Organic Syntheses

Discussion Addendum for:

(*S*)-(-)-2-Allylcyclohexanone (2-Allylcyclohexan-1-one]

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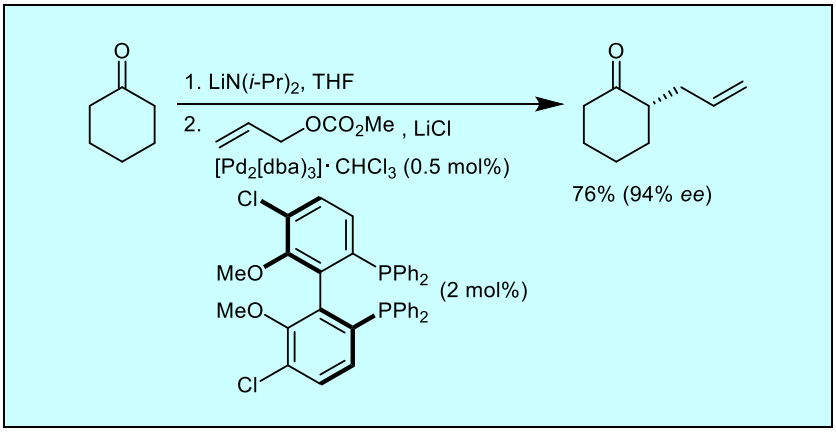

The protocol for the synthesis of (*R*)- and (*S*)- 2-allylcyclohexanone had been chosen for demonstrating that preformed, non-stabilized lithium enolates are suitable nucleophiles for palladium-catalyzed asymmetric allylic alkylations – the so-called Tsuji-Trost reaction.[2] This method is a direct alternative to the intramolecular variant, the decarboxylative asymmetric allylic alkylation that starts from allyl β-ketoesters or allyl enol carbonates. This intramolecular approach, which was pioneered by the research groups of Stoltz, Trost and others,[3] has been published as an Organic Syntheses procedure on (*S*)-2-allyl-2-methylcyclohexanone in 2009.[4] This manuscript was followed by an addendum in 2018.[5] In both procedures, advantage was taken of the cyclohexanone skeleton that guaranteed the fixed *trans*-configuration of the lithium enolate.

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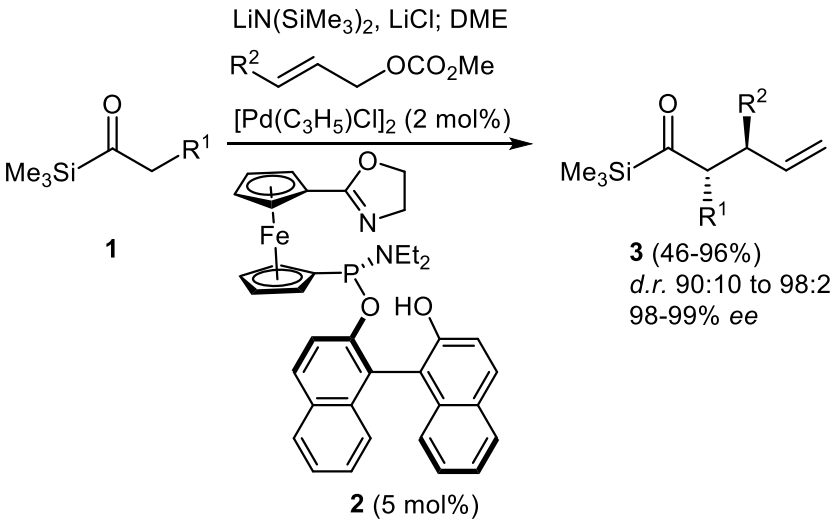
This discussion addendum emphasizes the progress and development of transition metal-catalyzed allylic alkylations for enantioselective and diastereoselective carbon-carbon bond formations by using preformed lithium enolates of various carbonyl and carboxyl derivatives.

After a diastereoselective and enantioselective allylation of mesityl ethyl ketone had been reported by us,[2b] the group of Hou studied the allylation of various acyclic ketones through their lithium enolates.[6] In a remarkable extension of their protocol, they used acylsilanes **1** as substrates and obtained allylation products **3** in high diastereoselectivity with excellent optical purity. The alkenes **3** are particularly valuable as they can be converted into carboxylic acids and esters, so that the protocol can be considered as an alternative to the allylation of ester enolates. In this palladium-mediated reaction, ferrocenyloxazoline ligand **2** served as the efficient, stereoselectivity-determining ligand (Scheme 1).[7]

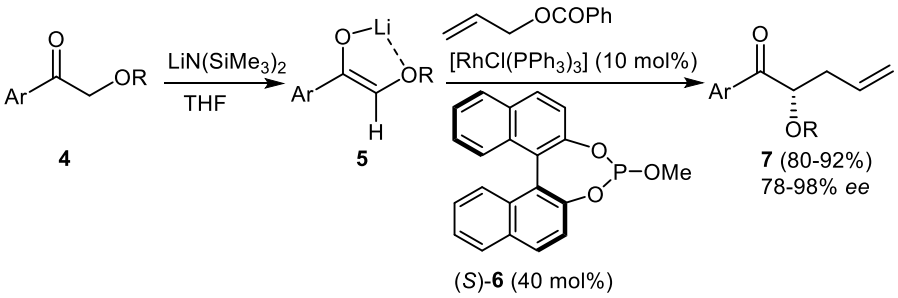


Scheme 1. Diastereoselective and enantioselective allylic alkylation of acylsilanes

More recently, Hou's group reported the palladium-catalyzed reaction of gem-alkyl-aryl-disubstituted allylic reagents with cyclic ketones through their lithium enolates. Remarkably, the branched products featuring a

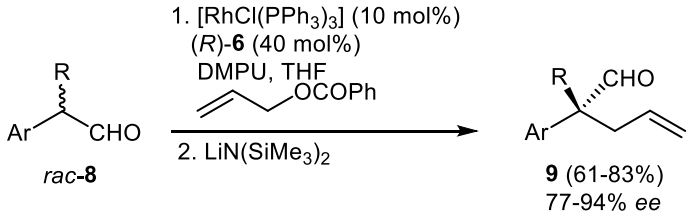
quaternary stereogenic center not only formed regioselectivity at the expense of the linear regioisomer, but also diastereoselectively.[8]

Rhodium-catalysis turned out to be the suitable tool for the enantioselective allylic alkylation of α-oxy-substituted ketones **4**, as demonstrated by Evans and coworkers. In this procedure, the monodentate phosphite ligand **6** was used, and allylation products **7** were obtained in fair to high enantioselectivity. A chelated structure **5** of the lithium enolate was postulated (Scheme 2).[9] Later, Hartwig and coworkers reported diastereoselective and enantioselective iridium-catalyzed allylic alkylations of α-alkoxy-ketones. Their primarily generated lithium enolates were trans-metalated into the copper enolates that are assumed to adopt a five-membered chelate structure.[10a] Recently, Trost and coworkers achieved an enantioselective allylation of 1,3-dioxaboroles, a special kind of boron enolates that serves as synthetic equivalent of α-hydroxyketones.[10b]



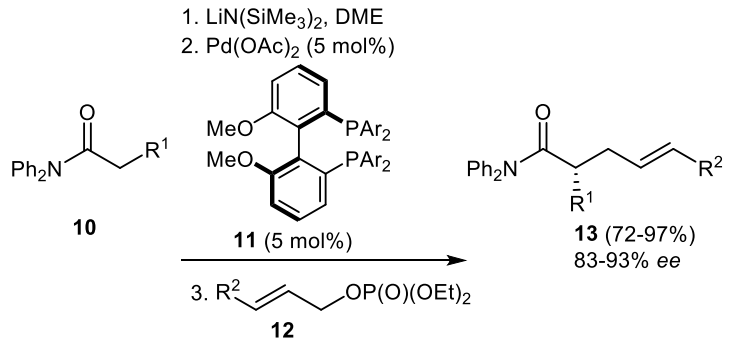
Scheme 2. Asymmetric rhodium-catalyzed allylic alkylation of α-oxy-substituted ketones

By also using rhodium catalysis in combination with (*R*)-configured ligand **6**, Evans and Wright achieved the allylation of aldehyde enolates for the creation of a stereogenic quaternary center in α-carbonyl position. It turned out that the particular lithium amide base used for deprotonation was crucial for the enantioselectivity. LiHMDS provided the highest *ee*-values. For obtaining satisfying chemical yields, the presence of the co-solvent DMPU was necessary, and the lithium base had to added dropwise – obviously for suppression of undesired side-reactions. (Scheme 3).[11] Surprisingly, the same enantiomer of alkenes **7** is formed, irrespective of the configuration of the lithium enolate.



Scheme 3. Racemic α-aryl aldehydes allylated by rhodium catalysis through their lithium enolates

After the asymmetric allylic alkylation of ketone enolates had been achieved, the group of Hou studied the extension to acyclic tertiary amides, whose lithium enolates are known to be as equally stable as ketone enolates. The method is illustrated in Scheme 4 for *N,N*-diphenyl carboxylic amides **10** that are deprotonated with LiHMDS and subsequently submitted to a palladium-catalyzed reaction with allylic phosphates **12**. The allylic alkylation was mediated by the commercially available MeO-BIPHEP-type ligand **11** and delivered amides 1**3**, whose *ee*-values ranged from 83 to 93%.[12]

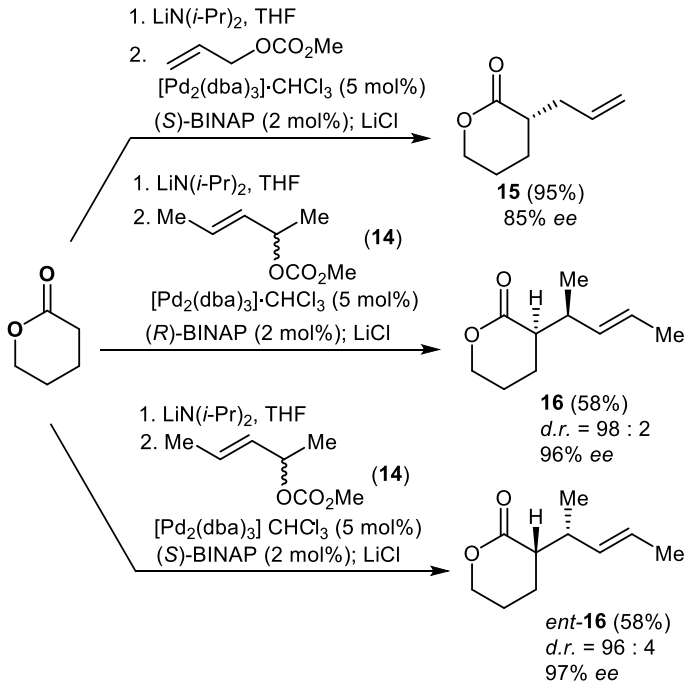


Scheme 4. Asymmetric allylic alkylation of amides 10 through their lithium enolates; Ar = 3,4,5-$(MeO)_3C_6H_2$

This disclosure was preceded by an asymmetric allylic alkylation of racemic α,α-disubstituted acyclic amides with similar degrees of enantioselectivity.[13] Previously, Trost and Frederiksen had reported that 3-aryl-substituted oxindoles can be allylated in an enantioselective manner through their lithium enolates.[14]

While the asymmetric allylic alkylation of amide enolates was elaborated, as outlined above, our research group next tackled a further class of non-

stabilized lithium enolates: deprotonated lactones. For this purpose, we applied conditions very similar to those used in the original Organic Syntheses procedure, and used, in particular, lithium chloride as an additive in the asymmetric allylation of δ-valerolactone (Scheme 5).

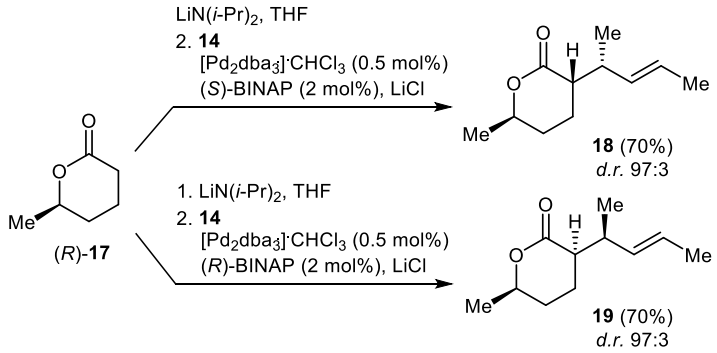


Scheme 5. Enantioselective and diastereoselective allylic alkylations of δ-valerolactone through the lithium enolate

The simple, readily available, classic BINAP ligand provided fair enantioselectivity in the formation of alkene **15** in the palladium-catalyzed reaction with allyl methyl carbonate. High enantioselectivity, combined with high diastereoselectivity was reached in the formation of lactones **16** and *ent*-**16** depending on the enantiomer of the chiral ligand BINAP. Thus, enantiomeric products **16** featuring contiguous stereogenic centers were obtained starting from racemic dimethylallyl carbonate **14**.[15]

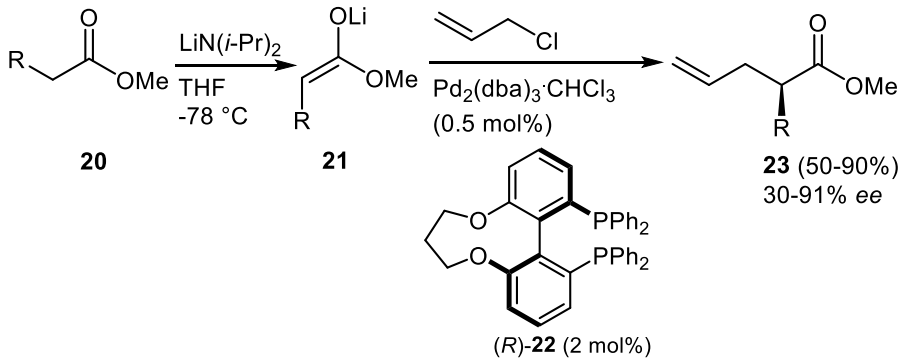
When enantiomerically pure δ-caprolactone (*R*)-**17** was submitted to this allylation protocol using either (*R*)- or (*S*)-BINAP as the chiral ligand at palladium, the stereochemical outcome was clearly determined by the

configuration of the catalyst. This protocol facilitated formation of diastereomeric products **18** and **19**, both as pure enantiomers (Scheme 6).[15]



Scheme 6. Catalyst-control in the allylic alkylation of (*R*)-δ-caprolactone

More fragile and sensitive than enolates of ketones, aldehydes, amides, lactams and lactones are lithium enolates of carboxylic esters that are thermally labile and tend to decompose under formation of ketene and alkoxide. So far, only chelated zinc or titanium enolates derived from α-amino acids or peptides proved themselves as versatile and suitable for enantioselective and/or diastereoselective Tsuji-Trost reactions.[16] Our group however, tackled the direct enantioselective allylic alkylation of non-chelated enolates of simple alkanoic-acid esters **20**. Prerequisite of that achievement was the selective generation of either *cis*- or *trans*-configured lithium enolates that was enabled by following the seminal contributions of Ireland and coworkers.[17] For this purpose, carboxylic esters **20** were deprotonated with LDA for generating *trans*-configured lithium enolates **21**. As in previous protocols, the presence of lithium chloride was found to be crucial for reactivity and stereoselectivity. However, instead of adding the salt in stoichiometric amounts, we used allylic chloride that forms lithium chloride gradually as the palladium-catalyzed allylation proceeds. Mediating the reaction with C_3-TUNEPHOS ligand (*R*)-**22** led to allylated esters **23** in fair to high yield and enantioselectivity up to 91 % *ee*. (Scheme 7).[18]

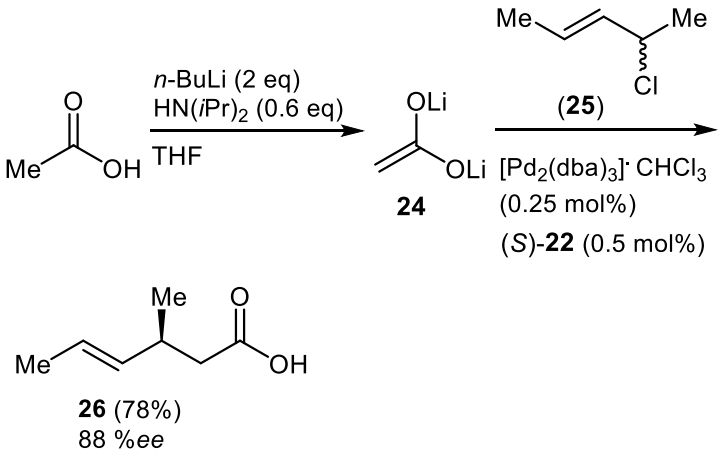


Scheme 7. Enantioselective allylic alkylation of alkanoic ester enolates

In our attempts to extend even further the Tsuji-Trost-reaction towards "harder" nucleophiles, we finally investigated doubly deprotonated carboxylic acids – truly hard enolates if one takes into account that the pK_a value of acetate was determined to amount to 33.5.[19] Dilithiated carboxylic acids $R_2C{=}C(OLi)_2$ had been disclosed by Creger;[20a,b] procedures for a more convenient generation were elaborated later by the groups of Mulzer[20c] and Parra.[20d] After having shown that carboxylic-acid dianions can indeed serve as nucleophiles in Tsuji-Trost reactions,[21] we studied the challenging allylic alkylation of doubly lithiated acetic acid – probably a highly aggregated species, whose mixture in THF has a milky consistence, expected to react sluggishly. After generation of doubly lithiated acetic acid **24**, a protocol similar to that described above for the allylation of carboxylic esters was applied. Thus, racemic dimethylallyl chloride **25** was used as allylation reagent and, simultaneously, as a source of lithium chloride. Again, TUNEPHOS ligand **22** was used. Under a remarkably low catalyst-loading, 3-methyl-4-hexenoic acid **26** was obtained in 88% *ee* (Scheme 8).[2i] The enantioselective allylic alkylation through doubly deprotonated carboxylic acids may be considered a direct alternative to the traditional Tsuji-Trost protocols that starts from malonates and uses the detour via saponification and decarboxylation of the allylation products to alkenyl monocarboxylic acids.

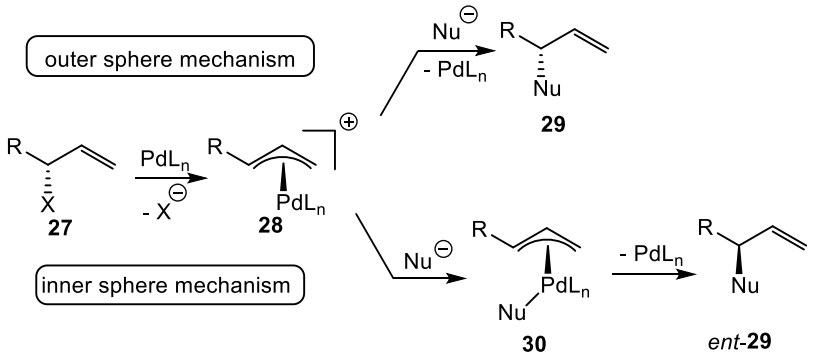
Nitriles are considered to be a derivative of carboxylic acids in the broader sense. Upon deprotonation, α-substituted benzyl nitriles form azaallenyl anions that were submitted to enantioselective rhodium-catalyzed

allylic alkylation – a protocol that leads to nitriles featuring a quaternary stereogenic center.[22]



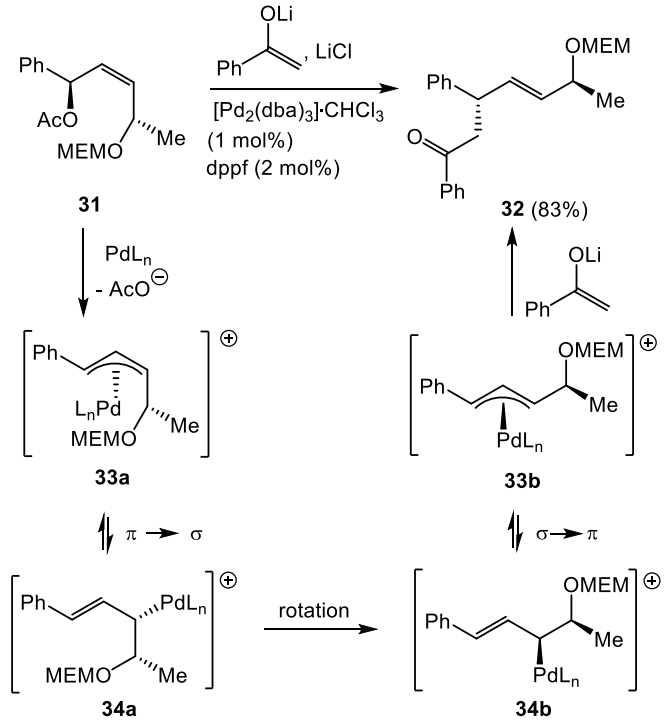
Scheme 8. Enantioselective allylic alkylation of doubly deprotonated acetic acid

Concerning the stereochemistry of the palladium-catalyzed allylic alkylation, two different pathways are discussed, as shown in Scheme 9: Both start with the intermediate π-allyl palladium complex **28** that forms from the racemic precursor **27** under inversion of configuration. Then, the outer-sphere mechanism postulates the nucleophile to approach from the face opposite to that occupied by the noble metal under formation of product **29**. According to the inner-sphere mechanism a pre-coordination of the nucleophile to palladium occurs to give intermediate **30** and, subsequently, the nucleophile approaches the allyl complex from the same face as the palladium is located, and the carbon-nucleophile bond forms under reductive elimination. As a stereochemical consequence, the outer-sphere mechanism leads to a net retention (product **29**), whereas the inner-sphere path results in net inversion (product *ent*-**29**) (Scheme 9). Early studies of the Tsuji-Trost reaction had revealed that "soft" carbon nucleophiles favor the outer-sphere mechanism, whereas "hard" carbon nucleophiles follow the inner-sphere mechanism, where a pK_a value of approximately 20 to 25 was considered – somewhat arbitrarily – the border between "hard" and "soft" nucleophiles.[23] In this context the lithium enolates derived from the carbonyl and carboxyl compounds discussed here are borderline cases.



Scheme 9. Competing mechanisms in the palladium-catalyzed allylic alkylation and their stereochemical outcome

In a first study, we used the diastereomerically and enantiomerically pure allylic acetate (*Z*)-**31** as a probe that was submitted to the palladium-catalyzed reaction with the lithium enolate of acetophenone according to our standard allylation procedure; however, achiral ligand dppf [1,1'-bis(diphenylphosphino)ferrocene] was used and the stereocontrol was dependent on the substrate. By means of this experiment, we tried to find out whether preformed lithium enolates follow the pathway of "soft" or "hard" nucleophiles. The reaction led to ketone **32** as a single diastereomer – a result that is significant in two ways: the new carbon-carbon bond had formed under overall inversion of the configuration, and the double bond has isomerized from (*Z*)-**31** to (*E*)-**32**. This stereochemical outcome is explained as follows: Firstly, the acetate leaving group in the starting material **31** is displaced by the noble metal under inversion. The intermediate π-allyl complex **33a** thus formed undergoes a conversion into the thermodynamically favored π-allyl complex **33b** through π-σ-π-interconversions involving the σ-complex **34a** and its rotamer **34b**. Finally, the lithium enolate attacks the π-allyl complex **33b** from the face opposite to the palladium. Thus, the observed overall inversion en-route from (*Z*)-**31** to (*E*)-**32** results from two substitutions each under inversion and the (*Z*)-(*E*)-double-bond isomerization (Scheme 10).[2f]



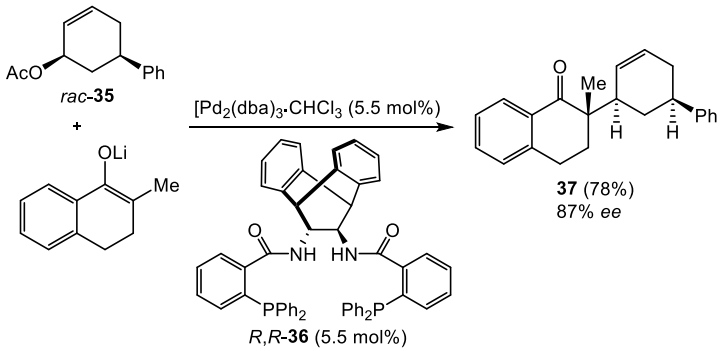
MEM = $CH_3O(CH_2)_2OCH_2$

Scheme 10. Palladium-catalyzed allylic alkylation of the probe (31). Evidence for the outer-sphere mechanism

The analogous stereochemical result was also observed with the lithium enolate of cyclohexanone. The mechanism proposed in Scheme 10 is furthermore supported by the fact that the (*E*)-diastereomer of alkene **31** reacts under overall retention when submitted to the palladium-mediated reaction with the lithium enolate of acetophenone. Clearly, the stereochemical result of these conversions supports the outer-sphere mechanism. In an earlier study,[24] we had submitted the acetate (*Z*)-**31** to a palladium-bis(diphenylphosphinomethane)-mediated reaction with malonate – a typical "soft" carbon nucleophile. The stereochemical result was the same as with the preformed enolates of acetophenone and cyclohexanone: Overall inversion under double bond isomerization.

These results were confirmed by a study of Trost, Xu, and Schmidt, who used the cyclic acetate *rac*-*cis*-**35** as a probe. The latter was submitted to an

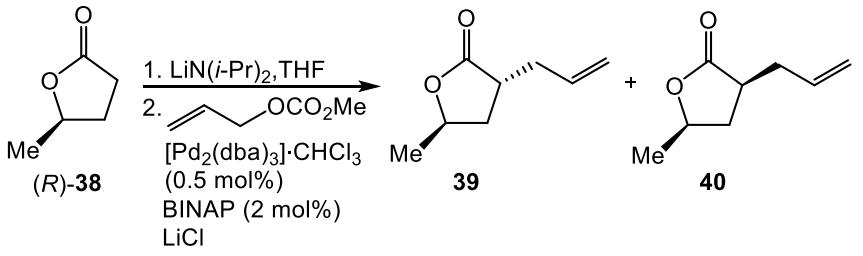
allylic alkylation with the lithium enolate of 2-methyltetralone. The reaction that was mediated by "Trost's ligand" (*R*,*R*)-**36** led to diastereomerically pure ketone **37** in 87% *ee*. Here again, the net retention in the allylic moiety results from a double inversion – a further proof of the outer-sphere mechanism (Scheme 11).[23b]



Scheme 11. Evidence for the outer-sphere mechanism by palladium-catalyzed allylation of 2-methyltetralone enolate with the probe rac-34

For obtaining a deeper insight into the mechanism of asymmetric allylic alkylations with preformed lithium enolates, Thiel and Patil performed theoretical calculations that are based on the results obtained by our group with (*R*)-γ-valerolactone **38**. This enantiomerically pure compound was submitted to our allylation protocol in the presence of lithium chloride using (*R*)- and (*S*)-BINAP as chiral ligands at the palladium. We noticed a clear mismatched combination in the reaction with (*R*)-BINAP resulting in a 56:44-ratio of diastereomeric products **39** and **40** (Table 1, entry 1). The matched combination of (*R*)-lactone **38** with (*S*)-BINAP, on the other hand, led to a high preference for the *trans*-diastereomer **39** over *cis*-**40** (entry 2).[15]

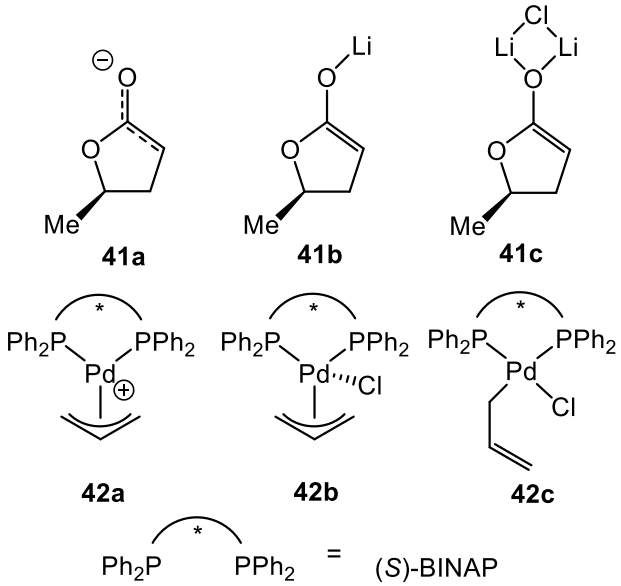
Table 1. Experimental and calculated diastereoselectivities of alkenes 39 and 40 obtained by allylic alkylation of (*R*)-γ-valerolactone 38



Entry	Ligand	Experimental diastereoselectivity *trans*-**39** : *cis*- **40**	Calculated* diastereoselectivity *trans*-**39** : *cis*- **40**
1	(*R*)-BINAP	56 : 44	62 : 38
2	(*S*)-BINAP	91: 9	90:10

*Calculated diastereomeric ratios obtained from the free energy differences of the two diastereomeric transition states, computed at the B3LYP-IV level

DFT calculations at B3LYP-I to B3LYP-IV levels were performed based on these experimental data in order to study the mechanism, while a focus was put on the role of lithium chloride. Three structures were considered in the calculation for the enolate of γ-valerolactone **38**: the ion pair **41a** with the negative charge delocalized, the O-bound tautomer **41b**, and the mixed aggregate **41c** with lithium chloride. On the other hand, the [(η^3-C_3H_5)Pd-(*S*)-BINAP] cation **42a** as well as the complexes [(η^3-C_3H_5)PdCl-(*S*)-BINAP] (**42b**) and [η^1-C_3H_5)PdCl-(*S*)-BINAP] (**42c**) were taken into account as reactive palladium complexes. (Fig. 1).[15,25]



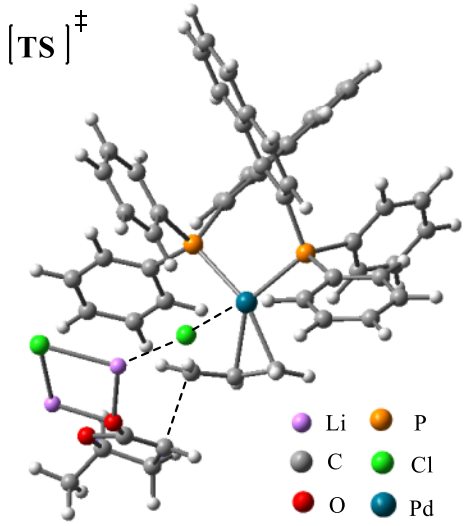


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Figure 1. Structures 41 and 42 considered in DFT calculations and calculated transition state for the allylic alkylation of lactone (*R*)-38 with palladium-(*S*)-BINAP

Based upon these structures, five different pathways for the approach of the enolate to allyl palladium complex were calculated and the relevant transition states were located. The experimental outcome in the combination of lactone **38** with (*S*)-BINAP (Table 1, entry 2) exclusively matched with the permutation of the mixed aggregate **41c** with the η^3-complex **42b** wherein chloride is bound directly to palladium. Moreover, the transition state leading to *trans*-lactone **39** has the lowest free energy of all the transition states calculated.

The transition-state model **43** resulting from the calculations, also shown in Figure 1, clearly supports the outer-sphere mechanism. The approach of the enolate to the allyl moiety from the face opposite to the transition metal is facilitated by a "tether" consisting of chlorine bound at palladium and lithium of the Li-O-Li-Cl-square. The fact that experimental and calculated product ratios of *trans*-**39**:*cis*-**40** also agree for the mismatched pair (*R*)-**39** with (*R*)-BINAP (Table 1, entry 1) underlines the reliability of the theoretical calculations.[15,25]

Compared to lithium enolates, silyl enol ethers and silyl ketene acetals that may be considered as silicon enolates are in general more stable and robust – at the expense, however, of diminished reactivity or even sluggishness. For being used in transition metal-catalyzed allylic alkylations, silyl enol ethers require an activation by fluoride. Protocols that provide high enantioselectivity were elaborated using palladium[3b,26] or iridium[27] catalysis. The more nucleophilic silyl ketene acetals that function as ester-enolate equivalents were used in asymmetric allylic alkylations partly without activation under palladium,[28] copper,[29] or iridium[30,31] catalysis.

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