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Palladium-Catalyzed Diastereoselective and Enantioselective Allylic Alkylations of Ketone Enolates

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Abstract: Lithium and magnesium enolates of cyclohexanone undergo palladium-catalyzed allylic alkylations under mild conditions. Diastereoselectivity and enantioselectivity are observed when the diphenyl- and dimethyl-substituted allylic substrates **1a** and **1b** are reacted with cyclohexanone or ethyl mesityl ketone. The lithium enolates of cyclohexanone, cyclopentanone and α-tetralone lead to the alkylations products **12**–**14** in an enantioselective manner. Axially chiral biphenyl- and binaphthyl-bisphosphanes provide high enantioselectivity and/or diastereoselectivity. In the case of the lithium enolates, the presence of lithium chloride is also crucial to reactivity and stereoselectivity. The stereochemical outcome of the allylic alkylation of cyclohexanone and acetophenone has been investigated by the palladium-catalyzed reaction of their lithium enolates with the *cis*/*trans* isomeric alkenes (*Z*)-**18** and (*E*)-**19**. It turns out that the preformed, non-stabilized enolates attack π-allyl-palladium complexes generated *in situ* from the face opposite to the noble metal thus following the stereochemical pathway of soft, stabilized carbanions.

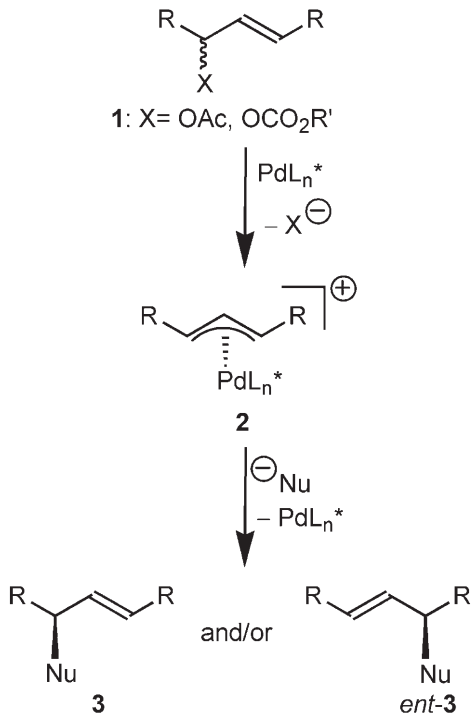
Keywords: allyl complexes; asymmetric synthesis; lithium; nucleophilic additions; stereoselectivity

Introduction

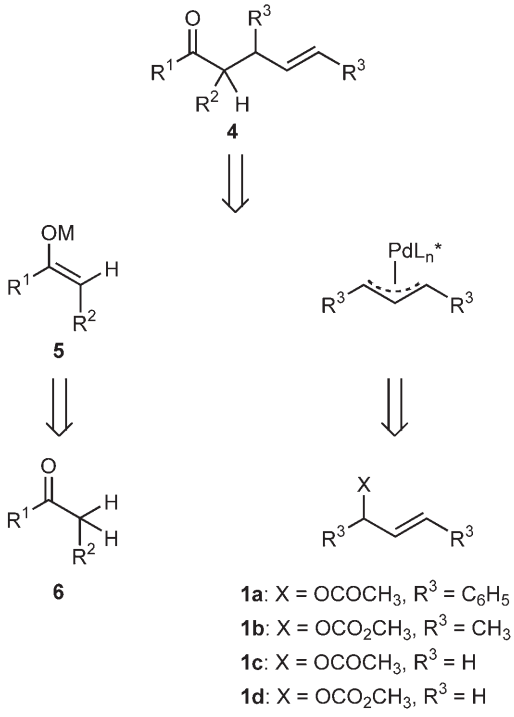
The palladium-catalyzed allylic alkylation, the Tsuji–Trost reaction, has developed into an exceptionally useful and versatile method for carbon-carbon and carbon-heteroatom bond formation.[1] This holds in particular for the numerous enantioselective variants developed in recent years. In general, the asymmetric allylic alkylation follows the route outlined in Scheme 1. Racemic starting material **1** is converted into non-racemic product **3** or *ent*-**3** due to chiral ligands L* at the noble metal that direct the approach of the nucleophile predominantly to one of the diastereotopic termini of the π-allyl complex **2**. As far as carbon nucleophiles are concerned, there has been a substantial limitation: For about two decades, almost exclusively "soft", stabilized carbanions have been used as carbon nucleophiles. Among them, symmetrically substituted nucleophiles were applied preferentially, and the allylation of malonates [Nu=CH-$(CO_2R')_2$] became a kind of standard protocol of the Tsuji–Trost reaction (Scheme 1), which was applied very frequently when the performance of novel ligands L* was tested. It is evident that this protocol leads to the formation of just one stereogenic center in the allylic position.[2]

If, on the other hand, synthesis is aimed at alkenyl ketones **4** with stereogenic centers in the homoallylic ($R^2 \neq H$, $R^3 = H$) or in both the allylic and the homoallylic position ($R^2 \neq H$, $R^3 \neq H$) the suitable prochiral nucleophiles are preformed, non-stabilized ketone enolates **5**,[3] as shown in the retrosynthetic Scheme 2.

In spite of the obvious synthetic utility of this approach, only very few attempts have been made to combine preformed enolates with *in situ* generated allyl-palladium complexes.[4] In recent years, a few enantioselective protocols have been elaborated for the palladium- and iridium-catalyzed allylic alkylation of ketones, most of them using the corresponding enol stannanes[5], enol silanes[6a,b] and enamines.[6c] Although it has been shown that lithium enolates can also serve as nucleophiles,[5a,c–e] there remained still substantial limitations inasmuch as most enolate precursors chosen for this purpose contain just one acidic proton, so that double or multifold alkylation as well as later racemization can be excluded *per se*. Thus, the enantioselective allylic alkylation of "unrestricted" ketones still remained as an unsolved problem.[7]



Scheme 1. "Standard" version of an enantioselective Tsuji–Trost allylic alkylation, $Nu = CH(CO_2R')_2$.

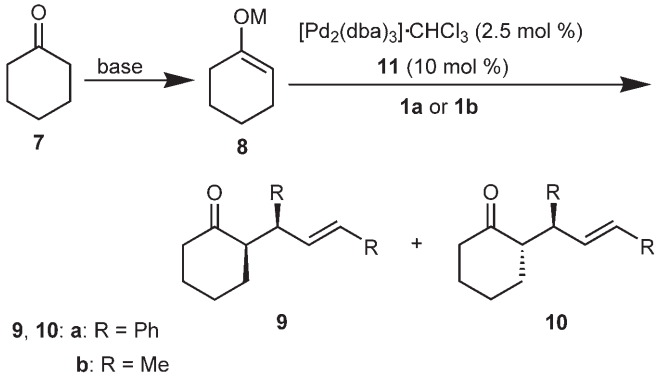


Scheme 2. Retrosynthesis of alkenyl ketones **4** based on ketones **6** and allylic substrates **1a–d** *via* enolates **5** and allylpalladium complexes. R^1 = alkyl, aryl, R^2 = alkyl.

However, a detour has been elaborated recently based on ketone-derived allyl enol carbonates or allyl β-keto esters that liberate an enolate upon treatment with a palladium catalyst under concomitant extrusion of carbon dioxide.[8] Here, we describe the direct stereoselective palladium-catalyzed reaction of allylic substrates **1a–d** with magnesium and lithium enolates of unrestricted ketones.[9]

Results and Discussion

Cyclohexanone **7** was chosen as the suitable representative of a ketone that offered the advantage of a fixed configuration (*E*) of the enolate **8**. Its reactions with racemic disubstituted allylic substrates **1a** and **1b** were investigated first with respect to diastereoselectivity that should be obtained when two adjacent stereogenic centers are formed in alkenyl ketones **9** and **10**. Then, the problem of enantioselectivity was tackled (Scheme 3).



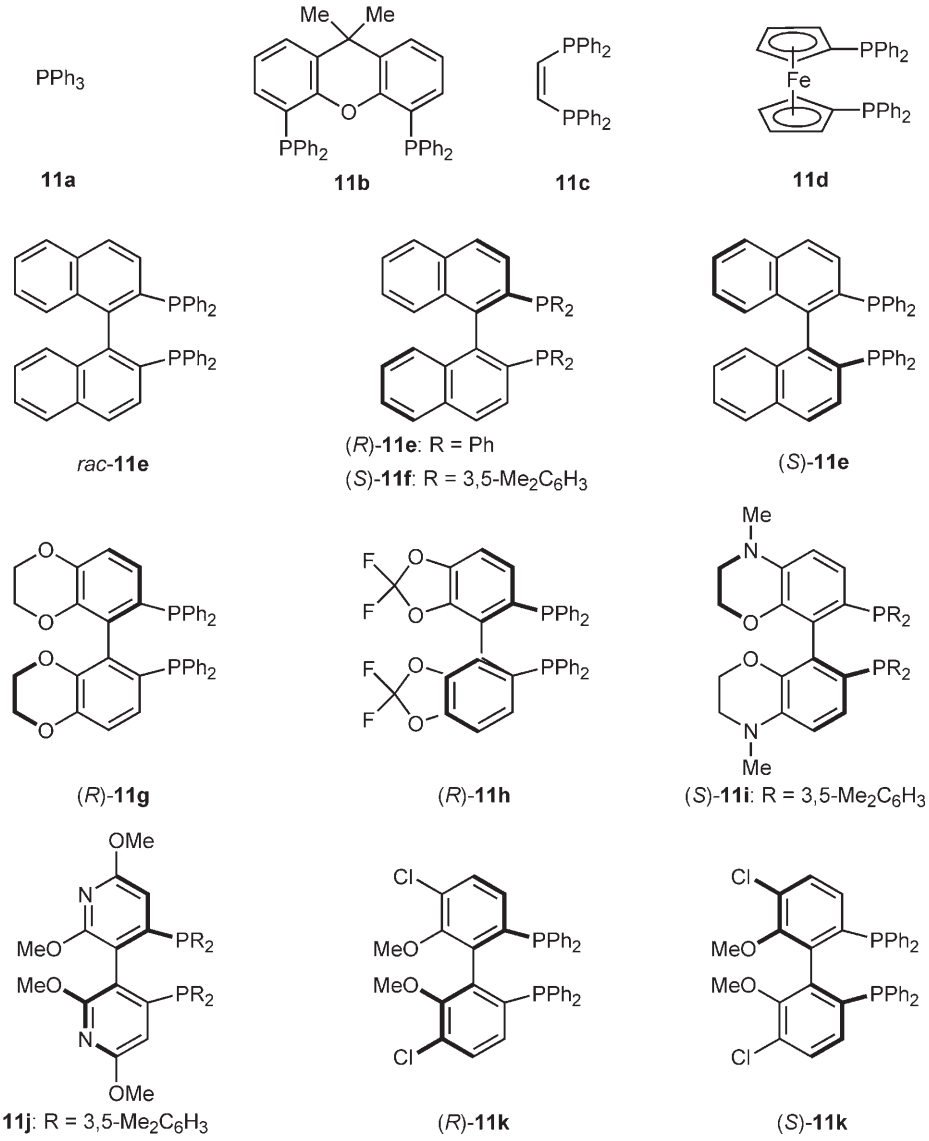
Scheme 3. Diastereoselective and enantioselective palladium-catalyzed allylic alkylation of cyclohexanone.

Thus, the influence of the base, used for the deprotonation of the ketone, the ligand at the palladium and the effect of additives were investigated; the results are shown in Table 1. In all cases, tris(dibenzylideneacetone)dipalladium-chloroform ($[Pd_2(dba)_3]\cdot CHCl_3$)[10] was used as the precursor of the catalyst that formed upon treatment with the corresponding phosphane or bisphosphane ligands **11a–k**, shown in Scheme 4.[11] They exhibit a major influence on diastereoselectvity. In all cases, the *syn* diastereomer formed predominantly. Thus, all bisphosphane ligands **11b–d** were superior to triphenylphosphane (Table 1, entries 1–5), the ferrocene derivative **11d** being the most efficient (entries 4 and 5). The use of lithium or potassium hexamethyldisilazide (entries 6 and 7) did not improve the diastereoselectivity. The additive lithium chloride led to a significant enhancement of the diastereoselectivity (entry 8). Further improvement resulted when, instead of the lithium, the magnesium enolate was used (entry 9) in the combination with the dppf ligand **11d**. As aside from diastereoselectiv-

Table 1. Palladium-catalyzed diastereoselective and enantioselective allylic alkylation of cyclohexanone.

Entry	Substrate	Base/Additive	Ligand	Temperature [°C]	Product	Conversion [%][a]	*dr*	*ee*
1	**1a**	LiN(*i*-Pr)$_2$	**11a**	0	**9a**, **10a**	45	53:47	-
2	**1a**	LiN(*i*-Pr)$_2$	**11b**	0	**9a**, **10a**	>97	81:19	-
3	**1a**	LiN(*i*-Pr)$_2$	**11c**	0	**9a**, **10a**	>97	83:17	-
4	**1a**	LiN(*i*-Pr)$_2$	**11d**	20	**9a**, **10a**	>97	85:15	-
5	**1a**	LiN(*i*-Pr)$_2$	**11d**	0	**9a**, **10a**	>97	87:13	-
6	**1a**	LiN(SiMe$_3$)$_2$	**11d**	0	**9a**, **10a**	>97	90:10	-
7	**1a**	KN(SiMe$_3$)$_2$	**11d**	0	**9a**, **10a**	>97	60:40	-
8	**1a**	LiN(*i*-Pr)$_2$/LiCl	**11d**	0	**9a**, **10a**	>97	92:8	-
9	**1a**	ClMgN(*i*-Pr)$_2$	**11d**	0	**9a**, **10a**	>97	97:3	-
10	**1a**	ClMgN(*i*-Pr)$_2$	*rac*-**11e**	0	**9a**, **10a**	>97	99:1	-
11	**1a**	ClMgN(*i*-Pr)$_2$	(*R*)-**11e**	0	**9a**, **10a**	>97 (67)[b]	99:1	99[c]
12	**1b**	LiN(*i*-Pr)$_2$/LiCl	*rac*-**11e**	−15	**9b**, **10b**	95	90:10	-
13	**1b**	LiN(*i*-Pr)$_2$/LiCl	(*R*)-**11e**	−78 to −8	**9b**, **10b**	35[b]	97:3	96[d]

[a] Determined from the ^{1}H NMR spectra of the crude reaction mixture.
[b] Isolated yield.
[c] Determined by HPLC on a chiracel OJ column.
[d] Determined by GC on a Lipodex E column.



Scheme 4. Ligands used for stereoselective allylic alkylations of ketone enolates.

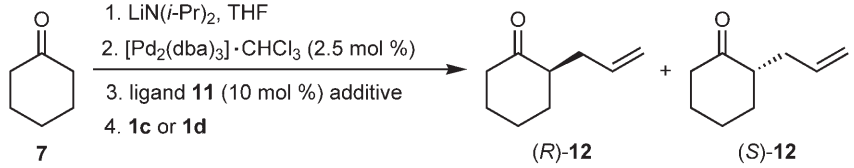
ity, enantioselectivity, was targeted in addition, the search for a chiral phosphane ligand was obvious. Thus racemic BINAP (**11e**) was tested and led to a diastereomeric ratio of 99:1, when the magnesium enolate of cyclohexanone was used (entry 10).

Consequently (*R*)-BINAP (**11e**) was used as an enantiomerically pure ligand to bring about enantioselectivity in the allylic alkylation. Indeed, the *syn*-configured diastereomer **9a** was obtained not only in a high diastereoselectivity but also in a remarkable enantiomeric excess of 99% *ee*, as determined by HPLC on a chiral column.

Most of palladium-catalyzed allylic alkylations with various ligands have been investigated using the 1,3-diphenyl-disubstitution pattern of the allylic substrate **1a**. On the contrary, the 1,3-dialkyl-substituted analogues have been employed by far less frequently. Thus, racemic carbonate **1b** was submitted to the palladium-catalyzed reaction with the lithium enolate of cyclohexanone. With this substrate, the magnesium enolate reacted in a very sluggish manner, and, in case of the lithium enolate, the additive lithium chloride was also essential for reactivity and selectivity. Thus, diastereoselective formation of *syn*-product **9b** was observed when the reaction was mediated with racemic BINAP (**11e**), the diastereomeric ratio amounting to 90:10 (entry 12). Whereas a high degree of conversion was obtained with the racemic ligand **11e**, a remarkably lower yield was reached with the optically pure ligand (*R*)-**11e**. However, both remarkable diastereoselectivity was observed and the enantiomeric excess of the isolated product **9b** amounted to 96% *ee* (entry 13) The low yield combined with the fact that recovered starting allylic carbonate **1b** was enantiomerically enriched suggest the idea of a kinetic resolution in course of the allylic alkylation.[12]

The palladium-catalyzed reaction of the enolate **8** with allyl acetate **1c** and allyl methyl carbonate **1d** was investigated next. As the reaction leads to the formation of just one stereogenic center, this type of enantioselective allylation of simple ketones appears to be rather facile. There is, however, no restriction that prevents double allylation and particularly a later racemization, so that just the simplicity of the cyclohexanone substrate makes it very challenging.

As the axially chiral bisphosphane ligands had proved themselves to be most efficient in the diastereoselective and enantioselective allylic alkylations with the substrates **1a** and **1b**, this type of ligand was also applied in the enantioselective allylation of cyclohexanone, shown in Scheme 5. In all cases the lithium enolate **8** was used as the nucleophile. Among the ligands tested, BINAP (**11e**) provided substantial enantioselectivity. However, the selectivity was strongly influenced by the metal salts used as additives (Table 2, entries 1 and 6 *vs.* entries 2–5 and 7–13). Best results



Scheme 5. Palladium-catalyzed enantioselective allylation of cyclohexanone.

Table 2. Palladium-catalyzed enantioselective allylation of cyclohexanone.

Entry	Substrate	Ligand	Additive	Temperature [°C]	Product	Yield[a]	*ee*
1	**1c**	(*S*)-**11e**	-	−30	(*S*)-**12**	40	32
2	**1c**	(*S*)-**11e**	$ZnBr_2$	−20	(*S*)-**12**	15	70
3	**1c**	(*S*)-**11e**	LiCl	−78	(*S*)-**12**	53	75
4	**1d**	(*S*)-**11e**	LiCl	−78	(*R*)-**12**	73	97
5	**1d**	(*S*)-**11e**[b]	LiCl	−78	(*S*)-**12**	87	80
6	**1d**	(*R*)-**11e**	-	−78	-	-[c]	-[d]
7	**1d**	(*S*)-**11f**	LiCl	−78	(*R*)-**12**	68	94
8	**1d**	(*R*)-**11g**	LiCl	−78	(*R*)-**12**	65	91
9	**1d**	(*R*)**11h**	LiCl	−78	(*R*)-**12**	40	92
10	**1d**	(*S*)-**11i**	LiCl	−78	(*S*)-**12**	71	93
11	**1d**	(*S*)-**11j**	LiCl	−78	(*S*)-**12**	74	95
12	**1d**	(*S*)-**11k**	LiCl	−78	(*S*)-**12**	76	98
13	**1d**	(*R*)-**11k**	LiCl	−78	(*R*)-**12**	72	>98

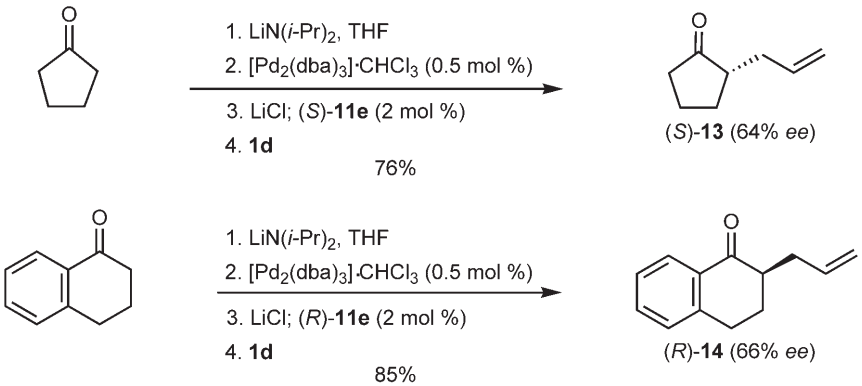
[a] Isolated distilled products.
[b] Catalyst loading: 0.025 mol% $[Pd_2(dba)_3]\cdot CHCl_3$, 0.1 mol% ligand.
[c] Traces.
[d] Not determined.

were obtained again with lithium chloride (entries 3–5 and 7–13). In addition, the use of allyl carbonate **1d** instead of allyl acetate **1c** brought about an improvement of enantioselectivity (entries 3 and 4). Thus, allylation occurred in 97% *ee*, when mediated by (*R*)-BINAP (**11e**). Remarkably, the reaction smoothly occurred at −78 °C. Under these conditions, the additive lithium chloride was also crucial to reactivity: in the absence of the salt, no reaction took place (entry 6) at that temperature, a result that clearly underlines the enhanced reactivity of the lithium enolate due to the known[13] desaggregation by lithium chloride. As a consequence, racemization of the allylation product **12** was widely suppressed. The standard catalyst loading was 2.5 mol% of $[(Pd_2(dba)_3]\cdot CHCl_3$ and 10 mol% of the chiral ligand. However, the amount of palladium could be as low as 0.05 mol% and 0.1 mol% of the ligand, as shown by the allylation that was mediated by (*S*)-BINAP (**11e**) and gave (*S*)-**12** in 80% *ee* and 87% isolated yield (entry 5). Under the standard conditions that included the presence of lithium chloride and a reaction temperature of −78 °C, various axially chiral bisphosphane ligands that are commercially available were tested. The results are shown in entries 7–13 of Table 2. As a result of the optimization study, the BIPHEP-type ligand (*R*)- and (*S*)-**11k** provided the highest degrees of enantioselectivity and permitted us to obtain enantiomeric (*R*)- and (*S*)-allylcyclohexanone in 98% and >98% *ee*, respectively, the chemical yields ranging from 72 to 76%.[14] It should be mentioned that the source of the precatalyst $[(Pd_2(dba)_3]\cdot CHCl_3$ has substantial influence on the enantioselectivity.

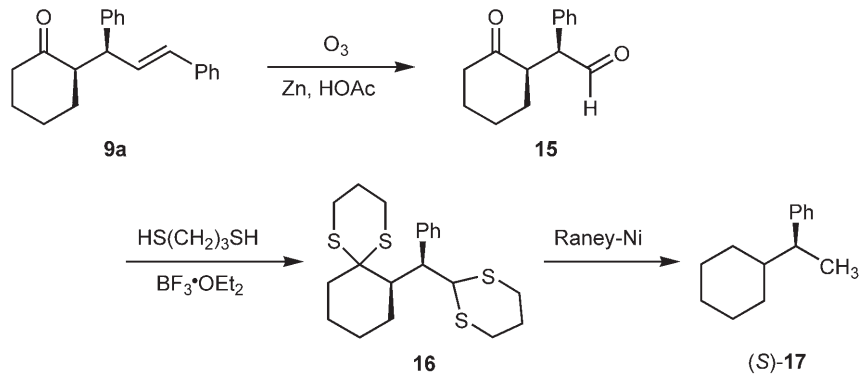
The enantioselective allylation was also studied with cyclopentanone and α-tetralone to give the olefinic ketones **13** and **14** in 64 and 66% *ee*, respectively, when the reaction was mediated with (*S*)- and (*R*)-BINAP (**11e**), as shown in Scheme 6. Particularly in the case of allyltetralone **14** a partial racemization might be responsible for the relatively low enantiomeric excess.

The determination of the absolute configuration of the allylation products **12**–**14** was possible based on the comparison of their optical rotations with the data described in the literature.[15] In addition, the CD spectrum of (*R*)-**12**, displayed a significant positive Cotton effect at 285 nm, again in agreement with known data.[15b] For the allylation products **9** and **10**, the relative configuration had to be assigned first. In case of the diphenyl derivative **9a** that formed as the major diastereomer, a crystal structure analysis revealed the *syn*-configuration.[9a] The absolute configuration of the product **9a**, obtained when the allylation was mediated by (*R*)-BINAP (**11e**), was determined to be (*2R,1′S*) by the following chemical correlation (Scheme 7). The ozonolysis of **9a** led to the keto aldehyde **15** that was converted without purification into the thioacetal **16** by treatment with 1,3-propanedithiol, obtained in 13% yield after a relatively tedious chromatography. Finally, the desulfurization with Raney nickel gave the crude hydrocarbon **17**, which showed an optical rotation $[\alpha]_D^{20}$ of +6.8. As the rotation of (*R*)-**17** has been reported to be −8.6,[16] the (*S*)-configuration has to be assigned to the degradation product **17** and – as a consequence of a change in priorities – the stereogenic α-carbonyl carbon of the allylation product **9a** is (*R*)-configured.

In the case of the allylation products **9b**/**10b**, prepared previously by different routes,[8a,17] the *syn*-configuration was assigned to the major diastereomer **9b**. This stereoisomer has been obtained from an addition of 1-pyrrolidino-1-cyclohexene to CpMo(NO)(CO)(η^3-dimethylallyl) cation and subsequent decomplexation with moderate diastereoselectivity.[17b] Nevertheless, the diastereomers differ in some of the ^{1}H NMR signals, so that a comparison permits us to assign the *syn*-configuration to the main product **9b**, obtained form the palladium-catalyzed reaction. Another support for this assignment comes from the comparison of the ^{1}H NMR spectra of the diastereomeric ketones **9b** and **10b** with those of *syn*- and *anti*-2-(1-methyl-2-propenylcyclohexanone), the chemic shift of the vinylic 2′-H being characteristic.[8a] The ab-



Scheme 6. Enatioselective allylation of cyclopentanone and α-tetralone.

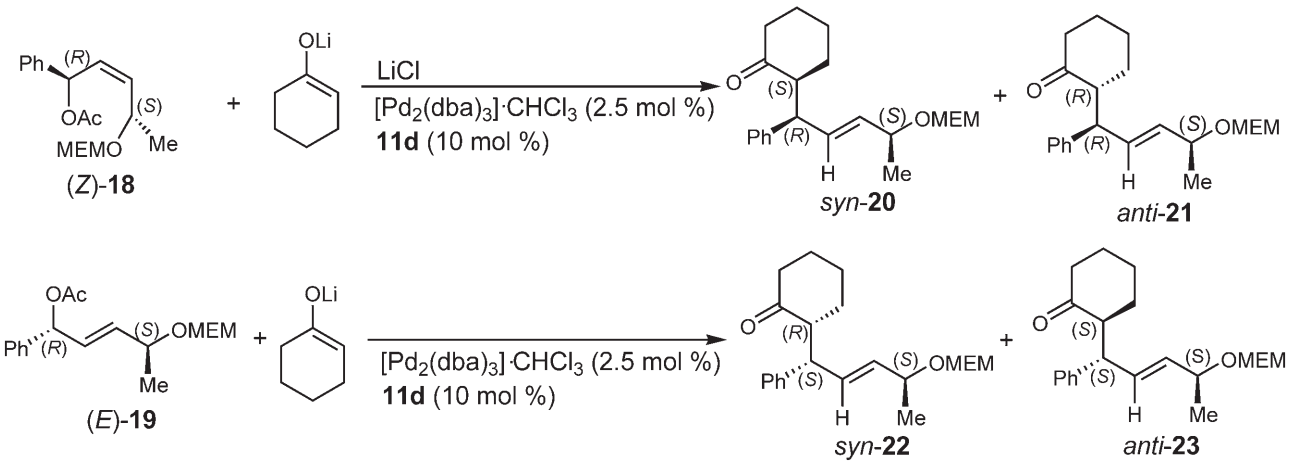


Scheme 7. Assignment of configuration to alkenyl ketone **9a** by chemical correlation.

solute configuration of **9a** was finally determined to be (*2R,1′S*) by CD spectroscopy. Similarly to (*R*)-allylcyclohexanone **12**, it shows a strong positive Cotton effect at 290 nm. As this effect is determined principally by the stereogenic center at the α-carbonyl carbon atom, it unambiguously shows that the ketones (*R*)-**12** and (*2R,1′S*)-**9b** are homochiral with respect to that center.

For the reaction of a nucleophile with π-allylpalladium complexes, two different paths have been discussed: The nucleophile either approaches the π-allyl moiety from the face opposite to the palladium, as outlined in Scheme 1, or it is first coordinated to the transition metal and attacks the π-system from the same face. It is generally accepted and supported by manifold evidence that "soft" carbon nucleophiles follow the first pathway, whereas "hard" nucleophiles have been shown to react through a precoordination, thus following the second route.[1,2] Although somewhat arbitrarily, a border between the two types of carbon nucleophiles has been set in such a way that conjugate bases of carbon acids with $pK_a < 25$ have been classified as "soft" nucleophiles, whereas the "hard" species are derived from carbon acids with $pK_a > 25$.[2c] Cyclohexanone, whose allylation was investigated here is a borderline case in this context inasmuch as its pK_a value amounts to 26.4 according to Bordwell's scale.[18] Thus, we have studied the stereochemical outcome of its palladium-mediated allylation because, at a glance, it is not predictable whether is will react like a "hard" or a "soft" nucleophile. It should be pointed out, however, that in early studies the lithium and the potassium enolates of acetone have been shown to attack π-allyl-palladium complexes from the face opposite to the noble metal.[4a,b] As the desaggregation with lithium chloride seems to play an important role in our approach, the stereochemical outcome was investigated with the lithium enolate of cyclohexanone in the presence and in the absence of lithium chloride.

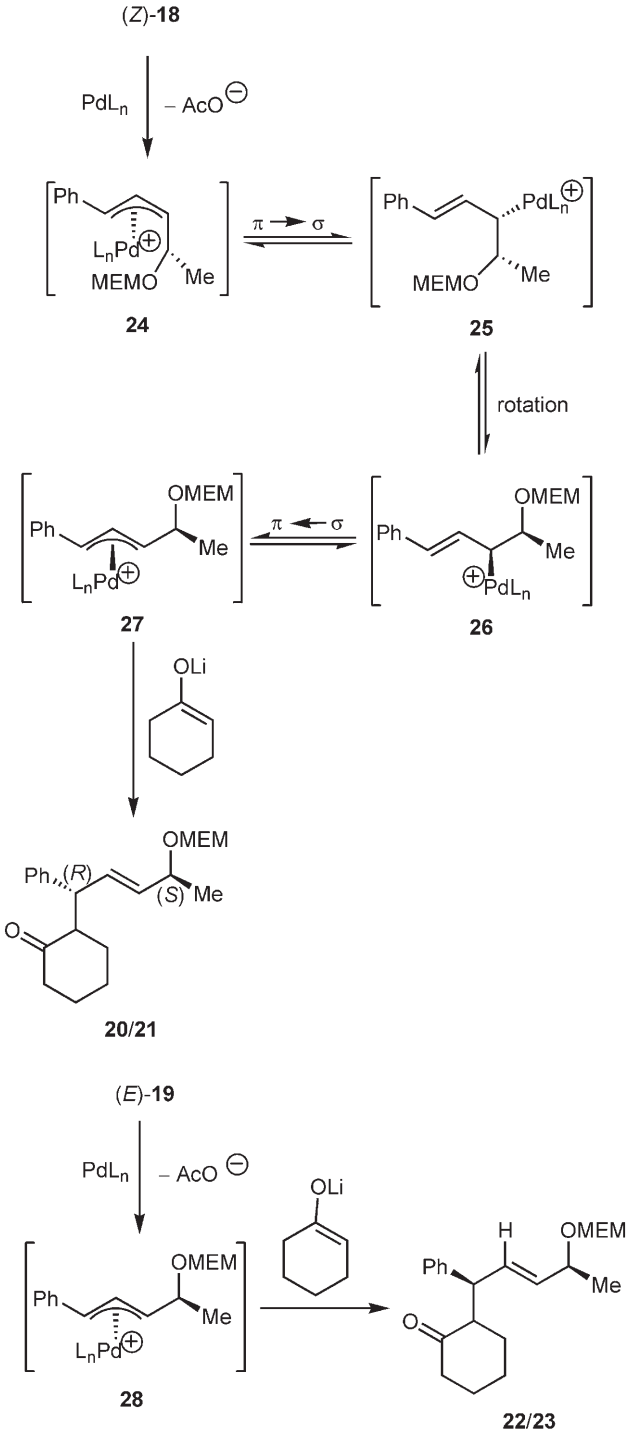
The enantiomerically and diastereomerically pure alkenes (*Z*)-**18** and (*E*)-**19** served as probes to study the stereochemical outcome.[19] They are acyclic and unrestricted, identical in the configuration of their stereogenic carbon centers, but they differ in the configuration of the double bond. Their stereogenic center adjacent to the MEM ether group should not be touched during the allylic substitution (Scheme 8).



Scheme 8. Formation of diastereomeric products **20–23** from palladium-catalyzed reactions of cyclohexanone enolate with (*Z*)-**18** and (*E*)-**19**, respectively.

When the reaction of the lithium enolate **8** (M = Li) of cyclohexanone with (*Z*)-**18** was mediated by $[Pd_2(dba)_3]\cdot CHCl_3$ and the achiral ligand **11d** in the presence of lithium chloride, a mixture of *syn*-**20** and *anti*-**21** resulted in a ratio of 79:21. The analogous reaction with (*E*)-**19**, preformed in the absence of lithium chloride, led to the diastereomeric products *syn*-**22** and *anti*-**23**, in a 57:43-mixture. Both mixtures were separated by column chromatography. The assignment of the relative configurations in the *syn*/*anti*-diastereomers **20**/**21** and **22**/**23** was possible based on the ^{1}H NMR spectra. The characteristic differences in shift and coupling constants were exhibited by the α-carbonyl, the benzylic and the vinylic protons in each of the diastereomers. To give an example, the signal (ddd) of the vinylic proton (indicated in the formulas **20**–**23**) shows up at lower field in the *syn*-isomers **20** and **22**, and at higher field in the *anti*-diastereomers **21** and **23**. This also holds for the diastereomers *anti*-**10a** and *syn*-**9a**, the configuration of which was determined unambiguously by a crystal structure analysis. The configuration of the stereogenic center at the α-carbonyl carbon atom was determined by CD spectroscopy. Thus, the diastereomers *syn*-**20** and *anti*-**23** showed a negative Cotton effect at 295 nm, indicating the (*S*)-configuration in the cyclohexyl ring. Accordingly, *anti*-**21** and *syn*-**22** displayed a positive Cotton effect at the same wavelength, so that in analogy to (*R*)-allylcyclohexanone **12** the (*R*)-configuration could be assigned to the α-carbonyl center. This result clearly shows that in the reaction of (*Z*)-**18**, the leaving group has been replaced under inversion of the configuration, whereas, starting from (*E*)-**19**, the allylic substitution has occurred under retention in the allylic moiety. In both reactions the enantiofacial selectivity of the enolate was lower than that observed with the substrates **1a** and **1b**.

The stereochemical outcome is rationalized as follows: The substrate (*Z*)-**18** reacted with the nucleophile in an overall inversion due to a π–σ–π-interconversion,[20] observed already previously with that substrate,[19] as shown in Scheme 9. This is clearly indicated by the conversion of the (*Z*)-double bond in the starting material into (*E*)-configured products **20** and **21**. Thus, the π-complex **24** formed initially from the substrate (*Z*)-**18** was converted *via* the σ-intermediate **25** and its rotamer **26** into the π-complex **27**. This is finally attacked by the enolate from the face opposite to the palladium. Thus, the overall inversion results from two substitutions occurring each under inversion and an interconversion of the (*Z*)- into an (*E*)-double bond through the π–σ–π-mechanism.



Scheme 9. Rationale for the stereochemical outcome in the reaction of allylic substrates (*Z*)-**18** and (*E*)-**19** with the lithium enolate of cyclohexanone.

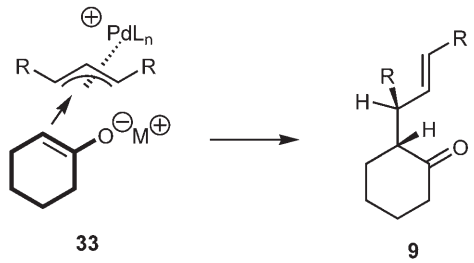
The formation of diastereomeric products **22** and **23** from the substrate (*E*)-**19** is plausibly rationalized by a two-fold inversion: First, in the formation of the π-complex **28** and, second, by an approach of the nucleophilic enolate. In this case, there is no "need" for a thermodynamically controlled (*Z*)- to (*E*)-interconversion. As a result, it has been shown that the lithium enolate of cyclohexanone, despite the presence or absence of lithium chloride, attacks π-allyl-palladium complexes from the face opposite to the noble metal,

thus following the stereochemical pathway of "soft" nucleophiles.

This stereochemical outcome was also proven for the lithium enolate of acetophenone, using again the isomeric alkenes (*Z*)-**18** and (*E*)-**19** as probes. In both experiments, lithium chloride was used as an additive, and dppf (**11d**) served as the achiral ligand. As shown in Scheme 10, alkenyl ketones **30** and **32** were obtained upon treatment of the lithium enolate **29** with (*Z*)-**18** or (*E*)-**19**, respectively. The products formed in a regioselective and diastereoselective manner, and the ratio of these isomers surpassed 95:5 in both cases. They are also pure enantiomers, as their synthesis started from the enantiomerically pure alkenes (*Z*)-**18** and (*E*)-**19**.

Here again, the products **30** and **32** differ with respect to the configuration of the benzylic stereogenic center: the former diastereomer results from an overall inversion, the latter from an overall retention. Analogously to the case of cyclohexanone, the formation of the diastereomer **30** is explained by an inversion during the formation of the π-allylpalladium complex, a π–σ–π-conversion, which leads to (*Z*)- to (*E*)-isomerization, and a final inversion occurring during the attack of the nucleophile to the π-allyl-palladium complex (*cf.* Scheme 9). The overall retention, on the other hand, that is observed in the formation of the diastereomer **32** from (*E*)-**19** is rationalized as the result of a double inversion. The configurations at the stereogenic centers formed upon the allylic alkylation were proved by ozonolysis of the alkenes **30** and **32** which gave the enantiomeric aldehydes (*R*)- and (*S*)-**31**, respectively. As their optical rotation is known,[21] a comparison permitted us to assign the absolute configuration to them and, as a consequence, to determine the relative configuration to the allylation products **30** and **32**. Thus, it has been demonstrated that the lithium enolates of both acetophenone and cyclohexanone follow the stereochemical pathway of "soft" nucleophiles in the palladium-catalyzed allylic alkylation.

Based thereupon, the diastereoselectivity observed in the reaction of cyclohexanone with the diphenyl- and dimethyl-substituted allylic systems **1a** and **1b**, is rationalized by assuming the "closed" transition state model **33**. It seems to be plausible that in this approach of the enolate to the π-allyl-palladium complex, a Coulomb attraction between the negatively charged oxygen of the enolate and the complexed allyl cation moiety might be effective (Scheme 11).

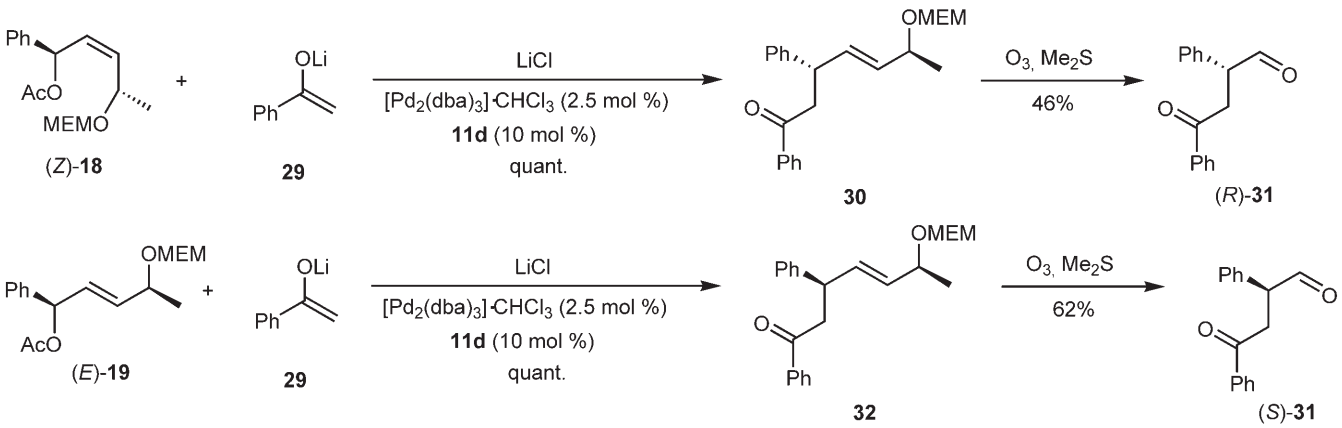


33 **9**

M = Li, MgCl; R = Ph, Me

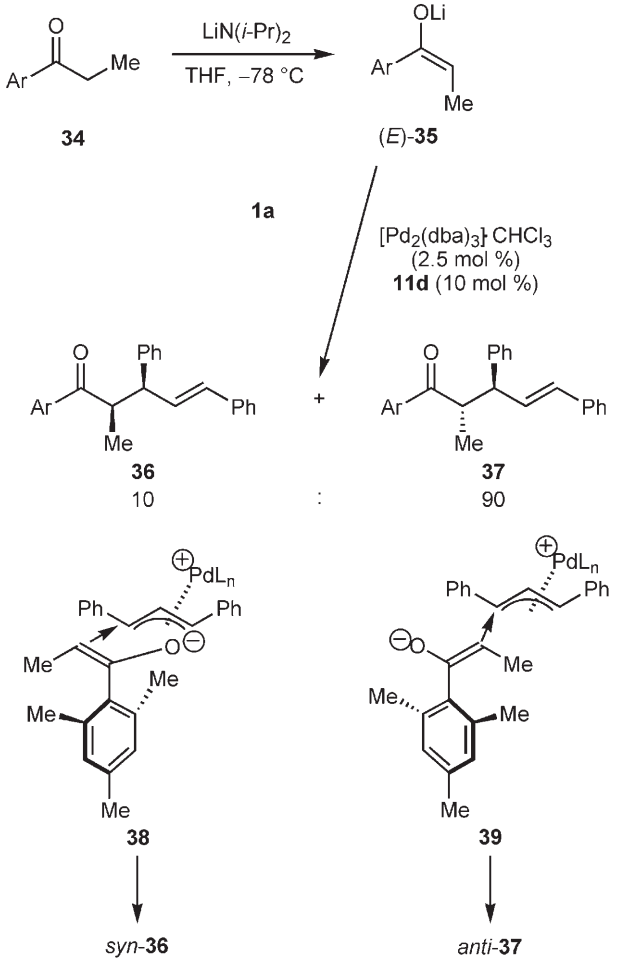
Scheme 11. Transition-state model for the diastereoselective allylic alkylation of cyclohexanone enolate **8**.

In order to support this model, the enolate **35** of ethyl mesityl ketone **34** was submitted to a reaction with allyl acetate **1a** following the above protocol and using the achiral ligand dppf (**11d**). The treatment of the ketone **34** with lithium diisopropylamide is known[3] to give the (*E*)-configured enolate **35** in a highly selective manner. This was proven by a determination of the *E*:*Z* ratio that amounted to 96:4 and changed only slightly (to 92:8) under the influence of $[Pd_2(dba)_3]\cdot CHCl_3$, shown by quenching with chlorotrimethylsilane. As both the enolate **35** and the deprotonated cyclohexanone **8** have *E*-configuration, the predominant formation of *syn*-product **36** was expect-



Scheme 10. Formation od diastereomeric products **30** and **32** from the palladium-catalyzed allylation of acetophenone with (*Z*)-**18** and (*E*)-**19** through the lithium enolate **29**.

ed at the expense of *anti*-**37**. Surprisingly however, the latter diastereomer was found to be the major product, and the *syn*-**36**:*anti*-**37** ratio was determined to be 10:90 (Scheme 12). The structure of the main diastereomer **37** was assigned based on a crystal structure analysis.[7a]



Scheme 12. Diastereoselective allylic alkylation of ethyl mesityl ketone **34** and transition-state models.

It seems to be possible that a torsion of the mesityl group with respect to the enolate plane leads to an unfavorable steric interaction between the allyl moiety and one of the *ortho* methyl groups in the cyclic transition-state model **38**. The alternative open transition-state model **39** could avoid this type of interaction so that it becomes at least less unfavorable than the reaction pathway through **38**. When the allylation of the enolate **35** with diphenylallyl acetate **1a** was mediated with (*R*)-BINAP (**11e**), the *syn*-diastereomer **36** formed in 88% *ee*, as shown by NMR measurement in the presence of the chiral shift reagent $Eu(hfc)_3$.

Conclusions

It has been shown, in summary, that palladium-catalyzed allylic alkylations are feasible with preformed, non-stabilized lithium and magnesium enolates of simple ketones. Not only diastereoselective but also highly enantioselective protocols have been elaborated. In the case of lithium enolates, the presence of lithium chloride permits us to perform the allylation at low temperatures due to an enhancement of reactivity by desaggregation of the enolate structures. Enantioselectivity is provided by using axially chiral bisphosphane ligands of the BINAP and BIPHEP types. Thus, it becomes more and more evident that tools are now available that permit to combine allylpalladium and preformed enolate chemistry.

Experimental Section

Characterization data are available in a supporting information file. $[Pd_2(dba)_3]\cdot CHCl_3$ was purchased from Strem Chemicals, Inc. Allyl acetate **1c** and methyl allyl carbonate **1d** are commercially available. (*E*)-1,3-Diphenylprop-2-enyl acetate (**1a**) was prepared according to ref.[22]

(*E*)-Methyl (Pent-3-en-2-yl) Carbonate (1b)[23]

A 500-mL three-necked flask was equipped with a dropping funnel, closed with a septum, a magnetic stirrer, a septum, an inlet thermometer and a connection to the combined nitrogen/vacuum line. The air in the flask was replaced by nitrogen and a 3 M solution of CH_3MgCl in THF (100 mL, 300 mmol) was added through a cannula. The solution was diluted with THF (125 mL) and cooled to 0 °C. Under stirring, (*E*)-crotonaldehyde (18.0 g, 255 mmol) was added through the dropping funnel at such a rate that the temperature did not exceed 3 °C. The dropping funnel was then rinsed with THF (5 mL) that was added to the reaction mixture. After stirring at room temperature for 2 h, the solution was cooled to −78 °C. Methyl chloroformate (24 mL, 29 g, 312 mmol) was added through the dropping funnel while keeping the temperature below −70 °C. After rinsing of the dropping funnel with THF (5 mL), the mixture was allowed to warm up to room temperature within 18 h under stirring. It was poured into a buffer solution (150 mL, pH 7). The organic layer was separated and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$ and concentrated in a rotary evaporator. The residue was purified by distillation under reduced pressure to give colorless **1b**; yield: 29.7 g (81%). The spectroscopic data are in accodance with those describerd in the literature.[24]

(1*R*,2*Z*,4*S*)-{4-[(2-Methoxyethoxy)methoxy]-1-phenyl-2-penten-1-yl} Acetate [(*Z*)-18]

To a solution of (1*R*,2*Z*,4*S*)-4[(2-methoxyethoxy)methoxy]-1-phenyl-2-penten-1-ol[19] (5.4 g, 20.3 mmol) in CH_2Cl_2 (10 mL), stirred at 0 °C under nitrogen, was added an ice-cold mixture of triethylamine (2.8 g, 28 mmol), acetic anhy-

dride (2.8 g, 28 mmol), 4-(dimethylamino)pyridine (10 mg, 0.08 mmol) and CH_2Cl_2 (30 mL). The solution was stirred at room temperature for 23 h and poured into water. The organic layer was separated and the aqueous phase was extracted three times with CH_2Cl_2. The combined organic layers were washed with 2 N NaOH solution and with water and dried with $MgSO_4$. The solvent was removed in a rotary evaporator and then in oil-pump vacuum and the residue was purified by distillation under reduced pressure to give colorless, oily (*Z*)-**18**; yield: 5.647 g (90.3%)

(1*R*,2*E*,4*S*)-{4-[(2-Methoxyethoxy)methoxy]-1-phenyl-2-penten-1-yl} Acetate [(*E*)-19]: Also obtained according to this procedure from (1*R*,2*E*,4*S*)-4-[(methoxyethoxy)methoxy]-1-phenyl-2-penten-1-ol[19]; yield: 56.7%.

(2*R*,1′*S*,2′*E*)-2-(1,3-Diphenylallyl)cyclohexanone (9a)

Through the magnesium enolate of cyclohexanone: Under nitrogen, diisopropylamine (0.15 mL, 1.1 mmol) dissolved in 1 mL of dry THF was allowed to react with 1.1 mmol of methylmagnesium chloride (0.37 mL of 3 M solution in THF) at −16 °C. After 30 min, cyclohexanone (0.11 mL, 1.1 mmol) dissolved in 1 mL of dry THF was added dropwise, and stirring was continued for 30 min at −16 °C. The enolate thus generated was injected into a solution of **1a** (252 mg, 1 mmol), $[Pd_2(dba)_3]\cdot CHCl_3$ (25.9 mg, 25 μmol) and (*R*)-BINAP **11e** (62 mg, 100 μmol) in 2 mL of dry THF. After stirring for 16 h at 0 °C, the mixture was hydrolyzed by addition of phosphate-buffer (pH 7) and extracted three times with CH_2Cl_2 (50 mL each). The combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated in a rotary evaporator to give the crude product; yield: 285 mg (98%).

(*S*)-2-Allylcyclohexanone (12); Typical Procedure for the Allylic Alkylation of Lithium Enolates in the Presence of Lithium Chloride

A 100-mL two-necked flask was equipped with a magnetic stirrer and charged with $[Pd_2(dba)_3]\cdot CHCl_3$ (25.9 mg; 25 μmol), (*S*)-**11k** (65.8 mg, 101 μmol), and LiCl (0.51 g, 12 mmol). The flask was closed with a septum, connected to a combined nitrogen/vacuum line, evacuated for 5 h at 25 °C and filled with nitrogen. A solution of **1d** (0.581 g, 0.57 mL, 5.0 mmol) in THF (13 mL) was added by syringe. The deep purple mixture was stirred at 25 °C for approximately 0.5 to 1 h. In the course of this, the color changed to yellow. A 100-mL two-necked flask was equipped with a magnetic stirrer, a resistance thermometer, a connection to the combined nitrogen/vacuum line and a septum. The air in the flask was replaced by nitrogen, and diisopropylamine (0.7 mL, 5.0 mmol) and THF (10 mL) were injected. After cooling to −78 °C, a 1.6 M solution of *n*-BuLi in hexane (3.1 mL, 5.0 mmol) was added, whereby the temperature was kept below −70 °C. After stirring at 0 °C for 30 min, it was cooled again to −78 °C and treated with distilled, degassed cyclohexanone (0.52 mL, 5.0 mmol) in 5 mL of THF. After stirring at 0 °C for 30 min, the solution was cooled to −78 °C and added by syringe to the first flask. After stirring at −78 °C for 40 h, the mixture was poured into 100 mL of phosphate buffer (pH 7) and extracted four times with CH_2Cl_2 (50 mL each). The combined organic layers were dried with $MgSO_4$ and evaporated at 40 °C and a pressure that did not fall below 10 mbar. The flask was connected by glass tubes with two subsequent traps that were cooled to 0 °C and −196 °C, respectively. When the flask containing the crude product was heated to 50 °C at 0.07 mbar, pure product was collected in the 0 °C trap. Yield of (*S*)-**12**: 0.497 g (72%); 98% *ee* according to chiral GC.

According to this procedure, the following compounds were prepared:

(2*R*,1′*S*,2′*E*)-2-(1-Methyl-but-2-enyl)cyclohexanone (9b): Obtained from cyclohexanone (**7**) and methyl pentenyl carbonate (**1b**); the reaction was mediated by the ligand (*R*)-**11e**; yield: 35%, diastereomeric ratio **9b**:**10b** = 97:3; 96% *ee*. The ^1H and ^{13}C NMR data measured in $CDCl_3$ are in accordance with those described in the literature[8a] for racemic **9b** and **10b**, respectively.

(*S*)-2-Allylcyclopentanone (13): Obtained from cyclopentanone and allyl methyl carbonate (**1d**); the reaction was mediated by (*S*)-**11e**; yield: 76%. The ^1H NMR data are in accordance with those described in the literature.[25]

(*R*)-2-Allyl-1-tetralone (14): Obtained from α-tetralone and allyl methyl carbonate (**1d**); the reaction was mediated by (*R*)-**11e**. In the work-up procedure, 10% citric acid was used instead of the buffer solution. Yield: 85%. The ^1H NMR data are in accordance with those described in the literature.[15e]

(2*S*,1′*R*,2′*E*,4′*S*)- and (2*R*,1′*R*,2′*E*,4′*S*)-2-{4-[(2-Methoxyethoxy)methoxy]-2-phenylpent-2-enyl}cyclohexanone (*syn*-**20** and *anti*-**21**): Obtained from cyclohexanone (**7**) and (*Z*)-**18**; the reaction was performed through the lithium enolate in the presence of lithium chloride and mediated with the ligand **11d**, quantitative conversion. The diastereomeric ratio of *syn*-**20** and *anti*-**21** amounted to 79:21, according to GC-MS. Diastereomerically pure samples were obtained by column chromatography on silica gel ($CHCl_3$/ethyl acetate, 5:1).

(2*R*,1′*S*,2′*E*,4′*S*)- and (2*S*,1′*S*,2′*E*,4′*S*)-2-{4-[(2-Methoxyethoxy)methoxy]-1-phenylpent-2-enyl}cyclohexanone (*syn*-**22** and *anti*-**23**): Obtained from cyclohexanone (**7**) and (*E*)-**19**; the reaction was performed through the lithium enolate without an additive and mediated with the ligand **11d**; quantitative conversion. The diastereomeric ratio of *syn*-**22** and *anti*-**23** was determined to be 57:43. Diastereomerically pure samples were obtained by column chromatography on silica gel ($CHCl_3$/ethyl acetate, 5:1).

(3*S*,4*E*,6*S*)-6-[(Methoxyethoxy)methoxy]-1,3-diphenyl-4-hepten-1-one (30): Obtained from acetophenone and (*Z*)-**18**; the reaction was performed through the lithium enolate in the presence of lithium chloride and mediated with the ligand **11d**; quantitative conversion. The NMR spectra did not show the presence of diastereomers or regioisomers. The crude product was purified by column chromatography on silica gel ($CHCl_3$/ethyl acetate, 5:1) to give pure **30**; yield: 83%.

(3*R*,4*E*,6*S*)-6-[(Methoxyethoxy)methoxy]-1,3-diphenyl-4-hepten-1-one (32): Obtained from acetophenone and (*E*)-**19**; the reaction was performed through the lithium enolate in the presence of lithium chloride and mediated with the ligand **11d**. Conversion 95%. The NMR spectra and the GC did not show the presence of diastereomers and or regioisomers to an extent of more than 2%. The crude prod-

uct was purified by column chromatography on silica gel ($CHCl_3$/ethyl acetate, 5:1) to give pure **32**; yield: 25%.

***anti*-2-Methyl-3,5-diphenyl-1-(2,4,6-trimethylphenyl)-4-penten-1-one** (**36**): Obtained from ketone **34** by deprotonation with lithium diisopropylamide and subsequent reaction with **1a**. The reaction was performed without an additive and mediated with the ligand **11d**; quantitative conversion. The diastereomeric ratio of *anti*-**37** and *syn*-**36** was determined to amount to 90:10. The major product *anti*-**37** was obtained as a pure diastereomer upon column chromatography on silica gel (*n*-hexane/ethyl acetate, 10:1); yield: 85%.

(1-Cyclohexylethyl)benzene (17)

By means of a frit, a stream of ozone in oxygen was passed through a solution of the alkene (*2R,1′S*)-**9a** (389 mg, 1.34 mmol) (99% *ee*) in CH_2Cl_2 (40 mL) at −78 °C until the blue color persisted. Then, the solution was treated with a stream of oxygen and nitrogen. Dimethyl sulfide (831 mg, 13.4 mmol) was added, the mixture was allowed to reach room temperature overnight and poured into a buffered aqueous solution (pH 7). The organic layer was separated and the aqueous layer was extracted with three 50 mL portions of CH_2Cl_2. The combined organic layers were dried with $MgSO_4$, the solvent was removed in a rotary evaporator, and the residue was exposed to oil pump vacuum to give crude oily (2-oxocyclohexyl)phenyl-acetaldehyde **15**; yield: 210 mg (72%).

Under nitrogen, a solution of crude **15** (210 mg, 0.97 mmol) in CH_2Cl_2 (5 mL) was stirred in a 25-mL flask, equipped with a septum, a magnetic stirrer, an inlet thermometer and a connection to the combined nitrogen/vacuum line at 0 °C. 1,3-Propanediol (0.18 mL, 2.5 mmol) was injected and, thereafter, boron trifluoride-etherate (0.12 mL, 1.0 mmol) was added dropwise by syringe. The mixture was allowed to warm up to room temperature and stirred for 1 h. After the addition of 1 N aqueous NaOH, the mixture was extracted three times with CH_2Cl_2. The combined organic layers were washed with water, dried with $MgSO_4$ and concentrated in a rotary evaporator. The crude product was purified by two-fold column chromatography on silica gel to give bis-thioacetal **16**; yield: 50 mg (13%).

A suspension of Raney nickel in water (10 mL) was decanted, methanol was added and the supertenant liquid was decanted. This procedure was repeated five times. To the remaining suspension, a solution of **16** (50 mg, 0.13 mmol) in methanol (40 mL) was added. The mixture was refluxed for 10 h and thereafter filtered through celite 577, which was rinsed with CH_2Cl_2. The combined filtrates were washed with water and dried with $MgSO_4$. Evaporation of the solvent gave crude **17** (yield: 23 mg, 94%) as a yellowish oil, whose NMR spectroscopic data were in accordance with those described in the literature,[16]

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