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Palladium-catalyzed addition of hydroxylamine derivatives to Baylis–Hillman acetate adducts☆

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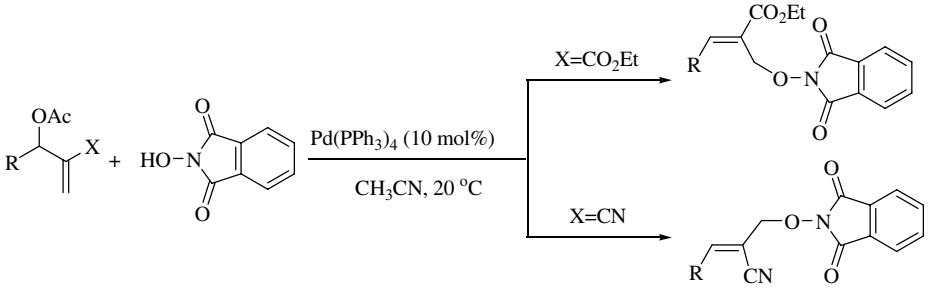
Abstract—The first use of hydroxylamine derivatives as the aminoxy equivalent of nucleophiles in palladium catalyzed addition to Baylis–Hillman acetate adducts is described. The reaction proceeds smoothly to give the substituted allyloxy amines in good yield and selectivity.

Palladium-catalyzed allylic substitution has been used in a wide variety of synthetically useful reactions involving various nucleophiles.[1] However, few studies have been reported in which hydroxylamines are used as oxygen atom (aminoxy equivalent) nucleophiles for allylic substitution reactions.[2] Interestingly, there is no report in the literature on allylic substitution of Baylis–Hillman acetate adducts using hydroxylamines. These findings encouraged us to study the reaction of hydroxylamines with Baylis–Hillman acetates. The products obtained also serve as intermediates for making useful allyloxy amines/aminoxy esters and their derivatives.[3]

The products of Baylis–Hillman reactions (BH adducts) are multifunctional allylic alcohols and have been used as precursors in synthesizing several useful compounds.[4] In particular, the acetates of Baylis–Hillman adducts have proved to be very useful synthons for addition reactions with different nucleophilic reagents.[5] In continuation of our interest in the reactions involving Baylis–Hillman adducts,[6] we studied the nucleophilic addition of hydroxylamine derivatives to Baylis–Hillman acetate adducts in the presence of 10 mol % $Pd(PPh_3)_4$ (Scheme 1).

We first examined the reaction of *N*-hydroxyphthalimide **1b** with Baylis–Hillman adduct **1a** in the presence of 10 mol % $Pd(PPh_3)_4$ in acetonitrile at room temperature to afford the corresponding allyloxy phthalimide **1c**. The reaction was complete in 1 h and product **1c** was



Scheme 1.

Keywords: Palladium; Baylis–Hillman adduct; Hydroxylamines.
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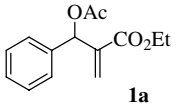
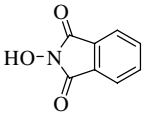
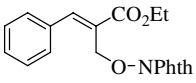
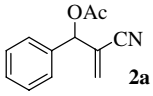
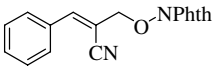
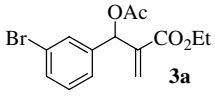
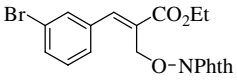
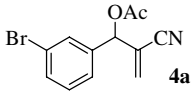
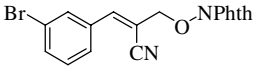
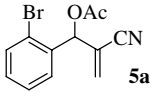
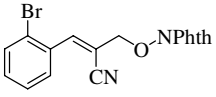
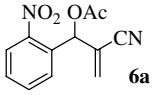
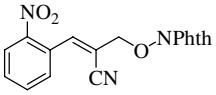
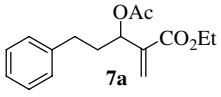
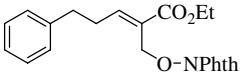
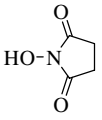
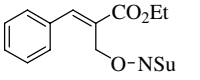
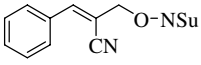
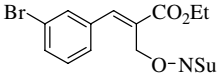
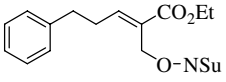
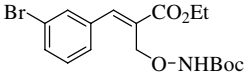
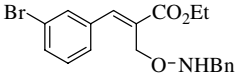
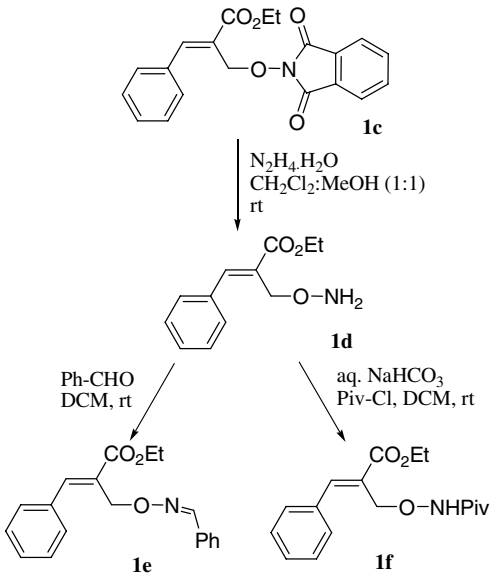
Table 1. Addition of hydroxylamines to Baylis–Hillman acetate adducts[9]

Entry	BH acetate adduct (**a**)	Hydroxylamine derivative (**b**)	Time (h)	Product (**c**)[a]		Yield[b] (%)
1	 **1a**	 **1b** (HO-NPhth)	1		**1c**	80
2	 **2a**	**1b**	1		**2c**	71
3	 **3a**	**1b**	2		**3c**	68
4	 **4a**	**1b**	2		**4c**	70
5	 **5a**	**1b**	2		**5c**	62
6	 **6a**	**1b**	1.5		**6c**	68
7	 **7a**	**1b**	1		**7c**	71
8	**1a**	 **2b** (HO-NSu)	1.5		**8c**	70
9	**2a**	**2b**	2		**9c**	65
10	**3a**	**2b**	2		**10c**	66
11	**7a**	**2b**	1		**11c**	67
12	**3a**	HO–NHBoc **3b**	1.5		**12c**	34
13	**3a**	HO–NHBn **4b**	1.5		**13c**	28

[a] The products were characterized by ^{1}H NMR, mass and IR spectra.
[b] Isolated yields.

obtained in 80% yield with exclusive (*E*)-selectivity (entry 1). The stereochemistry of the product was established based on extensive 2D NMR studies including DQCOSY, NOESY and TOCSY experiments.[7]

In the absence of a catalyst, no reaction occurred even at reflux. Next, the reaction of Baylis–Hillman acetate adduct **2a**, derived from acrylonitrile, with *N*-hydroxyphthalimide under similar reaction conditions gave the



Scheme 2.

corresponding product, **2c** in 71% yield with exclusive (*E*)-selectivity (entry 2).[7] To prove the generality of the method, we reacted other Baylis–Hillman acetate adducts with *N*-hydroxyphthalimide **1b** and succinimide **2b** (entries 3–11). The results are summarized in Table 1. In all cases, the reaction proceeded smoothly and afforded the products in reasonably good yields with good selectivity. As shown in Table 1, Baylis–Hillman acetate adducts derived from ethyl acrylate gave the corresponding products having the aryl group trans to the ester, whereas the adducts derived from acrylonitrile gave products having the aryl group cis to the nitrile. The olefin geometry was established based on ^{1}H and ^{13}C NMR chemical shifts and by comparison with literature values.[8] However, reaction with *N*-Boc-hydroxylamine and *N*-benzyl hydroxylamine gave low yields of the desired products with (*E*)-selectivity (entries 12 and 13).

We also investigated the transformations of **1c** into useful substituted allyloxy amine/aminoxy ester **1d** and its derivatives **1e** and **1f** (Scheme 2). Further applications of these products to prepare pseudo-γ-amino acids are underway.

In conclusion, we have developed a palladium-catalyzed addition of hydroxylamine derivatives to Baylis–Hillman acetate adducts.[9] The selective formation of substituted allyloxy amine products was observed and these products may find use in organic synthesis.

Acknowledgements

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References and notes

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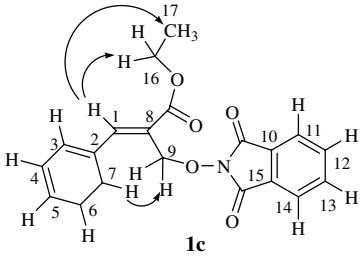
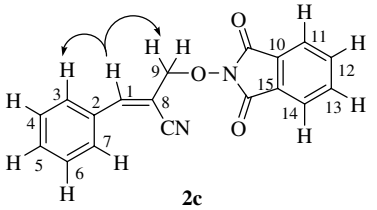
7. (a) The (*E*)-stereochemistry of **1c** was assigned on the basis of ^{1}H and ^{13}C NMR chemical shifts in comparison with literature values.[8] The structure was supported by NOE cross peaks between H7–H9, H1–H16 and H1–H17. *Spectral data for* **1c**: Off white solid; mp 74–78 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.13 (1H, s, H1), 7.83 (2H, dd, $J = 3.5$, 5.5 Hz, H11, 14), 7.73 (2H, dd, $J = 3.5$, 5.5 Hz, H12, 13), 7.70 (2H, d, $J = 7.0$ Hz, H3, 7), 7.43–7.45 (3H, m, H4, 5, 6), 5.11 (2H, s, H9), 4.28 (2H, q, $J = 7.0$ Hz, H16), 1.32 (3H, t, $J = 7.0$ Hz, H17); ^{13}C NMR (75 MHz, $CDCl_3$); δ 166.7, 163.2, 148.1, 134.3, 133.8, 129.9, 129.8, 128.7, 128.6, 125.4, 123.3, 71.5, 61.3, 14.0. IR ($CHCl_3$): ν 1727, 1620, 1106, 794 cm^{-1}; LC MS (*m*/*z*): 352 $(M+H)^+$; HRMS (EI): *m*/*z* Calcd for $C_{20}H_{18}NO_5$ 352.1185 $[M+H]^+$. Found 352.1181.



1c

(b) The structure was supported by NOE cross peaks between H1–H3 and H1–H9. *Spectral data for* **2c**: Off white solid; mp 158–161 °C ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.85 (2H, dd, $J = 3.0$, 5.38 Hz, H11, 14), 7.82–7.80 (2H, m, H3, 7), 7.76 (2H, dd, $J = 3.0$, 5.38 Hz, H12, 13), 7.44 (3H, dd, $J = 2.1$, 5.1 Hz H4, 5, 6), 7.37 (1H, s, H1), 4.93 (2H, s, H9); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.3, 149.7, 134.7, 132.4, 131.4, 129.4, 128.9, 128.7, 123.7, 117.2, 104.7, 78.5. IR ($CHCl_3$): ν 2230, 1725, 1502, 1219, 771 cm^{-1}; LC MS (*m*/*z*): 327 $(M+Na)^+$; HRMS (EI): *m*/*z* Calcd for $C_{18}H_{12}N_2O_3Na$ 327.0746 $[M+Na]^+$. Found 327.0749.



2c

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9. *General experimental procedure*: To a stirred solution of Baylis–Hillman acetate adduct (1 mmol) in acetonitrile (3 mL) was added *N*-hydroxyphthalimide (148 mg, 0.9 mmol) and the reaction mixture was cooled to 20 °C. Palladium tetrakis(triphenyl-phosphine) (0.1 mmol) was added to the above reaction mixture which was stirred for the given time (see Table 1). After completion of the reaction (monitored by TLC), the solvent was evaporated in vacuo and the crude was purified by column chromatography to afford the corresponding product. Spectroscopic data for selected products: Product **3c**: Pale yellow solid; mp 110–114 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00 (1H, s), 7.20–7.85 (6H, m), 7.55 (1H, d, $J = 8.6$ Hz), 7.4 (1H, t, $J = 7.8$ Hz), 5.05 (2H, s), 4.3 (2H, q, $J = 7.2$ Hz), 1.35 (3H, t, $J = 7.2$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.3, 163.1, 146.1, 135.9, 134.3, 132.6, 132.4, 130.2, 128.7, 128.4, 126.9, 123.3, 122.6, 71.1, 61.46, 14.0; IR ($CHCl_3$): ν 1733, 1637, 770, 665 cm^{-1}; LC MS (*m*/*z*): 430 $(M+H)^+$, 432 $[(M+2)+H]^+$; HRMS (EI): *m*/*z* Calcd for $C_{20}H_{17}BrNO_5$ 430.0290 $[M+H]^+$. Found 430.0286. Product **4c**: Pale yellow solid; mp 143–146 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75–7.87 (6H, m), 7.55 (1H, d, $J = 8.6$ Hz), 7.32–7.36 (2H, m), 4.9 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.3, 147.5, 134.8, 134.2, 130.5, 128.6, 127.4, 123.8, 122.9, 116.6, 106.5, 78.1; IR ($CHCl_3$): ν 2213, 1618, 698, 622 cm^{-1}; LC MS (*m*/*z*): 405 $(M+Na)^+$, 407$[(M+2)+Na]^+$; HRMS (EI): *m*/*z* Calcd for $C_{18}H_{11}BrN_2O_3Na$ 404.9851 $[M+Na]^+$. Found 404.9848.