Novel Use of Ring Strain to Control Regioselectivity: Alkene-Directed, Palladium-Catalyzed Allylation

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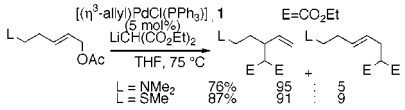
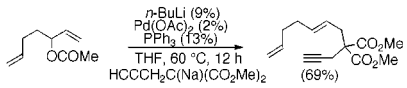
Palladium-catalyzed allylations of soft nucleophiles are a powerful synthetic transformation.[1,2] While the stereo- and regiochemical consequences of the allylation have been well-studied, questions still remain. The major factors influencing regioselectivity are nucleophile type, steric bulk of the groups at the allylic termini, electronic nature of allyl substituents, stability of the η^2-alkene palladium(0) complex resulting from the nucleophilic addition to the π-allyl moiety, and steric and electronic effects from the other ligands on the metal center. Much attention has recently been given to external ligand control over the regiochemical outcome, in particular, as it pertains to asymmetric catalysis of the transformation.[3,4] We have demonstrated that allylic acetates possessing a thioether or dimethylamino substituent in the homoallylic position directed the addition of malonate to the allylic terminus proximal to the heteroatom.[5] We proposed that chelation of the heteroatom played an integral role in determining the regiochemical outcome. This internal (intramolecular) ligand control represents an additional factor in the regioselectivity-defining process (Scheme 1). We anticipated that other nonheteroatom containing functional groups capable of coordination to a metal would direct the regiochemistry of allylation. *Herein we describe the novel use of an alkene as a directing group in Pd-catalyzed allylations, the stereochemistry of the process, and mechanistic insight provided by a crystal structure of the putative alkene-bound Pd(+2) intermediate.*

Scheme 1



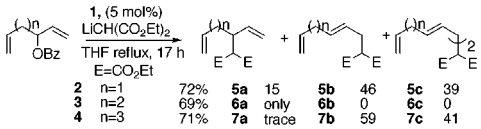
A number of examples of palladium-catalyzed reactions of alkene bearing substrates exist. One example is very relevant to the results described herein (eq 1). In the presence of a large excess of phosphine, Pd(0) catalyzes allylic alkylation at the less substituted terminus of the allyl moiety despite the presence of an alkene in a position to bind to the metal center (eq 1).[6] The



(1)

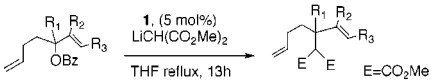
opposite regioselectivity of allylation is obtained when a Pd/P ratio of 1 is used (vide infra), suggesting an influential role of the alkene. Coordination of a pendant alkene to the metal center in the π-allyl intermediate resulting from inter- or intramolecular diene dimerizations has been demonstrated.[7−9] Interestingly, the presence of a remote double bond has been proposed to influence the direction of β-elimination of a palladacycle, whereas in the presence of phosphines the opposite alkene isomer predominated.[10]

The results of the palladium-catalyzed reaction of malonate anion with allylic acetates **2**−**4** show a surprising change in regioselectivity as the tether length between the alkene and allylic acetate increases from one to three atoms. In the reactions of **2**



2	n=1	72%	**5a**	15	**5b**	46	**5c**	39
3	n=2	69%	**6a**	only	**6b**	0	**6c**	0
4	n=3	71%	**7a**	trace	**7b**	59	**7c**	41

and **4** the major products arise from substitution at the unsubstituted terminus of the allylic acetate. However, the only isomer obtained from the reaction of allylic acetate **3** was diene **6** where substitution had taken place on the more substituted allylic position proximal to the tethered alkene. In light of our results with heteroatom-directed allylation, it is evident that alkene coordination to the metal center is responsible for the observed high selectivity. Support for the influential capacity of the alkene is derived from observation of the regioselectivity of reaction of **3** in the presence of DPPE in which almost complete disruption of the remote alkene effect is observed, giving a 14:48:38 ratio of **6a**:**6b**:**6c** in 90% yield. The dichotomy of results when the reaction is performed in the presence of 1 versus 2 or more equiv of phosphine per palladium atom strongly implicates coordination of the alkene as the regiochemical determining factor. Reactions of allylic benzoates **8**, **9**, and **10** suggest the generality of the directing effect. Substituents at the allylic terminus distal to the



8,	R_1=H, R_2=H, R_3=CH_3	13h	**11**	95:5	61%
9,	R_1=H, R_2=CH_3, R_3=H	17h	**12**	>95:5	85%
10,	R_1=CH_3, R_2=H, R_3=H	48h	**13**	>95:5	65%

directing alkene or at the central allylic carbon have no effect on the regiochemical outcome. Tertiary allylic acetate **10** undergoes reaction to generate a quaternary stereocenter in high yield with complete regiocontrol, although disubstitution at one allylic terminus may impact the result.[11,12] It is striking that, even when the distal terminus is unsubstituted, reaction occurs at the more substituted end proximal to the tether which is contrary to the normal steric guidance over substitution. Alkyl substitution at the internal position of the directing alkene has a minimal effect on the regioselectivity; however, 1,2-disubstituted and 1,1,2-trisub-

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Table 1

PR_3	time (h)	yield **6a** (%)	PR_3	time (h)	yield **6a** (%)
$P(C_6F_5)_3$	1	79[a]	$P(OPh)_3$	3	91
PCy_3	16	44[b]	PPh_3	17	69[a]

[a] Small amounts of starting material remained. [b] Starting material and other unidentified compounds were present.

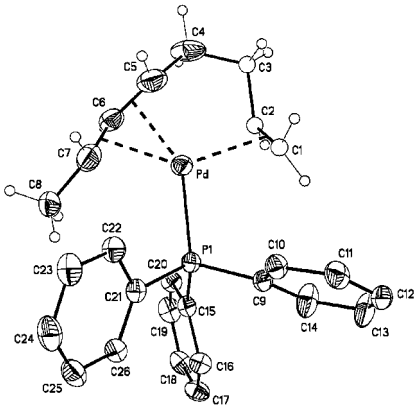
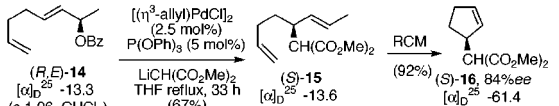


Figure 1. Thermal ellipsoids drawing of η^3,η^2-allyl ene complex **18**; H atoms of the phenyl rings were removed for clarity. Drawing with part 1 of the disorder (C1−C3). Selected bond lengths (Å): Pd−C5 2.189, Pd−C6 2.148, Pd−C7 2.177, Pd−C2 2.274, Pd−C1 2.316.

stituted alkenes are detrimental to the outcome of the highly selective allylation. Reaction of the sodium salt of diethyl methylmalonate with **8** gave rise to a 93:7 mixture of regioisomers where substitution at the allylic terminus proximal to the directing alkene predominated.

In an attempt to ascertain the role of the external ligand in influencing the regiochemical outcome, phosphorus ligands of different electronic nature were employed (Table 1, allylic acetate **3**, $[(\eta^3\text{-allyl})PdCl]_2$ (2.5 mol %), PR_3 (5 mol %), $LiCH(CO_2Me)_2$, THF, 75 °C). Evidently, a trans influence from the phosphine ligand[12] is not responsible for the observed regioselectivity as only one isomer was obtained regardless of the electronic nature of the ligand.

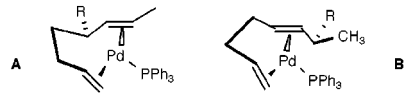
The stereoselectivity of the alkene-directed substitution is high and has been demonstrated to be retention of configuration, suggesting a double inversion process as is normally observed in Pd-catalyzed allylations (eq 2). Allylic acetate (*R*,*E*)-**14** underwent allylation to give (*S*,*E*)-**15** which, after ring-closing metathesis using Grubbs' catalyst,[13] provided the known cyclopentene (*S*)-**16**.[14]



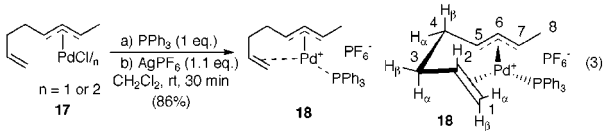
(2)

In an attempt to probe the mechanism and provide support for alkene coordination, cationic complex **18** was synthesized and characterized by ^{1}H NOE spectroscopy and X-ray diffraction analysis (eq 3).[15,16] The ^{1}H NMR spectrum of allylic complex **17** showed broad peaks suggesting an equilibrium between monomeric and oligomeric complexes. However, the ^{1}H NMR spectrum of **18** revealed a distinct 4:1 mixture of two compounds where conformational rigidity and binding of the alkene to the metal center, as determined by an upfield shift of the terminal alkene

Scheme 2



hydrogens (δ 4.67 and 4.26 ppm), were evident. ^{1}H NOE enhancements between H_5 and $H_{3\alpha}$ and between $H_{1\beta}$ and $H_{3\alpha}$ suggest the major conformer resides in a chairlike conformation in solution. Not surprisingly, reaction of one equiv of **18** with one equiv of sodio dimethylmalonate at room temperature resulted in a 65% yield of diene **11** along with 5% of the regioisomeric addition product. Thus, the results are identical when the reaction



(3)

is performed under either catalytic or stoichiometric conditions. X-ray diffraction analysis revealed disorder in the tethered alkene part of the ligand. A thermal ellipsoid drawing of one of the two allyl complexes is shown in Figure 1.

A number of factors are known to contribute to regioselectivity in Pd-catalyzed allylations.[1,3] However, in these cases an influential role of the alkene, presumably ligated, must be an integral part of the explanation. With due consideration given to all aspects of the mechanistic manifold, ring strain-induced selective activation of one of the allylic termini with concomitant influence in the direction of rotation of the allyl ligand is the factor most likely required in a rationalization of the regiochemical outcome.[3] Nucleophilic addition at C5 (**18**, eq 3) associated with a counterclockwise rotation of the allyl moiety out of the coordination plane during the change in hapticity, with simultaneous shifting of the π-system to generate the elusive alkene complex,[17] relieves ring strain as the chelate ring is effectively enlarged (Scheme 2, A). Reaction at C7 would require a clockwise rotation of the allyl moiety during hapticity change with simultaneous shift of the π-system to the right, thus causing an increase in ring strain as the effective ring size is decreased (Scheme 2, B).

In summary, a novel use of internal ring strain to drive reaction selectivity has been described. Using a tethered alkene as a nontraditional control element, regioselective addition to π-allyl Pd complexes is possible. The directing effect overcomes the normal steric bias, and reaction can occur at the more substituted terminus of a monofunctionalized π-allyl moiety. X-ray diffraction analysis of the alkene-bound intermediate sheds light on the mechanism by providing structural evidence for alkene binding. Further work in this area is currently underway.

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Supporting Information Available: Experimental information for all compounds; X-ray crystallographic information for **18** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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