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Palladium-Catalyzed Asymmetric Allylic α-Alkylation of Acyclic Ketones

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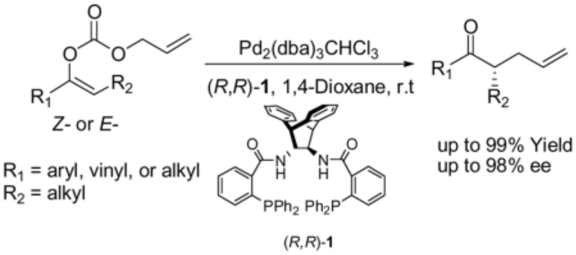
Abstract



The first example of Pd-catalyzed asymmetric allyl alkylation of the conformationally non-rigid acyclic ketone enolates is reported with excellent yields, regioselectivity and enantioselectivity. The double bond geometry of the allyl enol carbonates affects its reactivity, selectivity as well as the absolute configuration of the products. An opposite enantioselectivity from what is predicted by a direct attack of the enolate on the allyl moiety of the π-ally-Pd complex was observed. An alternative mechanism was proposed, which involves an inner sphere process of coordination of the enolate to Pd followed by reductive elimination.

Regio- and stereoselective formation of new carbon-carbon bonds is a fundamental problem in synthetic organic chemistry. One of the important C-C bond formation reactions is the α-alkylation of ketone enolates.[1] However, metal catalyzed asymmetric alkylation of unstabilized ketone enolates remains one of the most challenging reactions because the enolate equilibration during the reaction can lead to loss of regio-selectivity, polyalkylation, and in the case of creating tertiary centers, racemization of product.[2] While there has been some recent progress in the case of cyclic ketones,[3] to our knowledge there are no examples of asymmetric alkylation of the conformationally non-rigid acyclic ketones, in which the specific issue of the relationship of enolate geometry to asymmetric induction must be addressed. Herein, we report the first such examples and some mechanistic insights.

We initially selected ligand **1** and $Pd_2(dba)_3CHCl_3$ **2** to catalyze the reaction of (*Z*)-allyl 1-phenylprop-1-enyl carbonate **3** in toluene at ambient temperature (Table 1). The reaction went to completion in 3 h and led to alkylated product **4** in 68% yield and 75% ee. The by-products detected by GC were ketone **5** and dialkylated product **6** in 24% and 4% yield respectively. Changing the solvent to THF increased the ee value of the product to 88% but did not improve the yield. One the other hand, improvement occurred by switching to 1,4-dioxane: only 6% of **5** and no dialkylated product were detected by GC. The ee of **4** also increased to 94%. These results are significantly superior to those using dppe or dppb as ligand[4] (Table 1 entry 4, 5 and 6). Thus, proton transfer is significantly eliminated by using our chiral ligand in 1,4-dioxane.

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The reaction scope is summarized in Table 2. In general, excellent yields and ee's were obtained for various aromatic ketones. While the reaction can tolerate a broad range of substitution groups on the aromatic ring, some electronic effect was observed. Substrates bearing more electron-rich aromatic ring (entries 10, 13) had better enantiomeric excess (98%) than those possessing more electron-deficient aryl rings (entry 11, 73% and 12, 82%). The length of the alkyl chain at R_2 does not affect the results of the reaction (entries 2 and 3). However, an α-branched group significantly slows the reaction and decreases the ee (entry 4). The yield and ee was restored in the case of a β-branched R_2 (entry 5). Replacing the aryl ring by a vinyl group retained an excellent yield and high enantiomeric excess (entries 17 and 18). In the challenging case of the unsymmetrical aliphatic ketones such as **7** where R_1 = cyclohexyl and R_2 = methyl (Scheme 1), no loss of regioselectivity was observed in both the *E*- and *Z*- enol carbonates,[5] although the *Z* isomer reacted more sluggishly and had a lower ee (60%) than the aromatic (entry 1, 94%) or enone (entry 17, 88%) cases even though the steric size of these three R_1 groups should be close. This may suggest that the enantio-recognition step involves not only steric effects of R_1 and R_2, but also some electronic effects such as π-stacking interactions between the substrate and the ligand.

By using (*E*)-allyl 1-cyclohexyl-1-propenyl carbonate (Scheme 1) as the substrate, we can generate the corresponding mono-allyl alkylated aliphatic ketone in almost quantitative yield exclusively as one regioisomer in 97% ee. The double bond geometry of the enol carbonate **7** controls not only the enantiomeric excess but also the configuration of the resulting ketone (see Scheme 1). The double bond geometry also affects the reaction rate. Thus, *E*-**7** was more reactive that its *Z* isomer. The same effect was also observed in the case of 1-mesityl-1-propenyl carbonate (entry 15 and 16); the reaction of *E*-isomer went to completion in 6 h with a quantitative yield and 96% ee but only trace amount of product was detected in 16 h for the *Z*-isomer.

The absolute configuration of **4** was determined to be *S*- by Pd-$CaCO_3$ catalyzed hydrogenation of the C=C double bond and comparison of the optical rotation of the product with the known enantiomer.[6] This result conflicts with the model of intermolecular nucleophilic attack of the enolate on the π-allyl-Pd complex possessing ligand **1**, by which the *R*- enantiomer is preferred.[7] The same conflict was found in our previous studies.[3a] In the case of allylenol carbonate, since the π-allyl-Pd cation is the only counterion of the *in situ* generated enolate, it is likely that there is coordination between the enolate and palladium. According to the work of Hartwig et al, either C- or O-bound arylpalladium enolates, can undergo reductive elimination to generate the corresponding α-aryl ketones.[8] Therefore, under our reaction conditions, a reasonable explanation invokes a shift of mechanism from a direct attack of the enolate on the allyl moiety to an inner sphere process of coordination and reductive elimination (Scheme 2).

The distinctive solvent effect in favor of 1,4-dioxane may be explained by the fact that it is much better in forming solvent caged contact ion pairs than THF.[9] The proton sources in the bulk solution, mainly the mono-alkylated product itself or trace amounts of water, may react more slowly in 1,4-dioxane relative to collapse to product, so that very little proton transfer occurs between the enolate and these proton sources. The conjecture is supported by the reaction of **3** in 1,4-dioxane in the presence of one equivalent of dimethyl methylmalonate, dimethyl malonate or acetylacetone. The reaction with dimethyl methylmalonate was identical to the control. A small amount (9%) of dimethyl allylmalonate was detected in the run with dimethyl malonate and the yield of by-product **5** slightly increased to 10%, but the ee of the reaction remained high (93%) (entry 2). In entry 3 high yields of **5** (83%) and allyl acac (91%) were detected with the loss of yield (17%) and ee (81%) of the product **4**. A similar trend was observed in THF with the addition of a significant amount of diallyl acac also being observed. With the increase of the acidity of the additive, the ability to intercept the solvent caged contact ion pair relative to collapse to **4** increases. Thus the amount of byproducts increases.

In summary, we report the first palladium catalyzed asymmetric α-allyl alkylation of acyclic ketones. The reaction proceeds under very mild conditions and generates an α-tertiary stereogenic center with excellent yield, regio-selectivity and enantiomeric excess. Based on our experimental results we propose an intramolecular mechanism involving an inner sphere reductive elimination, quite distinct from the usual behavior of π-allyl-Pd complexes. Further investigation of the mechanism and the application of the reaction in organic synthesis are underway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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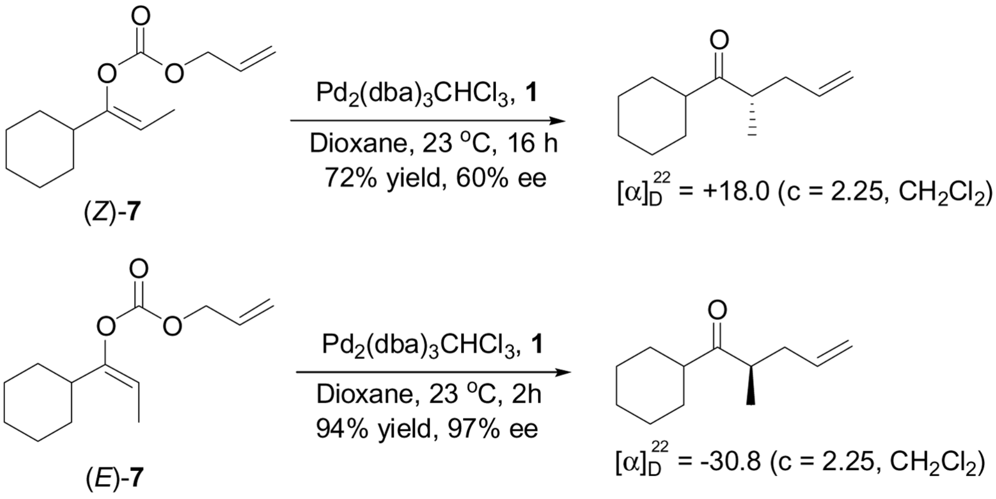
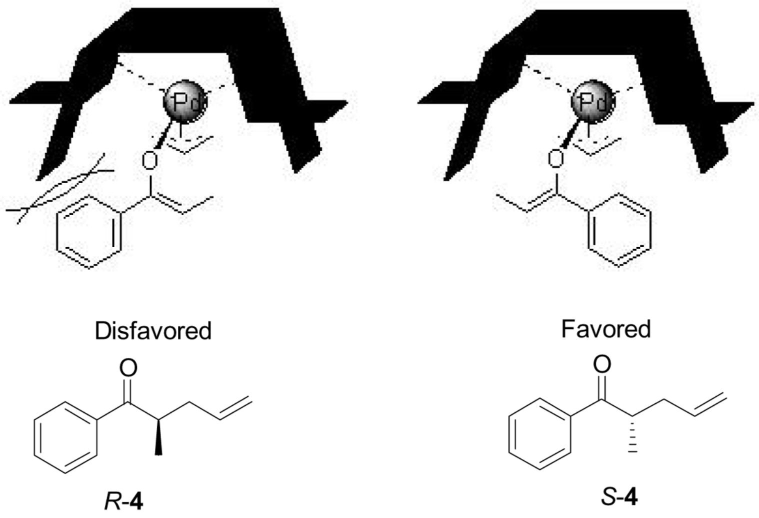
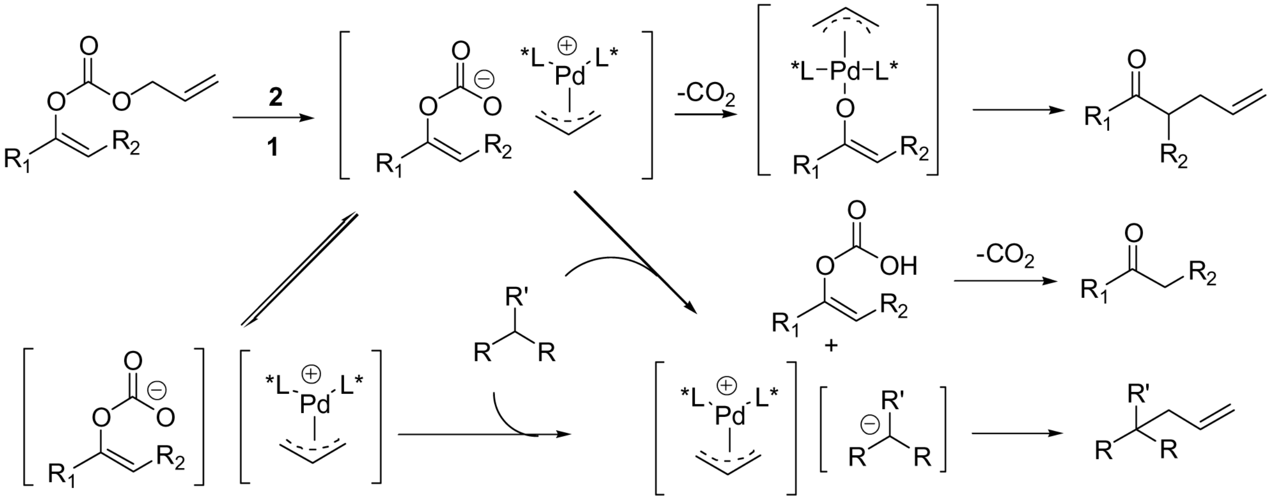


Scheme 1.
Double bond geometry controls the configuration and enatiomeric excess of product.



Scheme 2.

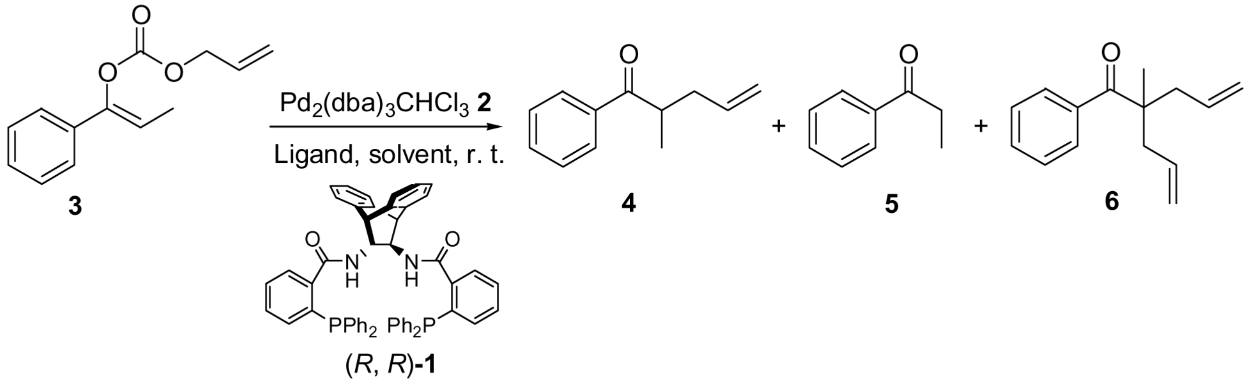
Model for the enantioselectivity of **4**.



Scheme 3.
Proposed mechanism for the reaction.

Table 1

Selected Optimization Studies.[a]

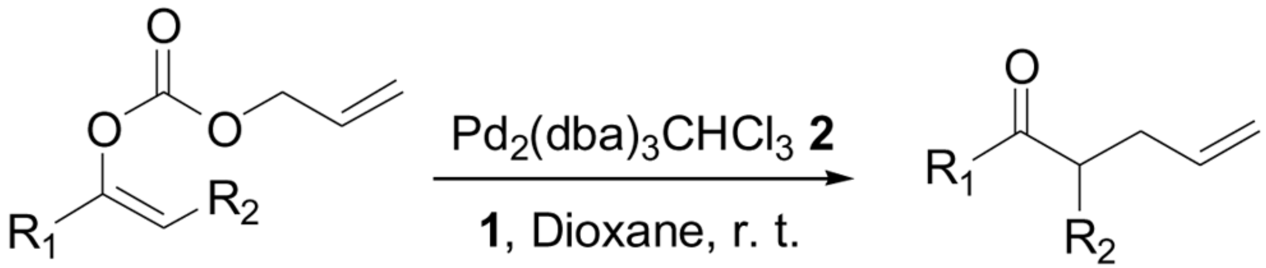


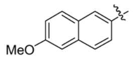
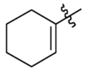
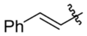
	Ligand	solvent	Time	yield% (ee) of 4	yield% of 5	yield% of 6
1	**1**	Toluene	3 h	68(75%)	24	4
2	**1**	THF	1 h	61(88%)	25	14
3	**1**	Dioxane	30 min	94(94%)	6	0
4	Dppe	Dioxane	10 min	61	24	14
5	Dppb	Dioxane	10 min	67	20	13
6	Dppb	Toluene	3 h	53	38	9

[a] Unless otherwise indicated, all reactions were performed at 23 °C on a 0.3 mmol scale at 0.1 M using 2.5 mol% **2** and 5.5 mol% ligand; yields are determined by quantitative GC analysis using decane as internal reference; ee of **4** was determined by chiral HPLC on a Chiralcel®OD-H column eluted with 2000:1 heptane: 2-proanol.

Table 2

Reaction of Various Allyl Enol Carbonates of acyclic ketones[a]



	R$_1$	R$_2$	*Z/E*[b]	time	yield	ee
1	Ph	Me	>98/2	2 h	94%	94%
2	Ph	Et	>98/2	2 h	94%	94%
3	Ph	C_5H_{11}	>98/2	16 h	93%	92%[c]
4	Ph	*i*-Pr	>98/2	24 h	30%	32%[c]
5	Ph	CH_2Ph	>98/2	1 h	75%	88%
6		Me	>98/2	1 h	90%	95%
7	2′-F-Ph	Me	>98/2	1 h	80%	94%
8	3′-Cl-Ph	Me	>98/2	1 h	97%	93%
9	4′-Br-Ph	Me	>98/2	1 h	94%	93%
10	2′-OMe-Ph	Me	>98/2	16 h	99%	98%[c]
11	Pyridyl	Me	>98/2	1 h	95%	73%[c]
12	3′-NO_2-Ph	Me	>98/2	1 h	83%	82%
13	Furyl	Me	>98/2	4 h	89%	88%
14	2′-CF_3-Ph	Me	>98/2	2 h	94%	92%
15	Mesityl	Me	5/95	6 h	99%	96%[c]
16	Mesityl	Me	96/4	16 h	trace	NA
17		Me	>98/2	5 h	94%	88%
18		Me	25/1	0.3h	93%	91%

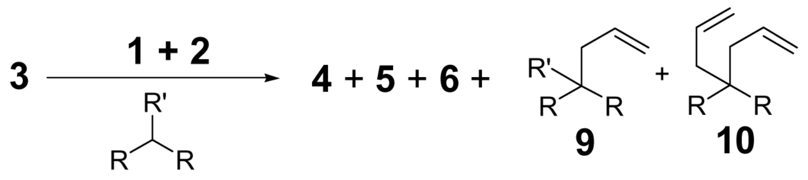
[a] Unless otherwise indicated, all reactions were performed on a 0.3 mmol scale at 0.1 M in 1, 4-dioxane at 23 °C using 2.5% **2** and 5.5% ligand **1**; the yields were isolated yields and ee values were determined by chiral HPLC.

[b] *Z/E* ratio was determined by ^{1}H-NMR.

[c] The ee values were determined by analysis of the derivative described in supporting information part.

Table 3

Reactions with proton sources.



	R	R′	solvent	time min	4 %(ee)	5 %	6 %	9 %	10 %
1	CO_2Me	Me	dioxane	30	94(94)	6	0	0	0
2	CO_2Me	H	dioxane	15	90(93)	10	0	9	0
3	$COCH_3$	H	dioxane	15	17(81)	83	0	91	0
4	CO_2Me	H	THF	10	71(87)	27	2	22	0
5	$COCH_3$	H	THF	<5	8(63)	92	0	76	14