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Palladium Catalysed Allylic Substitution Reactions of Prochiral and Racemic Allyl Acetates

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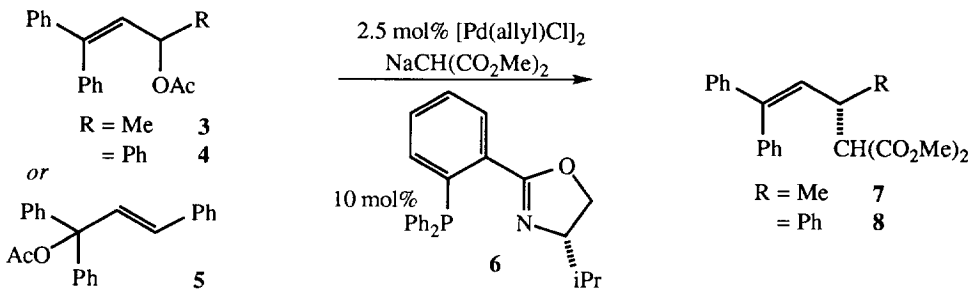
Abstract: The palladium catalysed reaction between non-symmetrical allyl acetates and sodiodimethylmalonate proceeds in high yields and enantioselectivities (up to 99% ee) using a diphenylphosphinoaryl oxazoline ligand.

In the last few years, there have been many new ligands reported which provide high levels of enantiocontrol in palladium catalysed allylic substitution reactions.[1] We[2] and others[3] have contributed with the development of oxazoline ligands tethered to an auxiliary donor ligand.

Substrates for palladium catalysed allylic substitution are often chosen because they proceed *via* a symmetrical allyl complex **1**. Herein, we report that the use of substrates which proceed *via* non-symmetrical[4] allyl complexes **2** afford high levels of asymmetric induction with an oxazoline ligand.

Treatment of the racemic allyl acetates **3** or **4** or the prochiral allyl acetate **5** with sodiodimethylmalonate in the presence of 2.5 mol% palladium allyl chloride dimer and 10 mol% of the ligand **6** under the conditions identified in the Table afforded the substitution products (*S*)-**7** or (*S*)-**8**.[5]



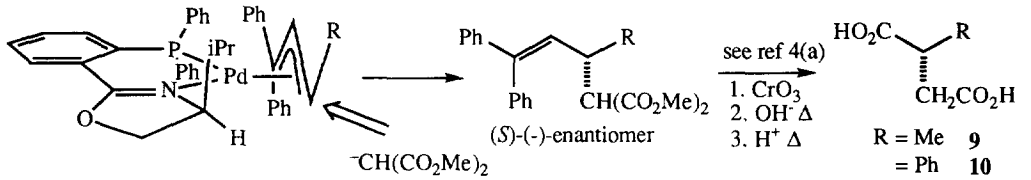
In no case was the alternative regioisomer detected, as expected on steric grounds and electronic grounds (the more conjugated alkene product is formed). The regiochemistry of the starting material (choice of **4** or **5**) has very little effect on the observed product yield and enantioselectivity, indicating a common palladium allyl intermediate in the catalytic cycle, as already demonstrated by Bosnich and co-workers.[4]

Table: Enantioselective palladium catalysed formation of **7** and **8**

Substrate	*Solvent*	*Temp*	*Time*	*Product*	*ee (%)*[a]	*Yield (%)*
3	THF	reflux	5hr	7	80	91
3	THF	20 °C	24hr	7	95	95
3	DMF	80 °C	5hr	7	86	92
4	THF	reflux	5hr	8	62	95
4	DMF	80 °C	5hr	8	68	96
5	THF	20 °C	24hr	8	95	97
5	THF	reflux	5hr	8	64	98
5	THF[b]	reflux	5hr	8	68	94
5	DMF	20 °C	24hr	8	99	88
5	DMF	80 °C	5hr	8	65	92

[a] The ee of **7** was determined from Hnmr spectra in the presence of $Eu(hfc)_3$, and the ee of **8** was determined by chiral hplc (Chiralcel OJ, heptane:iPrOH:Et_2NH, 96.9:3:0.1)
[b] This reaction was performed using an alternative protocol, using $CH_2(CO_2Me)_2$ with BSA (bistrimethylsilylacetamide) and KOAc in place of $NaCH(CO_2Me)_2$.

Based on the crystal structure obtained by Helmchen's group of a related palladium allyl complex,[3] and the knowledge that the π-accepting diphenylphosphino group generates a more electrophilic carbon *trans* to itself,[6] then it seems likely that the sense of asymmetric induction is explained by the process indicated. We assume that alternative π-allylpalladium complexes are able to interconvert by the well known π–σ–π mechanism.[4]



We have shown that substrates in which the termini of the palladium allyl intermediate are non-equivalent afford enantioselective reactions with ligand **6**. This is especially important if the R substituent is valuable.

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5. The (*S*)-configuration of the products was determined by conversion (see ref 4(a)) into (*R*)-methylsuccinic acid **9** $[\alpha]_D^{20}$ = +13.9 (c=1, EtOH), lit.7 $[\alpha]_D^{22}$ = +15.5 (c=2.8, EtOH) and (*S*)-phenylsuccinic acid **10** $[\alpha]_D^{20}$ = +148 (c=0.9, EtOH), lit.4a (for (R)-enantiomer), $[\alpha]_D^{25}$ = –145.5 (c=1.3, EtOH).
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