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LETTERS

Palladium Catalysed Regio and Stereoselective Reduction of Baylis-Hillman Coupling Products Derived Allylic Acetates[1]

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Abstract: Acetates derived from a variety of the Baylis-Hillman products undergo reduction with HCOOH in the presence of Et_3N, $Pd(OAc)_2$, and dppe (or tri-isopropylphosphite) to yield the corresponding trisubstituted Z-olefins in good yields displaying high regio and stereoselectivity. © 1998 Published by Elsevier Science Ltd. All rights reserved.

Baylis-Hillman products are readily accessible[2,3] allylic alcohols bearing an electron withdrawing group such as an ester, a cyano, a carbonyl or a sulfonyl group on the double bond. Hydrogenolysis of the hydroxy group or a derivative such as an acetate of the Baylis-Hillman products would lead to di or trisubstituted olefins depending on whether or not the double bond migrates during the hydrogenolysis. Recently, Basavaiah *et al.*[4] have reported the reduction of a variety of Baylis-Hillman products with $LiAlH_4$ where they observed remarkable reversal of stereochemistry ($Z \rightarrow E$) going from nitrile containing Baylis-Hillman products to ester containing ones *en route* to trisubstituted olefins. Although the cyano group remained unaffected, the ester moiety, as expected, was reduced to a primary alcohol. Our continued interest[5] in developing synthetic methods using palladium catalysis has led us recently[5(vi)] to report C-C bond formation with Baylis-Hillman products under Heck reaction conditions as well as via π-allyl intermediates with dimethyl malonate. The latter reactions had indicated rate enhancement under milder conditions with palladium catalysis than without it and offered high degree of regio and stereoselectivity leading to trisubstituted olefins with migration of the double bonds. Further, palladium catalysed reduction of allylic compounds with formic acid or ammonium formate, as popularised by Tsuji *et al.*,[6] has been well utilised in organic synthesis.[7] These reactions offer a fairly high degree of regioselectivity and employ cheaper reducing agents. We, therefore, reasoned that reduction of the Baylis-Hillman products or their acetates under palladium catalysis with formic acid or formate ions would occur without affecting the electron withdrawing groups commonly present on the Baylis-Hillman products and thus offer an alternative to $LiAlH_4$ reductions. Further, it would be interesting to find the stereochemical outcome of such reductions *vis-a-vis* $LiAlH_4$ reductions.

In this letter we wish to report that acetates derived from Baylis-Hillman products undergo high regio and stereoselective reductions to form trisubstituted *Z*-olefins bearing a methyl group and an electron with-

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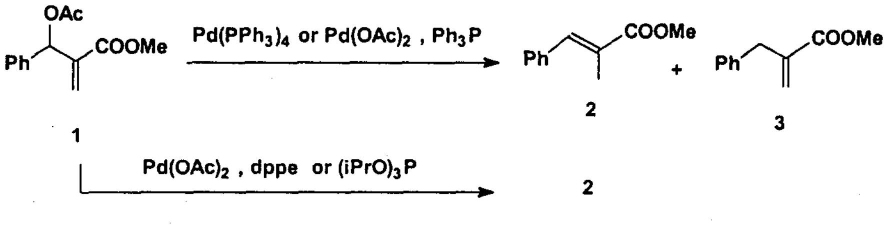
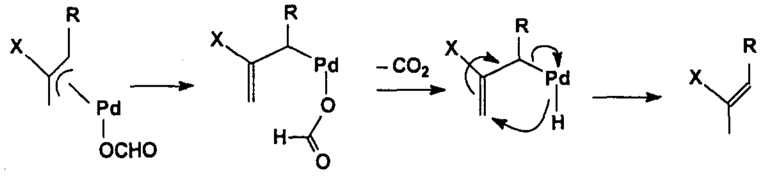
drawing group geminally disposed. Initial experiments using 1 (Scheme 1) with $Pd(Ph_3P)_4/HCOOH/Et_3N$ combination and Ph_3P or tri-*o*-tolylphosphine as a ligand in solvents like THF, CH_3CN or dioxane yielded a regioisomeric mixture of olefins 2 and 3 in a 1:1 ratio (Scheme 1). However, reduction of 1 with the $HCOOH$-Et_3N combination in the presence of $Pd(OAc)_2$ and 1,2-bis(diphenylphosphino)ethane (dppe) or triisopropyl phosphite as a ligand gave exclusively the trisubstituted olefin 2 in 85% yield. Although, it is generally observed[7] that formate ion based palladium catalysed reductions involve hydride attack at secondary or tertiary carbons leading to less substituted olefins, in our case, with proper choice of ligands it is the more substituted olefin that forms as the major product. It is likely that the presence of an electron withdrawing group at the middle carbon in Baylis-Hillman products is responsible for the regioselective hydride attack. It is noteworthy that blank experiments without using a palladium catalyst, for a prolonged time, did not lead to any reduction. This clearly indicates the importance of the formation of π-allyl palladium intermediates[8] prior to hydride transfer in the present cases. The formation of *Z*-olefins as the major/or the sole product as well as the above mentioned regioselectivity suggests the involvement of intermediates[9] as shown in Scheme 2. A variety of Baylis-Hillman products undergo similar reductions to form trisubstituted *Z*-olefins in good yields. Our results are summarised in Table 1. Interestingly, the *Z*-selectivity is observed with Baylis-Hillman products possessing aromatic substitutents only and not aliphatic substituents (cf. entry 9, Table 1). The high *Z*-selectivity could possibly[9] be due to coordination between the aromatic substitutent and the palladium intermediate which stabilises the *Z*-conformation. Such a coordination is obviously not possible with Baylis-Hillman products having aliphatic substiutents. Under these conditions functional groups such as a cyano, an ester or a ketone remain unaffected. A Baylis-Hillman product containing a non-conjugated diene unit (cf. entry 10, Table 1) also undergoes a regio and stereoselective reduction to form a conjugated 1,3-diene which should serve as a diene in Diels-Alder reactions with inverse electron demand. Studies related to the



Scheme 1



Where X: -CN, -COOMe or -COMe

Scheme 2

Table 1: Palladium Catalysed Reduction of Baylis-Hillman Products

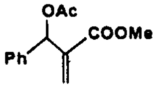
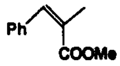
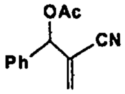
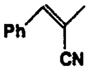
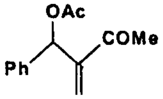
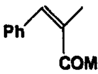
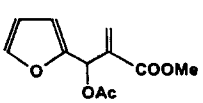
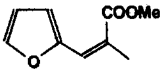
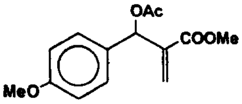
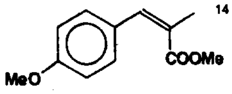
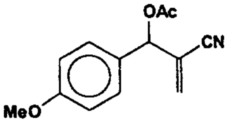
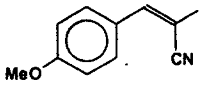
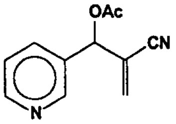
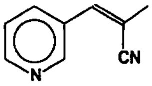
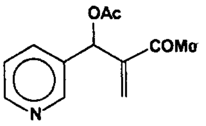
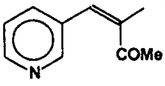
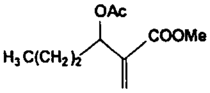
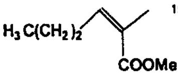
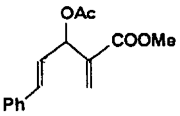
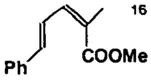
Entry	*Allylic acetate*	*Reduced Product (E/Z Ratio)*	*% Yield*
1		 [10] (7/93)	85
2		 [11] (0/100)	71
3		 [12] (0/100)	84
4		 [13] (0/100)	65
5		 [14] (3/97)	77
6		 [15] (0/100)	61
7		 [15] (0/100)	68
8		 [15] (0/100)	60
9		 [15] (45/55)	64
10		 [16] (0/100)	61

Table 2

Entry	Solvent	% Yield
1	THF	84
2	Dioxane	77
3	DMF	60
4	CH_3CN	48
5	DMSO	44
6	$CHCl_3$	00
7	Benzene	00
8	CCl_4	00

effect of solvents were conducted with a Baylis-Hillman product corresponding to entry 3 (Table 1) and accordingly THF was found to be the best solvent for such a transformation (cf. Table 2). A general experimental procedure is as follows: To a solution of an allylic acetate (1.28 mmol) in dry THF (3 ml) was added $Pd(OAc)_2$ (10 mg, 0.06 mmol), dppe (78 mg, 0.20 mmol), HCOOH (176 mg, 3.8 mmol) and Et_3N (388 mg, 3.8 mmol). This mixture was refluxed for 2 h following which it was extracted in diethyl ether (3x15 ml). The combined organic layers were washed with 3N HCl (10 ml), saturated $NaHCO_3$ (till neutral), water (3x10 ml), brine (10 ml) and then dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a crude product which was purified by column chromatography. In view of the fact that the Baylis-Hillman products are readily available[2,3] and trisubstituted olefins are useful intermediates,[17] we believe that the present study will find use in organic synthesis.

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