Chiral Recognition for Control of Alkene Geometry in a Transition Metal Catalyzed Allylic Alkylation

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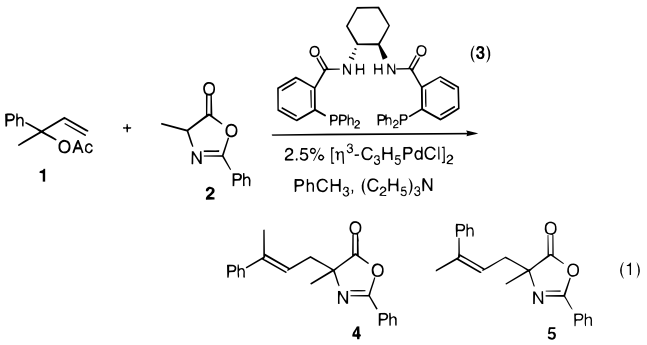
The efficient and stereoselective synthesis of alkenes is an important goal in organic synthesis. Olefination protocols continue to be one of the most general methods but frequently have problems controlling double bond geometry in creating trisubstituted alkenes.[1] Hydrometalation of alkynes followed by cross-coupling is a more atom economical strategy but does raise questions of regioselectivity.[2] We report a new paradigm for controlling alkene geometry in the metal-catalyzed allylic alkylation[3] based upon chiral recognition that has led to a synthesis of the thermodynamically less stable *Z*-trisubstituted alkenes.

Our initial studies centered on the palladium-catalyzed reaction of racemic allyl acetate **1** and azlactone **2**[4] (eq 1 and Table 1).

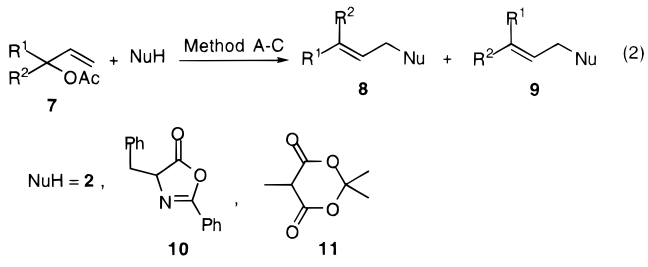


(1)

Two observations were striking. The first (Table 1, entries 1 and 2) was that a nearly equimolar mixture of the two alkene isomers **4**[5] and **5**[5] was obtained and only the *Z*-isomer, which was isolated pure in 47% yield, showed high ee (97%) with the enantiomerically pure ligands *R,R*-**3** or *S,S*-**3**. The second (Table 1, entry 3) was that a high preference for the *Z*-isomer **5** was obtained when the racemic version of the ligand **3** was employed. The assignment of the alkene geometry derived from ^{13}C shifts of the alkene methyl group (**4** δ 16.3, **5** δ 25.9) and nOe's. An achiral ligand like triphenylphosphine, as expected, favors formation of *E*-alkene **4** (entry 4).

The ability to control alkene geometry to favor formation of the thermodynamically less stable product with a chiral racemic ligand compared to a chiral nonracemic ligand led us to optimize this reaction. Choice of palladium source, π-allylpalladium chloride dimer or tris (dibenzylideneacetone) dipalladium (chloroform) (**6**), had little effect. Little variation occurred by changing solvent (acetonitrile, methylene chloride, benzene, toluene) except some enhancement in the ratio occurred by using THF. The biggest effect occurred by varying base. For example, use of sodium hydride with racemic ligand led to an 85:15 *E:Z* ratio, the inverse of that observed with triethylamine. A sterically more hindered tertiary amine, Hunig's base, saw a deterioration in the *Z*-selectivity compared to triethylamine, but a sterically less hindered base, *N*-methylpyrrolidine, increased it.

We subsequently settled upon *N*-methylpiperidine as base and **6** as palladium source in THF as solvent with racemic ligand **3**. Table 2 and eq 2 summarize the results. As the size of the group



(2)

R^2 of the acetoxyalkene increased, the diastereoselectivity in favor of the *Z*-isomer **9** increased (entries 1, 3, and 5). Increasing the size of the R^1 has the opposite effect (entries 1, 7, and 9). Increasing the bulk of the alkyl group on the azlactone nucleophile

Table 1. Alkylation of 3-Acetoxy-3-phenyl-1-butene (**1**) with Azlactone **2**

entry	ligand	isolated yield, %	*E*:*Z*[a]
1	*R,R*-**3**	88	50[b]:50[c]
2	*S,S*-**3**	97	55[d]:45[c]
3	*R,R*-**3** + *S,S*-**3**	83	15:85
4	Ph_3P	85	84:16

[a] Determined by NMR spectroscopy on the crude mixture. [b] The ***E***-isomer had 12% ee. [c] The ***Z***-isomer had 97% ee. [d] The ***E***-isomer had 9% ee.

Table 2. Alkylation of Acetoxyalkenes **7** with Nucleophiles **2**, **10**, and **11**[a]

entry	R^1	R^2	NuH	method[b]	isolated yield, %	*E*:*Z*[c] (**8**:**9**)
1	Ph	CH_3	**2**	A	95 (**8a**+**9a**)	4:96
2	Ph	CH_3	**2**	B	89 (**8a**+**9a**)	89:11
3	Ph	C_2H_5	**2**	A	91 (**8b**+**9b**)	2:98
4	Ph	C_2H_5	**2**	B	80 (**8b**+**9b**)	43:57
5	Ph	$(CH_3)_2CHCH_2$	**2**	A	96 (**8c**+**9c**)	1:99
6	Ph	$(CH_3)_2CHCH_2$	**2**	B	85 (**8c**+**9c**)	35:65
7	β-naphthyl-	CH_3	**2**	A	91 (**8d**+**9d**)	15:85
8	β-naphthyl-	CH_3	**2**	B	90 (**8d**+**9d**)	93:7
9	$CH_3C{\equiv}C$	CH_3	**2**	A	91 (**9e**)	0:100
10	$CH_3C{\equiv}C$	CH_3	**2**	B	82 (**8e**+**9e**)	22:78
11	Ph	CH_3	**10**	A	95 (**8f**+**9f**)	7:93
12	Ph	CH_3	**10**	B	81 (**8f**+**9f**)	69:31
13	Ph	CH_3	**11**	C	88 (**8g**+**9g**)	14:86
14	Ph	CH_3	**11**	B	96 (**8g**)	100:0

[a] All reactions were run using 2.5% $Pd_2(dba)_3{\cdot}CHCl_3$ with a 1:2 ratio of acetoxyalkenes **7** to nucleophile **2**, **10**, and **11**. [b] Method A employs 7.5% ligand **3** (racemic) and 1-methylpiperidine in THF; Method B employs 7.5% dppe and 1-methylpiperidine in THF; Method C employs 7.5% ligand **3** (racemic) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in toluene. [c] Ratio determined by ^1H NMR spectroscopy of the crude reaction mixture.

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(5) All new compounds have been characterized spectroscopically, and elemental composition has been established by combustion analysis.

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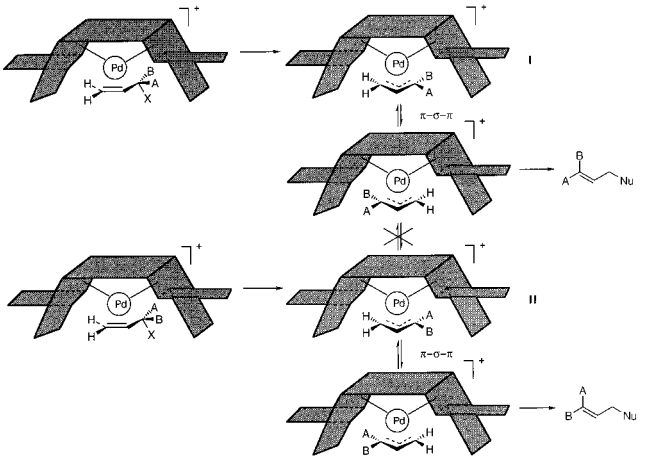

Figure 1. Cartoon representing the reaction of racemic allyl esters with enantiomerically pure catalyst.

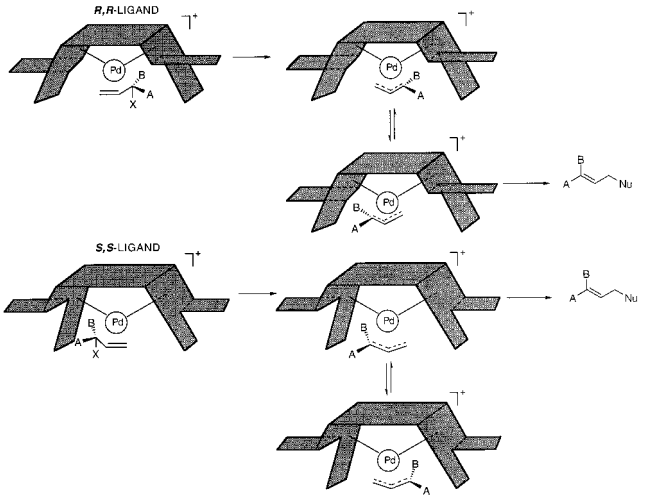

Figure 2. Cartoon representing the reaction of racemic allyl esters with racemic catalyst.

(e.g., **10**) caused a small decrease in *Z*-selectivity (entry 1 vs 11). Meldrum's acid derivative **11** also showed a *Z*-selectivity (entry 13). In this case, better selectivity was observed by switching to DBU as base.

The results demonstrate that variation of ligand from an achiral one to a chiral racemic one can switch alkene geometry from *E* to *Z* in a synthetically useful fashion. The dichotomy between chiral nonracemic and chiral racemic ligands, at first glance, seems peculiar. However, closer examination provides a reasonable rationale as illustrated in Figures 1 and 2.[3g] In the case of a chiral nonracemic ligand, the resultant complex must operate on both enantiomers of the substrate as depicted in Figure 1. As a result, the ionization event must eventually generate an equimolar mixture of the two diastereomeric complexes when run to completion. As long as diastereomer I does not interconvert with diastereomer II, a 50:50 mixture of the two alkenes should result. Since equilibration of I and II requires formation of a σ-C−Pd bond at a tertiary center, it is reasonable to believe that such an interconversion would be slow. Our experimental results agree with this prediction. In this picture, one ionization represents a "matched" event in which one enantiomer of the starting racemate will ionize faster with the enantiomerically pure catalyst than the other, the latter being a "mistmatched" event. However, since the reaction is run to 100% conversion, this kinetic difference in ionization has no effect on the product.

When racemic catalyst is employed, a "matched" ionization event is now possible with *both* enantiomers of the allyl ester as shown in Figure 2. If the *R,R*-catalyst will form a "matched" ionization with one enantiomer of the substrate, the *S,S*-catalyst will form a "matched" ionization with the mirror image allyl ester. In this scenario, the two diastereomers generated are simply the mirror images of each other. Thus, both give the same achiral product. The alkene geometry of the product then depends on the preference for aryl vs alkyl to adopt the A or B position in the π-allylpalladium intermediates. In this "matched" ionization step, the B group is in the sterically more encumbered position. The effective steric bulk of the phenyl group depends on conformation, which has led to the demonstration that it has a smaller effective steric bulk than a methyl group.[6] In the chiral pocket of the complexes in Figures 1 and 2, the ability of the phenyl group to adopt a conformation wherein it is rotated so that one of its π-faces encounters one of the "walls" of the pocket also would make its effective steric bulk smaller than methyl. As a result, for substrate **1**, A becomes methyl and B becomes phenyl preferentially. The degree of this bias then determines the *Z*-selectivity. This model nicely accommodates the observed trends (vide supra).

In conclusion, a new method to exercise control of alkene geometry has been disclosed.[7] Chiral ligands provide opportunities to affect selectivity beyond asymmetric induction. In allylic alkylations, the family of chiral ligands being developed in these laboratories[3f,g] exercise regiocontrol in unsymmetrical substrates that may override the intrinsic regioselectivity observed with achiral ligands.[8] The present case demonstrates an ironic twist wherein chiral enantiomerically pure ligand provides no geometrical selectivity but the racemic ligand does. This new mechanism for *Z*-selectivity provides an opportunity to access thermodynamically less stable alkenes in a very simple fashion using transition metal catalyzed allylic alkylations. Synthetically, access to either alkene geometry of the product from the same starting materials only requires changes of catalyst ligand. Increasingly, this family of catalysts are functioning more like an active site of an enzyme, forcing a substrate to conform its shape to that of the chiral pocket—in this case by adopting a particular allyl geometry.

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Supporting Information Available: Experimental procedures for the preparation of **4**, **5**, **8b**−**g**,and **9b**−**g** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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