[6] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC-140701 (**Ni-5b**), and CCDC-140702 (**Zn-5a**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).
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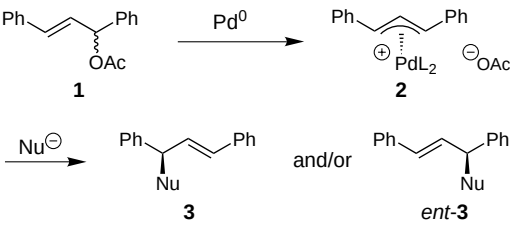
Diastereoselective and Enantioselective Palladium-Catalyzed Allylic Substitution with Nonstabilized Ketone Enolates**

Manfred Braun,* Frank Laicher, and Thorsten Meier

Dedicated to Professor Rolf Huisgen on the occasion of his 80th birthday

The utility of transition metal mediated allylic substitutions in organic syntheses has been proven by numerous applications in the past three decades. A particularly efficient way of carbon–carbon bond formation was opened up by the reaction of carbon nucleophiles with allylpalladium complexes, the generation of which is accomplished in situ and requires only catalytic amounts of the transition metal.[1] After mechanistic studies had treated the problem of stereochemistry,[2] considerable efforts were directed towards enantioselective variants,[3] most of this work focussed on symmetrically substituted racemic allyl compounds such as **1**. The attack of a nucleophile on the palladium complex **2**, formed from **1**, can be directed in an enantioselective way by means of chiral ligands (L*) so that either one of the substitution products, **3** or *ent*-**3**, can be prepared in a controlled manner [Eq. (1)].[4]



(1)

Despite this impressive progress, the main limitation of this concept is that the carbon nucleophiles used so far have been almost exclusively "soft", stabilized carbanions.[3] Although the chemistry of "preformed" enolates[5] evolved at the same time as that of allylpalladium chemistry, attempts to combine both concepts have been very rare, and their success rather limited. An early report on palladium-catalyzed reactions of ketone enolates with cyclic allyl acetates[6] was questioned later.[7] Furthermore, these attempts were plagued by the inevitable double allylations, low reactivities, and moderate yields.[8a] These difficulties were partly overcome by the employment of enol stannanes instead of lithium enolates,[8] an approach which led to the first enantioselective variant.[9]

Recently, stereoselectivity was obtained in the reaction of an enantiopure allyl acetate with a chelated zinc enolate.[10] However, the problem of producing a palladium-mediated allylation of enolates which provides both diastereoselectivity and catalyst-induced enantioselectivity has so far not been solved. Herein we report, as a solution to this problem, a method that is applicable to cyclic and acyclic ketone enolates.

Two adjacent stereogenic centers are created in the reaction of an α-substituted enolate and the meso complex **2**, which is formed in situ from the racemic acetate **1** [Eq. (1)]. Thus, we decided to tackle the problem of diastereoselectivity first. For this purpose, cyclohexanone was deprotonated with various bases in tetrahydrofuran to generate the enolate **4**; the advantage of this intermediate is its fixed enolate geometry (*E*, Scheme 1). The enolate **4** was allowed to react with the acetate **1** in the presence of 5 mol % of the palladium catalyst generated in situ from tris(dibenzylideneacetone)dipalladium–chloroform ($[Pd_2(dba)_3] \cdot CHCl_3$)[11] and the corresponding phosphane ligands **5**. In all the cases that are listed in Table 1 there was smooth and quantitative conversion into the diastereomeric ketones **6a** and **7a**, which can clearly be distinguished from one another by the chemical shifts of their allylic protons (3.88 and 3.98 ppm, respectively) in the ^{1}H NMR spectra.

The diastereoselectivity was influenced not only by the ligands **5a–d**[12] on the transition metal but also by the enolate counterion and the base used for the deprotonation. For the lithium enolate, substantial diastereoselectivity resulted from the use of chelating phosphane ligands (Table 1, entries 1

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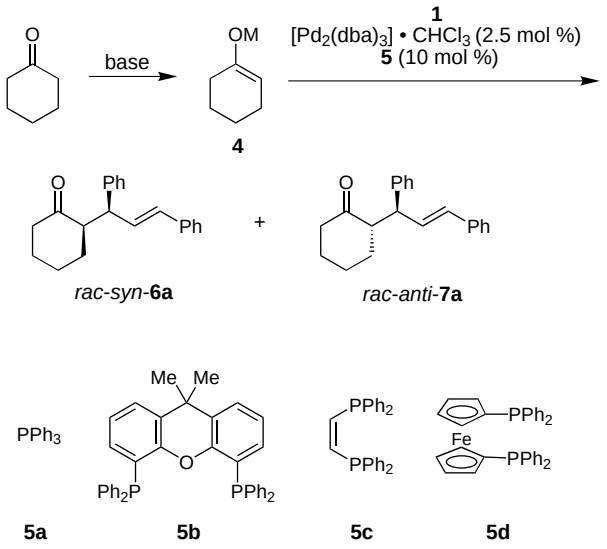


Scheme 1. Palladium-catalyzed diastereoselective allyl substitution with cyclohexanone.

Table 1. Diastereoselective palladium-catalyzed reaction of ketones with allylic acetate **1**.

Entry	Ketone	Base	Ligand **5**	*syn*-**6**:*anti*-**7**
1	$(CH_2)_5CO$	LiN*i*Pr	**5a**[a]	**6a**:**7a** 57:43
2	$(CH_2)_5CO$	LiN*i*Pr	**5b**[b]	**6a**:**7a** 81:19
3	$(CH_2)_5CO$	LiN*i*Pr	**5c**[b]	**6a**:**7a** 83:17
4	$(CH_2)_5CO$	LiN*i*Pr	**5d**[b]	**6a**:**7a** 87:13
5	$(CH_2)_5CO$	LiN*i*Pr/LiCl	**5d**[b]	**6a**:**7a** 92:8
6	$(CH_2)_5CO$	$LiN(SiMe_3)_2$	**5d**[b]	**6a**:**7a** 90:10
7	$(CH_2)_5CO$	$KN(SiMe_3)_2$	**5d**[b]	**6a**:**7a** 60:40
8	$(CH_2)_5CO$	ClMgN*i*Pr	**5d**[b]	**6a**:**7a** 97:3
9	$Me_3C_6H_2COEt$	$LiN(SiMe_3)_2$	**5d**[b]	**6b**:**7b** 33:67
10	$Me_3C_6H_2COEt$	$LiN(iPr)_2$	**5d**[b]	**6b**:**7b** 10:90

[a] 20 mol %. [b] 10 mol %.

versus 2–6), with the ferrocene derivative **5d** being the most efficient (entries 4–6). Disaggregation of the enolate by addition of one equivalent of lithium chloride[13] led to a small but clear enhancement of the diastereomeric ratio (entry 5), whereas no further improvement came from the use of lithium hexamethyldisilazide ($LiN(SiMe_3)_2$; entry 6). Since the use of the supposedly more polar potassium enolate led to a considerable decrease in stereoselectivity (entry 7), the next logical step was a change to magnesium. Indeed, the product **6a** was obtained from the magnesium enolate in high diastereoselectivity (entry 8). The *syn* configuration of the main product **6a**, obtained as a diastereomerically pure racemic compound after recrystallization, was unambiguously determined by a crystal structure analysis (Figure 1).[14] In contrast to the normally favored equatorial conformation of 2-methylcyclohexanone, the side chain of the ketone **6a** occupies the axial position, thus avoiding steric interaction of the bulky diphenylpropene substituent and the carbonyl oxygen atom.[15]

To test the versatility of our method it was applied to an open-chained ketone. Mesityl ethyl ketone was chosen (mesityl ethyl ketone = 1-(2,4,6-trimethylphenyl)propan-1-one), which, depending on the deprotonation conditions used,

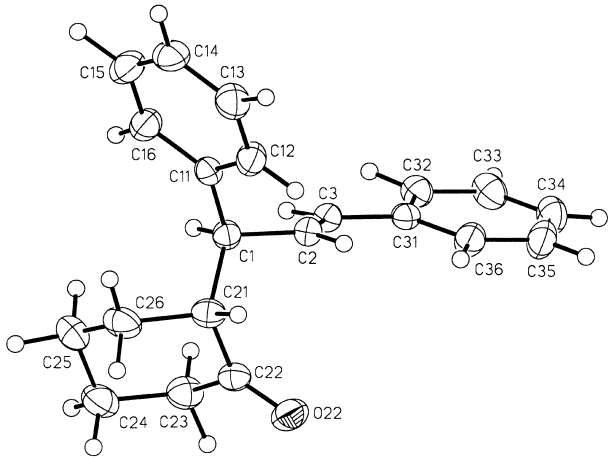
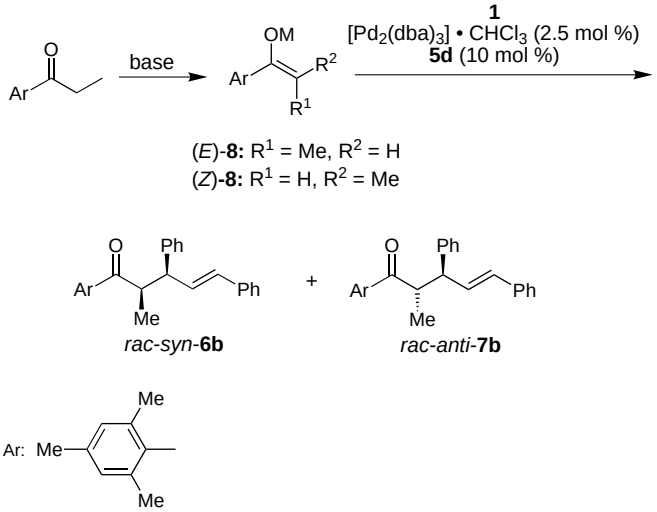


Figure 1. Crystal structure of *syn*-**6a** (SHELXTL-Plus; 25% probability displacement ellipsoids).

can give either of the stereoisomers of the enolate **8**.[5] When $LiN(SiMe_3)_2$ was used for deprotonation, predominantly (*Z*)-**8** was formed (Scheme 2).[16a] The subsequent palladium-catalyzed allylation was controlled by the chelating ligand **5d** and afforded the stereoisomers **6b** and **7b** with only moderate



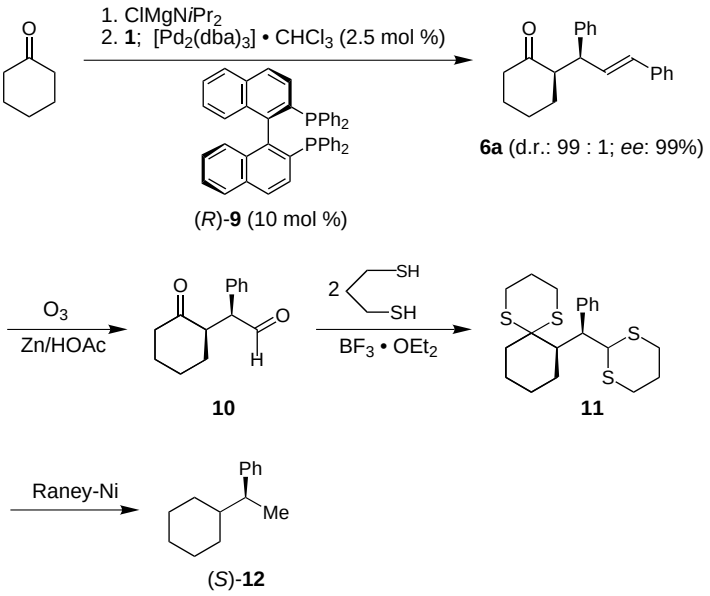
Scheme 2. Palladium-catalyzed diastereoselective allyl substitution with an acyclic ketone.

diastereoselectivity (entry 9). On the other hand, use of the *E*-configurated enolate **8**,[16b] which is generated by metalation of mesityl ethyl ketone with lithium diisopropylamide, enhanced the *syn*:*anti* ratio of the products **6b**:**7b** to 10:90 (entry 10). Thus unexpectedly, despite having the opposite configuration of the enolate **8**, the same stereoisomeric product **7b** was formed in excess (entries 9, 10). A possible explanation could come from the observation that, under the conditions of the allylic substitution reaction (that is, $[Pd_2(dba)_3]\cdot CHCl_3$; ligand **5d**, without **1**; THF; 0 °C), a slow conversion of (*Z*)-**8** into the thermodynamically more stable (*E*)-**8** occurs,[17] as shown by the formation of the corresponding enolsilanes ((*Z*)-**8**/(*E*)-**8**, M = $SiMe_3$). In contrast, the configuration of the *E* enolate **8** remains unchanged under

these conditions. Thus, the low diastereoselectivity obtained from the use of $LiN(SiMe_3)_2$ might stem from competing allylic substitution pathways of the *E* and *Z* enolates **8**, each of which lead to the other diastereomer of **6b** and **7b**.

The configuration of the major stereoisomer **7b** was determined by a crystal structure analysis, which unambiguously revealed it to be that of the *anti*-diastereomer. The major products **6a** and **7b**, formed from cyclohexanone and mesityl ethyl ketone, respectively, have opposite relative configurations, which is surprising in view of the identical enolate geometries in both enolates ((*E*)-**4** and (*E*)-**8**). A possibile explanation is the existance of two different types of transition state (closed versus open) for the two different types of ketone, this has yet to be confirmed experimentally.

Finally, we addressed the problem of enantioselectivity. For this purpose, the magnesium enolate **4** of cyclohexanone was allowed to react with the acetate **1** in the presence of the palladium–(*R*)-BINAP complex (BINAP = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl) generated in situ from $[Pd_2(dba)_3]\cdot CHCl_3$ (2.5 mol %) and the chiral (*R*)-BINAP ligand (*R*)-**9** (10 mol %) as shown in Scheme 3. The reaction



Scheme 3. Palladium-catalyzed enantioselective allyl substitution with cyclohexanone.

turned out to be very efficient in three respects. First, quantitative conversion of the starting material **1** was observed; second the diastereoselectivity was enhanced even compared to that obtained with the achiral ligand **5d** (Table 1, entry 8); third, exceptional enantioselectivity was reached. Thus, the enantiomeric excess of the major diastereomer **6a** was determined to be 99 % *ee* by HPLC on a chiralcel OJ column. The diastereomeric ratio of **6a**:**7a** was 99:1.

The absolute configuration of the ketone **6a** was elucidated by correlation with the hydrocarbon **12** as follows: The keto aldehyde **10** was generated in 72 % yield by ozonolysis of the alkene **6a**. Subsequent thioacetalization provided the bisdithiane **11**, which was isolated after (a material consuming) column chromatography in 13 % yield. Finally, (*S*)-**12** was obtained in 94 % crude yield by desulfurization with Raney–nickel. Since the optical rotation of (*R*)-**12** was known,[18] a comparison permitted us to assign the *S* configuration to the hydrocarbon **12** obtained from ketone **6a**.

A brief investigation revealed that by using the method described above open-chained ketones can react enantioselectivity too. Thus, the reaction of the lithium enolate (*E*)-**8** with the acetate **1** was mediated by the palladium-(*R*)-BINAP catalyst. Again, the diastereomeric ratio was maintained (10:90). Furthermore the main diastereomer **7b** was formed in 88 % *ee*, as determined by ^1H NMR spectroscopy in the presence of the chiral shift-reagent $[Eu(hfc)_3]$.[19]

To conclude palladium-catalyzed allylic substitution is feasible with nonstabilized preformed lithium and magnesium enolates of cyclic and open-chained ketones. For the first time, this reaction could be performed in such a way that the chiral ligand of the transition metal induced not only a high degree of diastereoselectivity but also enantioselectivity.

Experimental Section

Typical procedure: Methylmagnesium chloride (1.1 mmol, 0.37 mL; 3 M solution in THF) was added dropwise to diisopropylamine (0.15 mL, 1.1 mmol) dissolved in dry THF (1 mL) at −16 °C under nitrogen. After 30 min, cyclohexanone (0.11 mL, 1.1 mmol) dissolved in THF (1 mL) was added dropwise, and stirring was continued for 30 min at −16 °C. The enolate thus generated was injected into a solution of **1** (252 mg, 1 mmol), $[Pd_2(dba)_3]\cdot CHCl_3$ (26 mg, 25 μmol), and (*R*)-BINAP (62 mg, 100 μmol) in dry THF (2 mL). After stirring the mixture for 16 h at 0 °C it was hydrolyzed by addition of a phosphate-buffer (pH 7) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated in vacuo. The residue was dissolved in *n*-hexane and filtered through celite 557 in a suction filter. Evaporation of the solvent led to the crude product. NMR spectroscopy revealed signals corresponding to the clean and quantitative conversion of the substrate **1.** An analytically pure sample of **6a** (195 mg, 67 %) was obtained by flash chromatography on silica gel (*n*-hexane:ethyl acetate, 10:1). The enantiomeric excess was determined by HPLC on a chiralcel OJ column (*n*-hexane:isopropanol, 96:4).

Selected physical and spectroscopic data: **6a**: m.p. 93 °C; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 2.87$ (ddd, $J = 9.5, 9.5, 4.9$ Hz, 1H, 2-H), 3.88 (dd, $J = 9.5, 7.6$ Hz, 1H , 1′-H), 6.33 (d, $J = 15.8$ Hz, 1H, 3′-H), 6.44 (dd, $J = 15.8, 7.6$ Hz, 1H, 2′-H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 23.93, 28.52, 32.17, 42.42, 48.39, 55.82, 126.45, 126.55, 127.14, 128.51, 128.60, 128.83, 130.46, 131.91, 137.33, 141.88, 212.46$; elemental analysis calcd for $C_{21}H_{22}O$ (%): C 86.85, H 7.64; found: C 86.91, H 7.62. The minor diastereomer **7a** differs in: ^1H NMR (500 MHz, $CDCl_3$): $\delta = 3.98$ (dd, $J = 9.0, 9.0$ Hz, 1H), 6.26 (dd, $J = 15.7, 9.0$ Hz, 1H), 6.45 (d, $J = 15.7$ Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 24.42, 28.30, 31.84, 42.15, 48.32, 55.55, 130.97, 131.21, 137.16, 143.24, 211.43$. (1′*S*,2*R*)-**6a**: $[\alpha]_D^{20} = 68.5$ ($c = 0.2$ in $CHCl_3$); **7b**: m.p. 110.3 °C; ^1H NMR (500 MHz, $CDCl_3$): $\delta = 1.22$ (d, $J = 7.3$ Hz, 3H, CH-CH_3), 1.99 (s, 6H, Ar-CH_3), 2.24 (s, 3H, Ar-CH_3), 3.40 (dq, $J = 7.3, 7.8$ Hz, 1H, 2-H), 4.10 (dd, $J = 8.2, 7.8$ Hz, 1H, 3-H), 6.43 (dd, $J = 15.7, 8.2$ Hz, 1H, 4-H), 6.48 (d, $J = 15.7$ Hz, 1H, 5-H); elemental analysis calcd for $C_{27}H_{28}O$ (%): C 88.00, H 7.66; found: C 87.89, H 7.76. The minor diastereomer **6b** differs in: ^1H NMR (500 MHz, $CDCl_3$): $\delta = 0.95$ (d, $J = 7.0$ Hz, 3H), 2.21 (s, 3H), 3.49 (dq, $J = 9.7, 7.0$ Hz, 1H), 3.99 (dd, $J = 9.7, 6.4$ Hz, 1H), 6.34 (dd, $J = 16.0, 6.4$ Hz, 1H), 6.63 (d, $J = 16.0$ Hz, 1H).

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[16] The ratio of (*E*)-**8**:(*Z*)-**8** was determined by conversion into the enolsilanes at −78 °C. a) 7:93; b) 96:4.

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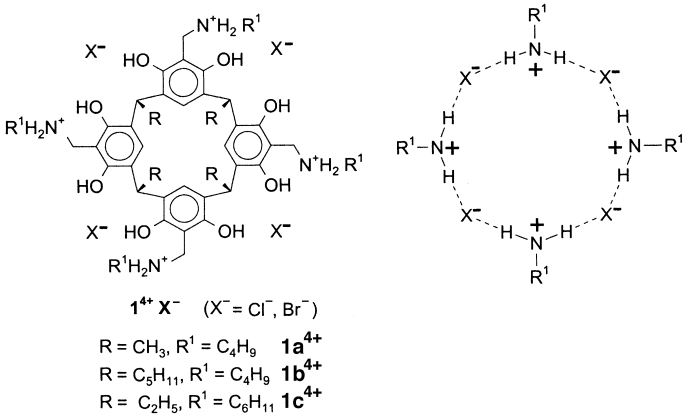
[19] [Eu(hfc)$_3$] = tris[3-(2,2,3,3,4,4,4-heptafluoro-1-hydroxybutylidene)-D-camphorato]europium (Aldrich).

Hydrogen-Bonded Analogues of Cavitands**

Alexander Shivanyuk,* Thomas P. Spaniol, Kari Rissanen, Erkki Kolehmainen, and Volker Böhmer

Multiple hydrogen-bonding interactions are widely used for the design of hollow self-assembled structures capable of molecular encapsulation.[1] In particular, intermolecular hydrogen bonds between urea functions are responsible for the stability of dimeric calixarene capsules,[2] while the slow exchange of guests in self-folded caviplexes is caused by a seam of intramolecular hydogen bonds between amide groups.[3]

Herein we describe a novel type of self-assembled concave structures $\mathbf{1}^{4+} \cdot 4X^-$ in which the shallow socket of a resorcarene is extended by a cyclic hydrogen-bonded array of four halide ions and four ammonium ions attached to the wide rim of the macrocycle. We demonstrate also that $\mathbf{1}^{4+} \cdot 4Cl^-$, but not $\mathbf{1}^{4+} \cdot 4Br^-$, is able to complex certain alcohols in $CDCl_3$ through the formation of hydrogen bonds and inclusion into the π-basic resorcarene cavity.



$\mathbf{1}^{4+}\,X^-$ ($X^- = Cl^-, Br^-$)

R = CH_3, $R^1 = C_4H_9$ **1a**$^{4+}$
R = C_5H_{11}, $R^1 = C_4H_9$ **1b**$^{4+}$
R = C_2H_5, $R^1 = C_6H_{11}$ **1c**$^{4+}$

Condensation of resorcarenes[4] with primary amines and formaldehyde readily gives the corresponding tetrabenzoxazine derivatives.[5] The subsequent cleavage of the benzoxazine rings with HCl or HBr (*n*-butanol, 80 °C) yields the tetraammonium salts $\mathbf{1}^{4+} \cdot 4X^-$ ($X^- = Cl^-$,[6] Br^-) in 80 – 90 % yield.

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