

Phosphonium Salt Catalyzed Henry Nitroaldol Reactions

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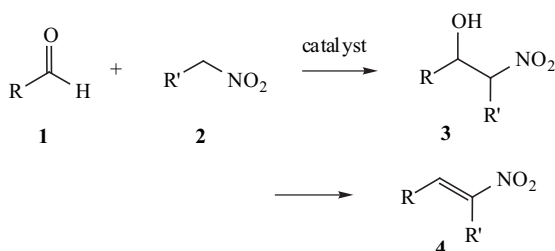
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Abstract: Trihexyl(tetradecyl)phosphonium decanoate was shown to be an effective promoter for the Henry nitroaldol reaction of nitromethane with aromatic aldehydes. A mechanism is proposed involving Lewis acid activation of the carbonyl group proceeding through a trigonal-bipyramidal intermediate. Evidence in accord with the postulated pathway as opposed to a base or phase transfer-mediated route involving proton transfer from the nitroalkane is presented.

Keywords: Nitroaldol, Henry reaction, phosphonium salt, organic catalysis.

The Henry [1] nitroaldol reaction is one of the reliable, classical aldol-type addition reactions involving the reaction of a carbonyl compound (**1**) with a nitroalkane (**2**) to give first a nitroaldol intermediate (**3**) often leading to a nitroolefin (**4**) upon dehydration. The extent of the reaction varies considerably with the nature of the catalyst chosen as well as with reactions conditions as described in several comprehensive reviews on the reaction [2,3,4]. In addition, the extent of reaction also depends upon the electronic nature of the carbonyl component involved [5]. A large variety of catalysts have been employed successfully in this reaction ranging from alkali metal bases, simple amines and ammonium salts to electrophilic activators such as alumina [6,7], silica [4,8] and chiral Lanthanum-binaphthol complexed Lewis acids, through which asymmetric nitroaldol additions have been effected [9].



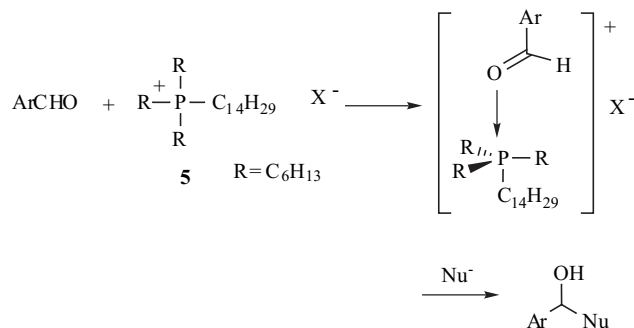
Scheme 1. The Henry nitroaldol reaction.

Recent work in our laboratories has focused on applications of phosphonium salts [10] (room temperature ionic liquids) as solvents and promoters for various reactions. We were attracted to the possibility that commercially available phosphonium salts based on the trihexyl(tetradecyl)phosphonium ion (**5**) might function as a mild Lewis acid and thus promote classical carbonyl addition processes. In this Letter, we show that this is indeed the case and that these new “organic catalysts” promote the addition of both nitromethane and diethylzinc to aromatic aldehydes without elimination side products.

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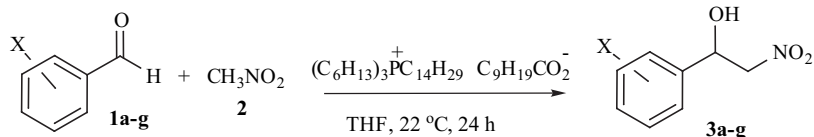


As outlined in Scheme 2, we envisioned that complexation of the carbonyl compound to the phosphonium salt might proceed *via* a phosphorane-type, trigonal-bipyramidal intermediate, possibly as a π -complex, activating the carbonyl towards the addition process. In addition to their employment in Suzuki coupling reactions [10], phosphonium salts have recently been used as solvents for hydroformylation [11], transfer hydrogenation [12] and Diels-Alder reactions [13]. In addition, one recent report describes the use of a phosphonium salt as a solvent and promoter for the addition of trimethylsilyl cyanide to aldehydes [14]. It is likewise possible that the latter two reactions proceed through related phosphorane-type dienophile and carbonyl activation processes.



Scheme 2. Postulated mechanism for phosphonium salt mediated carbonyl activation

Our initial experimentation consisted of screening a variety of trihexyl(tetradecyl) phosphonium salts containing a range of anionic partners through which we identified the decanoate salt as the most efficient promoter of the addition reaction. As an example, the reaction of 4-nitrobenzaldehyde (**1a**) in dry THF containing nitromethane (Table 1, entry a) and trihexyl(tetradecyl)phosphonium decanoate (2 mol%), proceeded to give the nitroaldol product (**3a**) in 100% yield [15]. The reaction was thus proven to be catalytic in respect to the phosphonium salt (50 turnovers) and no trace of the corresponding nitroolefin (**4a**) was detected in the reaction conducted under these conditions.

Table 1. Trihexyl (Tetradecyl) Phosphonium Decanoate Mediated Nitroaldol Reactions

Entry	X	Yield, %
a	4 -NO ₂	100
b	4 -Cl	96
c	H	95
d	4 -CH ₃	89
e	4 -OH	0
f	4 MeO-	65
g	3,4 - OCH ₂ O-	70

The Henry reaction was found to proceed to a high degree of completion with electron deficient aldehydes (entries a and b) under these conditions [15]. Benzaldehyde itself and the simple 4-methyl derivative also reacted under our general conditions providing good isolated yields of nitroaldols. The reaction did not proceed when a free phenolic hydroxyl was present on the aromatic ring (entry e) however both 4-methoxybenzaldehyde and piperonal (entries f and g) reacted to provide good yields of the corresponding nitroaldols. Once again, no nitroolefins are produced in these latter two reactions. We investigated the reaction of 4-methoxybenzaldehyde (1.0 mmol) and nitromethane (10.0 mmol) in THF under various conditions. The isolated yield of nitroaldol (**3f**) ranged narrowly from 59-65% when the catalyst loading was varied incrementally from 2 to 50 mol%. Increasing the amount of nitromethane from 10 to 25 equivalents relative to the aldehyde increased the yield to 69%. These data appear to indicate that an equilibrium has been established and show that the phosphonium salt is functioning in true catalytic fashion having, in this case, about 60% of the nitroaldol (**3f**) at equilibrium under the standard conditions.

Further evidence in accord with the Lewis acid mediated carbonyl activation hypothesis was obtained from the following experiments. We felt it necessary to differentiate this outlined possibility from an obvious alternate pathway involving the reaction of the phosphonium decanoate as a simple base or even a phase transfer catalyst, although as far as we can tell, a single phase is involved in the reaction. The addition of diethylzinc to benzaldehyde proceeds very slowly in toluene at 0 °C; however, the addition of even a mild Lewis acid is enough to promote this addition [16]. In our hands, the reaction of benzaldehyde (0.25 mmol) with diethylzinc (0.50 mmol) in dry toluene (0.70 mL) at 0 °C in the presence of 10 mol% trihexyl(tetradecyl)phosphonium decanoate (0.025 mmol) proceeded overnight to give the addition product in 71% isolated yield. An identical control experiment was performed with the omission of the phosphonium salt that provided a mere 1.5% isolated yield of the addition product. In this case, base mediated nucleophilic activation is not possible and it clearly appears that the phosphonium ion is activating the carbonyl group in Lewis acid fashion.

Given the recent advances made in the field of metal-free organocatalytic reactions [17], we feel that phosphonium salts, and in particular chiral phosphonium salts are likely to be of great interest as mild organocatalytic Lewis acids that might possibly mediate asymmetric carbonyl addition reactions. These leads are being actively pursued in our laboratories at the present time.

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- [15] Representative procedure: Trihexyl(tetradecyl) phosphonium decanoate (0.05 mmol, 0.02 eq) was dried under high vacuum for 1h and dissolved in dry THF (5.0 mL) under argon followed by the addition of 4-nitrobenzaldehyde (2.5 mmol, 1.0 eq). Upon cooling to 0 °C, nitromethane (25 mmol, 10 eq) was added and the solution stirred at 0 °C for one hour followed by a further 18 h at room temperature. The solvents were removed and the residue purified over silica gel (eluant hexanes:ethyl acetate 4:1) to give 2-nitro-(4'-nitrophenyl)-ethanol as a clear colorless oil. ¹H-NMR (CDCl₃): 3.24 (br s, 1H), 4.61 (m, 2H), 5.63 (dd, J=7.8, 4.4 Hz, 1H), 7.65 (d, J=8.6 Hz, 2H), 8.29 (d, J=8.6 Hz, 2H). ¹³C-NMR

(CDCl₃): 70.4, 81.0, 124.6, 127.3, 145.3, 148.5. EIMS m/z (% rel.): 165 (27.0), 151 (100), 150 (96.3), 105 (27.7), 77 (64.2), 76 (25.9), 51 (65.8), 50 (38.5). HREIMS: Calcd. For C₈H₈N₂O₅

212.0433; found 212.0433. FTIR (KBr); 3506, 2920, 2851, 1554, 1520, 1381, 1349, 1084, 857 cm⁻¹.

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