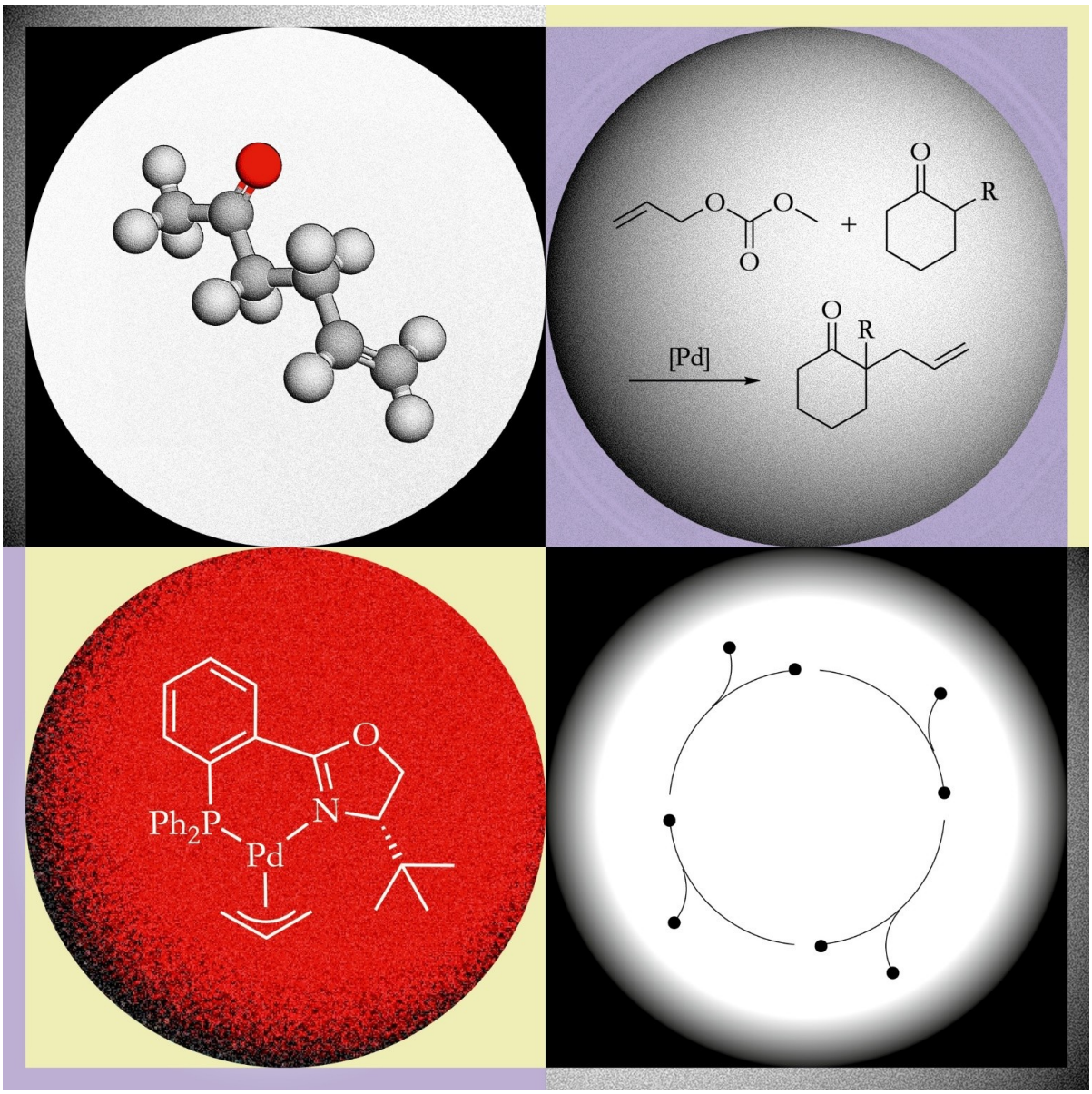
The Allylic Alkylation of Ketone Enolates

Lukas Junk and Uli Kazmaier*[a]

Dedicated to Prof. Dr. Günter Helmchen on the occasion of his 80th birthday



The palladium-catalyzed allylic alkylation of non-stabilized ketone enolates was thought for a long time to be not as efficient as the analogous reactions of stabilized enolates, e.g. of malonates and β-ketoesters. The field has experienced a rapid development during the last two decades, with a range of new, highly efficient protocols evolved. In this review, the early developments as well as current methods and applications of palladium-catalyzed ketone enolate allylations will be discussed.

1. Introduction

Transition metal catalyzed reactions are among the most utilized reactions in organic synthesis. Besides the very common palladium catalyzed sp^2-sp^2 and sp^2-sp couplings,[1] the Pd-catalyzed allylic alkylation, developed by Tsuji and Trost, provides an efficient way to react π-allyl Pd complexes with various nucleophiles, allowing also the formation of C(sp^3)–C (sp^3) bonds.[2]

First described as stochiometric couplings of π-allyl-Pd complexes with malonates by Tsuji *et al.* in 1965,[3] the group of Trost developed numerous protocols for a catalytic and enantioselective version of this reaction in the last decades.[4] Besides Pd, also many other transition metals (e.g. Ru, Rh, Ir) are able to catalyze the reaction,[5] all providing their own benefits regarding the regio- and stereoselective outcome of the reaction.

In early days of allylic alkylations, it was assumed that only "soft", stabilized enolates, e.g. those of malonates and β-ketoesters, can be employed in the reaction. In recent years however, many protocols emerged for the Pd-catalyzed allylic alkylation of non-stabilized enolates obtained from esters, amides, aldehydes or ketones.[6] The latest comprehensive review covering allylations of ketones was prepared in 2006,[6a] and we therefore see the need to summarize the newest developments in this interesting field. We will give an overview over the allylation of ketone enolates and equivalent *C*-nucleophiles such as enamines. We will structure this article according to enolate formation. Recent applications of ketone allylations in natural product syntheses will also be highlighted.

2. Allylic Alkylations of Ketone Enolates

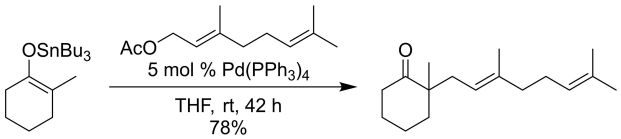
In general, ketones can be deprotonated by strong bases, for example lithium hexamethyldisilazide (LHMDS), lithium diisopropylamide (LDA) or metal hydrides such as NaH or KH. These alkali metal enolates can be transmetalated to less reactive species, which are usually better suited for Pd-catalyzed allylic alkylations.

2.1. Early Examples

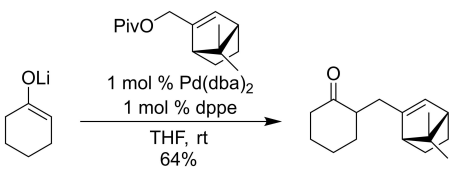
The very first example of a ketone enolate allylic alkylation was described by Trost and Keinan in 1980.[7] They found that the reaction of the lithium enolate of acetophenone with allylic acetates yielded mainly the double alkylated product via deprotonation of the primarily formed desired product and subsequent second allylation. In contrast, when a silyl enol ether was employed, the mono-alkylated product was obtained almost exclusively. The reaction was however more or less limited to unsubstituted allyl acetate, while it was sluggish with more complex substrates. When the silyl moiety was replaced by a tributyltin group, the reaction proceeded much more rapidly, even with densely substituted allylic acetates (Scheme 1). A highly regioselective attack at the least substituted end of the allyl fragments was observed, and the (*E*)-product was formed regardless of the configuration of the allyl substrate. This is typical for Pd-catalyzed allylic alkylations, where the Pd-allyl complex formed rapidly equilibrates *via* π-σ-π-isomerization. The regioselectivity is probably also controlled by the high steric demand of the tributyltin group.

Shortly thereafter, Fiaud and Malleron reported a method for the selective monoalkylation of lithium enolates derived from simple ketones.[8] By using 1,2-bis(diphenylphosphino) ethane (dppe) and bis(dibenzylideneacetonato)palladium (Pd $(dba)_2$) as the catalytic system, the enolates, e.g. of cyclohexanone, acetophenone or acetone could be alkylated in reasonable yields (Scheme 2).

In 1982, a method for the allylic alkylation of lithium enolates with allyl triethylammonium bromides was described by Hirao *et al.*,[9] and one year later, Negishi *et al.* reported the allylic alkylation of boron enolates (Scheme 3).[10] Potassium enoxyborates (**1**) were obtained from the corresponding ketone on treatment with a potassium base followed by the addition of



Scheme 1. First successful allylic alkylation of tin enolates.



Scheme 2. First allylic alkylation of Li enolates.

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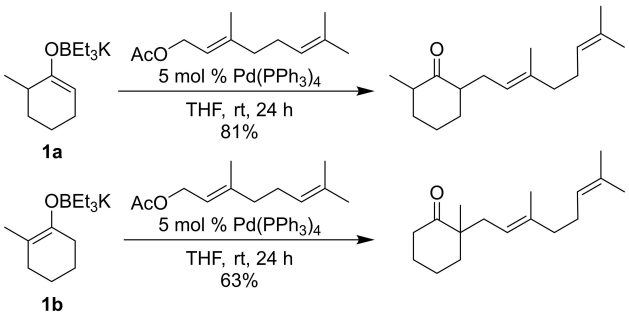


Scheme 3. Allylic alkylation of enoxybarates.

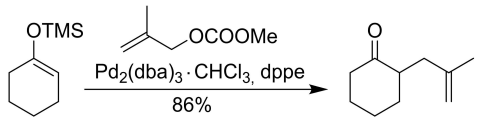
BEt_3. The kinetic (**1 a**) and the thermodynamic (**1 b**) enolates could be obtained selectively by deprotonation with KHMDS or KH, respectively. The allylic alkylations with geranyl acetate proceeded with high regio- and stereoselectivity. While screening different counter cations, Negishi and coworkers found that only zinc enolates provided similar results to the enoxyborates, whereas magnesium, titanium and silicon enolates resulted in less promising results.

In the same year, Tsuji and coworkers reported the allylic alkylation of silyl enol ethers.[11] They used dppe as an accelerating ligand, allowing them to alkylate cyclic and acyclic silyl enolates with high regioselectivity (Scheme 4).

In the following two decades after these pioneering examples, not much has been reported on the allylic alkylation of ketones. But with the emergence of chiral ligands and asymmetric catalysis in the early 2000's, ketone enolates found a resurgence as useful nucleophiles in the allylic alkylation. We will structure the following examples based on the nature of the enolate counter cation.

2.2. Tin Enolates

After the initial report of Trost and Keinan, only few examples using tin enolates were reported. In 1995, Shi *et al.* described the allylic alkylation of the tin enolate of 2-methylcyclohexanone with fluorinated allylic substrates



Scheme 4. First successful allylic alkylation of silyl enol ethers.

(Scheme 5).[12] The attack of the enolate occurred preferentially at the non-fluorinated terminus of the allyl fragment. The products could be obtained in reasonable yields and good to excellent regioselectivities.

The first enantioselective allylic alkylation of ketone enolates was described by Trost and Schroeder in 1999.[13] They developed a ligand derived from 1,2-diaminocyclohexane (**L1a**, Scheme 6), which shields the Pd-allyl complex in a C_2-symmetric fashion, enabling discrimination of the enantiotopic faces on the nucleophile. An enantiomeric excess (*ee*) of 86% was achieved for the alkylation of 2-methyl-1-tetralone with allyl acetate, but this protocol could also be expanded to some other substituted cyclohexanones.

This protocol was also employed in the synthesis of natural product hamigeran B.[14] To obtain the required configuration on the cyclopentene core, ligand **L1a** provided the required enantiomer with high *ee* (Scheme 7). This first stereogenic center controlled the formation of the two others during the further synthesis.

Another example of a tin enolate allylation was accomplished during Williams' synthesis of 7-hydroxyquinine (**3**).[15] Here, an allylic alkylation of a ketone enolate was used to form the bicyclic quinuclidine ring system (Scheme 8). The tin enolate was generated *in situ* from a silyl enol ether (**2**) using Bu_3SnF, which then reacted intramolecularly with an allyl benzoate forming the required ring system. Reduction of the resulting ketone and silyl ether cleavage afforded **3**.

2.3. Alkali Metal Enolates

The alkali metal enolates of ketones are readily obtained by deprotonation with nitrogen bases like NaHMDS, LHMDS or

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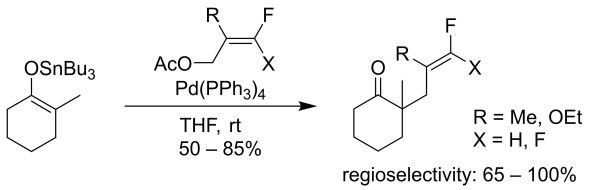
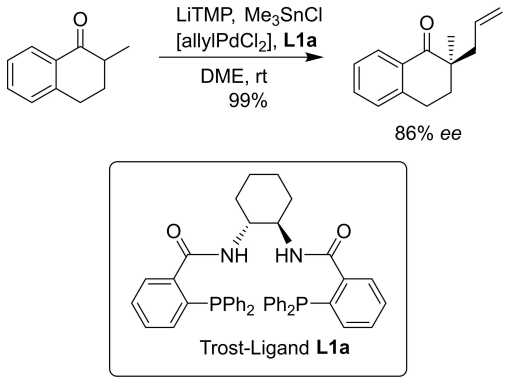
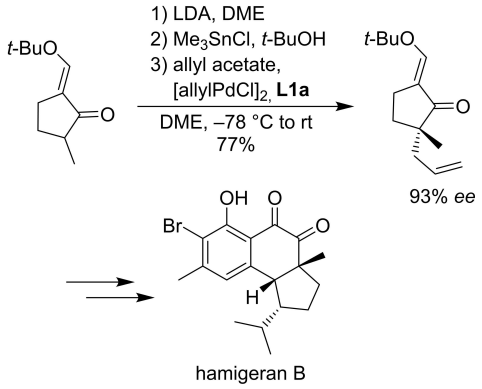
Uli Kazmaier studied chemistry at the University of Stuttgart where he obtained his PhD 1990 while working with U. Schmidt. Afterwards he joined the groups of M. T. Reetz (Marburg) and B. M. Trost (Stanford) as postdoctoral fellow. In 1992, he moved to Heidelberg, starting his own scientific work under the mentorship of G. Helmchen. In 2000, he received a Novartis Chemistry Lectureship and in 2001 an offer for a full professorship at Saarland University. His current research interest is focused on new organometallic reagents and reactions especially for amino acid and peptide synthesis, and their application to natural product synthesis.



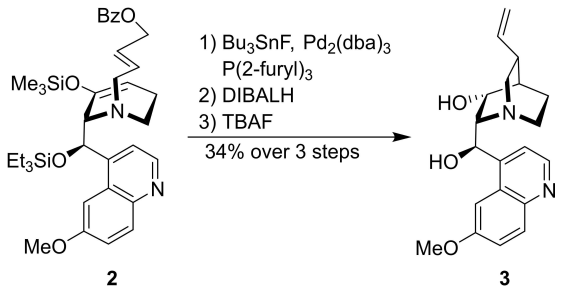
Scheme 5. Allylic alkylation of tin enolates with fluorinated allyl acetates.



Scheme 6. First example of an enantioselective ketone allylation.



Scheme 7. Asymmetric tin enolate allylation in the synthesis of hamigeran B.



Scheme 8. Intramolecular tin enolate allylation in the synthesis of 7-hydroxyquinine.

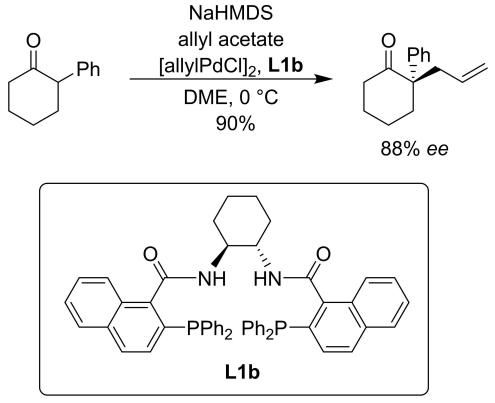
LDA. Due to the high electropositivity of Li and Na, these enolates are usually highly reactive. Since the emergence of catalytic systems comprised of highly elaborate ligands, these enolates can in some cases be tamed for allylic alkylations.

In 2002, Trost and coworkers reported the first asymmetric allylation of sodium enolates. 2-Aryl-cyclohexanones could be alkylated enantioselectively using ligand **L1b** (Scheme 9), which is similar to that previously employed for the allylation of tin enolates.[16]

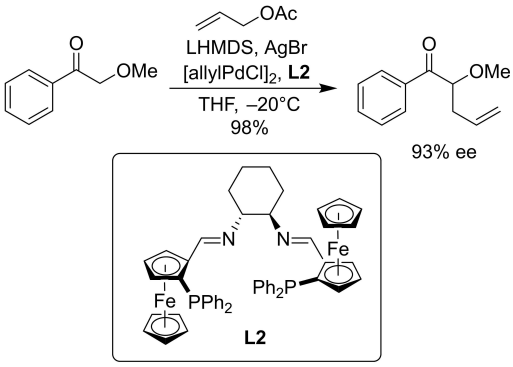
The group of Hou developed elaborate "chiral pocket" ligands (**L2**) for Pd-catalyzed allylations of cyclic ketones.[17] In 2005, they also reported their successful application in asymmetric allylations of linear ketones.[18] This method worked especially well on α-alkoxy substituted aryl ketones, and the addition of AgBr as Lewis acid improved the enantioselectivity of the reaction (Scheme 10).

Two years later, the enantioselective allylation of linear ketones without α-alkoxy substituents was reported by the same group using another ferrocene-based ligand **L3a** (Scheme 11).[19] For the allylic alkylation with cinnamyl carbonate, LHMDS was used as a base and LiCl as a Lewis acid additive. The branched products were obtained selectively, which is rather unusual for Pd catalyzed allylic alkylations. The same ligand was later on used for the allylic alkylation of α-fluorinated ketones.[20] In this case, NaOAc was the most beneficial additive. Furthermore, the protocol was used for the allylation of acyl silanes.[21]

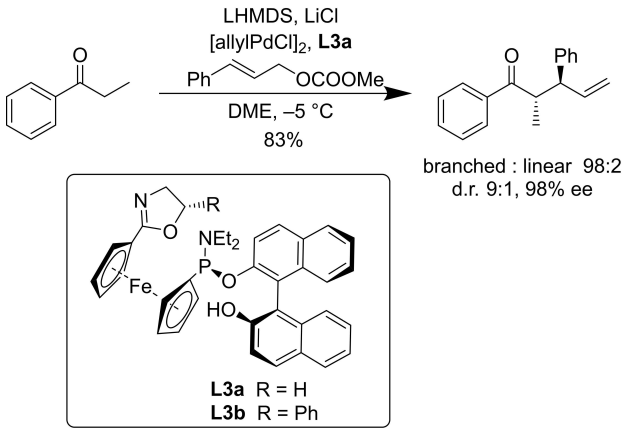
Based on the same ligand architecture, a kinetic resolution of lithium enolates derived from cyclic ketones was developed (Scheme 12).[22] When 2-substituted quinolones were reacted with allyl phosphate and the catalytic system of $[allylPdCl]_2$ and



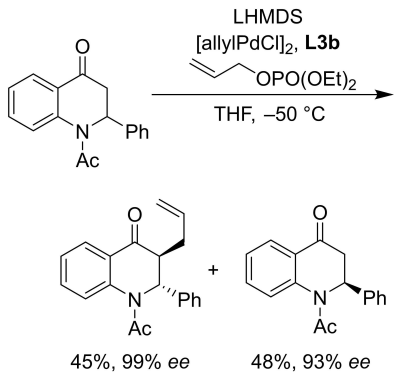
Scheme 9. Asymmetric allylic alkylation of 2-aryl cyclohexanones.



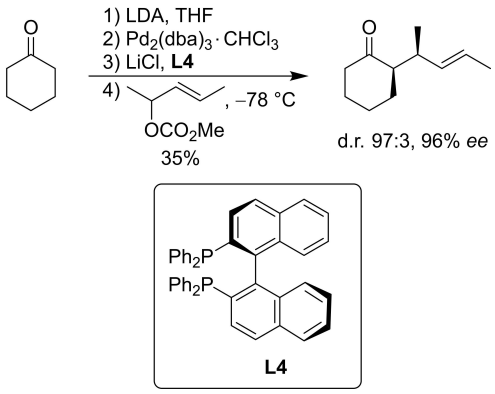
Scheme 10. Asymmetric allylic alkylation of α-alkoxy ketones.



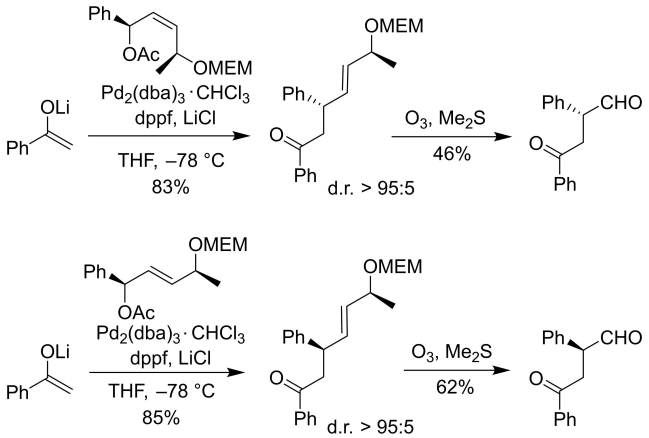
Scheme 11. Enantioselective allylic alkylation of acyclic lithium enolates.



Scheme 12. Kinetic resolution of quinolone derivatives.



Scheme 13. Stereoselective allylic alkylation of cyclohexanone.



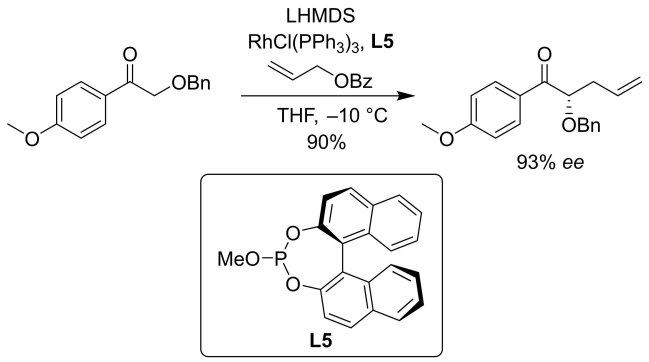
Scheme 14. Allylic alkylation of acetophenone with (*Z*) and (*E*) allylic acetates; dppf: 1,1′-bis(diphenylphosphino)ferrocene.

L3b at −50 °C, the (*R*)-enantiomer of the starting material was alkylated preferentially, leading to high yields and enantiomeric excesses in both the product and the remaining starting material. Allyl acetates and carbonates did not perform as well as the phosphates, possibly due to the low reaction temperature, since allylic phosphates tend to ionize at a lower temperature than esters or carbonates.

Braun and coworkers investigated the diastereo- and enantioselectivity of the allylic alkylation of cyclic Li ketone enolates.[23] Cyclohexanone was deprotonated with LDA and reacted with different allylic carbonates. For the allylation with a symmetrical carbonate, (*R*)-BINAP (**L4**) as a ligand delivered the highest enantio- and diastereoselectivities (Scheme 13). The procedure for this reaction was furthermore published in *Organic Syntheses*, which underlines its reproducibility and versatility.[23b,c]

For the allylation of the Li enolate of acetophenone, they used a more complex, enantiomerically enriched allylic substrate (Scheme 14),[24] and discovered that the stereochemical outcome of the reaction depended on the configuration of the double bond in the allylic substrates. While the (*Z*)-substrate reacted under total inversion (via double inversion and (*Z*)-(*E*)-isomerization), the (*E*) isomer reacted under a total retention (via double inversion) of the stereochemistry. The resulting products could then be converted to valuable 1,4-dicarbonyl compounds by ozonolysis.

Another example for the asymmetric allylic alkylation of α-alkoxy ketones was reported by Evans and coworkers.[25] They used monodentate phosphite ligand **L5** along with Wilkinson's catalyst, a Rh(I) complex (Scheme 15). Benzoates proved to be superior leaving groups compared to carbonates. When conducted at–10 °C, the allylation provided the allylated



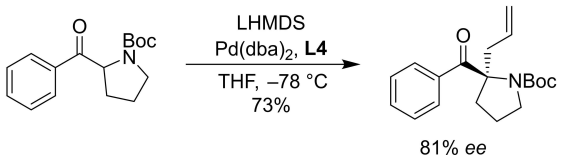
Scheme 15. Rh-catalyzed allylic alkylation of α-alkoxy ketones.

products with excellent enantioselectivities. Control experiments with configurationally fixed silyl enol ethers indicated that the (*Z*)-enolate is formed exclusively *via* chelation of the Li atom by the two oxygens of the α-alkoxyketone, thus resulting in the high selectivities.

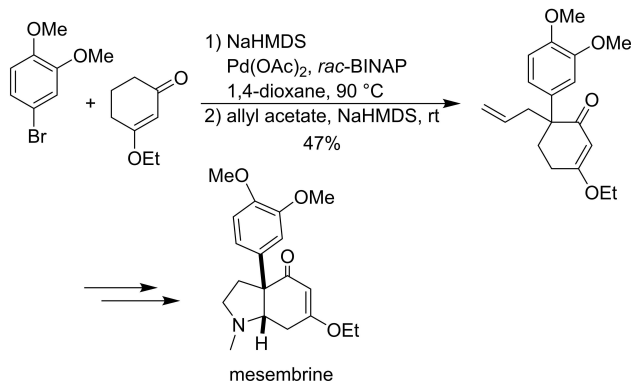
A study on silyl ether bearing allyl phosphates in the allylation of lithium ketone enolates showed that these substrates react regioselectively, while the position distal to the silyl ether oxygen is attacked preferentially in this reaction.[26]

Proline derived α-amino ketones are valuable precursors of natural products if they can be alkylated stereoselectively. Zhang *et al.* used these ketones to access 2,2-disubstituted pyrrolidine derivatives.[27] During their reaction optimizations, they noticed that LHMDS as a base in combination with a Boc *N*-protecting group led to the highest enantiomeric excesses in the products (Scheme 16). They attributed this effect to the preferential formation of the (*Z*)-enolate due to an interaction between Li^+ and the oxygen atoms of the enolate and the Boc group. Using (*R*)-BINAP **L4** as a ligand, an enantiomeric excess of up to 81% could be obtained.

The so far only example, in which an alkali metal enolate was used for the synthesis of a natural product was in the synthesis of mesembrine by Zhang *et al.*[28] The remarkable key step of the synthesis was a one pot Pd-catalyzed enolate arylation/allylation forming the connection between the aryl and cyclohexenone ring (Scheme 17). The enolate was first formed with NaHMDS and coupled to an aryl bromide. Then, another equivalent of NaHMDS was added along with allyl acetate resulting in 2,2-disubstitution of the ketone. However, no substantial enantiomeric excess could be obtained in this reaction. (±)-Mesembrine could be assembled in only 3 further steps.



Scheme 16. Allylic alkylation of proline derived ketones.



Scheme 17. Sequential enolate arylation and allylic alkylation for the synthesis of mesembrine.

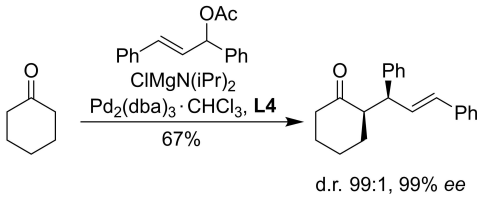
2.4. Alkaline Earth Metal Enolates

In 2000, Braun and coworkers described the diastereoselective allylic alkylation of cyclohexanone enolates with racemic, symmetrical allylic acetates.[29] During their optimization studies, they observed that the highest diastereoselectivity for the *syn* product could be obtained when the enolate was formed with $ClMgNiPr_2$. Using (*R*)-BINAP (**L4**) as a ligand, an enantiomeric excess of up to 99% could be obtained (Scheme 18). This represented the first application of a Mg ketone enolate in Pd-catalyzed allylic alkylations.

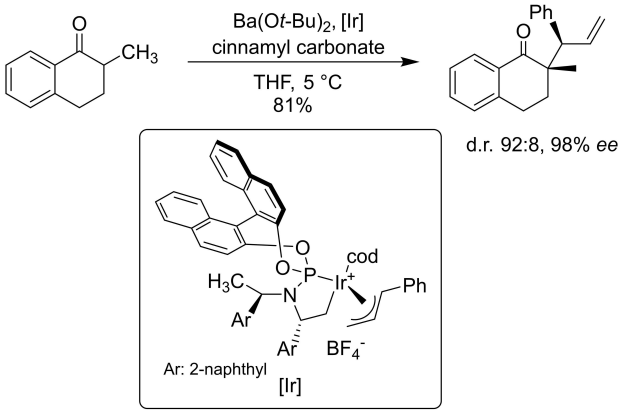
For the Ir-catalyzed allylic alkylation of cyclic ketone enolates, Hartwig *et al.* investigated different alkaline earth metal bases in the enolate formation step.[30] They could show that the highest diastereoselectivities and yields could be obtained when the enolates were formed with $Ba(Ot\text{-}Bu)_2$, thus providing the first application of barium enolates in allylic alkylations (Scheme 19). In their initial experiments, $[Ir(cod)Cl]_2$, phosphoramidite ligands and complex silver phosphates were used to optimize the reaction. To evaluate the effect of the silver salts, a preformed iridium complex [Ir] was used as a catalyst. Since the selectivities and yields were almost the same also without silver salts, the authors concluded that the silver salts only promote the formation of the catalytically active species.

2.5. Silyl Enol Ethers

Silyl enol ethers can be regarded as tamed versions of alkali metal enolates. In general, they can be isolated and are



Scheme 18. Diastereo- and enantioselective allylic alkylation of a Mg enolate.



Scheme 19. Ir-catalyzed allylic alkylation of barium enolates.

configurationally stable, however they are less nucleophilic and require additives or special catalytic systems to react smoothly in allylic alkylations.

The first application of silyl enol ethers derived from ketones was described by Tsuji in 1983 (see above, Scheme 4).[11] One of the advantages of silyl enol ethers is that the reaction conditions can in principal be maintained completely neutral, thus allowing a high functional group tolerance.

In a report from 1990, Pd on silica was used as a heterogenous catalyst system by Baba *et al.* for the allylic alkylations of silyl enol ethers.[31] However, this protocol was not suitable for stereoselective allylations.

The stereochemical outcome of the reaction can be controlled by neighboring groups, as described in the total synthesis of a vitamin D building block by Wicha *et al.*[32] They utilized a (*Z*)-configured allyl carbonate, which isomerized during the reaction to yield the (*E*)-configured allylated product (Scheme 20). The reaction proceeded diastereoselectively, delivering 90% of the desired *anti*-isomer.

Silyl enol ethers can also be allylated using Rh(I) catalysts. While symmetrical allyl substrates yield the desired allylated ketones in high yields, unsymmetrical substrates result in low regioselectivities and provide mixtures of linear and branched products.[33]

The first enantioselective allylation of cyclic silyl enol ethers was reported by Behenna and Stoltz in 2004.[34] They found that the phosphinooxazoline ligand **L6a** ((*S*)-*t*-Bu-PHOX) provided the highest enantiomeric excesses and yields of the allylated ketones (Scheme 21). $Bu_4N^+Ph_3SiF_2^-$ (TBAT) was used in substochiometric amounts as an initiator of the reaction.

This protocol was broadly used in different applications, e.g. in the allylation of fluorinated cyclic silyl enol ethers.[35] Since the enantiomeric excesses of the products ranged from 83 to 92% with **L6a** as ligand, novel phosphinooxazoline ligands were also developed for the allylation of fluorinated silyl enolates.[36]

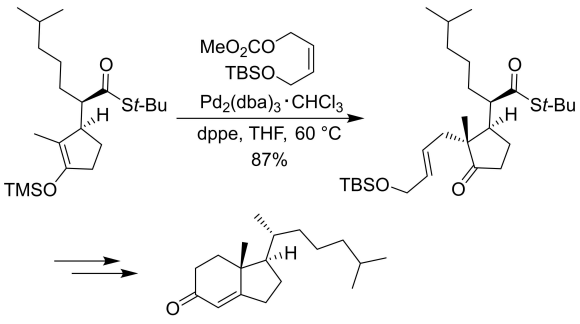
In order to apply the asymmetric allylic alkylation to α-hydroxy carbonyl compounds, Stoltz *et al.* made use of 1,4-dioxanone enol ethers.[37] Since the enolate geometry is fixed in these cyclic silyl enolates and the rest of the molecule is also conformationally locked, high enantioselectivities could be obtained (Scheme 22). The allylated products could further be modified to yield, for example, α-hydroxy β,γ-unsaturated esters.

This method was further used to generate a highly substituted cyclopentenol derivative (Scheme 23).[38] This building block was later used as a precursor for synthetic approaches towards polycyclic diterpenes like inelangolide.[39] Furthermore, the same approach was used for the synthesis of (+)-eucomic acid.[40]

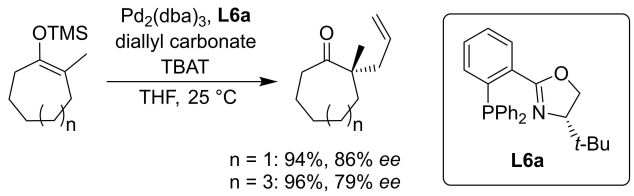
The asymmetric silyl enol ether allylation was also applied in the synthesis of the marine sesquiterpenoides drechslerine A and B by Stoltz *et al.*.[41] The silyl enol ether **4** could be allylated with ligand **L6a** leading to an excellent diastereoselectivity. Further steps including cyclization gave access to drechslerine A and B, respectively (Scheme 24).

For the synthesis of antiviral agents, Oguri *et al.* utilized a silyl enol ether allylation followed by a thermal Cope rearrangement to generate densely substituted tetrahydropyridines (Scheme 25).[42] In this case, 1,2-bis(diphenylphosphino)benzene (dppbz) was used as a bidentate ligand.

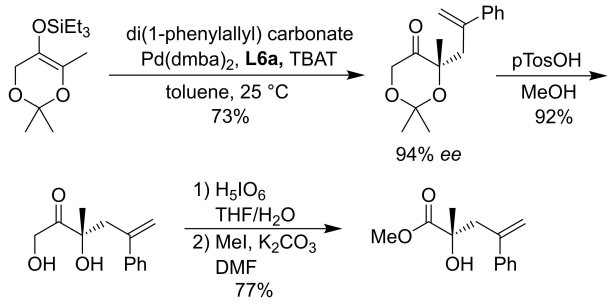
Iridium catalyzed allylic alkylations have the advantage that (in contrast to Pd) they provide the branched products preferentially in most cases. In the reaction of the silyl enolate



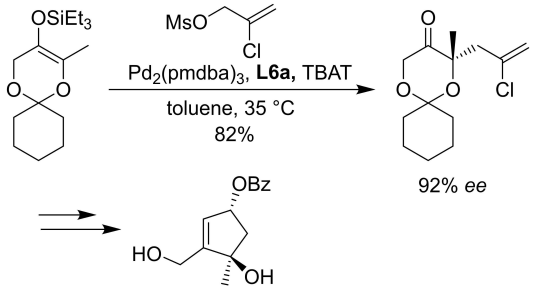
Scheme 20. Silyl enol ether allylation for the synthesis of vitamin D building blocks.



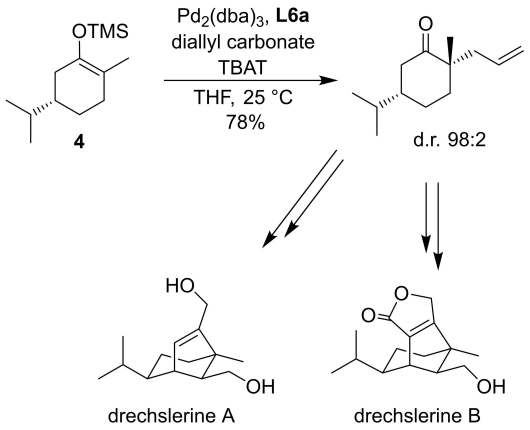
Scheme 21. First example of enantioselective silyl enol ether allylation.



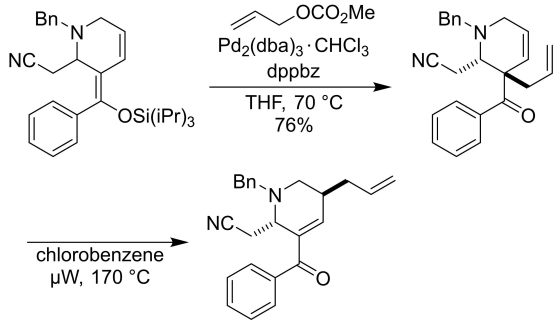
Scheme 22. Application of enantioselective silyl enol ether allylation for the synthesis of α-hydroxyesters; dmba: bis(3,5-dimethoxybenzylidene)acetone.



Scheme 23. Enantioselective silyl enol ether allylation followed by synthesis of a complex cyclopentenol derivative; pmdba: 4,4′- methoxydibenzylideneacetone.



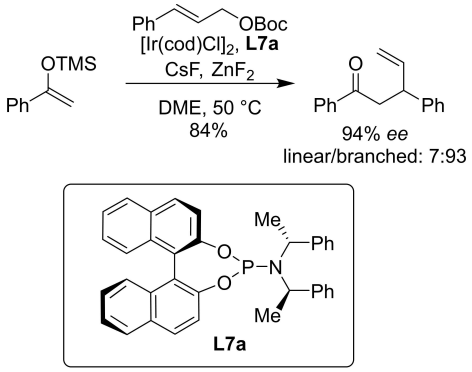
Scheme 24. Application of enantioselective allylation for the synthesis of drechslerines A and B.



Scheme 25. Silyl enol ether allylation followed by cope rearrangement to afford densely functionalized tetrahydropyridines.

of acetophenone with cinnamyl carbonate, the branched product was obtained selectively using $[Ir(cod)Cl]_2$ in the presence of CsF and ZnF_2, as described by Hartwig *et al.* (Scheme 26).[43] The fluoride additives seem to assist in the formation of the catalytically active species. Ligand **L7a** provided the highest enantioselectivities.

For the Ir-catalyzed allylic alkylation of silyl enolates derived from α,β-unsaturated ketones, Chen and Hartwig used $[Ir(cod)_2Cl]_2$ in combination with ligand **L7a**.[44] The optimal fluoride additive in this case was KF in combination with crown

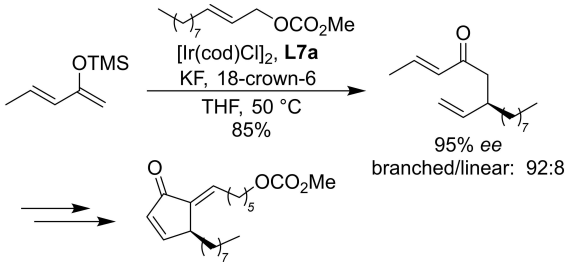


Scheme 26. Ir-catalyzed allylation of silyl enol ethers.

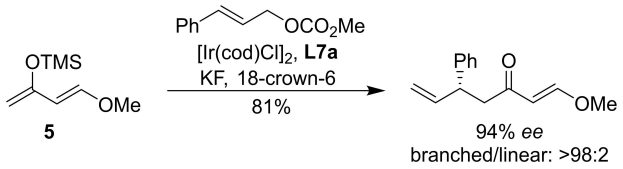
ether. Also here, the branched products were obtained selectively (Scheme 27). This protocol was also applied in a short total synthesis of a prostaglandin derivative.

Chen and Hartwig later expanded this protocol to silyl enol ethers derived from vinylogous esters and amides.[45] For example, Danishefsky's diene **5** could be allylated enantioselectively using different allylic carbonates under Ir-catalysis with the branched products being formed selectively (Scheme 28). KF apparently activates the catalyst by forming an active iridacyclic complex. In addition, the silyl enol ethers seem to be activated by the alkoxide released from the allylic carbonates.

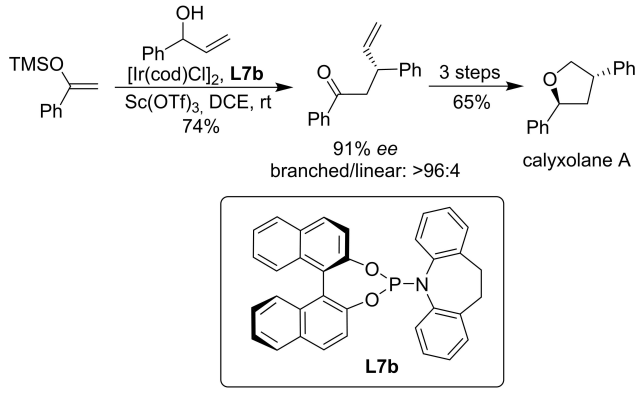
Yang *et al.* described the Ir-catalyzed allylic alkylation of silyl enol ethers using allylic alcohols instead of carbonates (Scheme 29).[46] With ligand **L7b** and $Sc(OTf)_3$ as a promoter, the branched products could be obtained in good yields and excellent enantioselectivities. In addition, this protocol was applied in the synthesis of all four diastereomers of calyxolanes A and B, confirming also the absolute configuration of calyxolane A.



Scheme 27. Ir-catalyzed allylation of α,β-unsaturated silyl enol ethers.



Scheme 28. Ir-catalyzed allylation of silyl enol ethers derived from a vinylogous ester.



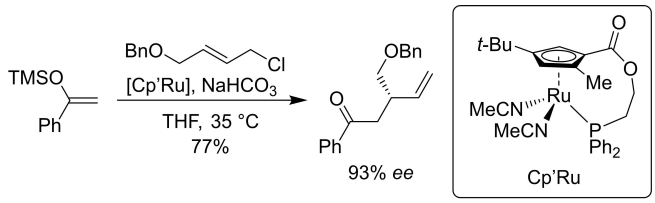
Scheme 29. Ir-catalyzed allylation of silyl enol ethers with allylic alcohols and synthesis of calyxolane A.

The allylic alkylation of silyl enol ethers can also be accomplished with planar chiral Ru complexes. Kanbayashi *et al.* reported that the silyl enolate derived from acetophenone could readily be reacted with substituted allylic chlorides to yield the branched products selectively.[47] The planar chiral Ru complex Cp'Ru provided products with up to 93% *ee* (Scheme 30).

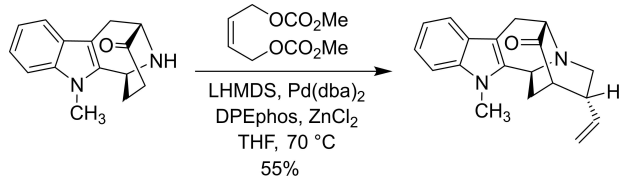
2.6. Zinc Enolates

In general, zinc enolates of esters and amides are considered to be less reactive than their lithium counterparts.[48] The group of Kazmaier has been involved in the development of different methods involving zinc enolates of amino acid esters or amides. These are suitable nucleophiles for various standard enolate reactions, but also transition metal-catalyzed allylic alkylations.[49]

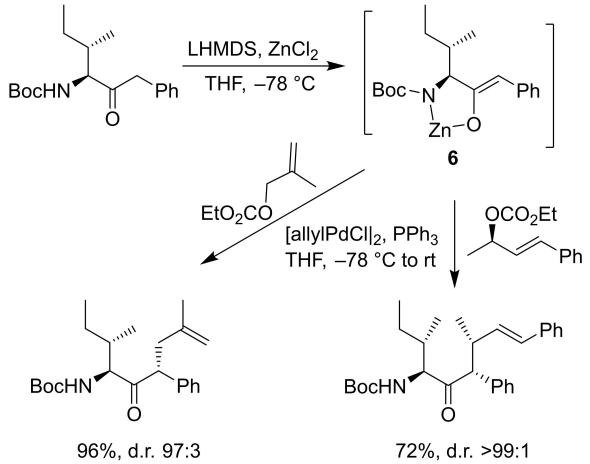
The first examples of allylic alkylations of zinc ketone enolates were reported by Cook *et al.* in 2007 in the synthesis



Scheme 30. Ru-catalyzed asymmetric silyl enol ether allylation.



Scheme 31. Construction of the quinuclidine core of neosarpagine *via* combined *N*- and ketone allylation.



Scheme 32. Allylic alkylation of chelated amino ketone Zn-enolates.

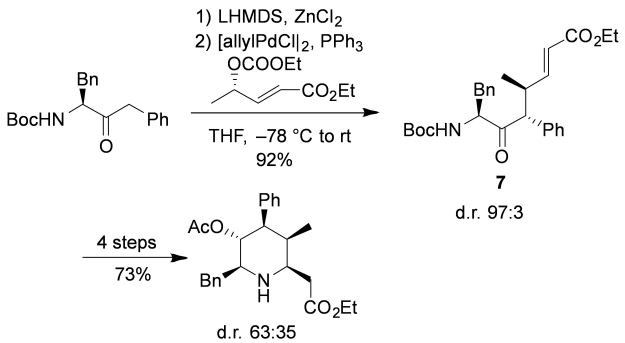
Chiral α-amino ketones can easily be obtained from proteinogenic amino acids. Kazmaier *et al.* investigated the allylic alkylation of these species.[51] When these ketones are deprotonated with LHMDS in the presence of $ZnCl_2$, probably chelated exocyclic (*Z*)-enolates such as **6** are formed almost exclusively, avoiding 1,3-allyl strain between the phenyl group and the sidechain of the amino acid (Scheme 32). Most likely, in these enolates one diastereotopic face of the nucleophile is shielded by the side chain, explaining the excellent stereoselectivities (>97%) observed in their reactions.

Recently, this method was extended to allylic substrates bearing electron withdrawing groups like ester or nitrile groups, allowing subsequent cyclizations *via* 1,4-addition.[52] The resulting ketones **7** were subjected to a sequence of ketone reduction, *N*-deprotection and Michael-type addition furnishing highly substituted piperidines and homopipecolic acid derivatives, respectively (Scheme 33).

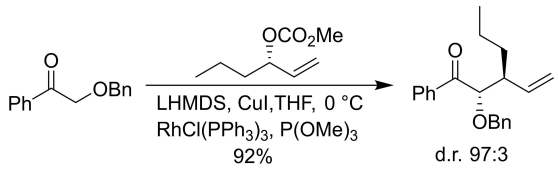
2.7. Copper Enolates

Cu(I) enolates generated *via* transmetalation of Li enolates have only rarely been used in allylic alkylations. Evans and Leahy first reported on the Rh-catalyzed allylic alkylation of ketone Cu(I) enolates in 2003.[53] In this initial study, different allylic carbonates were used for the allylation of acetophenone.

In a follow up study, they investigated the diastereoselectivities in allylic alkylations of α-benzyloxy acetophenone.[54] Using Wilkinson's catalyst and $P(OMe)_3$ as a ligand, the *anti* products were favored in all cases (Scheme 34). The authors postulated that, in analogy to the zinc enolates, a chelation of the α-alkoxy ketone by Cu(I) takes place, thus fixing the enolate geometry resulting in the high diastereoselectivities observed.



Scheme 33. Allylic alkylation of chelated amino ketones and transformation into homopipecolic acid.



Scheme 34. Rh catalyzed allylic alkylation of Cu(I) enolates.

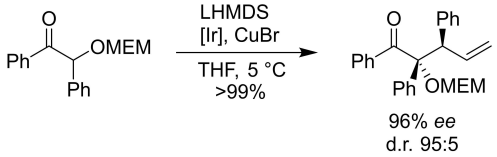
An Ir-catalyzed asymmetric allylic alkylation of copper (I) enolates was described by Hartwig *et al.* in 2016.[55] They reported that for the allylation of α-methoxy ketones, Cu(I) salts as additives yielded the best diastereoselectivities. Preformed iridium complex [Ir] (Scheme 19) was used for the allylation and the branched products were obtained selectively. Next to α-methoxy ketones, also MOM, MEM or PMB protected α-hydroxy ketones gave good results (Scheme 35). The allylated products are valuable precursors of densely substituted tetrahydrofurans.

3. Decarboxylative Allylic Alkylations

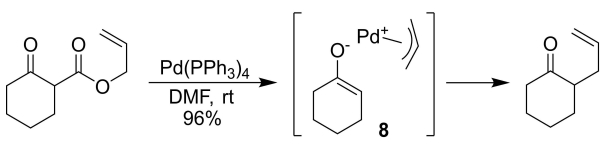
3.1. Decarboxylative Allylic Alkylations of Cyclic Ketones

The first examples for the decarboxylative allylic alkylation of ketones were described already in 1980 by the groups of J. Tsuji and T. Saegusa independently.[56] They investigated the Pd-catalyzed decarboxylative rearrangement of allyl β-ketoesters (Carroll rearrangement), which resulted in the α-allylated ketones. Saegusa *et al.* obtained the best yields for this reaction using cyclic ketones (Scheme 36),[56b] whereas Tsuji and co-workers also reported on the successful allylation of linear ketones.[56a] Both teams proposed Pd-allyl enolate complexes such as **8** as intermediates, which readily generate the allylated ketone.

The second approach for the decarboxylative allylation, introduced by Tsuji *et al.* in 1983, makes use of allyl enol carbonates.[57] When cyclohexanone was reacted with KO*t*-Bu and allyl chloroformate, allyl 1-cyclohexenyl carbonate (**9**) was obtained *via*



Scheme 35. Ir catalyzed allylic alkylation of Cu(I) enolates.



Scheme 36. First example of a decarboxylative allylic alkylation.

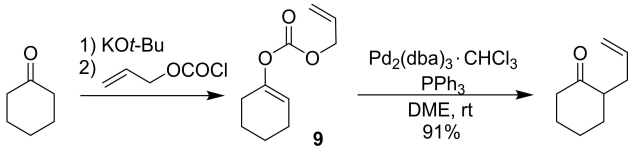
O-acylation (Scheme 37). When **9** was reacted in the presence of catalytic amounts of $Pd_2(dba)_3{\cdot}CHCl_3$ and PPh_3, the α-allylated cyclohexanone was formed. The reaction most likely proceeds *via* the same intermediate **8** as in the previous example. These two methods thus present different ways to accomplish the decarboxylative allylation of ketones, the main difference is the preparation of the starting material. While β-ketoesters can in general by synthesized by Claisen condensation, the allyl carbonates are prepared from the corresponding ketone and a chloroformate (Scheme 37).

In a follow-up study, Tsuji *et al.* could prove that the reaction proceeds *via* Pd-π-allyl complexes and not *via* a concerted rearrangement.[58] Therefore, asymmetric allylations were not a trivial issue until the development of chiral ligands.

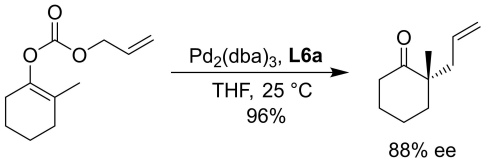
In 2004, the first enantioselective protocol for the decarboxylative allylic alkylation of ketones was described by Stoltz and Behenna, who used *t*-BuPHOX (**L6a**), a ligand previously successfully applied for the allylation of cyclic silyl enol ethers (Scheme 21).[34] The enol carbonate derived of 2-methylcyclohexane was used to optimize the reaction (Scheme 38), but the protocol was only applied to enol carbonates derived from cyclic ketones. The detailed protocol was later also described in an *Organic Syntheses* article and discussion addendum.[34b,c] In addition, it could be shown that the same ligand also performs well in the decarboxylative allylic alkylation of α-fluoroketones.[59]

Quantum chemistry calculations by Goddard *et al.* suggested, that the reaction proceeds via an inner-sphere mechanism and not through an external attack of the nucleophile onto the Pd-allyl electrophile, which is commonly observed for "soft" nucleophiles.[60] Stoltz and coworkers further identified complex **10** (Figure 1) as a plausible resting state intermediate of the reaction.[61] This complex probably is formed *via* oxidative addition, but before decarboxylation. Interestingly, this square planar Pd complex contains a η^1-allyl ligand bound *trans* to the nitrogen atom, which is in contrast to the generally observed η^3-π-allyl-Pd-complexes.

Extensive DFT calculation studies provided further insight into the reaction mechanism.[62] Most likely, a η^3-π-allyl complex is formed first, which then rearranges to complex **10**. This



Scheme 37. Decarboxylative allylic alkylation of an allyl enol carbonate.



Scheme 38. Enantioselective decarboxylative allylic alkylation of an allyl enol carbonate.

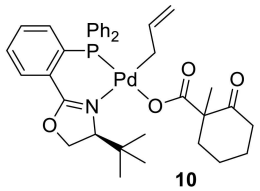


Figure 1. Isolable intermediate Pd-complex.

rearrangement might be the enantio-determining step of the reaction. A non-traditional reductive elimination via a seven-membered cyclic transition state finally forms the C–C bond.

A comprehensive overview over mechanistic studies on decarboxylative allylic alkylations was given by Guiry *et al.* in a recent review article from 2019.[63]

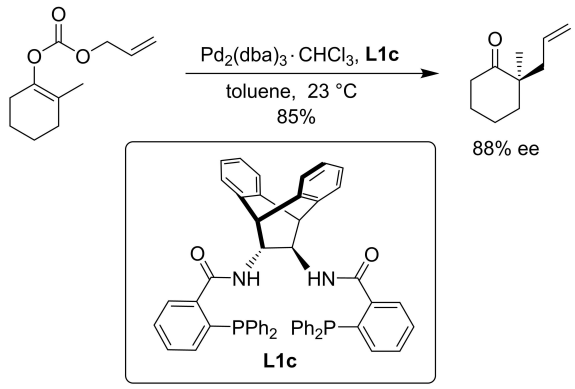
In 2005, Trost and Xu reported on the use of ligand **L1c** in the decarboxylative allylation of cyclic ketones.[64] In this reaction, ligand **L1c** seemed to be superior to the previously applied **L1a**, resulting in enantiomeric excesses ranging from 76% to more than 99% (Scheme 39). Interestingly, the configuration of the newly formed stereogenic center was opposite to that obtained with tin enolates and **L1a** (Scheme 6). For acyclic enol carbonates such as that derived from propiophenone, a solvent switch to dioxane led to the best yields and enantioselectivities.[65]

McFadden and Stoltz used the same protocol in the total synthesis of terpenoid natural product (+)-dichroanone (Scheme 40).[66] The quaternary stereogenic center in **11** could be generated enantioselectively (91% *ee*) using $Pd_2(dba)_3$/**L6a**. Nine further transformations were required to complete the synthesis. The enantiomer of **11** could be prepared using ligand ***ent*-L6a** and was used in the total synthesis of (+)-Liphagal in 2011.[67]

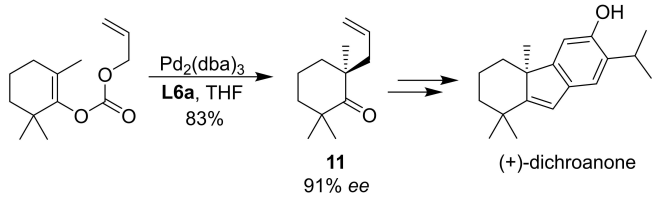
For the synthesis of diterpenoid (−)-cyanthiwigin F, Enquist and Stoltz presented the first stereoablative double alkylation of bis(β-ketoester) **12** (Scheme 41).[68] A 1:1 mixture of racemic and *meso* diasteromers of **12** were converted into the (*R,R*) isomer of **13** diastereo- and enantioselectively by $Pd(dmba)_2$/**L6a**. Since in this double ketone allylation two of the three stereogenic centers of the natural product were formed, the synthesis of (−)-cyanthiwigin could be completed in only six further steps. The same approach was later used by Stoltz *et al.* for the construction of the gagunin diterpenoid carbocyclic backbone.[69] A few years later, the double allylic alkylation was optimized for scale-up, providing 1,4-diketone **13** in multigram quantities.[70]

The decarboxylative allylic alkylation of a cyclohexanone-derived β-ketoester with ligand **L6a** was also used by Zhu *et al.* for the total synthesis of several monoterpene indole alkaloids.[71] Among others, (−)-scholarisine G could be constructed from the allylated product **14** in nine synthetic steps (Scheme 42).

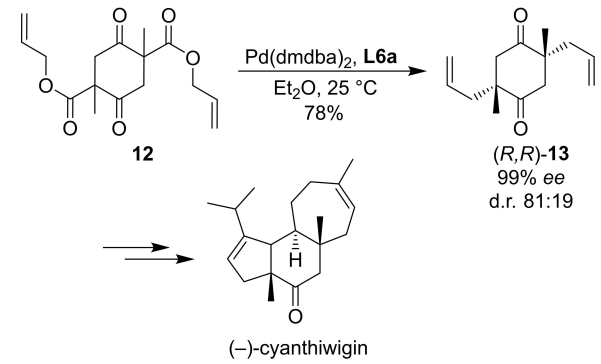
An interesting approach towards cyclohepta-1,4-diones was developed by Blechert and Schulz.[72] They used a tandem reaction consisting of fragmentation and decarboxylative allylic alkylation to transform bicyclo[3.2.0]heptan-2-ones to cycloheptane-1,4-diones (Scheme 43). The reaction proceeded *via* a DeMayo-type fragmentation, forming the enolate of cycloheptane-1,4-dione, which was trapped by a Pd-allyl complex. Enantioselectivity could be introduced into the reaction with ligand **L6a**.



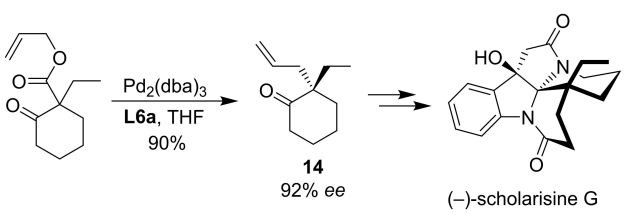
Scheme 39. Cyclic allyl β-ketocarboxylates in asymmetric decarboxylative allylic alkylation.



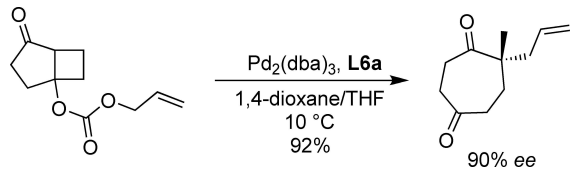
Scheme 40. Decarboxylative allylic alkylation for the total synthesis of (+)-dichroanone.



Scheme 41. Double allylic alkylation for the total synthesis of (−)-cyanthiwigin.



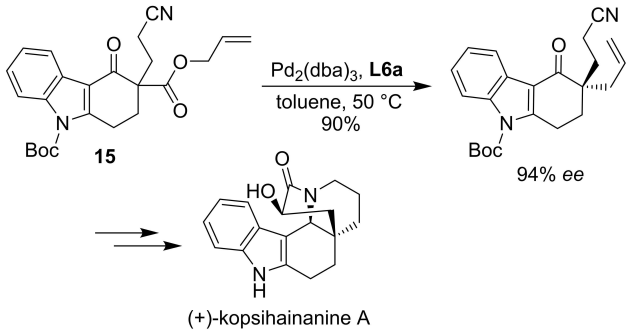
Scheme 42. Decarboxylative allylic alkylation for the total synthesis of (−)-scholarisine G.



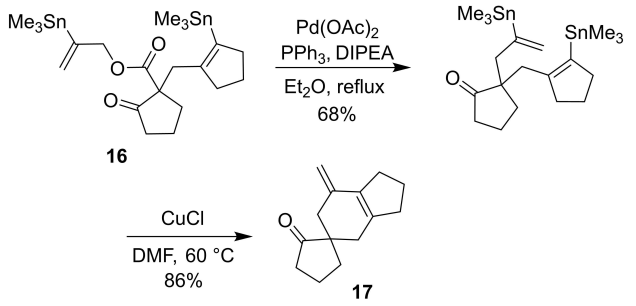
Scheme 43. Asymmetric ring-expanding allylic alkylation.

For the formal synthesis of (+)-kopsihainanine A, Gartshore and Lupton utilized the decarboxylative allylic alkylation of a carbazolone derived, cyanoethyl-substituted β-ketoester **15**.[73] Using **L6a**, the all-carbon quaternary stereogenic center could be constructed efficiently in the key step of the synthesis (Scheme 44).

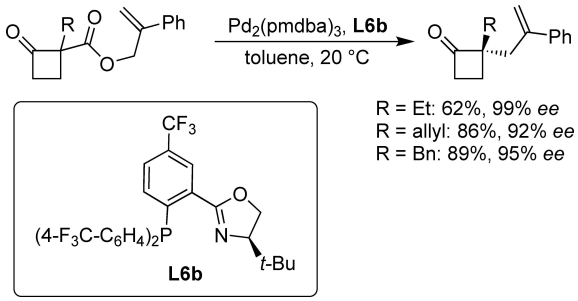
Although organotin compounds readily react in Pd(0)-mediated cross couplings, they are stable under the conditions



Scheme 44. Decarboxylative allylic alkylation of a carbazolone for the formal synthesis of (+)-kopsihainanine A.



Scheme 45. Decarboxylative allylation of stannylated β-ketoesters..



Scheme 46. Decarboxylative allylic alkylation of cyclobutanones.

used for allylic alkylations. Especially 2-stannylated allylic compounds were shown to be useful in the synthesis of various complex structures.[74] Piers and Romero showed that (2-trimethylstannyl)allyl β-keto esters can also be used for decarboxylative allylic alkylations.[75] When distannylated substrate **16** was used, the product could be cyclized with CuCl to yield spirocyclic compound **17** (Scheme 45).

In 2013, Stoltz *et al.* expanded the decarboxylative allylic alkylation to cyclobutanone-derived β-ketoesters.[76] They observed a positive effect of electron-deficient ligand **L6b** on the enantioselectivity. Different substrates were successfully transformed using this new protocol with enantiomeric excesses ranging from 86 to 99% (Scheme 46).

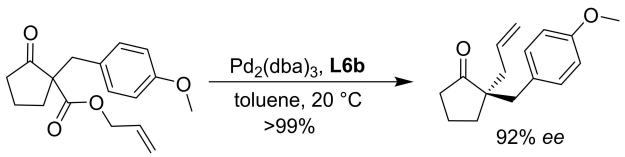
Analogously, ligand **L6b** provided the best result for the decarboxylative allylic alkylation of cyclopentanones (Scheme 47).[77] The α-quaternary ketones could be obtained in excellent yields and enantiomeric excesses. This protocol proved to be especially suited for the allylic alkylation of α-alkyl or α-benzyl cyclopentanones.

In 2015, Stolz *et al.* reported on the asymmetric allylic alkylation of cyclic Mannich adducts.[78] They found that **L6b** again led to the highest enantioselectivities. For example, a 4-piperidone derivative **18** could be transformed into the α-quaternary, allylated ketone in good yield and enantioselectivity (Scheme 48).

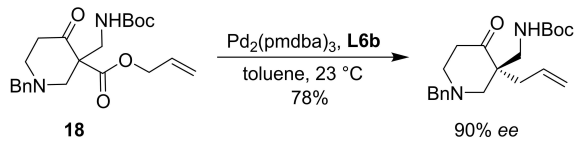
Guiry and coworkers observed that Stoltz's protocol for the allylic alkylation of cyclopentanones is not well suited for α-aryl substituted ketones.[79] After screening several ligands for the reaction, Trost's ligand **L1c** was found to deliver the best enantioselectivities (83% to >99.9% *ee*). Furthermore, they showed the utility of the protocol by providing a formal synthesis of (+)-tanikolide (Scheme 49).

Ligand **L6b** also proved to be beneficial in the decarboxylative allylic alkylation of nitrogen containing heterocyclic ketones.[80] Furthermore, Stoltz and coworkers used it for the allylic alkylation of tetralone derivative **19** in the total synthesis of hamigeran B (Scheme 50).[81]

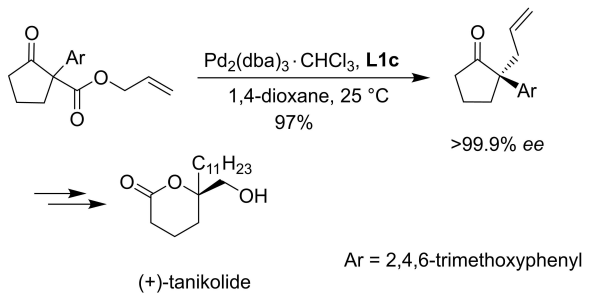
In order to improve the functional group compatibility of the method, Stoltz and coworkers developed a new protocol for an intermolecular allylic alkylation with decarboxylative enolate generation.[82] β-Ketoesters or enol carbonates are



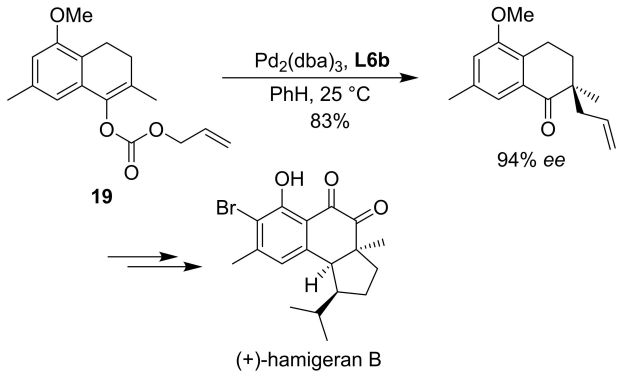
Scheme 47. Decarboxylative allylic alkylation of cyclopentanones.



Scheme 48. Decarboxylative allylic alkylation of β-aminoketones.



Scheme 49. Decarboxylative allylic alkylation of α-aryl cyclopentanones and formal synthesis of (+)-tanikolide.



Scheme 50. Decarboxylative allylic alkylation of and formal synthesis of (+)-hamigeran B.

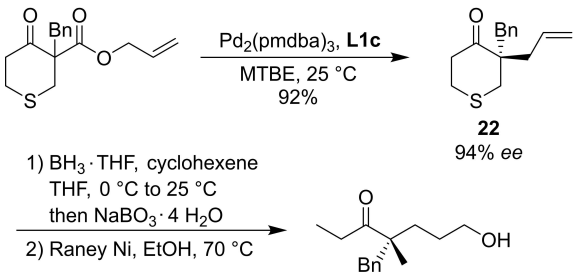
generally synthesized by the use of strong bases and the corresponding electrophiles, which is not compatible with all functional groups. An alternative is the application of 2-(trimethylsilyl)ethyl (TMSE) β-ketoester **20**, a fluoride source such as $Bu_4N^+Ph_3SiF_2^-$ (TBAT), and allylic carbonates. Under these conditions also complex and configurational labile allylic substrates such as **21** can be used (Scheme 51).

In 2017, Stoltz et al. described the decarboxylative allylic alkylation of thiopyranones, which can serve as precursors of linear, α,α-disubstitued ketones.[83] For this reaction, the PHOX ligands **L6a** and **L6b** led to little or no product formation. The allylation could however be optimized using Trost's ligand **L1c**. To illustrate the utility of this protocol, thiopyranone **22** was transformed into an acyclic ketone via hydroboration/oxidation and subsequent desulfurization with Raney Ni (Scheme 52).

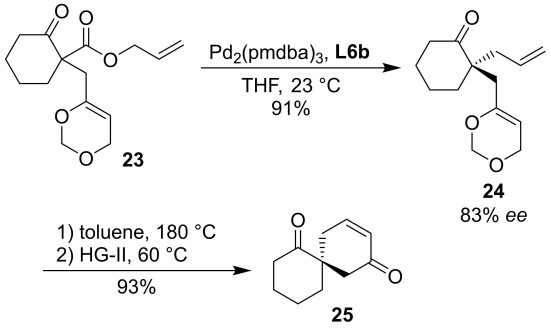
For the synthesis of spirocycles, a 4*H*-1,3-dioxin moiety **23** was used as a surrogate for a vinyl ketone.[84] Allylated product **24** could be converted into spirocycle **25** in excellent yield via thermal cleavage of the dioxin moiety followed by ring closing metathesis using Hoveyda-Grubbs II catalyst (HG-II) (Scheme 53).[85]

For the formal synthesis of (−)-platencin, Stoltz and co-workers used a cyclohexanone-derived β-ketoester for the construction of the quaternary center via decarboxylative allylation, followed by cyclization in order to build the bicyclic framework of the natural product.[86]

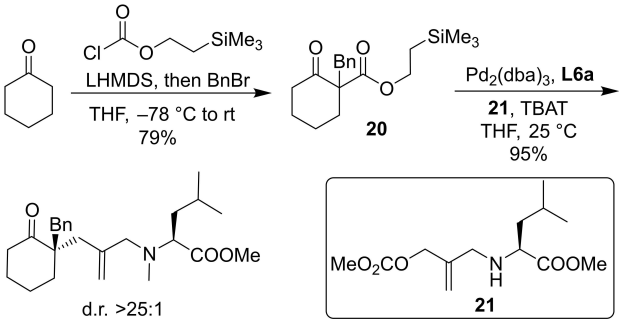
In the comparable synthesis of nigelladine A, application of ligand **L6b** generated the quaternary stereogenic center present in the natural product (Scheme 54).[87] Remarkably, the last step of the synthesis, an allylic C–H oxidation, was catalyzed



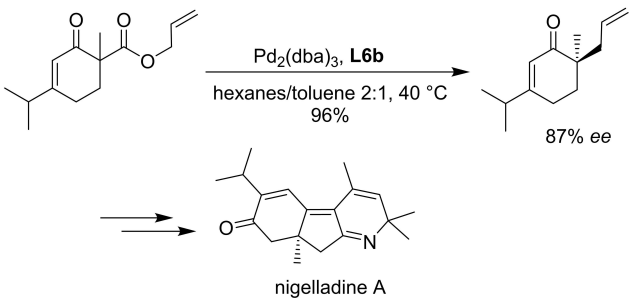
Scheme 52. Decarboxylative allylic alkylation of thiopyranones and follow-up chemistry.



Scheme 53. Decarboxylative allylic alkylation for the synthesis of spirocycles.



Scheme 51. Decarboxylative allylic alkylation of TMSE-β-ketoesters.



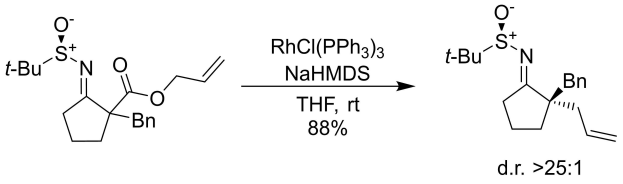
Scheme 54. Decarboxylative allylic alkylation for the synthesis of nigelladine A.

by a mutant P450 enzyme, which was optimized for allylic oxidations.

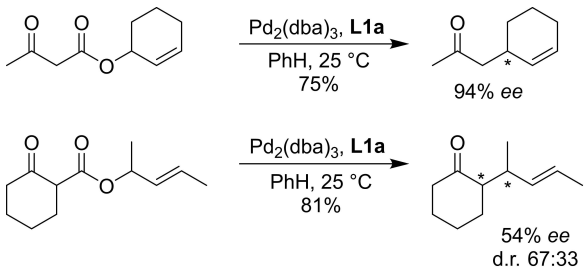
Recently, Liu *et al.* reported a protocol for the decarboxylative allylic alkylation of chiral sulfinimines, which can be transformed to the corresponding ketones.[88] This auxiliary-based protocol made use of Wilkinson's catalyst and delivered the allylated products diastereoselectively (Scheme 55). Since the chiral sulfinimine guides the attack of the electrophile, chiral ligands are not necessary in this case.

3.2. Decarboxylative Allylic Alkylations of Acyclic Ketones

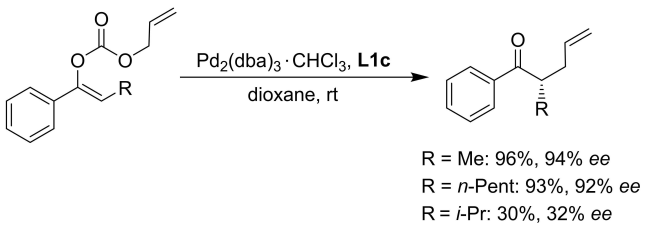
In general, the stereoselectivity of the allylic alkylation of cyclic ketone enolates is easier to control than in the case of acyclic ketones, mostly because of their conformational flexibility. The first report about the enantioselective decarboxylative allylic alkylation of acyclic ketones was published in 2004 by Tunge and Burger.[89] Remarkably, this work was published only a few days prior to Behenna's and Stoltz' work on asymmetric decarboxylative allylations (Aug. 27 vs. Sept. 13, 2004).[34a] They used Trost's ligand **L1a** for the asymmetric allylation of allyl β-ketocarboxylates. Remarkably, enolates of linear ketones, such as acetone, performed better in this reaction than cyclic enolates (Scheme 56).



Scheme 55. Diastereoselective decarboxylative allylic alkylation of chiral sulfinimines.



Scheme 56. Asymmetric decarboxylative allylic alkylation of allyl β-ketocarboxylates.



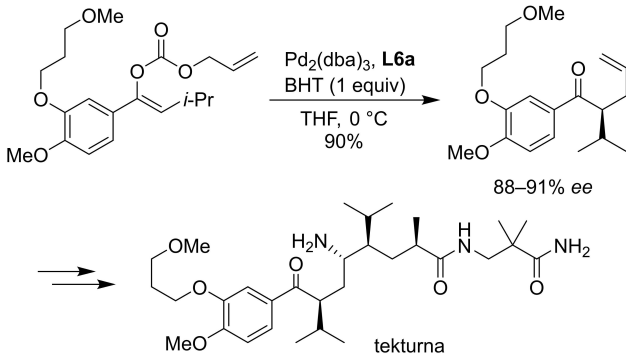
Scheme 57. Decarboxylative allylation of acyclic phenyl ketones.

Additional studies on acyclic phenyl ketones were reported by Trost and coworkers in 2009.[90] Again, anthracene-derived ligand **L1c** was found to be the superior one in this allylation (Scheme 57). They observed that phenyl ketones bearing linear alkyl residues R led to the best results regarding yields and enantioselectivities. However, when isobutyl phenyl ketone (R = *i*Pr) was used, the yield and enantioselectivity dropped significantly.

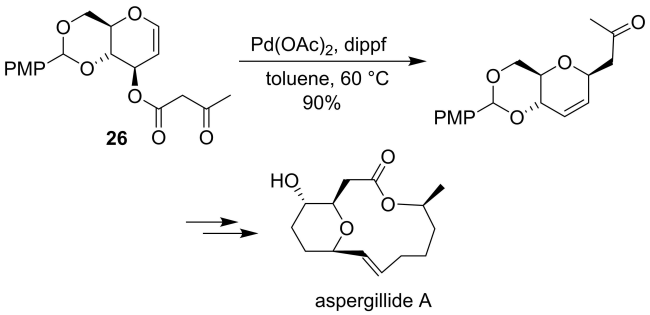
Stoltz *et al.* reported diminished yields and enantioselectivities in the allylic alkylations of acyclic ketones using their PHOX ligand **L6a**.[91] Hanessian and Chénard encountered the same problems for the allylic alkylation of a challenging isobutyl ketone in their synthesis of tekturna, a peptidomimetic renin inhibitor.[92] During reaction optimization they found that protic additives, especially 2,6-di-*tert*-butyl-*p*-cresol (BHT) accelerated the reaction significantly and led to enantiomeric excesses of 88% to 91% in the desired product (Scheme 58). The authors also noted a positive effect of the two alkoxy groups present in the aryl group of the substrate.

Liu *et al.* investigated the decarboxylative allylic alkylation of sugar derived acetoacetate **26** to provide a new way for β-C-glycosylations (Scheme 59).[93] They found that bis(diisopropylphosphino)ferrocene (dippf) as a ligand had a positive effect on the yield and diastereoselectivity of the reaction, and the β-isomer could be obtained as a single diastereomer. Furthermore, they could show that the product of the alkylation is a valuable precursor for the synthesis of aspergillide A.

Similar cyclic allylic substrates were used in the synthesis of decytospolides A and B as well as (±)-centrolobine.[94] The allylic



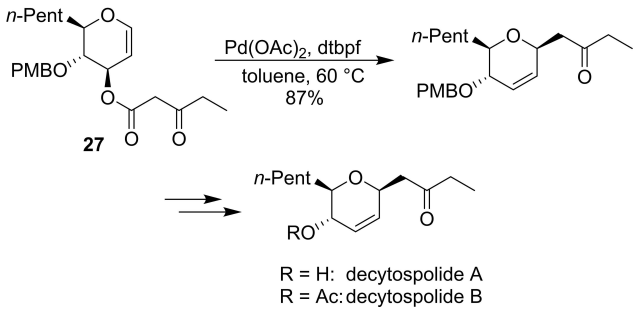
Scheme 58. Decarboxylative allylation of an acyclic aryl ketone.



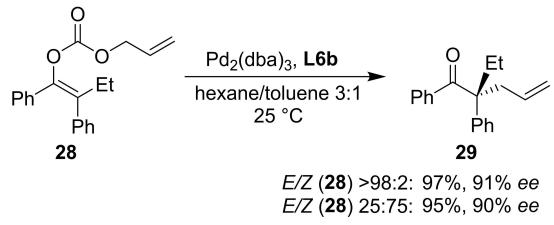
Scheme 59. Decarboxylative allylation of sugar derived acetoacetates for the formal synthesis of aspergillide A.

alkylation of precursor **27** was accomplished with $Pd(OAc)_2$ and 1,1′-bis(di-*tert*-butylphosphino)-ferrocene (dtbpf), yielding the 2,6-*cis* dihydropyrane selectively (Scheme 60). Only two further transformations afforded the natural product decytospolide A, which was acetylated to obtain decytospolide B.

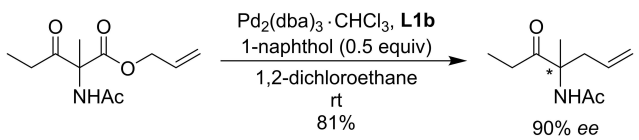
Enolate geometry is believed to be an important factor in the asymmetric allylic alkylation of acyclic ketones. In 2018, Stoltz *et al.* described a protocol for the synthesis of acyclic α-quaternary ketones via decarboxylative allylation.[95] They tried to bypass the enolate geometry problem by using (*E*)-enol carbonates derived from aryl benzyl ketones, which could be prepared selectively using a modified method of Gosselin *et al.* (Scheme 61).[96] After optimization of the reaction conditions, they found that the best enantioselectivities could be obtained with electron-deficient ligand **L6b** in non-polar solvents. The pure (*E*)-enol carbonate **28** yielded the alkylated ketone **29** with an enantiomeric excess of 91%. However, a control experiment with an *E*/*Z* mixture (25:75) of the enol carbonate **28** provided almost the same enantiomeric excess in the product. Stoltz *et al.* therefore proposed that a dynamic kinetic enolate equilibration happens during the reaction.



Scheme 60. Decarboxylative allylic alkylation for the synthesis of decytospolide A and B.



Scheme 61. Decarboxylative allylic alkylation for the synthesis of acyclic, α-quaternary ketones.



Scheme 62. Decarboxylative α-aminoketone allylation.

3.3. Decarboxylative Allylic Alkylations of α-Functionalized Ketones

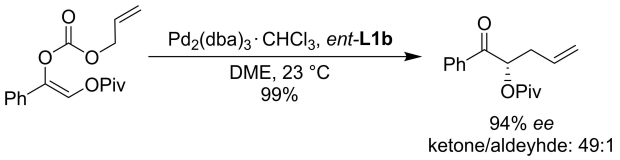
Murakami *et al.* observed a positive effect of phenol additives on the enantioselectivity of the decarboxylative allylation of α-acetamido ketones.[97] In this reaction, Trost's ligand **L1b** led to enantiomeric excesses of up to 90% in the products (Scheme 62).

For the decarboxylative allylic alkylation of α-fluorinated cyclic ketones *via* enol carbonates, an interesting effect was noted by Paquin and coworkers.[98] They used PHOX ligand **L6a** for the reaction and found that **L6a**/Pd ratios $<1:1.67$ had a positive effect on the yield and enantioselectivity of the allylation. This is unusual, since mostly L/Pd ratios of $>1:1$ are employed. In this case, even ratios as low as 1:4 were well accepted, while significantly lower *ee*'s were obtained if the ligand was used in excess. However, this effect seems to be limited to cyclic fluorinated allyl enol carbonates, but is not observed with other fluorinated substrates such as silyl enol ethers or β-keto allyl esters, where the L/Pd-ratio has no significant effect. Obviously, unlike other non-fluorinated enolate precursors, the different fluorinated precursors show different reactivity patterns and can not be considered equivalent.

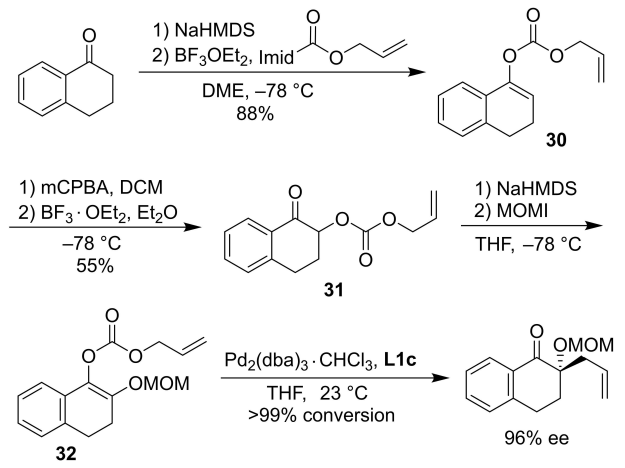
Trost *et al.* described the decarboxylative allylic alkylation of 1,2-enediol carbonates for the synthesis of α-hydroxylated, α-allylated ketones.[99] In this reaction, both the allylated α-hydroxyketone and the allylated α-hydroxy aldehyde can be formed *via* transfer of the *O*-protecting group. The choice of ligand and *O*-protecting group proved to be crucial to obtain good selectivities for the α-hydroxyketone. Naphthalene-derived ligand *ent*-**L1b** and ester protecting groups on the α-oxygen atom (Ac or Piv) led to the best chemo- and enantioselectivities for the allylated α-hydroxyketones (Scheme 63).

In 2012, the same group described a protocol for the conversion of simple ketones to α-hydroxylated, α-allylated ketones (Scheme 64).[100] The five-step sequence started with the formation of an enol carbonate **30**, which was then epoxidized by *meta*-chloro perbenzoic acid (mCPBA). The addition of $BF_3{\cdot}OEt_2$ resulted in a ring opening and rearrangement of the carbonate group. The carbonate **31** formed was then treated with NaHMDS and iodomethyl methyl ether (MOMI) to yield the MOM-protected 1,2-endiol carbonate **32** suitable for decarboxylative allylic alkylation.

α,α-Difluorinated ketones are medicinally important substructures since they are known inhibitors of serine and aspartyl proteases. Altman and coworkers developed a decarboxylative



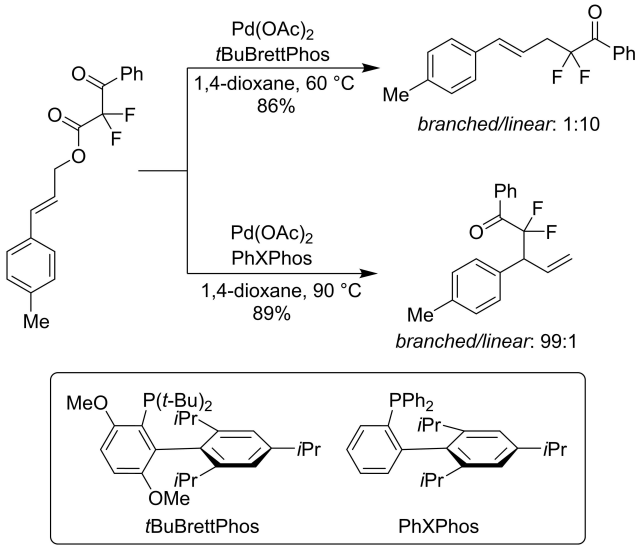
Scheme 63. Allylic alkylation of pivaloyl protected 1,2-enediol carbonates.



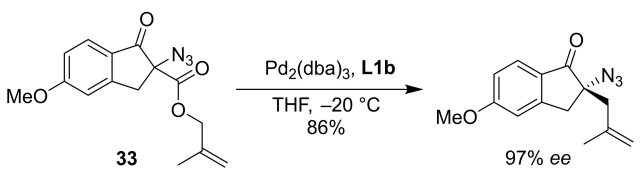
Scheme 64. Synthesis and decarboxylative allylic alkylation of MOM-protected 1,2-enediol carbonates; Imid = imidazole.

allylic alkylation of α,α-difluoroketones in 2015.[101] They observed that biaryl monophosphine ligands delivered the best results in this reaction. Interestingly, depending on the ligand, the branched or linear products could be obtained selectively (Scheme 65).

Waser and coworkers described the decarboxylative allylic alkylation of α-azido and α-cyano indanones **33**.[102] In these reactions, Trost's ligand **L1b** delivered the best results



Scheme 65. Decarboxylative allylic alkylation of α,α-difluoroketones.



Scheme 66. Decarboxylative allylic alkylation of 2-azidoindanones.

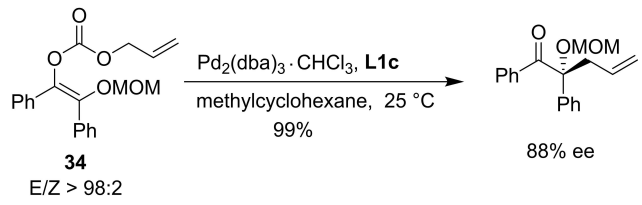
(Scheme 66). The enantiomerically enriched azides can be seen as precursors of amines or triazoles.

Stoltz and coworkers recently described the decarboxylative allylic alkylation of enediol carbonates such as **34** for the synthesis of acyclic, α-quaternary α-hydroxyketones (Scheme 67).[103] For this reaction they found that the enolate geometry is indeed crucial for obtaining high *ee*'s with ligand **L1c**, in contrast to the allylation of acyclic aryl-alkyl-substituted ketones with **L6b** (see Scheme 61). Ligand **L6b** was also used in the allylation of α-fluoro- and different α-trifluoroalkyl ketones. The best results were obtained in toluene at ambient temperature.[104]

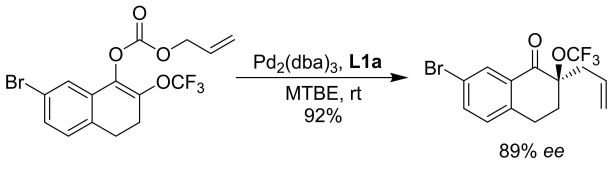
For the allylic alkylation of α-trifluoromethoxy ketones, Shibata *et al.* used also the approach via enol carbonates (Scheme 68).[105] They found that ligand **L1a** yielded the products in good yields and enantioselectivities. The OCF_3-group can be regarded as especially challenging in this reaction, because it is strongly electron-withdrawing.

Since difluoromethyl thioethers are also interesting for the development of new drugs, Shibata *et al.* reported a protocol for the allylic alkylation of α-SCF_2H ketones (Scheme 69).[106] They made use of Trost's ligand **L1a** and found that the best enantioselectivities could be obtained at −40 °C, while the (*S*)-configured product was formed preferentially.

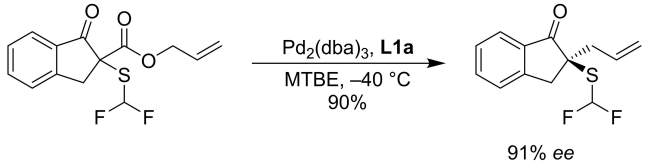
For the formal synthesis of (−)-cephalotaxine, Zhang *et al.* made use of the decarboxylative allylic alkylation of a cyclic α-aminoketone (Scheme 70).[107] The product **35** obtained could then be transformed into a known precursor of the natural product.



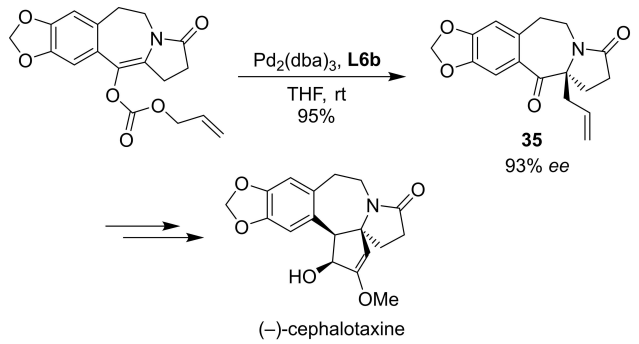
Scheme 67. Allylic alkylation of acyclic enediol carbonates.



Scheme 68. Decarboxylative allylic alkylation of 2-azidoindanones.



Scheme 69. Decarboxylative allylic alkylation of α-difluoromethyl thioketones.



Scheme 70. Decarboxylative allylic alkylation of a cyclic α-amino ketone for the formal synthesis of (−)-cephalotaxine.

3.4. Decarboxylative Allylic Alkylation of Vinylogous Esters and Thioesters

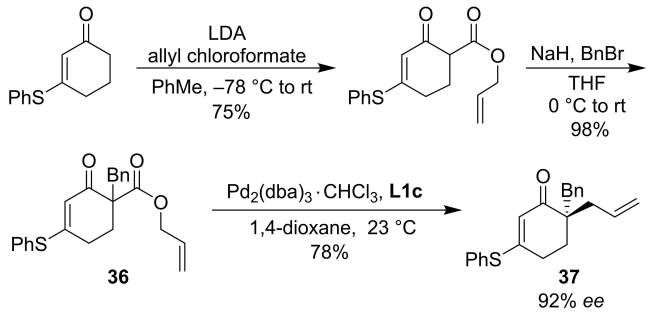
Trost and coworkers could apply the decarboxylative allylic alkylation also to cyclic β-alkoxy-substituted α,β-unsaturated ketones, vinylogous esters, which can be seen as masked 1,3-diketones.[108] Both approaches, via enol carbonates and via β-ketoesters, were investigated. The enol carbonates were however only obtained in low yields and β-ketoesters derived of these vinylogous esters reacted only sluggishly. Therefore, the corresponding sulfur analogues **36** were used, which are more reactive due to poorer orbital overlap between the sulfur and carbon atoms. These compounds could be readily converted to the allylated vinylogous thioesters **37** in good yields and high enantioselectivities using ligand **L1c** (Scheme 71).

This observation served as the starting point of the total synthesis of (−)-aspidophytine by Yang and Qiu in 2013 (Scheme 72).[109] The moderate enantiomeric excess of 85% in the allylated product **38** could be improved to an *ee* of 97% by recrystallization after hydrolysis of the thioenolether to the corresponding 1,3-diketone.

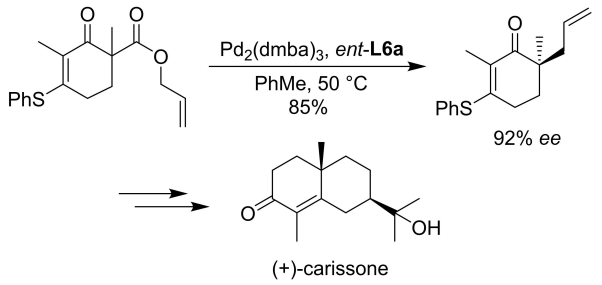
A similar approach was used by Stoltz and coworkers in the total synthesis of (+)-carissone (Scheme 73).[110] Best results were obtained with ligand *ent*-**L6a**, which provided the alkylated product with an enantiomeric excess of 92%. The sesquiterpenoid carissone could be synthesized in 10 further steps.

The same group further employed this method for the allylic alkylation of seven-membered vinylogous esters,[111] e.g. to obtain densely functionalized acyl cyclopentene **39**.[112] This compound could be used in the total synthesis of (−)-presilphiperfolan-1-ol and its C-9-epimer leading to the configurational revision of the stereogenic center in the natural product (Scheme 74).[113] Acyl cyclopentenes such as **39** are also promising precursors of the natural products hamigerans C and D.[114]

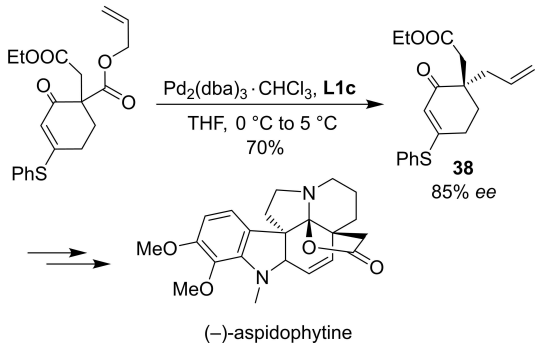
The vinylogous ester allylation was also applied in the synthesis of the naturally occurring sesquiterpenoid (+)-elatol.[115] Stoltz *et al.* also encountered problems in the reaction of an enol carbonate **40**, which only provided low yields and mediocre enantioselectivities. In this case, a chloro substituent on the allyl fragment seemed to cause the



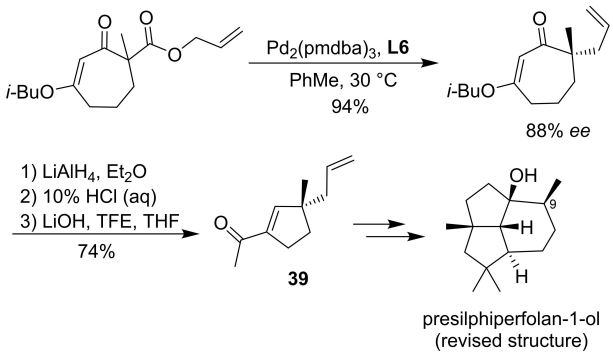
Scheme 71. Allylic alkylation of vinylogous thioesters.



Scheme 73. Allylic alkylation of a vinylogous thioester in the total synthesis of (+)-carissone.



Scheme 72. Allylic alkylation of a vinylogous thioester in the total synthesis of (−)-aspidophytine.



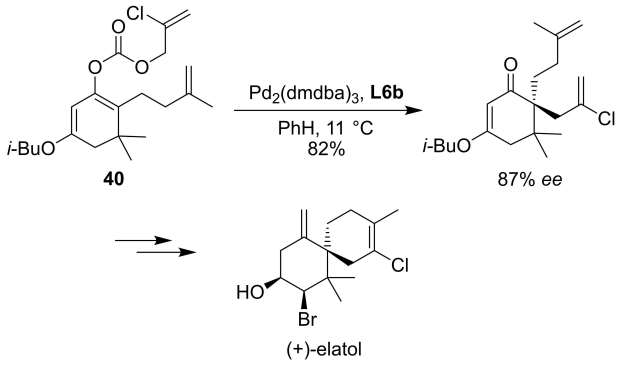
Scheme 74. Allylic alkylation of a vinylogous ester in the total synthesis of (−)-presilphiperfolan-1-ol; TFE: 2,2,2,–trifluoroethanol

problems, leading to slow alkylation. The reaction could be accelerated by addition of electron-deficient ligand **L6b**. This ligand increases the electrophilicity of the Pd-π-allyl complex and results in a faster reaction, providing the desired product in 82% yield and 87% *ee* (Scheme 75). The natural product (+)-elatol could be synthesized in only 4 further steps, showcasing the utility of vinylogous esters in total synthesis.

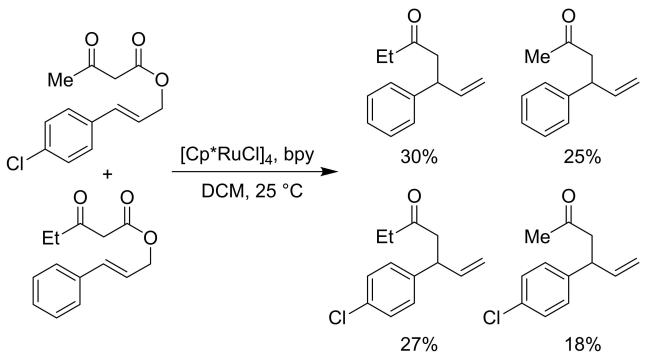
3.5. Ru- and Ir-Catalyzed Decarboxylative Allylic Alkylations

Decarboxylative ketone allylations can not only be catalyzed by palladium, but also by other transition metals such as ruthenium or iridium.

The first Ru-catalyzed decarboxylative allylation of ketones was described by Burger and Tunge in 2004.[116] They employed $[Cp^*RuCl]_4$ ($Cp^* = C_5Me_5$) and bipyridyl (bpy) for the decarboxylative allylation of cinnamyl β-ketoesters. It was observed, that the branched products were formed with a high selectivity. A cross-over experiment was performed with two different β-ketoesters to probe the mechanism of the reaction (Scheme 76). In this reaction, all four possible products were formed in almost equal quantities, clearly indicating that the reaction proceeds intermolecularly *via* free enolates and Ru-allyl complexes, which are attacked preferentially at the sterically more demanding position.



Scheme 75. Allylic alkylation using a vinylogous enol carbonate in the total synthesis of (+)-elatol.



Scheme 76. Crossover experiment for Ru-catalyzed decarboxylative allylic alkylation.

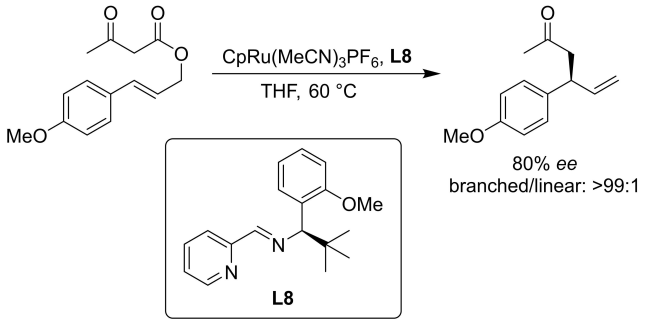
An asymmetric version of the Ru-catalyzed decarboxylative allylation was described by Lacour *et al.*[117] In this case, $CpRu(MeCN)_3PF_6$ ($Cp = C_5H_5$) and the pyridine-imine ligand **L8** were used for the enantioselective rearrangement of cinnamyl acetoacetates. Independent of whether linear or branched allylic esters were employed in the reaction, the branched products were formed regioselectively and with modest to good enantioselectivities (Scheme 77).

This method could be improved by Lou *et al.*, who used iridium complexes along with monodentate ligand *ent*-**L7a**.[118] In this case, the branched products were again formed preferentially with enantiomeric excesses of 89–96% (Scheme 78). A crossover experiment – similar to the one by Burger and Tunge (see above) – was performed, proving again that the reaction proceeds intermolecularly.

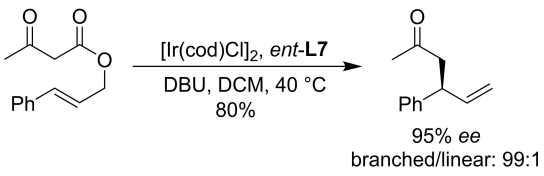
Recently, a new ligand for the Ru catalyzed decarboxylative allylic alkylation was introduced, which provided even better enantioselectivities. Kitamura and coworkers reported, that a Ru-complex formed from CpRu and chiral bisamidine **L9** provided nearly perfect enantioselectivity in the Ru-catalyzed rearrangement of cinnamyl acetoacetates (Scheme 79).[119] Remarkably, the reaction could be performed with 0.1 mol% of catalyst, which resulted in prolonged reaction times of 48 h (compared to 6 h with 1 mol% catalyst), but the products could still be obtained in high yields and enantiomeric excesses.

4. Deacetylative Allylic Alkylations

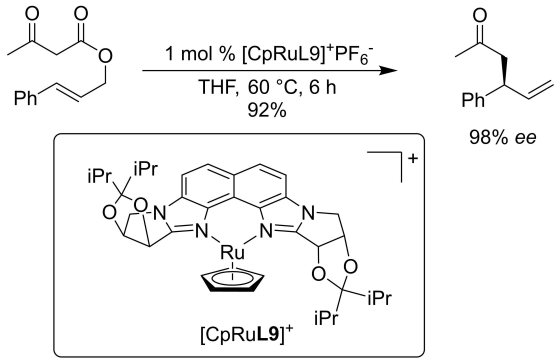
The first example of a deacetylative allylic alkylation of an enol acetate was described by Tsuji *et al.* in 1983.[120] The deacetylation was initiated by catalytic amounts of tributyltin methoxide which activates the enol acetate via formation of methyl acetate and the tin enolate, which can then react in the usual manner



Scheme 77. Asymmetric Ru-catalyzed decarboxylative allylic alkylation with pyridine imine ligand **L8**.



Scheme 78. Asymmetric Ir-catalyzed decarboxylative allylic alkylation.



Scheme 79. Asymmetric Ru-catalyzed decarboxylative allylic alkylation with bisamidine ligand **L9**.

with an allylic substrate forming the α-allylated ketone (Scheme 80).

Grenning and Tunge described a different approach based on a retro-Claisen addition.[121] They made use of allylic alkoxides, which attack a 1,3-diketone forming the corresponding enolate via deacetylation. In this process, the allylic acetate is formed *in situ*, generating a π-allyl complex with Pd^0. The best results were obtained with NaH as base (Scheme 81).

Two years later, Tunge *et al.* reported an enantioselective protocol for the allylic alkylation of 1,3-diketones derived from tetralone (Scheme 82).[122] They made use of the PHOX-ligands **L6a** and **L6b**, which resulted in acceptable enantiomeric excesses in the allylation products.

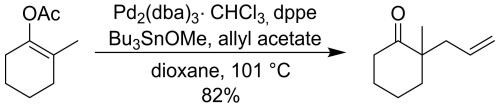
Wang *et al.* made also use of a *retro*-Claisen approach for the allylic alkylation of different nucleophiles *via* C–H functionalization.[123] The activation of simple alkenes to π-allyl-Pd complexes could be accomplished using $Pd(OAc)_2$, PPh_3 and 2,5-di-*tert*-butylbenzoquinone (2,5-DTBQ) as an oxidant, while Cs_2CO_3 and *tert*-butanol were used for deacetylation (Scheme 83). Using this new protocol, Wang *et al.* were able to alkylate not only different ketones and carboxylic acid derivatives, but also nitro compounds.

Inspired by Tsuji's early report and Tunge's work on deacetylative allylations, Aponick and coworkers developed a tin-free protocol for the enantioselective, allylic alkylation of enol acetates (Scheme 84).[124] Using ligand **L6b**, the products could be obtained in very good to excellent enantiomeric excesses. This approach was also used in a formal synthesis of (+)-hamigeran B.

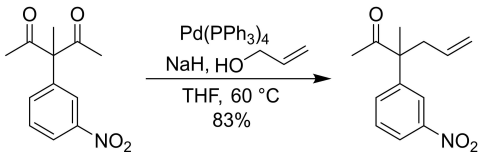
5. Allylic Alkylations of Enolates Formed in 1,4-Additions

In 1996, Noyori *et al.* presented a protocol generating zinc enolates from cyclic enones and zinc organyls.[125] In the presence of catalytic amounts of CuCN and a sulfonamide, diethylzinc undergoes a 1,4-addition onto a α,β-unsaturated ketone, forming a β-alkylated zinc enolate (Scheme 85). This enolate can then be trapped by electrophiles, e.g. with allyl acetate and Pd^0, forming the *trans*-diastereomer of the α,β-difunctionalized ketone preferentially.

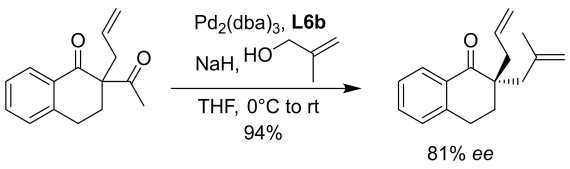
Feringa *et al.* described an enantioselective version of this reaction three years later.[126] A Cu-catalyzed 1,4-addition in the presence of ligand (*S,R,R*)-**L7a** provided the enantioenriched Zn-enolate, which could be allylated towards the enantioenriched product **41** in very good yield and *ee* (Scheme 86).



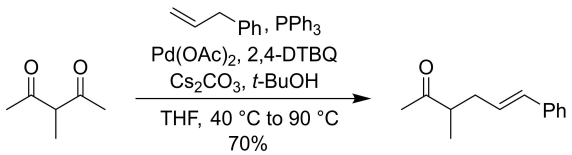
Scheme 80. Allylic alkylation of enol acetates catalyzed by Pd^0 and Bu_3SnOMe.



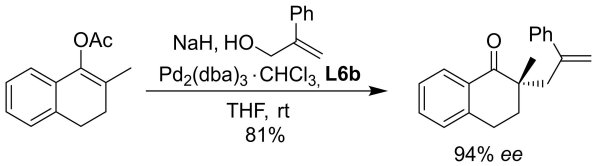
Scheme 81. Deacetylative allylic alkylation via retro-Claisen addition.



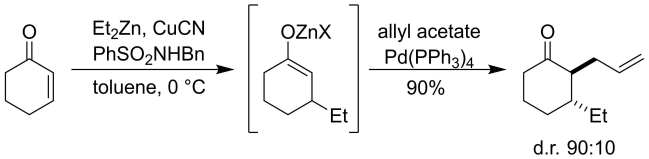
Scheme 82. Asymmetric deacetylative allylic alkylation via retro-Claisen addition.



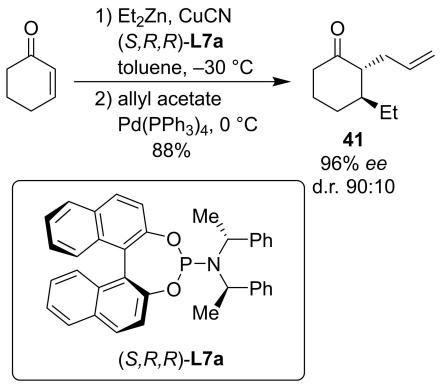
Scheme 83. Deacetylative allylic alkylation via C–H activation.



Scheme 84. Asymmetric allylic alkylation of enol acetates with allylic alcoholates.



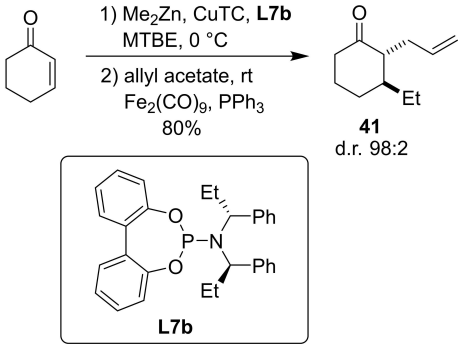
Scheme 85. Tandem 1,4-addition, allylic alkylation of cyclohexenone.



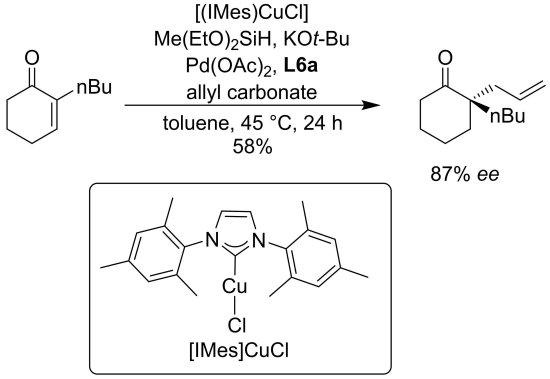
Scheme 86. Enantioselective tandem 1,4-addition, allylic alkylation of cyclohexenone.

Jarugumilli and Cook reported a tandem Fe-catalyzed allylic alkylation of zinc enolates, also formed by 1,4-addition to enones.[127] With $Fe_2(CO)_9$ and PPh_3 best results were obtained, a diastereomeric ratio of 98:2 was observed for **41**, which was unprecedented for this approach (Scheme 87). One year later, Cook *et al.* also described a protocol for the transition metal-free allylation by trapping the zinc enolates with allyl bromides and iodides.[51]

Riant and coworkers reported the tandem 1,4-reduction/allylic alkylation of cyclic enones in 2013.[128] Cu(I) *N*-heterocyclic carbene (NHC) complexes, silanes and catalytic amounts of KO*t*-Bu were used to generate the corresponding silyl enol ethers, which could be subjected to Pd-catalyzed allylic alkylations. Moderate to good enantiomeric excesses were obtained by using PHOX ligand **L6a** (Scheme 88).



Scheme 87. Tandem 1,4-addition, Fe-catalyzed allylic alkylation of cyclohexenone; CuTC = copper(I) thiophene-2-carboxylate.



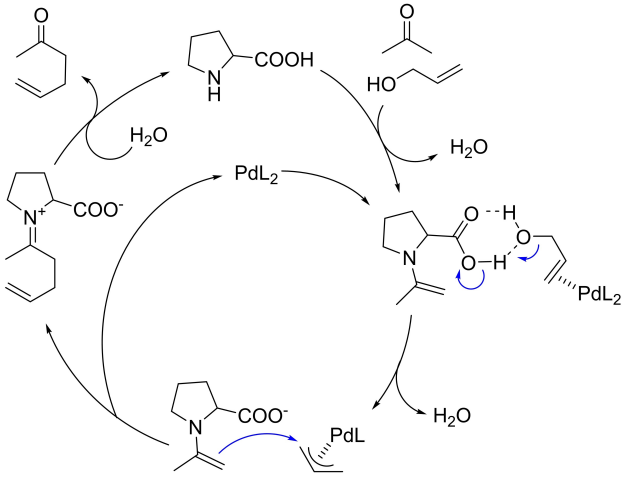
Scheme 88. One pot Cu/Pd-catalyzed 1,4-reduction, allylic alkylation.

6. Allylic Alkylation of Enamines

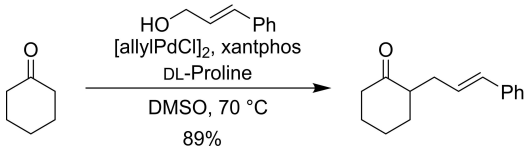
Enamines can be seen as surrogates for ketone (or aldehyde) enolates, which can be easily obtained from the carbonyl compounds and secondary amines. The first allylic alkylations of enamines were described for those derived from aldehydes in 2006 and 2007.[129] This chapter will however focus on the allylation of ketone enamines.

In 2007, Breit *et al.* reported the first protocol for the allylic alkylation of ketones with allylic alcohols (instead of allylic carbonates or esters) catalyzed by Pd^0 and a secondary amine such as proline.[130] In this reaction, the allylic alcohols are presumably activated *in situ* by proline and can thus be ionized by Pd^0 forming a π-allyl-Pd complex (Scheme 89). The amino functionality of proline then forms an enamine with the ketone, which acts as a nucleophile and attacks the π-allyl complex resulting in the allylated ketone. Using xantphos as a ligand, cyclohexanone could be reacted with cinnamyl alcohol to the allylated ketone in good yield (Scheme 90).

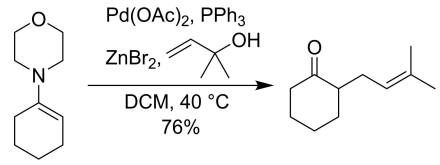
Rezgui *et al.* developed a method for the allylic alkylation of enamines with allylic alcohols using $ZnBr_2$ for the activation of the alcohols (Scheme 91).[131]



Scheme 89. Proposed reaction mechanism for the Pd-proline-catalyzed allylic alkylation of ketones.



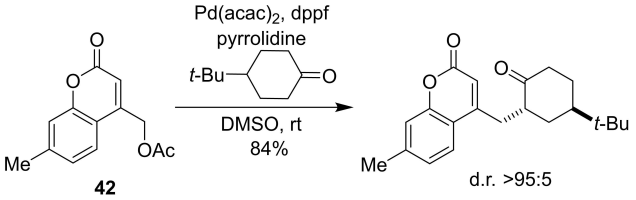
Scheme 90. Allylic alkylation of cyclohexanone *via* Pd-enamine dual catalysis.



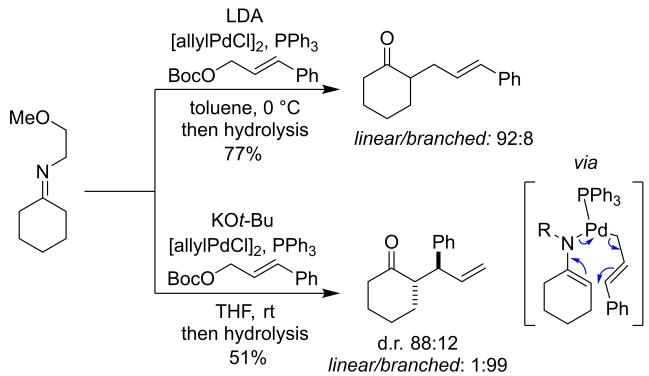
Scheme 91. Allylic alkylation of ketone enamines with allylic alcohols.

Tunge and coworkers employed the concept of Pd/pyrrolidine dual catalysis for the aryl methylation of ketones and aldehydes with coumarin derivatives.[132] In this reaction, a Pd-π-benzyl complex was formed from coumarin derivative **42**, which was reacted with an enamine generated from pyrrolidine and the corresponding ketone (Scheme 92).

Wu *et al.* reported the allylic alkylation of imines.[133] Imines can be deprotonated with strong bases to the corresponding aza-allyl anions. Depending on the nature of the base and solvent, either the branched or the linear products were obtained selectively. While KO*t*-Bu and cinnamyl *tert*-butyl carbonate in THF yielded the branched product, the linear product could be obtained using LDA in toluene (Scheme 93). In case of Li^+ as counter ion, the allylic alkylation most likely proceeds intermolecularly at the C-terminus of the ambident aza enolate (outer sphere attack). In contrast, in the presence of K^+ the deprotonated enamine probably coordinates to the π-allyl palladium complex, and the branched product is formed via [3,3']-reductive elimination (inner sphere attack). In the second case, better yields were obtained with cinnamyl chloride as electrophile, while the leaving group had no significant effect on the regioselectivity.



Scheme 92. Aryl methylation of ketones with Pd and pyrrolidine dual catalysis.



Scheme 93. Regioselective allylic alkylation of imines with Li or K bases.

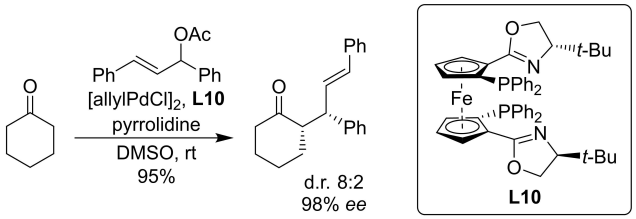
Shibasaki *et al.* reported on asymmetric allylic alkylation of ketones with allylic alcohols using chiral ligands consisting of a proline unit and a phosphine.[134] However, to reach a yield of 66% in the allylic alkylation of cyclohexanone, high concentrations of catalyst and ligands had to be used and the enantiomeric excess in the products ranged only from 36 to 66%.

In 2011, Zhang and coworkers described a protocol for the allylic alkylation of ketones and aldehydes using allylic acetates under Pd/pyrrolidine dual catalysis.[135] Pyrrolidine served as the organocatalyst, forming the enamine in substoichiometric amounts. Best results were obtained in the presence of ligand **L10** (Scheme 94).

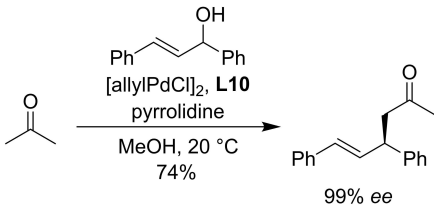
The same group also described similar allylations using allylic amines and allylic ethers as substrates.[136] They further extended this protocol to allylic alcohols using methanol as solvent.[137] The presence of ligand **L10** led to almost enantiopure product in the allylic alkylation of acetone (Scheme 95).

Lei *et al.* reported on the allylic alkylation of ketones with simple alkenes *via* allylic C–H-activation using Pd/amine dual catalysis (Scheme 96).[138] In this protocol, L-proline served as the organocatalyst forming catalytic amounts of enamine. Interestingly, despite the use of enantiopure L-proline, no chiral induction could be observed in the reaction.

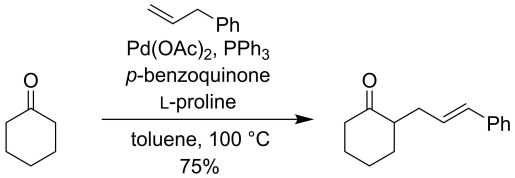
Lin *et al.* showed that unactivated alkynes can also be used for the allylation of ketones under analogous conditions



Scheme 94. Asymmetric allylic alkylation of cyclohexanone via Pd-enamine dual catalysis.



Scheme 95. Asymmetric allylic alkylation using allylic alcohols via Pd-enamine dual catalysis.

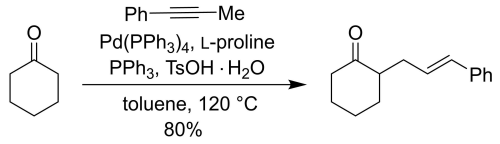


Scheme 96. Allylic alkylation with unactivated alkenes using Pd/proline dual catalysis.

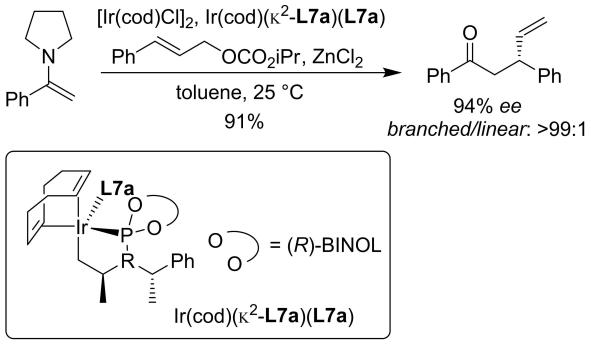
(Scheme 97).[139] The authors suggested that $Pd(PPh_3)_4$ and toluene sulfonic acid (TsOH) first form a palladium hydride species, which then undergoes hydropalladation of the alkyne triple bond. β-hydride elimination forms an allene, which then reacts with another palladium hydride complex to form a π-allyl complex.

In 2007, Weix and Hartwig reported an asymmetric Ir-catalyzed allylation of enamines derived from ketones (Scheme 98).[140] They found that a combination of preformed catalyst Ir(cod)(K^2-**L7a**)(**L7a**) and $[Ir(cod)Cl]_2$ resulted in the fastest reaction rates and highest yields for the reaction. As usual for Ir-catalyzed allylations, the branched product was formed selectively. $ZnCl_2$ was also added to the reaction mixture in order to trap the isopropanol released from the isopropyl carbonates used.

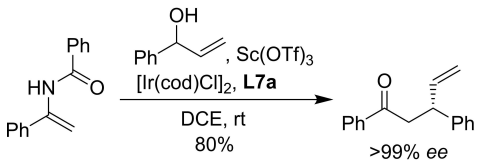
A similar protocol for the Ir-catalyzed allylic alkylation of enamides and enecarbamates derived from benzophenones was described by Yang *et al.* in 2019.[141] They made use of $[Ir(cod)Cl]_2$ and **L7a** as the catalytic system and could allylate benzophenones with allylic alcohols (Scheme 99). Scandium triflate was used as a Lewis acid for their activation. The branched products were obtained selectively.



Scheme 97. Allylic alkylation of ketones with alkynes via Pd/proline dual catalysis.



Scheme 98. Ir-catalyzed asymmetric allylic alkylation of ketone enamines.



Scheme 99. Ir-catalyzed asymmetric allylic alkylation of enamides.

7. Conclusions

Tremendous progress has been achieved for the allylic alkylation of ketones over the last four decades. While initial examples proving the feasibility of mono-allylations were provided as early as 1980, the original protocols were optimized for the use with chiral ligands in the early 2000s. With these novel protocols, enantiomerically enriched products can be obtained regio- and stereoselectively. The use of the deacetylative and decarboxylative approaches, 1,4-additions, enamines and chelated enolates has made the allylic alkylation of ketones a straight-forward transformation enabling the efficient construction of all-carbon stereogenic centers.

This is especially well exemplified by the many natural product syntheses which are based on ketone allylations for the efficient establishment of the desired stereochemistry.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: allylic alkylations · enolates · ketones · palladium · transition metals

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Manuscript received: June 12, 2020
Revised manuscript received: August 3, 2020