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Regioselective additions to Π-allyl metal complexes

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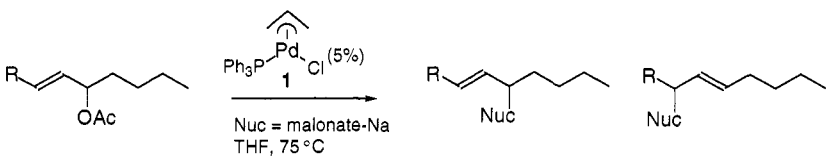
Abstract: Highly regioselective additions to allylic acetates, catalyzed by palladium (0), can be achieved by incorporation of a thioether or tertiary amine on the substrate. Reactions with malonate anion are highly selective for the terminus of the allyl moiety proximal to the heteroatom.

Palladium catalyzed allylations of stabilized nucleophiles is a well-established procedure which has been shown to be of great synthetic utility.[1,2,3] Substitutions of 1- or 3-substituted allylic acetates tend to be selective for the less substituted terminus (Scheme 1).[2] Reactions of 1,3-disubstituted allylic acetates can lead to a mixture of regioisomeric substitution products. The problems associated with substitution selectivity have been partially addressed in several ways. Polarizing functional groups such as carbonyl,[4] acetate,[5] alkoxide,[6] or alcohol[7] adjacent to the π-allyl complex promote addition distal to that group. Steric hindrance at one terminus of allyl moiety can direct the substitution away from that terminus.[8,9] In addition, enhanced control over the position of substitution has been achieved by the use of catalysts bearing sterically hindered bidentate ligands.[10,11] In spite of these efforts the problem has not been completely solved.

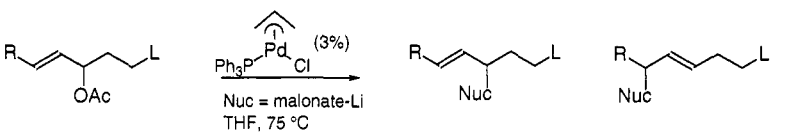
Scheme 1



R=Me	1	: 6
R=H	1	: 15

Regioselective addition can now be achieved by taking advantage of a tertiary amine or thioether in the homoallylic position of an allylic acetate (Scheme 2). Reactions of thioether or dimethylamino substituted allylic acetates with diethyl malonate anion (Li - BuLi, -78°C or Na - NaH, 0°C) in THF in the presence of palladium catalyst **1** (3-5%) at 75°C for 5h gave rise to the corresponding allylated malonates in 75 - 80% isolated yields. The major isomer resulted from addition to the terminus of the π-allyl Pd(+2) intermediate nearest the heteroatom. The regiochemistry is particularly striking in those cases where R=H. In spite of increased steric interactions, substitution occurs on the more substituted terminus. In the absence of the heteroatom, substitution occurs almost exclusively at the unsubstituted terminus (Scheme 1). Use of $Pd(PPh_3)_4$ as the catalyst in place of **1** led to more variable results.

Scheme 2

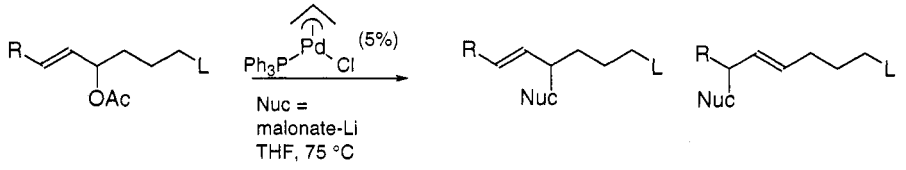


L	R	
NMe_2	Me	9 : 1
	H	19 : 1
SMe	Me	8 : 1
	H	10 : 1
OMOM	Me	1 : 10
	H	1 : 10

Isolated yields: 70-90%

An increase in the number of methylene units between the heteroatom and the allylic moiety led to a change in selectivity (Scheme 3). Under identical reaction conditions, the major product formed resulted from preferential substitution at the terminus of the allylic fragment distal to the heteroatom.

Scheme 3

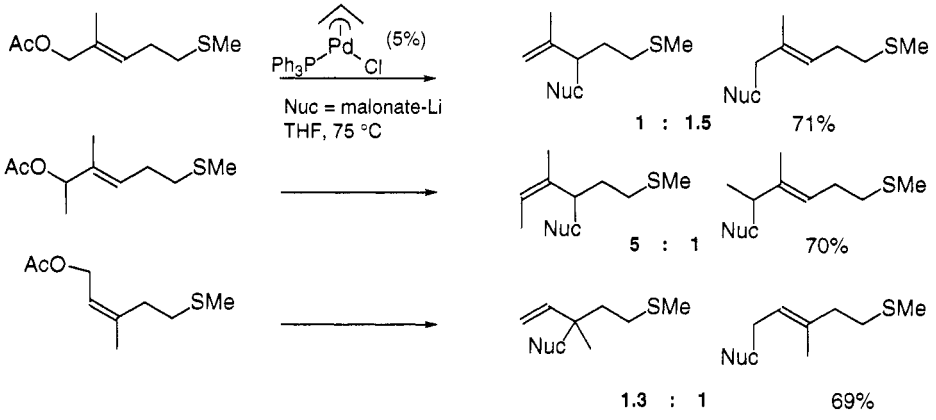


L	R		
NMe_2	Me	1	: 4
	H	1	: 5
SMe	Me	1	: 3
	H	1	: 6
OTBS	Me	1	: 10
	H	1	: 10

Isolated yields: 65-85%

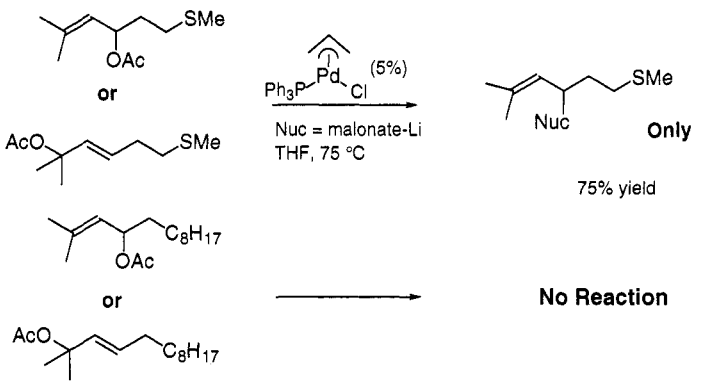
Additional substitution on the three carbons of the allylic moiety led to variable, but interesting, results (Scheme 4). Substitution of a methyl group on the central allyl carbon disrupted the directing effect and almost equivalent amounts of each regioisomer were obtained. Introduction of another methyl group at the terminal carbon restored some of the selectivity giving a 5:1 ratio of isomers where the major product resulted from substitution proximal to the heteroatom. Disubstitution at the internal carbon of the allyl moiety might have been expected to completely disrupt the heteroatom effect due the enhanced steric hindrance. However, the power of the directing effect is readily apparent as the major isomer still results from substitution at the terminus proximal to the heteroatom in spite of the increased steric interactions.

Scheme 4



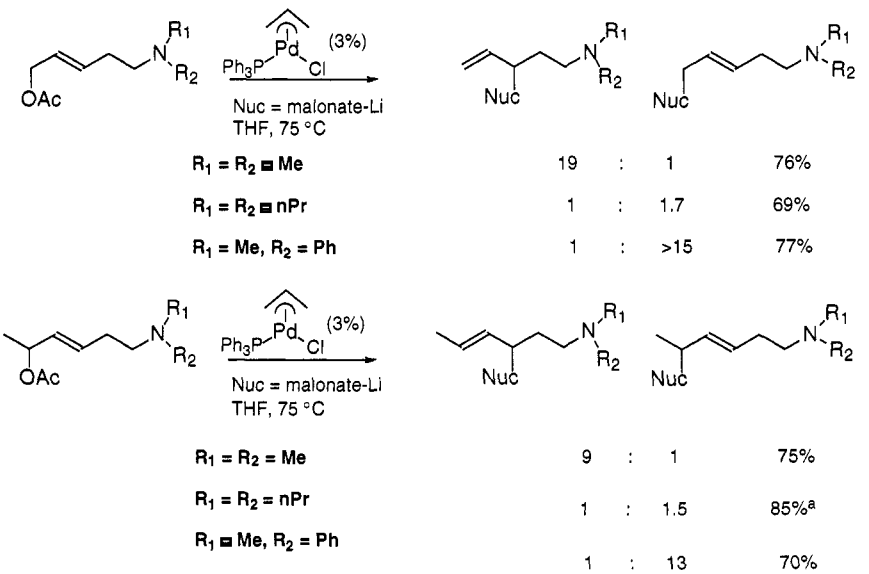
Interestingly, disubstitution at the terminus distal to the heteroatom yielded only the regioisomer resulting from addition at the terminus proximal to the heteroatom (Scheme 5). It is remarkable that, in the absence of the thioether, the analogous substrate does not undergo nucleophilic substitution and the starting allylic acetate is recovered unchanged. Both allylic acetate regioisomers were prepared in order to determine whether the failure of palladium to complex with the more hindered trisubstituted alkene was responsible for the lack of reactivity. These results suggest a dual role for the heteroatom - as an accelerating and a directing group.

Scheme 5



The effect of the size and electronic nature of the alkyl groups on the heteroatom was also studied (Scheme 6).[12] An increase in the size of the aliphatic group on the tertiary amine had a detrimental effect regardless of whether the allylic acetate was mono- or 1,3-disubstituted. The opposite selectivity observed with the aromatic amines, which would not be expected to coordinate efficiently to palladium,

Scheme 6



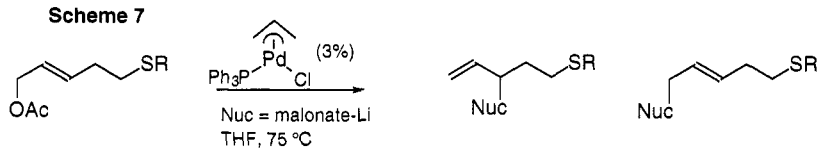
$R_1 = R_2$ = Me	19	:	1	76%
$R_1 = R_2$ = nPr	1	:	1.7	69%
R_1 = Me, R_2 = Ph	1	:	>15	77%

$R_1 = R_2$ = Me	9	:	1	75%
$R_1 = R_2$ = nPr	1	:	1.5	85%[a]
R_1 = Me, R_2 = Ph	1	:	13	70%

a) The reaction failed to proceed to completion under a variety of reaction conditions.

strongly suggests a different role for the heteroatom when compared to the substrates bearing the dimethylamino group. Of the tertiary amines, the dimethylamino group appears to provide the strongest directing effect. In the thioether cases (Scheme 7), the change in selectivity as a function of the alkyl substituent was not so dramatic. Even with the phenylthio ether influence from the heteroatom was apparently still observed.

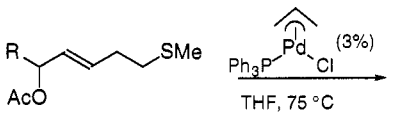
Scheme 7



R = Me	10	:	1	87%
R = iPr	7	:	1	63%
R = Ph	4	:	1	72%

Reactions with other stabilized nucleophiles gave expected results (Scheme 8). Sterically more bulky nucleophiles were less selective in the allylic substitution. The tetrasubstituted enolate, obtained from diethyl methyl malonate, also was less selective, in particular, with the terminal acetate. It is evident that the heteroatom still exerts an influence on the reaction outcome but significant steric factors can contribute to a disruption of the selectivity derived from the influence imparted by the heteroatom.

Scheme 8

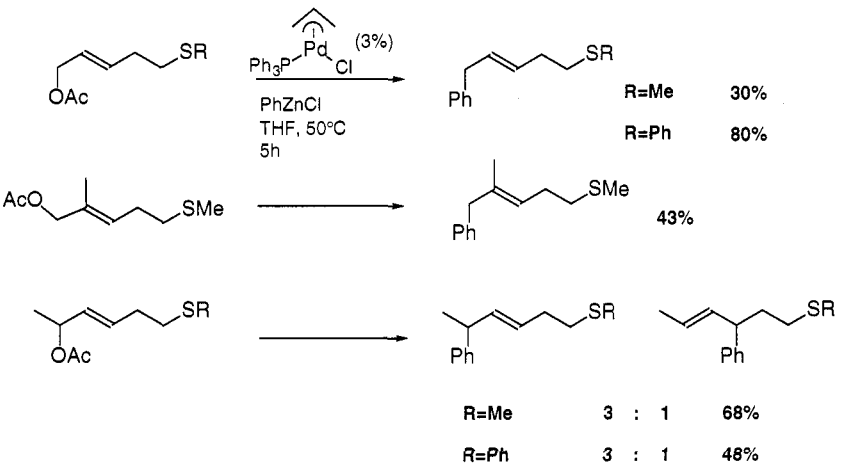


Nuc	R		
MeO(C=O)CH(Me)(C=O)OMe	H	15 : 1*	72
	Me	15 : 1	75
EtO(C=O)CH(Me)(C=O)OEt	H	10-15 : 1*	75
	Me	10-15 : 1	76
EtO(C=O)C(Me)(Me)(C=O)OEt	H	2.5 : 1	82
	Me	10 : 1	90
tBuO(C=O)CH(Me)(C=O)OtBu	H	4 : 1	83
	Me	6 : 1	90
$PhSO_2CH_2SO_2Ph$	H	3 : 1	70

* Mixture of mono and dialkylated malonate.

Analogous substitution reactions using alkylzinc reagents as nucleophiles led to high selectivity for the unsubstituted terminus of a monosubstituted π-allyl metal complex (Scheme 9). However, with a 1,3-difunctionalized π-allyl intermediate, transfer of an alkyl group from zinc led to a mixture of regioisomeric products where substitution on the sterically less hindered terminus was favored by a 3:1 margin.

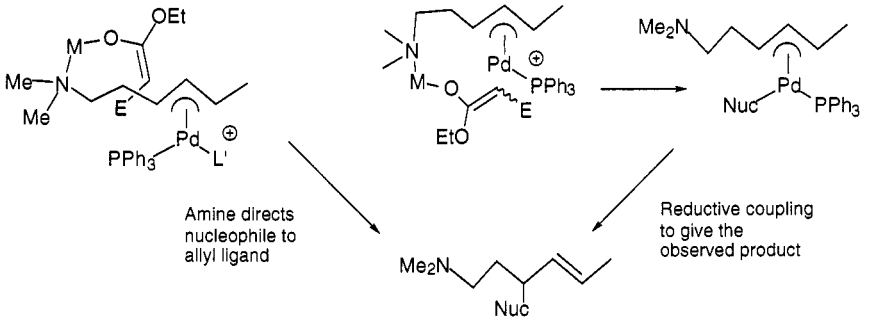
Scheme 9



Potential explanations for the observed high regioselectivity in the presence of the homoallylic tertiary amine or thioether are illustrated in Schemes 10 and 11. One possible scenario uses the amine or sulfide as a coordinating group to bring the nucleophile, *via* coordination to the counterion, to the allyl moiety or to the metal (Scheme 10). In the former case, the nucleophile would add to the terminus of the allyl residue closest to the heteroatom due to a proximity effect. Alternatively, the nucleophile could be

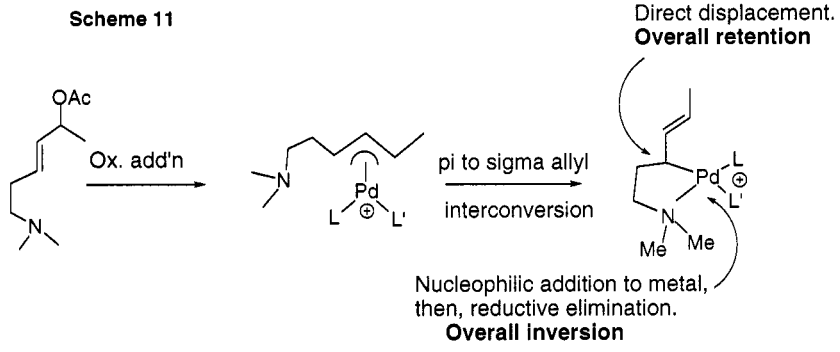
directed to the metal center followed by reductive coupling of the two carbon ligands on the metal. In both proposals, the ring size is large although recent reports[13] would suggest that reaction via a large ring is possible in this case. The stereochemical outcome would be overall retention in the former case and inversion in the latter one.

Scheme 10



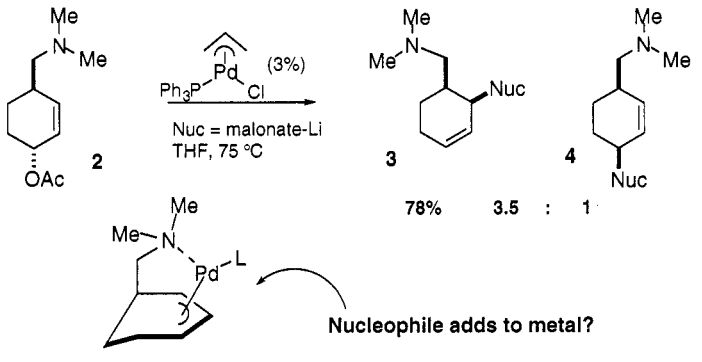
Another explanation is illustrated in Scheme 11. Coordination of the heteroatom to palladium could require slippage from a formal π–allyl toward a σ-allyl, then, nucleophilic addition to the metal followed by reductive elimination would yield an overall inversion of stereochemistry in the substitution product while direct displacement would result in overall retention of configuration. Thus, a study of the stereochemical outcome of the allylic substitution was clearly warranted.

Scheme 11



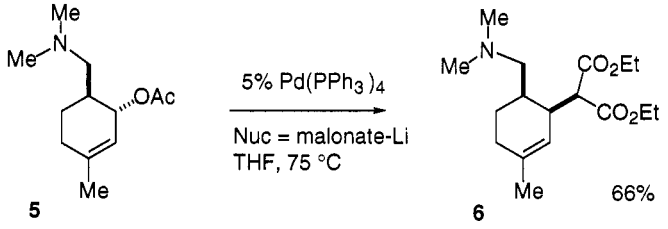
Stereochemical studies using a cyclic allylic acetate were chosen initially. Cyclohexenyl acetate **2** was synthesized using standard methods. Reaction with Pd catalyst **1** under the normal reaction conditions gave a 3.5:1 ratio of the 1,2 vs 1,4 substitution products, **3** and **4** respectively, both with *cis* orientation of the two groups on the ring (Scheme 12). Amine **3** is analogous to the major regioisomer obtained in the acyclic cases. It is notable that both adducts resulted from an overall inversion. A number of different reaction conditions were tried unsuccessfully in an attempt to increase the percentage of the 1,2-substitution product relative to the 1,4-substituted isomer.

Scheme 12



Finally, allylic acetate **5** was synthesized and treated with 5% $Pd(PPh_3)_4$ under the usual reaction conditions with lithiodiethyl malonate to yield exclusively the *cis* 1,2-disubstituted cyclohexene **6** in 66% yield (Scheme 13). No other regio- or stereoisomers could be detected by 500 MHz ^1H NMR spectroscopy.

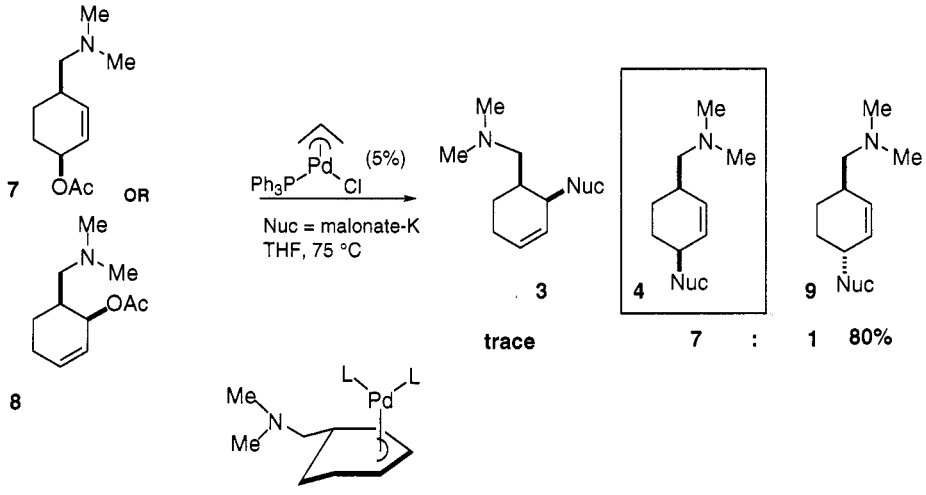
Scheme 13



Assuming an inversion of configuration for the initial displacement of acetate with palladium, the stereochemical outcome - overall inversion of configuration - can be used to rule out the use of the heteroatom to direct the nucleophile to the allyl intermediate (Scheme 10). It also rules out the direct displacement mechanism from the formal σ-allyl complex (Scheme 11). [A bicyclic ammonium salt on the mechanistic pathway does not fit the data from reactions of both amines **2** and **7** (below).]

Lastly, for comparison, dimethylaminomethyl substituted allylic acetates **7** and **8** were synthesized. Under the normal conditions, reaction with the potassium salt of diethyl malonate gave cyclohexene **4** as the major product and minor amounts of regio- and stereoisomers **3** and **9** respectively (Scheme 14). The major product, amine **4**, represents an overall retention of configuration which would be expected in the absence of a remote heteroatom effect.

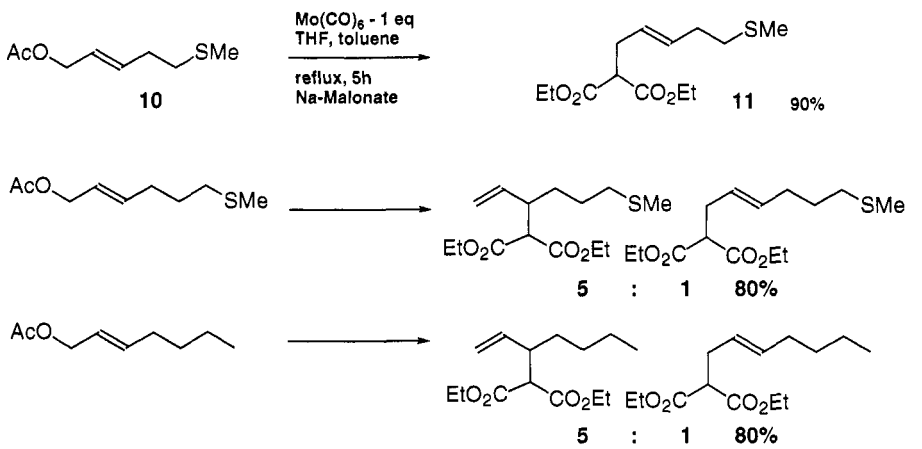
Scheme 14



To evaluate the importance of a remote heteroatom in other metal catalyzed allylations, we studied the analogous reactions catalyzed by $Mo(CO)_6$ (Scheme 15). With unsubstituted malonates and monosubstituted allylic acetates, $Mo(CO)_6$ normally promotes substitution at the more substituted terminus of the allylic moiety.[14] Reaction of homoallylic sulfide **10** with 1 equivalent each of $Mo(CO)_6$ and sodiodiethyl malonate in a 1:1 mixture of toluene/THF for 5h at reflux yielded exclusively allyl malonate **11**. This is in striking contrast to the reaction of the normal allylic acetate which gave a 5:1 ratio of isomers with the major product resulting from substitution at the more hindered allyl terminus. An increase in the tether length caused an apparent loss in the effectiveness of the heteroatom in directing

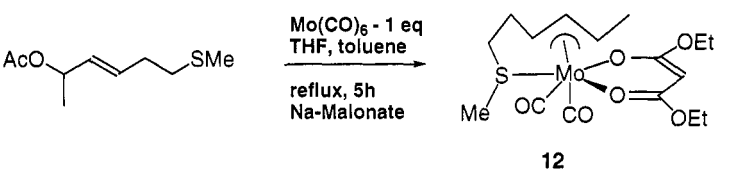
the reaction. The reaction outcome was identical to that obtained from the reaction of 2-heptenyl-1-acetate (Scheme 15).

Scheme 15



An increase in the substitution on the terminal allyl carbon resulted in the formation of complex **12** rather than the expected allylated malonate (Scheme 16).[15] Molybdenum complex **12** was relatively unstable in solution and decomposed upon standing, but, ^{1}H NMR spectroscopic evidence clearly shows the tridentate allyl ligand in the syn configuration. The stereochemistry at the metal center was not determined.

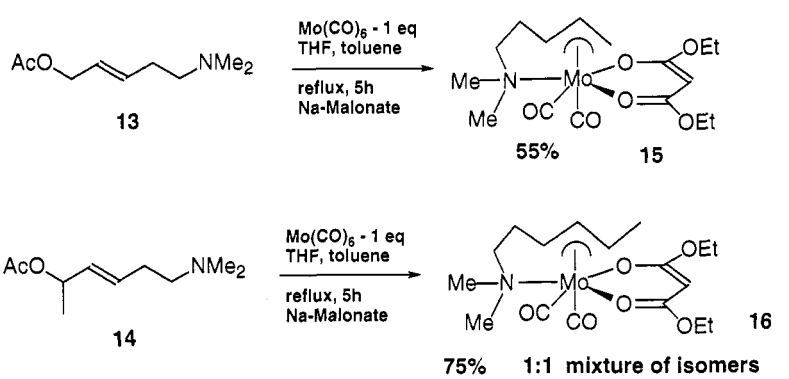
Scheme 16



12

Interestingly, reaction of the analogous homoallylic dimethylamines **13** and **14** gave only complexes **15** and **16** (Scheme 17). Both **15** and **16** were stable complexes and could be purified using silica gel chromatography. The stereochemistry of the allyl ligand was determined by ^{1}H NMR nOe experiments, but, the stereochemistry and the metal is, at this point, undefined.

Scheme 17



Summary: We have clearly identified an interesting and synthetically useful effect of a remote heteroatom on metal mediated allylations. Work is still in progress and results will be reported in due course.

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