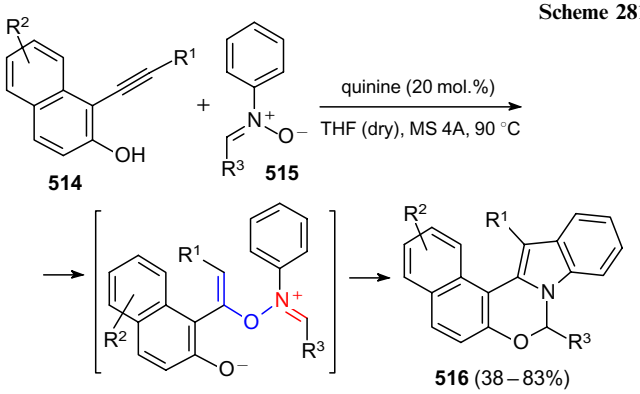
X = O, NH; R^1 = Me, F, Br; R^2 = H, Ph, Me; R^3 = Me, CH=CHAr (Ar = 4-$MeOC_6H_4$, 4-FC_6H_4, 4-$F_3CC_6H_4$, 3-$MeOC_6H_4$, 3-BrC_6H_4, 2-BrC_6H_4, 2-Fu)

Scheme 280



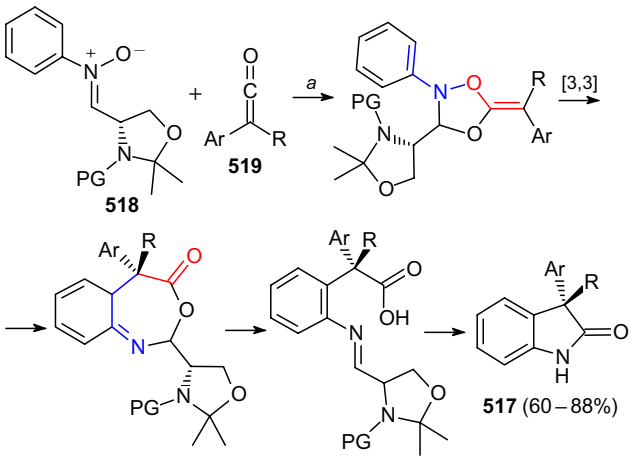
EWG = Ac, CF_3CO, 4-$NO_2C_6H_4$; R = Me, Ph; *n* = 1, 2;
BrettPhos is dicyclohexyl(2′,4′,6′-triisopropyl-3,6-dimethoxy-[1,1′-biphenyl]-2-yl)phosphine

Scheme 281



R^1 = Me, Ph, 3-MeC_6H_4, 4-FC_6H_4, 4-ClC_6H_4, 2-Th;
R^2 = OMe, Br; R^3 = Ph, 4-MeC_6H_4, 4-EtC_6H_4, 3,5-$Cl_2C_6H_3$, 4-$F_3CC_6H_4$, 1-Naph, 2-Th

Scheme 282



(*a*) 1) THF, −78 °C, 3 h; 2) NH_4Cl or HCl; R = Me, Et;
Ar = Ph, 4-$MeOC_6H_4$, 4-FC_6H_4; PG = Boc, Ts, TIPBS;
TIPBS is 2,4,6-triisopropylbenzene-1-sulfonyl

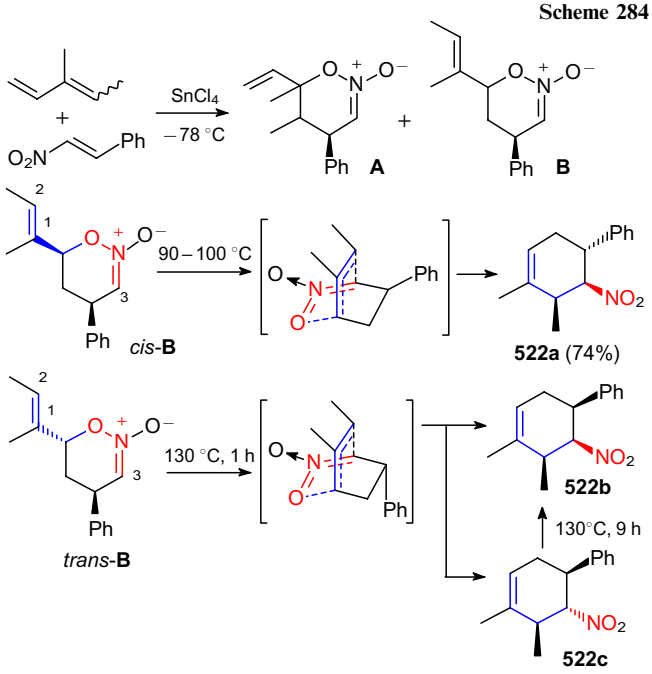
form polycyclic system **516** (Scheme 281). The key step is the scission of the N—O bond of nitrones *via* a [3,3]-sigmatropic rearrangement.

Oxindoles **517** can be prepared by the reaction of nitrones **518** with ketenes **519** (Scheme 282).[474] This reaction allows the synthesis of compounds with a predetermined configuration of the stereocenter defined by a sigmatropic rearrangement.

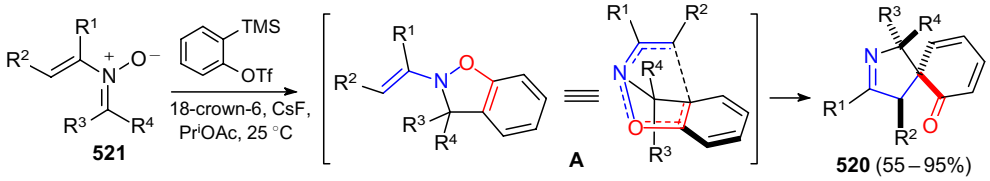
It was demonstrated that spirocyclic 1-pyrrolines **520** can be synthesized from nitrones **521** and *o*-(trimethylsilyl)-phenyl triflate (Scheme 283).[475] The reaction initially proceeds through the dipolar cycloaddition of *N*-alkenyl nitrone to dehydrobenzene generated during the reaction. The subsequent [3,3]-sigmatropic rearrangement of *N*-alkenylbenzisoxazolines **A** produces spirocyclic pyrroline cyclohexadienones.

β-Nitrostyrene reacts with (*E*)-3-methylpenta-1,3-diene in toluene in the presence of tin(IV) chloride as the catalyst (Scheme 284).[476] The reaction affords two major nitronic ester cycloadducts (**A** and **B**) in 27 and 29% yields, respectively. Cycloadducts **B**, derived from the reaction at the less substituted double bond of (*E*)-3-methylpenta-1,3-diene, can undergo a [3,3]-sigmatropic rearrangement on heating to afford 4-nitrocyclohexenes **522a**–**c**. It was assumed that the reaction occurs through a partially charge-separated dipolar transition state. Electron-donating groups at the carbon atoms in the 1 and 2 positions and electron-withdrawing groups at the C(3) atom have a significant effect on the possibility of this reaction.

Scheme 284



Scheme 283

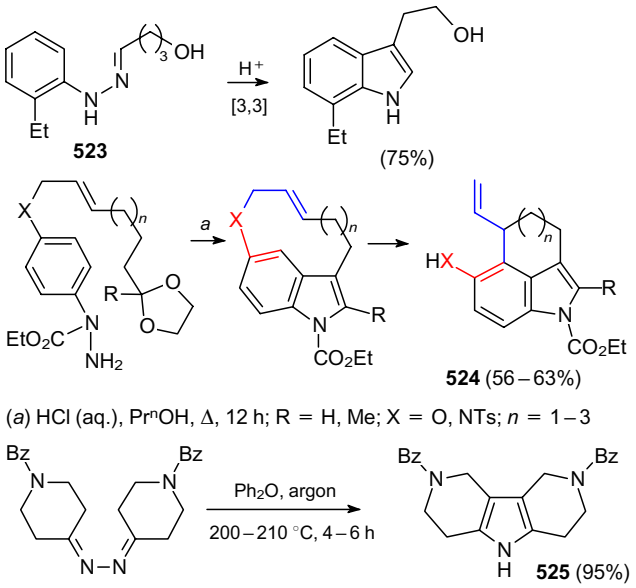


R^1 = Me, Bu^n, Ph; R^2 = Me, Et, Pr^i, $(CH_2)_4Cl$, Bu^n;
R^1–R^2 = $(CH_2)_4$, $(CH_2)_6$, $(CH_2)_2OCH_2$; R^3 = CO_2Me, CO_2Et, CF_3; R^4 = CO_2Me, CO_2Et

9. Rearrangements of N – N compounds

Numerous rearrangements of hydrazones and their derivatives were described in the literature. The Fischer indole synthesis is a widely known example of reactions of this class of compounds. Although this method has a huge synthetic potential, in some cases it cannot be applied to the synthesis of target compounds.[477] This gave impetus to the development of new procedures and(or) their modification, *e.g.*, the use of α-acyllactams for the synthesis of indole derivatives and their analogues.[478] An industrial method for the production of 7-ethyltryptophol by the Fischer reaction, involving a rearrangement of hydrazone **523** *via* a continuous flow reactor (Scheme 285), was described in the study.[479] Methods employing rearrangements can be employed in the synthesis of benzo[*cd*]indoles **524** (Ref. 480) and 1,2,3,4,6,7,8,9-octahydro-5*H*-pyrrolo[3,2-*c*:4,5-*c*′]-dipyridine **525**.[481]

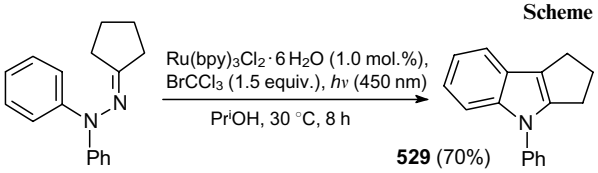
Scheme 285



An alternative method for the preparation of indoles is based on the reaction of arylhydrazines **526** with nitroalkenes (Scheme 286).[482] This cyclocondensation involves the reaction of arylhydrazines with nitroalkenes by using a combination of I_2 (20 mol.%) and diethyl phosphite (2 equiv.) at room temperature and affords N-protected and unprotected indoles **527** in yields of up to 95%. The reaction proceeds through a [3,3]-sigmatropic rearrangement of intermediate **528**.

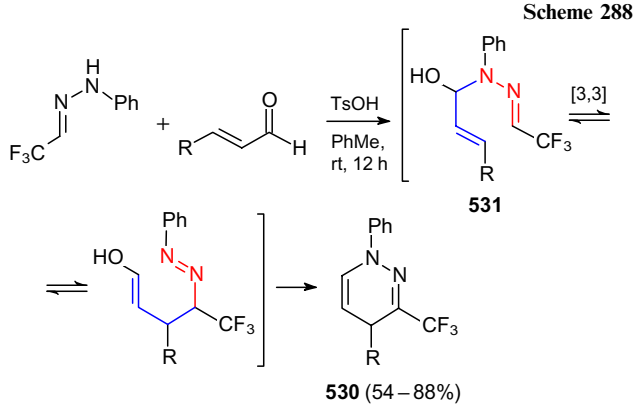
The Fischer method was modified by using photoactive catalysts (photoredox catalysis) under visible light irradiation. Product **529** was obtained under the same conditions even at 30 °C (Scheme 287).[483] N,N-Substituted diarylhydrazones are efficiently transformed into the corresponding indoles by the reaction with bromotrichloromethane in the presence of $Ru(bpy)_3Cl_2 \cdot 6H_2O$ (bpy is 2,2′-dipyridine) as the photocatalyst.

Scheme 287



Pyridazines show interesting and unique properties, due to which the chemistry of these compounds has attracted great interest in recent years.[484] 1,4-Dihydropyridazines **530** were synthesized using a rearrangement of hydrazones **531** (Scheme 288). Presumably, the reaction occurs *via* an electrocyclic mechanism or through a [3,3]-sigmatropic rearrangement of intermediates **531**, derived from unsaturated aldehydes and fluoral hydrazones.[485]

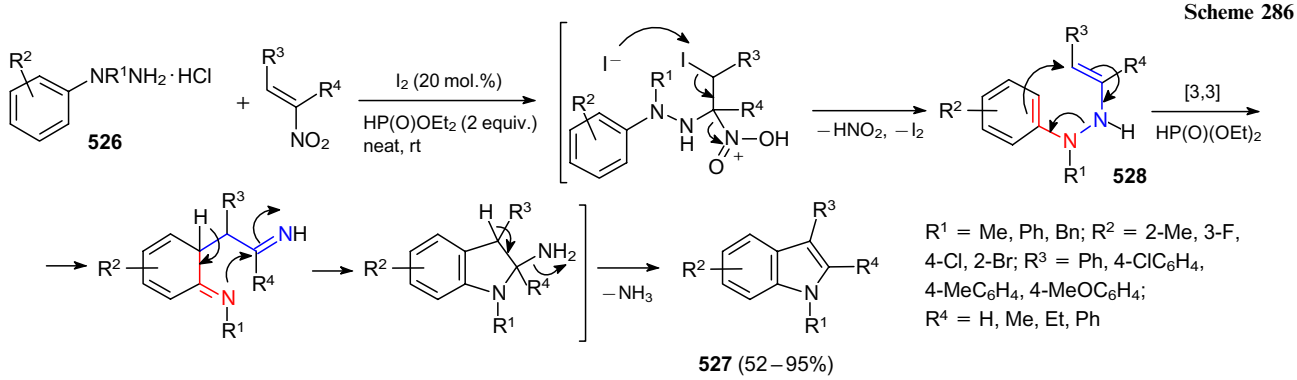
Scheme 288



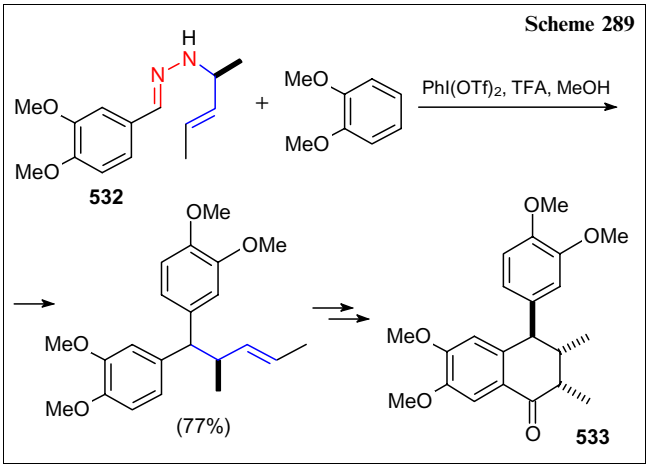
R = Me, Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$HalC_6H_4$, 4-NCC_6H_4, 2-Th

The rearrangement of hydrazones **532** was implemented in the synthesis of lignan **533** (Scheme 289).[486] Many compounds of this class exhibit antimalarial activity.

Scheme 286

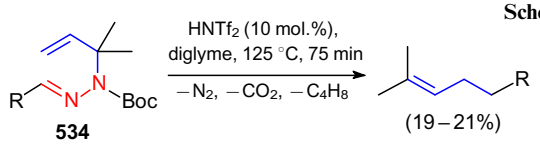


Scheme 289



Hydrazones are intermediates in the isoprenylation of aldehydes (Scheme 290).[487] Apart from *N*-Boc-*N*-(1,1-dimethylallyl)hydrazone, the reaction affords derivatives **534**, which are rearranged into target isoprenes in the presence of catalytic amounts of triflimide. These compounds can easily be isolated because only gaseous by-products are liberated during the synthesis.

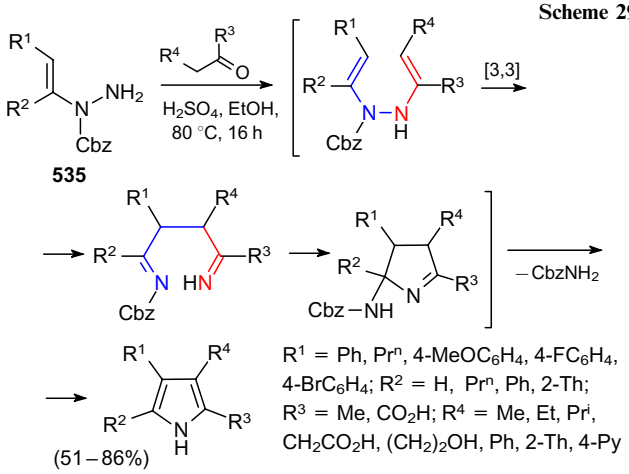
Scheme 290



R = n-C_7H_{15}, n-C_8H_{17}, n-C_9H_{19}, cyclo-C_5H_9, Cy, Ph

The CuI-catalyzed cross-coupling between vinyl halides and carbazates affords N-protected *N*-alkenylhydrazines **535** (Scheme 291) and the subsequent condensation of the latter with ketones under acidic conditions gives polysubstituted pyrroles.[488] The mechanism of this reaction is similar to the mechanism of the Fischer indole synthesis involving a [3,3]-sigmatropic rearrangement.

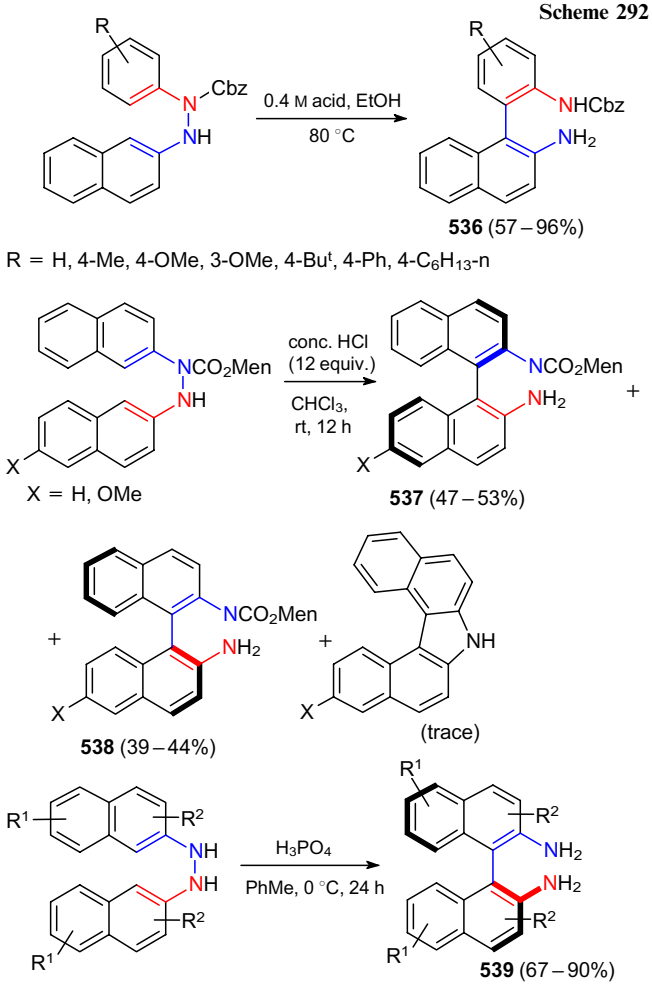
Scheme 291



R^1 = Ph, Pr^n, 4-MeOC$_6$H$_4$, 4-FC$_6$H$_4$, 4-BrC$_6$H$_4$; R^2 = H, Pr^n, Ph, 2-Th; R^3 = Me, CO$_2$H; R^4 = Me, Et, Pr^i, CH$_2$CO$_2$H, (CH$_2$)$_2$OH, Ph, 2-Th, 4-Py

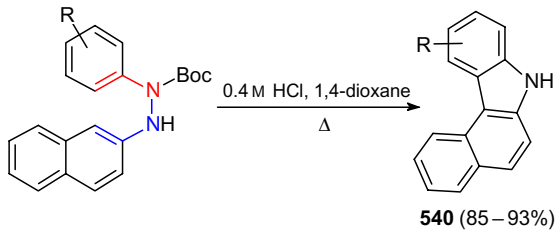
The construction of biaryl and polycyclic systems from substituted hydrazides relate to a separate area of application of rearrangements of N–N compounds. For example, compounds **536**–**539**, analogues of 2,2′-diamino-1,1′-binaphthyl (BINAM), were synthesized using a method based on a sigmatropic rearrangement of dinaphthylhydrazine derivatives (Scheme 292).[489–491] The resulting diastereomers can easily be isolated in the individual state.

Scheme 292



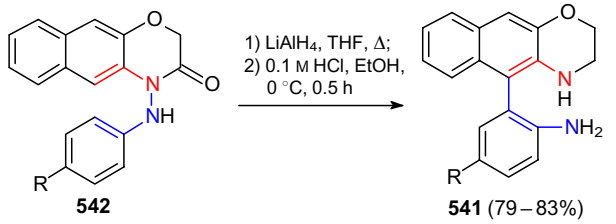
R^1 = H, OMe; R^2 = H, OMe, Pr^i; Men is (1*R*,2*S*,5*R*)-(−)-menthyl

Scheme 293



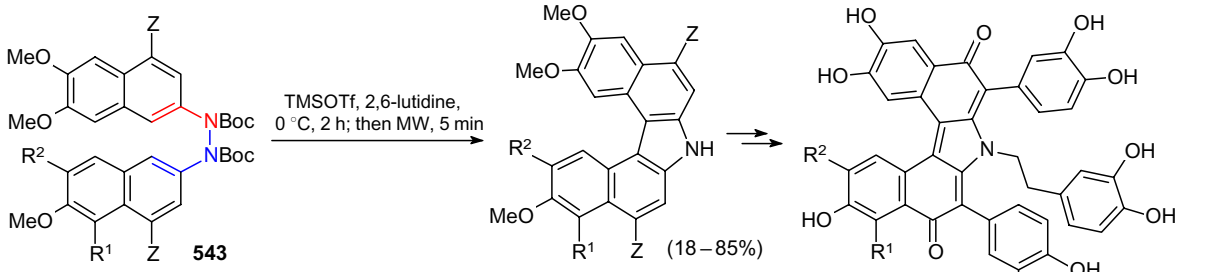
R = 5-Me, 5-OMe, 3-OMe, 5-Bu^t, 5-Ph, 5-C_6H_{13}-n

Scheme 294



R = Me, Bu^t, n-C_6H_{13}, OMe, Ph

Scheme 295



R^1 = H, R^2 = OMe; R^1 = OMe, R^2 = H; Z = Me, CO_2Et, NH_2, NHPiv

A rearrangement using hydrazides was also implemented in the synthesis of benzo[*c*]carbazoles **540** (Scheme 293).[492]

Oxazine-embedded biaryls **541** were synthesized *via* a rearrangement of compounds **542** depicted in Scheme 294.[493]

The total synthesis of the marine alkaloids ningalins D and G is based on a flexible synthetic strategy involving a [3,3]-sigmatropic rearrangement of dinaphthyl hydrazides **543** and cyclization of the resulting 2,2′-diamino-1,1′-dinaphthyls (Scheme 295).[494]

10. Rearrangements of thiocyanates, cyanates and azides

A [3,3]-sigmatropic rearrangement of allyl cyanates and thiocyanates is widely used to prepare allyl isocyanates and isothiocyanates. For instance, the rearrangement to appropriate isothiocyanates is an important key step in the synthesis of, *e.g.* uracil-3′-*epi*-polyoxin C,[495] castanospermine analogues[496] and jaspine B[497] (Scheme 296 presents their precursors **544**, **545** and **546**, respectively).

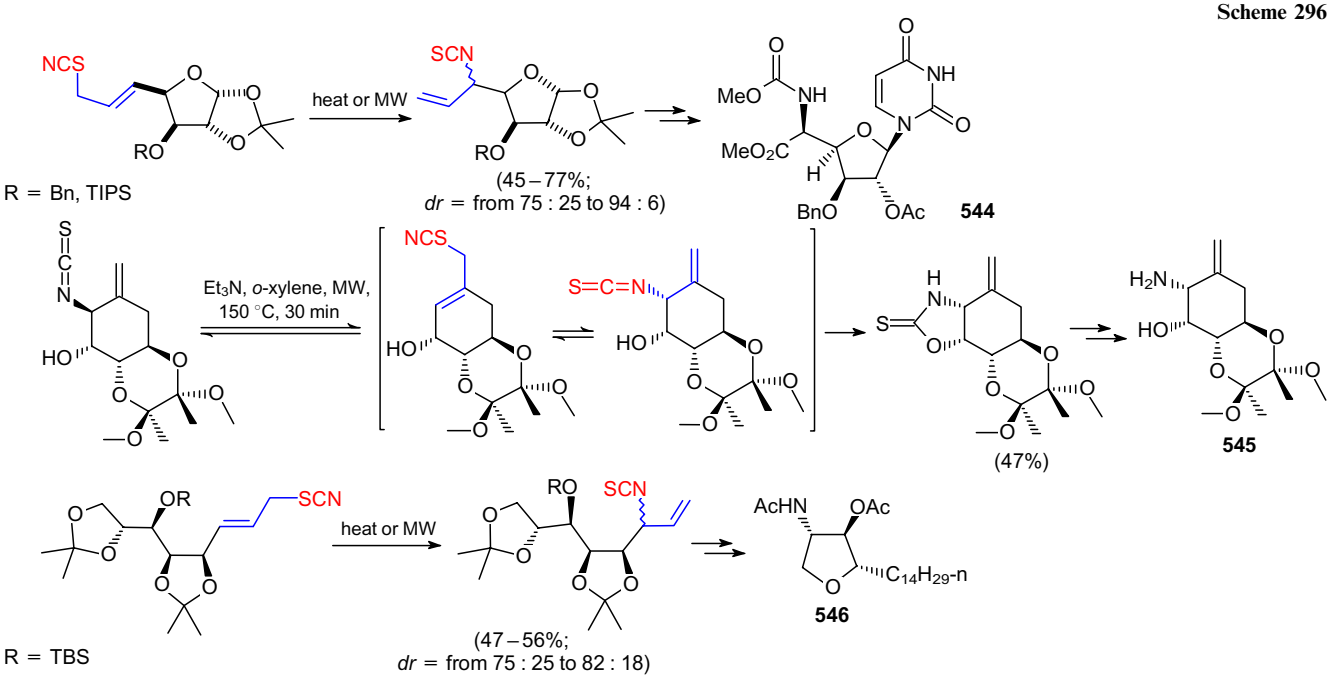
The amino acid-containing skeleton of phytosphingosines and related structures can be produced using rearrangements of thiocyanates **547** (Claisen rearrangement) and trichloroacetimidates **548** (Overman rearrangement) (Scheme 297).[498–506]

First examples of rearrangements of fluorinated cyanates and thiocyanates (Scheme 298) were reported in the study.[507] Long-chain 2-fluoroallylic alcohols **549** were converted to allyl cyanates, which immediately undergo a sigmatropic rearrangement to form fluorinated allyl isocyanates **A**. Without isolation, the latter were used to synthesize fluorinated ureas **550a** by the addition of amines. The heating of mesylates of fluorinated allylic alcohols **551** in THF with potassium thiocyanate afforded allyl isothiocyanates *via* a [3,3]-sigmatropic rearrangement of intermediate allyl thiocyanates. Major products **552a** were further reacted with amines to prepare fluorinated thioureas **550b**.

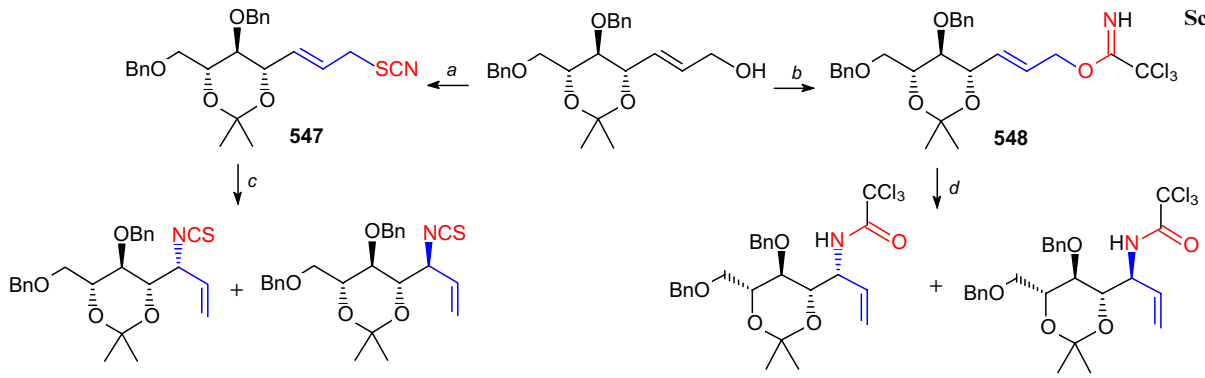
Spiroindolinones **553** were synthesized by the reaction of indolinones **554** with thiocyanatobutadiene **555** (Scheme 299).[508] Heterocyclic system **556** is a possible intermediate in this reaction. This transformation involves tandem sigmatropic rearrangement/Diels–Alder reaction. A chiral nickel(II) complex served as the catalyst. A series of cyclohexenyl isothiocyanates were synthesized in high yields with excellent diastereo- and enantioselectivities.

In most cases, rearrangements of cyanates **557** afford isocyanates **558** (Scheme 300).[509–519] These rearrangements are summarized in a special review[520] published in 2017. In these processes, the cyanate moiety is generated from the

Scheme 296

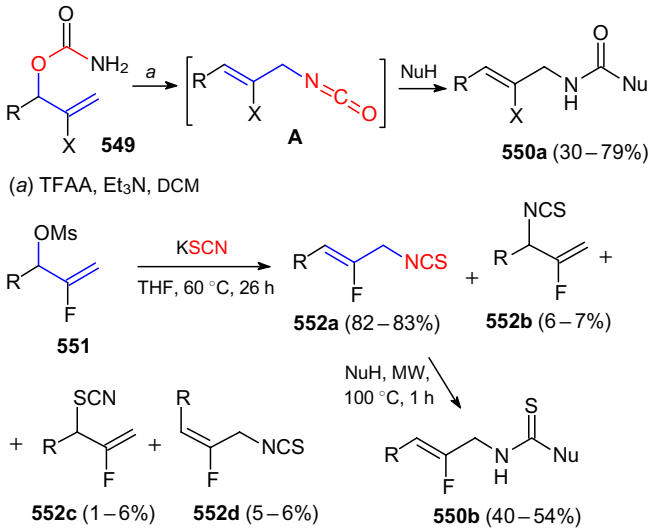


Scheme 297



(*a*) 1) MsCl, Et_3N, DCM, 0 °C to rt; 2) KSCN, MeCN, 0 °C to rt; (*b*) Cl_3CCN, DBU, DCM, 0 °C to rt; (*c*) n-heptane, 90 °C, Δ (60% yield) or MW (77% yield); (*d*) *o*-xylene, K_2CO_3, MW, 150 °C (85% yield) or 170 °C (94% yield)

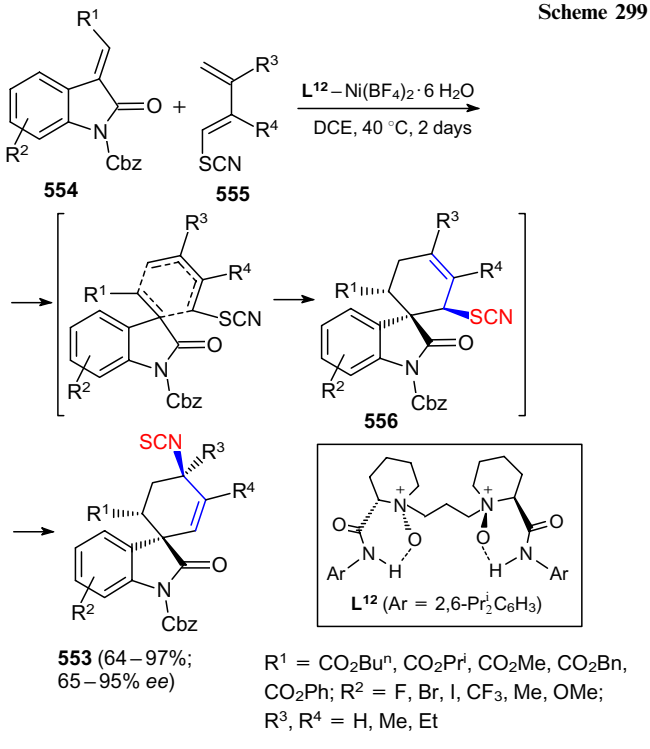
Scheme 298



(*a*) TFAA, Et_3N, DCM

R = n-C_7H_{15}, n-$C_{13}H_{27}$; X = H, F; NuH — aniline, piperidine

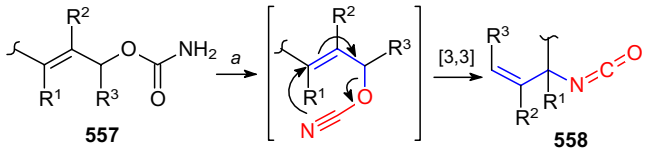
Scheme 299



553 (64–97%; 65–95% *ee*)

R^1 = CO_2Bu^n, CO_2Pr^i, CO_2Me, CO_2Bn, CO_2Ph; R^2 = F, Br, I, CF_3, Me, OMe; R^3, R^4 = H, Me, Et

Scheme 300

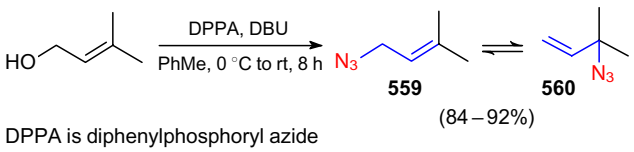


(*a*) TFAA, Et_3N, DCM or THF; R^1 = H, Me, CH_2OBn, $(CH_2)_2Ph$, TMS; R^2 = H, Alk; R^3 = H, Me, Ph, 4-$F_3CC_6H_4$; R^1–R^2 = CH_2, $(CH_2)_3$; R^1–R^3 = CH_2OCH_2

carbamate using trifluoroacetic anhydride[509–522] or the PPh_3–CBr_4–Et_3N system.[523–525] The rearrangement is possible when the substrate contains a double bond in the allylic position relative to the cyanate function. The resulting isocyanates can be isolated in the pure form[509] and, due to high electrophilicity, can be utilized in the synthesis of miscellaneous compounds.[509–520, 524, 525]

Isoprenyl azides **559** with a different number of isoprene units serve as the starting compounds for the construction of diverse triazole derivatives.[526] However, there is a problem of a spontaneous rearrangement of azides **559**, resulting in the formation of a mixture of regioisomers that are difficult to separate. The study of spontaneous rearrangements[526] led the authors to conclude that the preparation of pure isomers of isoprenyl azides is possible only using compounds containing the phenyl substituent at the double bond. In other cases, there is a dynamic equilibrium between rearranged product **560** and starting isoprenyl azide **559** during the synthesis (Scheme 301). The mechanism of the rearrangement of allylic azides (Winstein rearrangement) and the utilization of various compounds in this reaction were considered in the review.[527]

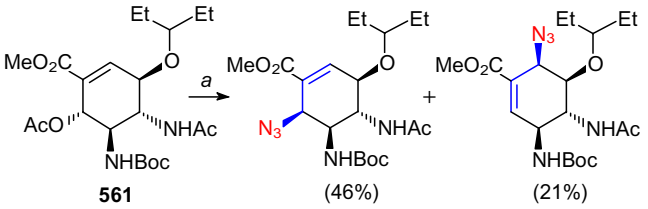
Scheme 301



DPPA is diphenylphosphoryl azide

A convenient route to the synthesis of triazole analogues of the drug Tamiflu was developed using cyclic acetate as a precursor for azide substitution *via* a suprafacial [3,3]-sigmatropic rearrangement of allylic azide **561** (Scheme 302).[528]

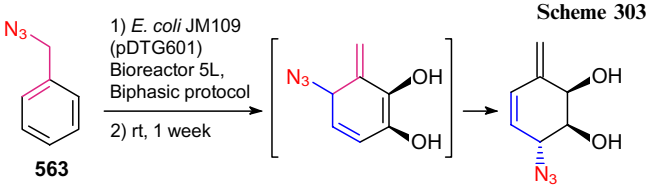
Scheme 302



(*a*) $TMSN_3$, Bu^tOH, 80–85 °C, 6 days

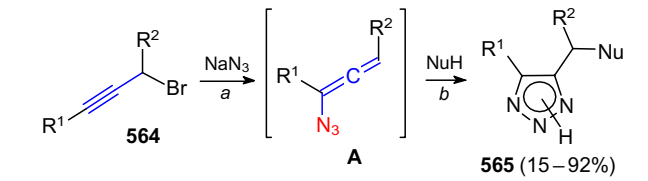
These rearrangements can also be performed using certain enzymes. For example, cyclohexadienediols **562** are produced by the dioxygenation of benzyl azides **563** catalyzed by *Escherichia coli* (Scheme 303).[529] The reaction involves the enzymatic dioxygenation and the azide transfer from the benzylic position.

Scheme 303



The reaction of propargyl bromides **564** with sodium azide produces propargyl azides, which undergo a [3,3]-sigmatropic rearrangement through the formation of short-lived allenyl azides **A** that cyclize to form triazafulvenes.[530] Electrophilic intermediates **A** can be trapped by addition of N- or O-nucleophiles giving triazoles **565** (Scheme 304). The mechanistic study summarized the general features of such reactions.[531] It was demonstrated that the [3,3]-sigmatropic rearrangement is the rate-determining step and has the highest activation barrier.

Scheme 304



(*a*) ~22–30 °C, 18–24 h; (*b*) 65–70 °C, 2–3 h;
R^1 = H, Me, n-$C_{10}H_{21}$, TMS; R^2 = H, n-C_5H_{11};
Nu = OH, OMe, OEt, OPr^n, OPr^i, OPh, OAc, NH_2, NHMe, N_3

11. Conclusion

In conclusion, we would like to say that there is a number of review papers dealing with non-classical rearrangements or rarely occurring atomic groups. Of such reviews, mention can be made of the review [532] devoted to rearrangements of functional groups containing heavy heteroatoms implemented in the synthesis of biologically active compounds and the review [533] on rearrangements of iodonium compounds.

The data summarized in this review demonstrate that [3,3]-sigmatropic rearrangements are important synthetic tools in organic chemistry. The application of rearrangements allows the improvement of atom economy, makes it possible to reduce the number of steps of the transformations and offers great potential for the synthesis of natural products and their analogues. In most cases, one can suggest a concerted mechanism for [3,3]-sigmatropic rearrangements through the formation of six-membered transition state. The relative predictability of the intermediate three-dimensional structure can be efficiently employed in the construction of target skeletons of complex molecules. Moreover, in the case of stereoselective reactions, it is possible to affect the stereo configuration of the product by varying the nature of the catalyst. Taking into account the fact that catalysis often reduces the need for heating or other activation of the reaction, multistep tandem transformations can be performed under rather mild conditions. Nevertheless, this approach has many undisclosed advantages, as confirmed by the discovery of new transformations based on sigmatropic rearrangements. For example, bulky chiral ligands in catalytic systems make it possible to prescribe the stereo configuration due to steric interactions; the presence of polyfluorinated substituents in the substrate leads to a significant decrease in the reaction time; the optimized reaction conditions enable the preparation of products on a kilogram scale. This review presents the most relevant and diverse data on [3,3]-sigmatropic rearrangements. We hope that this information will be useful in designing new synthetic protocols. It would be expected that these rearrangements will gain increasing importance in organic chemistry and the scope of their application will be continuously extended.

12. List of abbreviations and designations

Ad — 1-adamantyl,
AIBN — azobis(isobutyronitrile),
Ans — 4-methoxybenzenesulfonyl,
ATMM — azatrimethylenemethane,
AZADO — 2-azaadamantane-*N*-oxyl,
B — base,
BArF — tetrakis[3,5-bis(trifluoromethyl)phenyl]borate,
BHT — 2,6-di-*tert*-butyl-4-methylphenol,
BINAP — 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl,
Bnmim — 1-benzyl-3-methylimidazolium,
Boc — *tert*-butoxycarbonyl,
bpy — 2.2′-dipyridine,
BrettPhos — dicyclohexyl(2′,4′,6′-triisopropyl-3,6-dimethoxybiphenyl-2-yl)phosphine
Bs — 4-bromobenzenesulfonyl,
BSA — *N*,*O*-bis(trimethylsilyl)acetamide,
CaADH — clostridial alcohol dehydrogenase,
Cbz — benzyloxycarbonyl,
cod — cycloocta-1,5-diene,
COE — cyclooctene,
Cp — cyclopentadienyl,
Cy — cyclohexyl,
DABCO — 1,4-diazabicyclo[2.2.2]octane,
DAP — 1,3,2-diazaphospholenes,
dba — dibenzylideneacetone,
DBU — 1,8-diazabicyclo[5.4.0]undec-7-ene,
DCB — *o*-dichlorobenzene,
DCE — 1,2-dichloroethane,
DCM — dichloromethane,
DDQ — 2,3-dichloro-5,6-dicyano-1,4-benzothiophene,
de — diastereomeric excess,

DEAD — diethyl azodicarboxylate,
DIPEA — diisopopylethylamine,
DMAP — 4-dimethylaminopyridine,
DME — 1,2-dimethoxyethane,
DTBM-Segphos — (+)-5,5′-bis[di(3,5-di-*tert*-butyl-4-methoxyphenyl)phosphino]-4,4′-bi-1,3-benzodioxole,
DTBMP — 2,6-di-*tert*-butyl-4-methylpyridine,
DTBP — di-*tert*-butyl peroxide,
DPPA — diphenylphosphoryl azide,
dppe — 1,2-bis(diphenylphosphino)ethane,
dppf — 1,1′-bis(diphenylphosphino)ferrocene,
DQ — 3,3′,5,5′-tetra-*tert*-butyl-4,4′-biphenylquinone,
dr — diastereomeric ratio,
E_d — dissociation energy,
ECHIA — ethyl 2-cyano-2-(hydroxyimino)acetate,
EDC — 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide,
EDG — electron-donating group,
ee — enantiomeric excess,
er — enantiomeric ratio,
EWG — electron-withdrawing group,
fod — 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyloctane-3,5-dionate,
Fu — furyl,
HBpin — pinacolborane,
HBTU — 2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethylurea,
HFIP — 1,1,1,3,3,3-hexafluoroisopropanol,
HMDS — hexamethyldisilazide,
Hmim — 1-methylimidazolium,
HMPA — hexamethylphosphoramide,
HOBT — 1-hydroxybenzotriazole,
IBX — 2-iodobenzoic acid,
IPr — 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene,
Ind — indolyl,
JohnPhos — 2-(di-*tert*-butylphosphino)biphenyl,
LA — Lewis acid,
LDA — lithium diisopropylamide,
LiTMP — lithium 2,2,6,6-tetramethylpiperidide,
mCPBA — 3-chloroperoxybenzoic acid,
Men — (1*R*,2*S*,5*R*)-(−)-menthyl,
Mes — 2,4,6-trimethylphenyl (mesityl),
MOM — methoxymethyl,
MS — molecular sieves,
Ms — methanesulfonyl,
MVG — methyl 2-hydroxybut-3-enoate (methyl vinyl glycolate),
MW — microwave irradiation,
Naph — naphthyl,
NCS — *N*-chlorosuccinimide,
NHC — N-heterocyclic carbenes,
NOBIN — 2-amino-2′-hydroxy-1,1′-binaphthyl,
NPhth — phthalimido,
Ns — 4-nirobenzenesulfonyl,
Nu — nucleophile,
Oct — octyl,
octn — octanoate,
Pbf — 2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl,
PEG — polyethylene glycol,
PG — protecting group,
Piv — pivaloyl,
PMB — *p*-methoxybenzyl,
PMP — 4-methoxyphenyl,
PTAD — 4-phenyl-1,2,4-triazoline-3,5-dione,
Py — pyridyl,
RCM —ring-closing metathesis,
RICR — reductive iodonio-Claisen rearrangement,
rt — room temperature,
RuPhos — 2-dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl,
SS-FVP — solution spray flash vacuum pyrolysis,
$t_{1/2}$ — half-life,
TBAF —tetra-*n*-butylammonium fluoride,
TBDPS — *tert*-butyldiphenylsilyl,
TBS — *tert*-butyldimethylsilyl,
TC — thiophene-2-carboxylate,
TEMPO — 2,2,6,6-tetramethylpiperidine-1-oxyl,
TES — triethylsilyl,
Tf — trifluoromethanesulfonyl (triflyl),
TFA — trifluoroacetic acid,
TFAA — trifluoroacetic anhydride,
TFE — 2,2,2-trifluoroethanol,
Th — thienyl,
THP — tetrahydropyran-2-yl,
TIPBS —2,4,6-triisopropylbenzene-1-sulfonyl,
TIPS — triisopropylsilyl,
TMBA — 2,4,6-trimethylbenzoic acid,
TMS — trimethylsilyl,
TPP — *meso*-tetraphenylporphyrin,
TS — transition state,
Ts — *p*-toluenesulfonyl (tosyl),
UHP — hyperol (urea hydrogen peroxide clathrate),
US — ultrasound.

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