Pergamon

Tetrahedron Letters, Vol. 36, No. 41, pp. 7541-7544, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)01527-2

Stereoselective Cycloadditions of Chiral Acyl-Nitroso Compounds; Palladium(0) Catalyzed Allylic Displacement with Concomitant Loss of the Chiral Auxiliary

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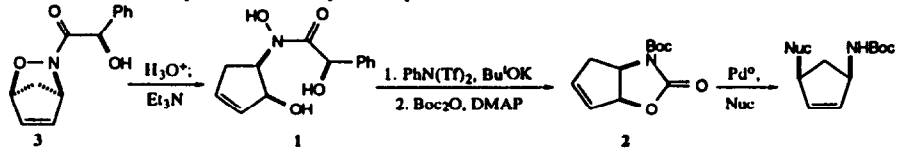
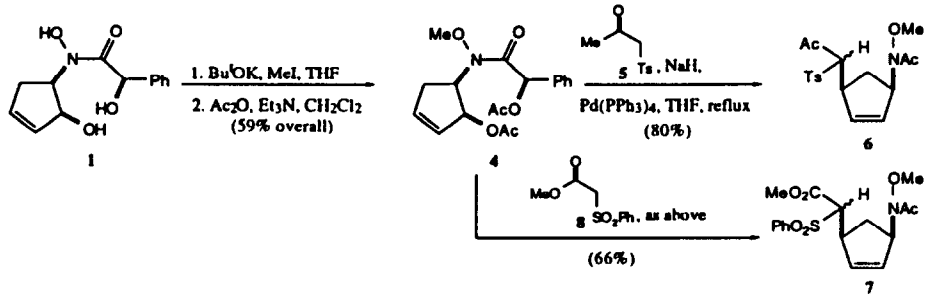
Abstract: The methylated diacetate **4**, derived from the readily available hydroxamic acid **1**, undergoes Pd^0 catalyzed nucleophilic allylic displacement under conditions which also result in the removal of the chiral auxiliary and its replacement with an easily removed acetyl group.

In the preceding paper, an unexpected reaction of the readily available hydroxamic acid **1** led to the formation of an oxazolidinone system, and the Boc derivative **2** was shown to be a substrate for Pd^0 catalyzed alkylation (Scheme 1).[1] This type of nucleophilic displacement is particularly useful in the context of the use of **1** in synthesis, as it re-establishes the 1,3-relationship of the stereocentres which was present in the original adduct **3**.[2] In this Letter we describe an alternative approach in which chiral auxiliary removal occurs in the same reaction vessel as the palladium catalyzed displacement.



Scheme 1

The hydroxamic acid **1** is easily obtained from the cycloadduct **3** in high yield,[1] and as both enantiomers of this cycloadduct are readily available in high enantiomeric excess, we are interested in uncovering efficient transformations of this material which should be useful in future synthetic applications. Selective methylation of **1** at the hydroxamic acid hydroxyl group is easily achieved, and the resulting methyl derivative can be converted into the diacetate **4** under standard conditions (Scheme 2). In principle diacetate **4** should be a



Scheme 2

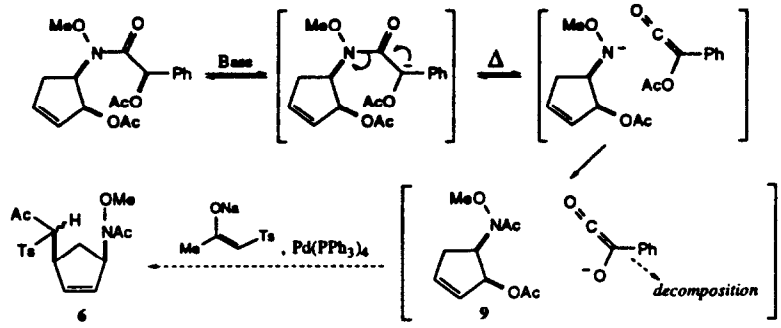
suitable substrate for Pd^0 catalyzed nucleophilic displacement of the allylic acetate. This was investigated using the ketone **5** as a model nucleophile, and on heating the reaction mixture to reflux a clean reaction was observed. The product was not that of the expected simple displacement, but corresponded to **6**, in which the anticipated displacement had occurred as usual with high selectivity, but in addition the chiral auxiliary had been replaced by an acetyl group. This reaction is not confined to nucleophile **5**, a similar product **7** is also obtained on reaction of the corresponding ester-sulphone **8**.[3]

Both the steps in this one-pot transformation, nucleophilic displacement and chiral auxiliary removal, are important for the application of this strategy in synthesis. In particular the removal of the chiral auxiliary is particularly troublesome in the case of cycloadducts from cyclopentadienes if the double bond is not removed prior to the cleavage of the chiral auxiliary.[4] In the reactions illustrated in Scheme 2 the auxiliary is removed in the course of the C–C bond forming reaction and the double bond is placed in the position which it occupied in the original cycloadduct **3**. Moreover, the reaction appears to be clean and capable of providing high yields.

In view of the potential usefulness of this transformation, and the unexpected nature of the chiral auxiliary removal, initial exploratory experiments were performed in an attempt to probe some of the mechanistic aspects of this process. The results of these experiments are outlined below, along with the tentative conclusions which we draw from them.

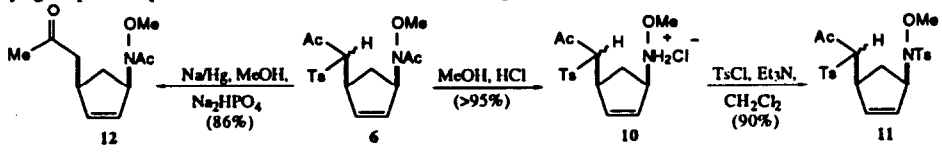
- The allylic acetate **4** appears to be largely unchanged on treatment with $Pd(PPh_3)_4$ alone under the reaction conditions (refluxing THF, 3 hrs.):- No allylic transposition of the allylic acetate was observed, suggesting that very little π-allyl palladium intermediate is formed, and that acetate **4** itself might be a poor substrate for the allylic displacement.
- The reaction appears to work equally well if 1.1 equivalents of the anion of **5** are used or if a molar excess of **5** is used to ensure that no excess NaH is present (2 equivalents of **5** and 1.1 equivalents of NaH):- The reaction presumably does not need two equivalents of base (i.e. one to cause loss of the chiral auxiliary and one for the formation of the anion of **5**), and NaH is unlikely to play a catalytic role.[5]
- Treatment of **4** with NaH (1 equivalent) in THF and stirring at room temperature followed by re-protonation causes epimerization adjacent to the phenyl group (along with some decomposition):- The anion of **4** is reasonably stable at room temperature.
- If the anion of **4**, generated as ion the preceding experiment, is refluxed in THF, a mixture of products is formed, in which the amide **9** appears to be the major identifiable component:- Amide **9** is not an unreasonable intermediate to propose in the reaction pathway.
- The chiral auxiliary appears to have decomposed completely:- Its removal is probably not a simple nucleophilic cleavage.

A reaction scheme which is consistent with these observations is outlined in Scheme 3, although it is not known at present what the basic species is which presumably initiates this reaction sequence.



Scheme 3

Irrespective of the mechanistic details of this interesting reaction, for future synthetic applications of this chemistry it would be of interest to be able to carry out certain selective reactions on systems such as **6** and **7**. Particularly important are the removal of the *N*-acetate and selective reductive cleavage of the toluenesulphonyl group without reduction of the N-O bond. These are can be achieved in high yield as illustrated in Scheme 4. The *N*-acetyl group can be removed efficiently by treatment with methanolic HCl, and further derivatization on nitrogen is straightforward as evidenced by the facile formation of tosylate **11**. Selective reductive cleavage of the tosyl group takes place on treatment with sodium amalgam in methanol to provide ketone **12**.



Scheme 4

In conclusion we have developed a simple synthetic sequence for the conversion of adducts from asymmetric acyl-nitroso cycloadditions to cyclopentadienes into systems which are interesting synthetic intermediates, which uses simple chemistry and which takes advantage of the unexpected and mechanistically interesting conversion of **4** into **6** and **7**. We are currently exploring the scope of this reaction, and developing synthetic applications of the products.

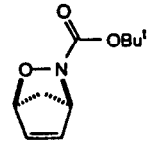
Acknowledgement: We thank the SERC (J.A.W.) and MRC (J.M.) for postdoctoral research assistantships.

References

1. Muxworthy, J.P.; Wilkinson, J.A.; Procter G preceding paper.
2. This structural motif can be found in various classes of potentially interesting synthesis targets, particularly carbacyclic nucleosides and analogues of nucleoside derivatives; for a review, see Agrofoglio, L.; Suhas, E.; Farese, A.; Condom, R.; Challand, S.R.; Earl, R.A.; Guedj, R. *Tetrahedron*, **1994**, *50*, 10611-10670.
3. To a solution of **4** (0.100 g, 0.29 mmol) and $Pd(PPh_3)_4$ (0.03 g, 0.03 mmol) in THF (1 ml), was added by cannula, the preformed sodium anion of **8** (from **8**, 0.061 g, 0.29 mmol, and sodium hydride 0.0115 g of a 60% dispersion, 0.29 mmol) in THF (1.5 ml). The mixture was heated at reflux for 1 h, cooled, quenched with aqueous ammonium chloride, and diluted with ethyl acetate (20 ml). The ethyl acetate layer was separated, washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. Flash column

chromatography (silica gel, ethyl acetate/petrol 1:1) yielded **7** (0.072 g, 66%) as an oil:- $[\alpha]_D$ -20° (1.1, $CHCl_3$); m/z (NH_3, C.I.) 368.1169, $C_{17}H_{22}NO_6S$ requires 368.1168; ν_{max} 1730, 1650 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$, two diastereoisomers, *ca.* 1.2:1, protons of major labelled as H*) 1.50 (1H, ddd, J 13.7, 5.6, 5.6 Hz), 1.99-2.16 (1H*, m), 2.09 (3H, s), 2.11 (3H*, s), 2.37 (1H, ddd, J 13.7, 8.5, 8.5 Hz), 2.48 (1H*, ddd, J 14.7, 8.7, 8.7 Hz), 3.17-3.28 (1H*, brm), 3.28-3.39 (1H, brm), 3.53 (3H, s), 3.61 (3H*, s), 3.63 (3H*, s), 3.66 (3H, s), 4.08 (1H, d, J 9.6 Hz), 4.10 (1H*, d, J 10.0 Hz), 5.41-5.54 (1H & 1H*, br), 5.63-5.66 (1H*, m), 5.78-5.81 (1H*, m), 5.83-5.85 (1H, m), 6.33-6.35 (1H, m), 7.55 (2H & 2H*, brdd, J 7.5, 7.5 Hz), 7.67 (1H & 1H*, brdd, J 7.5, 7.5 Hz), 7.85 (2H & 2H*, brd, J 7.5, 7.5 Hz).

4. It is our experience that attempts to hydrolyse cycloadducts such as **3**, derived from cyclopentadiene, in which the C≠C double bond is present result in either complex mixtures, or the formation of 'rearranged' products. This apparent instability under acidic conditions appears not to be restricted to cycloadducts derived from chiral acyl-nitroso compounds. For example, attempted removal of the Boc group from **13** under standard conditions (TFA, CH_2Cl_2, or HCl/MeOH) resulted in the formation of a mixture containing several components which were difficult to separate, whereas under similar conditions the reduced cycloaduct **14** underwent deprotection as normal.



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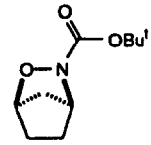

14

5. In a control experiment, treatment of **4** with catalytic amount of NaH in THF did not convert it cleanly into **9**.

(*Received in UK* 24 *July* 1995; *accepted* 11 *August* 1995)