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Palladium(0) Catalysed Allylation Reactions with Racemic and Enantiomerically Pure Allylic Sulfoximines.

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Abstract: Stabilised carbon and nitrogen nucleophiles can be efficiently allylated in a regioselective manner using allylic sulfoximines and palladium(0) catalysis. © 1997 Elsevier Science Ltd.

The palladium catalysed allylation reactions of nucleophiles with allylic substrates is well documented.[1] The asymmetric versions of these reactions is an exciting newer development, however products with high enantiomeric excess are generally only available from *meso*-substrates or allylic substrates that give rise to a symmetrical (η^3-allyl)palladium intermediates.[2] A variety of allylic substrates have been employed however, allylic acetates and carbamates seem to be the most useful.[1,2] Allylic sulfoximines have not been employed in these allylation reactions, although several studies on their S_N2 and S_N2' displacement reactions with organometallic reagents have been reported.[3] These substrates potentially offer a number of advantages over other allylic derivatives: (1) allylic sulfoximines are chiral and can be readily prepared in enantiomerically enriched form and thus lead directly to enantiomerically enriched products ; (2) allylic sulfoximines can be readily lithiated and their corresponding anions can be employed to prepare more complex structures in a highly diastereoselective manner through alkylation[4], aldol[5] and Michael addition[6] reactions and (3) allylic sulfoximines rapidly form (η^3-allyl)palladium complexes at room temperature.[4, 7-9]

We recently reported that allylic sulfoximines **A** undergo rearrangement to their isomeric allylic sulfinamides **D** in the presence of palladium(0) and that these reactions can be used to prepare *N*-tosyl allylic amines **E** (eq 1).[4,7-9] These reactions occur via nucleophilic attack of a liberated sulfinamide anion **C** on the resulting allylic cation-palladium complex **B**. In principle, allylic sulfoximines are good substrates for the allylation of an external nucleophile (Nu) if that nucleophile can compete with the sulfinamide anion **C** for the palladium(0) complex **B** or if the formation of **D** is reversible (eq 1). In this paper we report that stabilised carbon and nitrogen nucleophiles can be efficiently allylated in a regioselective manner using allylic sulfoximines and palladium(0) catalysis.

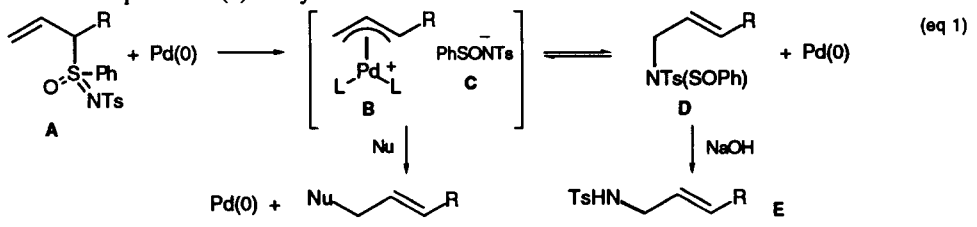
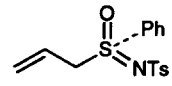
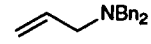
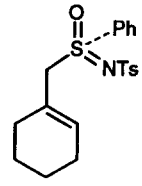
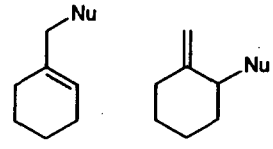
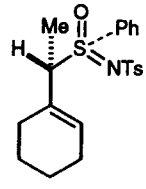
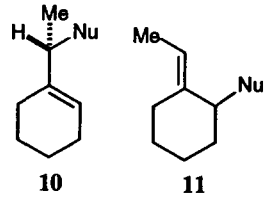
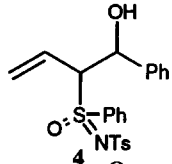
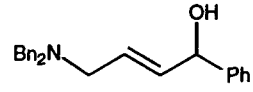
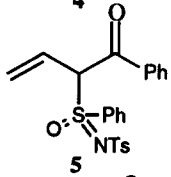
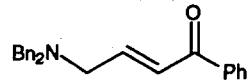
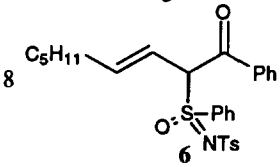
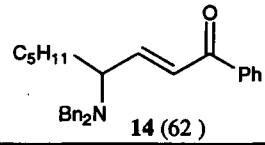


Table 1.

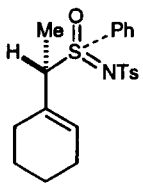
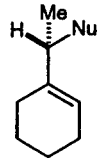
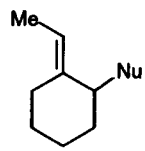
entry	substrate[a]	nucleophile[b]	products (yield[c] (%))
1	 **1**	A	 **7** (67)
2	 **2**	A	 **8** **9** Nu = Bn_2N (73); **8** : **9** = > 98 : < 2
3	**2**	B	Nu = $CH(CO_2Et)_2$ (77); **8** : **9** = 89 : 11
4	**2**	C	Nu = $CH(N{=}CPh_2)CO_2Bu^t$ (80); **8** : **9** = 94 : 6
5	 *rac*-**3**	C	 **10** **11** Nu = $CH(N{=}CPh_2)CO_2Bu^t$ (66); **10** : **11** = 90 : 10 (**10**; dr = 74 : 26)
6	 **4**	A	 **12** (66)
7	 **5**	A	 **13** (43)
8	 **6**	A	 **14** (62)

[a] Unless indicated all compounds are racemic. [b]Nucleophiles: A, dibenzylamine; B, sodium diethyl malonate and C, lithium salt of tert-butyl N-(diphenylmethylene)glycinate [c] After purification by column chromatography on silica gel.

Treatment of the racemic allylic sulfoximines **1-6**[10] with 5 mol% of tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$) in THF at room temperature for 10-30 min, in the presence of the nucleophiles, dibenzylamine, sodium diethyl malonate or the lithium salt of *tert*-butyl *N*-(diphenylmethylene)glycinate (BDMG) (1.2 molar equivalents) gave the allylated products **7-14** in generally good yields with a good to high regioselectivity (Table 1). In general, the nucleophile added to the least substituted and/or sterically less demanding position of the allylic moiety. In the case of allylic sulfoximine **1**, it was found that compound **7** could also be obtained in a similar yield by first converting **1** *in situ* to its isomeric allylic sulfinamide **D** (R = H, eq 1) by initial treatment of **1** with $Pd(PPh_3)_4$ in THF at room temperature for 15 min,[4] followed by the addition of dibenzylamine. Thus the allylic sulfinamide **D** (R = H, eq 1) is readily converted to its allylic cation **A** (R = H, eq 1) in the presence of Pd(0). The cyclic substrates **2** and **3**, like the reactions of their analogous allylic acetate[11] or allylic nitro compounds,[12] gave a mixture of regioisomers, **8** and **9** and **10** and **11**, respectively. The reaction conditions reported here were much milder (120°C was required for the allylic acetate analogous to **3**[11]) and the reaction times much shorter and this may explain the slightly better regioselectivities found in this study. In the case of the reaction of the allylic sulfoximine *rac*-**3** with the lithium salt of BDMG (Table 1, entry 5, Nu = $CH(N{=}Ph_2)CO_2Bu^t$)) a 90 : 10 mixture of regioisomeric adducts **10** and **11** resulted. The major regioisomeric product **10** (Nu = $CH(N{=}Ph_2)CO_2Bu^t$) was a 74 : 26 mixture of diastereoisomers.

The reactions of allylic sulfoximines **1-6** with dibenzylamine gave usefully protected *N, N*-dibenzyl allylic amines.[13,14] The reactions of the secondary allylic sulfoximines **2, 4-6** were completely regioselective (Table 1, entries 2, 6-8). The γ-amino-α,β-enones **13** and **14** are potentially attractive substrates for the synthesis of azasugars and structurally related alkaloids.[15]

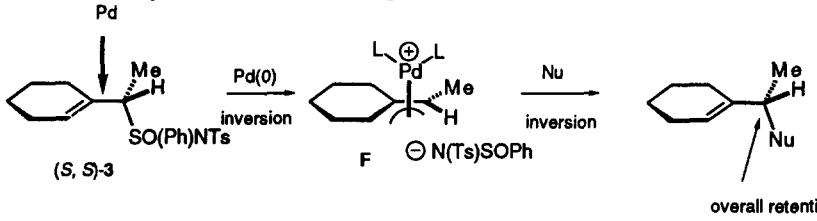
Table 2.

entry	substrate	nucleophile[a]	products (yield[b] (%))
1	 (*S, S*)-**3**	A	 **10**  **11** Nu = Bn_2N (60); **10** : **11** = > 98 : < 2 (**10**; ee > 98%)
2	(*S, S*)-**3**	B	Nu = $CH(CO_2Et)_2$ (62); **10**: **11** = 92 : 8 (**10**; ee > 98%)

[a]Nucleophiles: A, dibenzylamine; B, sodium diethyl malonate. [b] After purification by column chromatography on silica gel.

Treatment of enantiomerically pure (*S, S*)-**3**[4] with dibenzylamine or sodium diethyl malonate in the presence of palladium(0) gave the essentially enantiomerically pure (ee > 98 %) products (*S*)-**10** (Nu = Bn_2N) and (*S*)-**10** (Nu = $CH(CO_2Et)_2$) respectively (Table 2) as judged from ^1H NMR studies using the chiral shift agent europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate]. These studies resulted in two well resolved separate signals (doublets) for the methyl groups of racemic **10** (Nu = Bn_2N) and **10** (Nu =

$CH(CO_2Et)_2$), while only one set of doublets could be detected in the optically active versions of these compounds. Based on the sign of the specific rotation of **10** (Nu = Bn_2N, $[\alpha]^{27}_D$ +4 (c 0.9, $CHCl_3$))[16] the reaction of (*S, S*)-**3** with $Pd(PPh_3)_4$/dibenzylamine must have occurred with overall retention of configuration at the stereogenic carbon, consistent with attack of the nucleophile on the palladium allyl cation complex **F**, *anti* to the stericaly demanding palladium(II) moiety. The stereochemistry assigned to **10** (Nu = $CH(CO_2Et)_2$) was made by analogy to that of **10** (Nu = Bn_2N) and the known tendency of malonate nucleophiles to add *anti* to the palladium moiety in cations such as **F** (eq 2).[17]



(eq 2)

In summary, we have demonstrated that allylic sulfoximines are useful substrates for the palladium(0) catalysed allylation reactions and that these occur under very mild conditions and in a highly regioselective manner. In the case of (*S, S*)-**3**, products of high enantiomeric purities (> 98%) could be obtained.

Acknowledgment
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