Enantioselective Synthesis of and with Allenes

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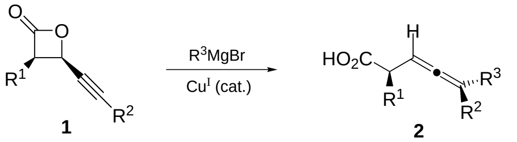
In recent years, allenes have gained increasing attraction as interesting building blocks in modern organic chemistry. Their synthetic utility is not only demonstrated by an abundance of regio- and stereoselective C–C-bond-forming transformations (e.g., Diels–Alder reactions), but they are also prone to transfer their axial chirality efficiently to one or several new stereogenic centers.[1] These characteristics, as well as the occurrence of allenic structures in a variety of natural products and pharmacologically active compounds, gave rise to ample interest in the stereoselective synthesis of allenes.[2] In this account, we report selected developments in the enantioselective synthesis of allenes and allenic natural products in the last two years, but by no means comprehensively.

A well-established, widely applicable access to various enantiomerically enriched and pure allenes relies on the S_N2' substitution of chiral propargylic derivatives with nucleophiles, in particular with organocuprates.[1–4] According to this principle, Wan and Nelson reported the use of optically active alkynyl-substituted β-lactones as highly reactive precursors for allenes through copper-catalyzed S_N2'-reactions with Grignard reagents [Eq. (1)].[4] The required enantiomerically enriched β-lactones **1** are readily accessible by condensation of propargylic aldehydes with acid halides and furnish, in a S_N2'-ring-opening process, the desired β-allenic carboxylic acids **2**. The latter were obtained in good yields and with high enantiomeric excesses, since the reaction occurs strictly *anti*-stereoselectively with complete chirality transfer from the stereogenic center of the lactone to the chirality axis of the resulting allene.



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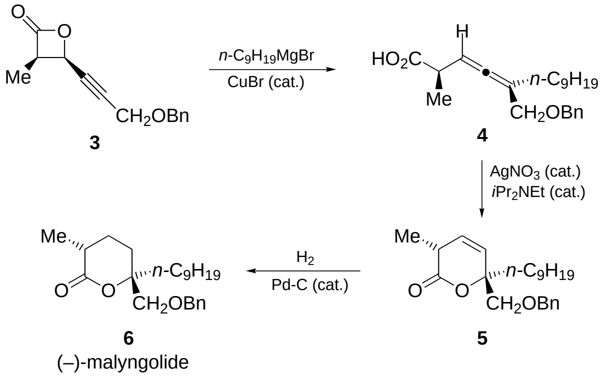
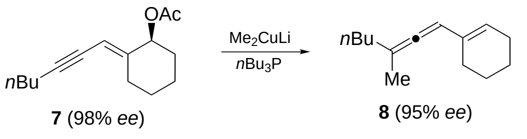
The authors showed the synthetic practicality of this reaction by using different nucleophiles (including a zinc ester enolate) and by the stereoselective synthesis of the natural product (−)-malyngolide (**6**), which was obtained from β-lactone **3** in only 3 steps with 64% overall yield (Scheme 1).[4]



Scheme 1. Synthesis of (−)-malyngolide (**6**). Bn = benzyl.

On the other hand, a direct access to enantiomerically enriched and pure vinylallenes was established by Krause and Purpura through 1,5-(S_N'')-substitution reaction of chiral enyne acetates with organocuprates.[5] Although the vinyl allenes **8** were mostly formed as a mixture of *E* and *Z* isomers, high enantiomeric excesses of up to 99% could be achieved starting from the respective enantiomerically enriched enyne acetates like **7** [Eq. (2)]. In this case, the presence of tri-*n*-butylphosphane or triethylphosphite as an additional ligand served to avoid racemization of the product by reactive copper species present in the mixture, and thus proved to be indispensable for high enantioselectivities. Since the enantioselectivity is controlled by a comparatively remote stereogenic center, this 1,5-substitution constitutes one of the few examples of "remote stereocontrol" in organocopper chemistry. Furthermore, the 1,5-substitution of chiral, nonracemic enyne acetates can be performed equally well with catalytic



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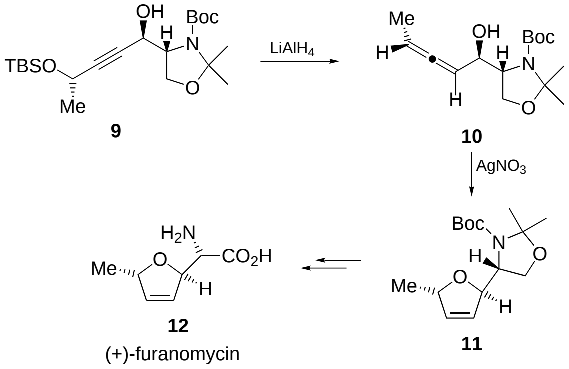
amounts of copper salts, a fact that is of special importance both from and economic and a preparative point of view.

The high stereoselectivity of many S_N2'-substitution reactions, as well as the possibility of utilizing the generated allenic moiety for a chirality transfer in subsequent transformations (often cyclizations[6–8]), make the sequence highly attractive for the synthesis of natural products. Thus, the formation of the α-hydroxyallene **10** and its silver-promoted cyclization to dihydrofuran **11** are key steps of the synthesis of (+)-furanomycin (**12**) described by VanBrunt and Standaert (Scheme 2).[8]

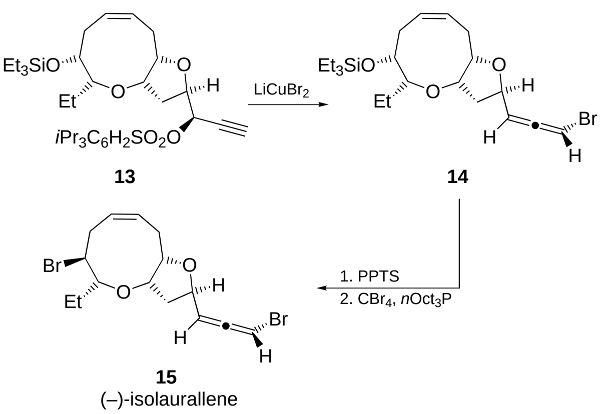


Scheme 2. Synthesis of (+)-furanomycin (**12**). TBS = *tert*-butyldimethylsilyl, Boc = *tert*-butoxycarbonyl.

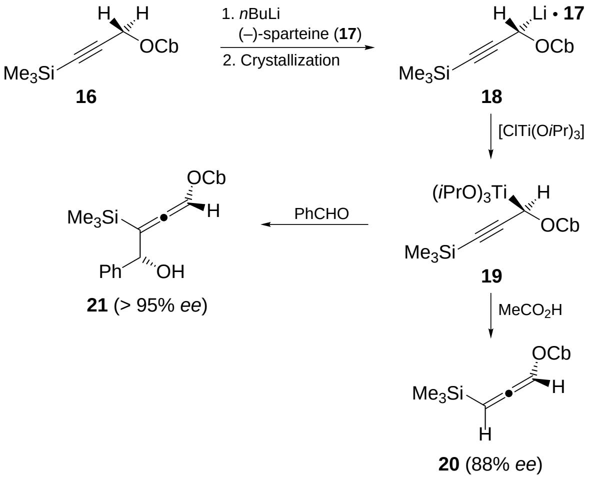
Starting from Garner's aldehyde, the authors prepared the propargylic silyl ether **9** by diastereoselective acetylide addition and converted this into the allenic alcohol **10** by an *anti*-stereoselective hydrometalation–elimination sequence with lithium aluminum hydride (Scheme 2). Although this transformation only gave a moderate yield, the subsequent diastereoselective cyclization to dihydrofuran **11** could be carried out with stoichiometric amounts of $AgNO_3$. Cleavage of the N,O-acetal and formation of the carboxy group finally led to (+)-furanomycin (**12**) in 12 % yield over eight steps.

Allenes are not only important as reactive key intermediates in organic synthesis, but also in their own right as natural products and pharmacologically active compounds.[1, 9, 10] An intriguing example of an allenic natural product is the bromoallene (−)-isolaurallene (**15**) which was isolated from marine red algae and was recently synthesized by Crimmins and Emmitte (Scheme 3).[9] The allenic moiety is again formed in a copper-mediated S_N2'-substitution reaction by making use of a triisopropylbenzenesulfonate (trisylate) as the leaving group. The precursor **14** was obtained in 67 % yield by treatment of trisylate **13** with $LiCuBr_2$ and was finally transformed into the target molecule **15** by cleavage of the silyl protecting group and introduction of the secondary bromide.

Conceptually rather different ways to enantiomerically enriched and pure allenes are based on the construction of the carbon skeleton (e.g., by enantioselective Wittig-Horner-Wadsworth-Emmons (WHWE) reactions of ketenes[11]) or on kinetic resolutions.[12, 13] Thus, Hoppe and co-workers[13] demonstrated that the deprotonation of prochiral secondary alkynyl carbamates **16** with *n*-butyllithium in the presence of (−)-sparteine (**17**) in pentane leads to the spontaneous crystallization of the diastereomerically pure complex **18** (Scheme 4), which could be transmetalated with $[ClTi(O\mathit{i}Pr)_3]$ under inversion of configuration into the corresponding titanate **19**. Subsequent protonation of **19** with acetic acid or a trapping reaction with an aldehyde finally furnished the allenes **20** and **21**, respectively, with high enantioselectivities.

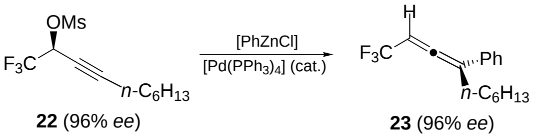


Scheme 3. Synthesis of (−)-isolaurallene (**15**). PPTS = pyridinium-*p*-toluenesulfonate.



Scheme 4. Synthesis of the allenes **20** and **21** by sparteine-mediated lithiation of the alkynyl carbamate **16**. Cb = $i\mathrm{Pr_2NCO}$.

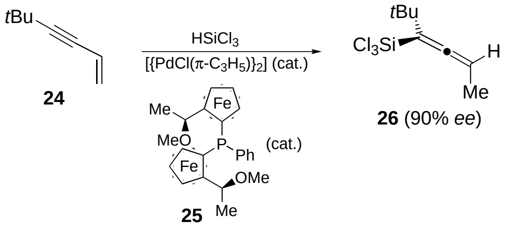
Besides the element copper, other transition metals (in particular palladium) can also be used to generate allenes through S_N2' substitution of chiral, nonracemic propargylic derivatives. In this case, the intermediate allenyl–Pd species, formed by oxidative addition and insertion steps, exists in equilibrium with the corresponding propargylic Pd intermediate. This equilibrium often results in a racemization of the allenic product, as observed recently by Tanaka and co-workers[14] in a Pd^0-catalyzed transformation of allylic alcohols into allenes. In contrast, Konno et al.[15] were able to obtain fluorinated allenes of type **23** with high optical purity by reaction of the corresponding enantiomerically enriched propargylic mesylates **22** with organozinc reagents in the presence of catalytic amounts of $[Pd(PPh_3)_4]$ [Eq. (3)]. Clearly, the formation of a propargylic Pd species and



22 (96% *ee*) **23** (96% *ee*) (3)

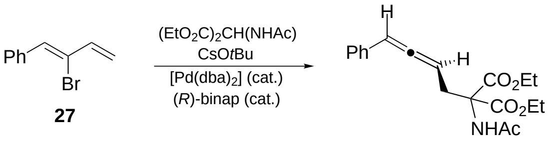
subsequent racemization are efficiently prevented by the presence of the perfluorinated alkyl group.

From an (atom) economical point of view, the generation of enantiomerically pure products from achiral precursors by stereoselective catalysis with catalytic amounts of both the transition metal and the chiral ligand is particularly desirable. However, no example of such a transition-metal-catalyzed synthesis of enantiomerically pure allenes existed until recently, even though the Rh- or Ni-catalyzed hydrosilylation of butadiynes reported by Tillack et al. gave the desired chiral allenes, albeit with low enantioselectivity.[16] The desired breakthrough in this field has now been achieved by Hayashi and co-workers, who developed two new, highly efficient catalytic allene syntheses. Thus, the palladium-catalyzed hydrosilylation of but-1-en-3-ynes **24** with trichlorosilane in the presence of the chiral ferrocenyl phosphane ligand **25** gave preparatively useful stereoselectivities of up to 90% *ee* [Eq. (4)].[17] In this case, a sterically demanding substituent at the triple bond of the enyne **24** was found to be crucial for high enantioselectivity. Furthermore, the resulting trichlorosilanes **26** can be converted not only into allenyl trimethylsilanes, but also (with chirality transfer) into preparatively valuable chiral homopropargylic alcohols.



24 **25** **26** (90% *ee*) (4)

The second catalytic enantioselective allene synthesis, also developed by Hayashi and co-workers,[18] relies on the palladium-catalyzed S_N2' substitution of prochiral 2-bromobuta-1,3-dienes like **27** with soft nucleophiles. In the presence of 10 mol% of (*R*)-2,2′-bis(diphenylphosphanyl)-1,1′-binaphthalene (binap) as the chiral ligand, CsO*t*Bu as base, and [Pd(dba)$_2$] as the precatalyst, the desired allene **28** was obtained with 89% *ee* [Eq. (5)]. Interestingly, the presence of dibenzylideneacetone (dba) in the reaction mixture proved to be indispensable for high enantiomeric excesses.



27 **28** (89% *ee*) (5)

As these examples demonstrate, the methods for the enantioselective synthesis of chiral allenes have recently achieved a high standard. The development of novel efficient catalytic protocols should lead to further applications of allenes in stereoselective syntheses, especially in those of natural products and pharmaceuticals.

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