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The Palladium Catalyzed Allylic Alkylation of Bis(trimethylsilyl) Substituted Propenyl Acetates or Carbonates in the Presence of Chiral Ligands

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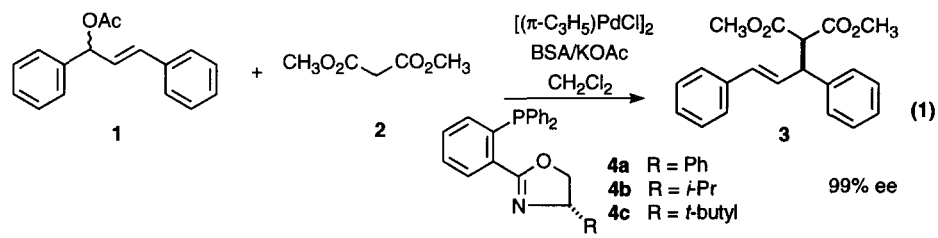
Abstract: Palladium catalyzed asymmetric allylic alkylations of a bis(trimethylsilyl) substituted propenyl acetate and carbonate were investigated using various chiral ligands and reaction conditions. The best enantioselectivity (86% e.e.) was obtained with the substrate 1-phenyl-3,3-bis(trimethylsilyl)propenyl carbonate **13** and the chiral oxazoline ligand **4c**. © 1997 Elsevier Science Ltd.

Recently there have been many reports of chiral ligands that afford high enantioselectivities in the palladium catalyzed allylic alkylation of the 1,3-diphenylallyl system, the "standard" test substrate (eq. 1).[1,2] This substrate is often selected because the π-allyl moiety is C_{2h} symmetric. High enantioselectivity results due to preferential attack of the nucleophile at one of the enantiotopic termini. Some of the best results to date have been obtained with chiral (phosphinoaryl)oxazoline ligands (**4**), wherein reaction of 1,3-diphenylpropenyl acetate (**1**) with dimethyl malonate in the presence of a catalytic amount of $[AllylPdCl]_2$ and **4a** (R = Ph), afforded the alkylated product (**3**) in 99% ee.[2a,b]

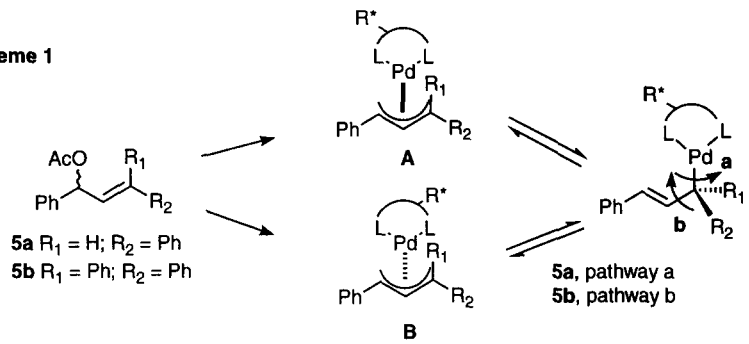


1 2 3 (1)

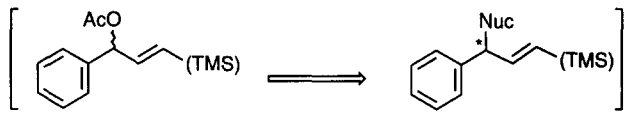
Although cases of unsymmetrical allyl moieties undergoing enantioselective alkylation have been reported,[3] the reaction is not generally useful because cases where the allylic termini are not substantially differentiated result in the formation of both possible regioisomeric products.[4] An exception is reported cases where one of the allylic termini has two identical substituents (Scheme 1, $R^1 = R^2$).[5] A close examination of the reaction mechanism provides an explanation for these observations.[6] Reaction of both enantiomers of symmetrical allylic acetate **5a** can give rise to two diastereomeric π-allyl complexes depicted as **A** and **B** (Scheme 1). These π-allyls can readily interconvert by the π-σ-π process via rotation about the allylic C-Pd bond which interconverts the enantioface of the η^3-allyl complex (Pathway a). Therefore, either of the starting enantiomeric allyl acetates can react through the same π-allyl to provide one enantiomer of the final product.

In the case of unsymmetrical π-allyls (i.e. $R^1 = H$; $R_2 \neq Ph$), interconversion via the π-σ-π process cannot occur; thus, except in special cases, both regioisomeric products are produced. Such unsymmetrical π-allyls can only interconvert when one of the termini is non-stereogenic (**5b**, i.e. $R_1 = R_2$). When this is the case, the palladium can switch enantiofaces by the π-σ-π process, this time via rotation about the C-C bond (Pathway b). If this interconversion is much more rapid than attack by nucleophile, high enantioselectivities will result if one of the π-allyl complexes reacts faster than the other.

Scheme 1

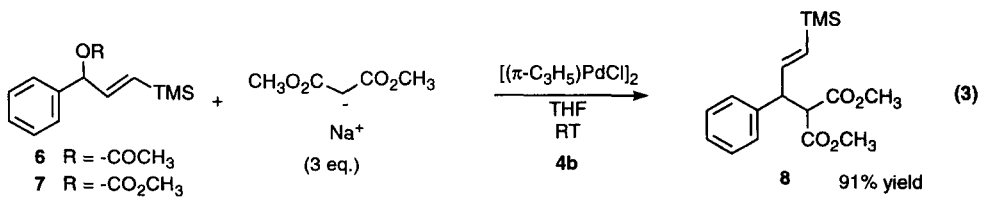


Herein we describe attempts to extend the utility of asymmetric palladium catalyzed allylic alkylation to unsymmetrically substituted allyls by investigating the alkylation of a π-allyl system wherein regiochemistry would be controlled. Previous work by Tsuji demonstrated that introduction of a regiocontrol element, such as a trimethylsilyl group, directs alkylation γ to the silicon atom.[7] Following the palladium catalyzed allylation, the trimethylsilyl group can be easily removed. An asymmetric version of this reaction, utilizing chiral palladium ligands would provide the equivalent of the chemical transformation depicted in eq. 2.[8, 9]



(2)

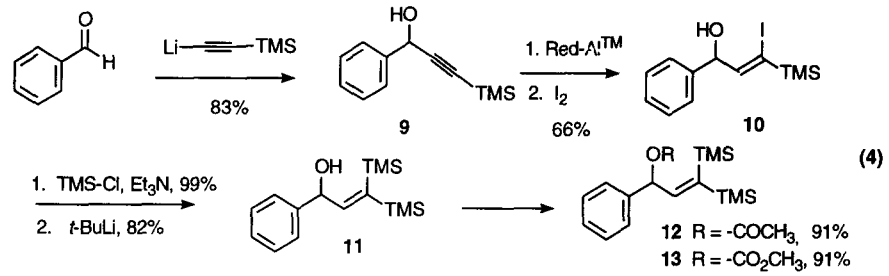
As expected from analysis of the reaction mechanism, treatment of silyl substituted allylic acetate **6** or carbonate **7** with dimethyl sodiomalonate in the presence of $[AllylPdCl]_2$ and **4b**, (eq. 3) afforded the alkylated product **8** in 91% yield but with no enantioselectivity.



(3)

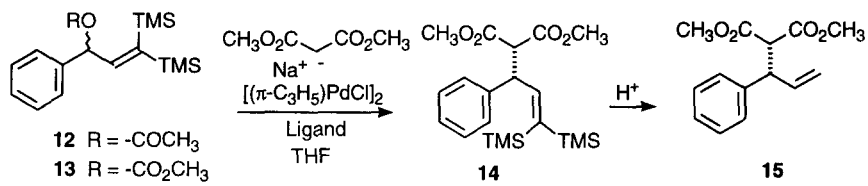
Thus we turned our attention to the reaction of an allyl system in which one of the allylic termini had two identical substituents. Following standard procedures,[10] an allylic acetate or carbonate containing two terminal trimethylsilyl groups was prepared (eq. 4). Treatment of benzaldehyde with lithium trimethylsilyl acetylide afforded the propargyl alcohol, **9**. Reduction of the acetylene with Red-Al™ followed by trapping with I_2 afforded vinyl iodide **10**. The alcohol was then silylated with TMSCl and the material was subjected

to metal halogen exchange by treatment with *t*-butyllithium. Internal transfer of the TMS moiety afforded vinylsilane **11** from which the requisite acetate **12** or carbonate **13** was prepared using standard conditions.



Alkylation of **12** or **13** with dimethyl sodiomalonate in the presence of chiral ligand **4b** afforded the alkylated product (*S*)-(-)-**14** in good yield and in 30% e.e. (Table 1).[11] When the bulkier ligand **4c** was used improved enantioselectivities were observed (86% e.e.). This ligand also proved effective in the alkylation of the acetate **12** affording the alkylated product in 66% e.e. In similar alkylations, alteration of the structure of the nucleophile via alteration of the counterion has resulted in improved enantioselectivities. Thus the reaction was attempted in the presence of 15-crown-5 in acetonitrile,[12a] but formation of product did not occur. Reaction did, however, proceed with the tetrahexylammonium salt of malonate in dichloromethane,[12b] but enantioselectivities were not improved. Treatment of the allylated product **14** with *p*-TsOH in refluxing acetonitrile afforded olefin **15** in 71% yield without erosion of enantiopurity.

Table 1. Enantioselective Alkylation of **12** and **13**

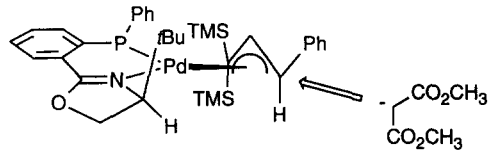


Entry	R	Ligand	Yield of **14** (%)	e.e. (%)
1	$CO_2CH_3/COCH_3$	4b	75	30[a]
2	CO_2CH_3	4c	69	86[b]
3[c]	$COCH_3$	4c	39	66[a]
4[d]	CO_2CH_3	4c	60	18[e]

[a]The e.e. values were determined by HPLC with Chirocel OD-H™, 0.25% 2-propanol/hexane, 1 mL/min. [b]The e.e. value was determined by HPLC with (R,R) WHELK-O™ column, 5% 2-propanol/hexane, 0.5 mL/min on compound **15**. [c]This reaction was run at 0°C to RT. [d]The sodium counterion was exchanged to tetrahexylammonium bromide in methylene chloride according to the procedure outlined in reference 12b. [e]The e.e. value was determined by ^1H NMR using 0.5 eq. of Eu(hfc)$_3$ in 1:1 $CDCl_3/C_6D_6$.

In conclusion, 1-phenyl-3,3-bis(trimethylsilyl)propenyl acetate or carbonate can be alkylated with sodiomalonate in the presence of chiral ligands with good enantioselectivity. After serving as regiocontrol elements, the trimethylsilyl groups can be easily removed affording the equivalent of products in which the nucleophile has attacked the more substituted carbon atom of the π-allyl system. The sense of asymmetric induction can be explained by the transition state depicted in Figure 1, which is consistent with previous proposals and a crystal structure of a similar palladium complex.[2e] Factors which may lead to improved enantioselectivity such as variation of the chiral ligand, or alteration of the reaction conditions remain to be investigated.[13]

Figure 1.



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