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Phosphine-catalyzed nitroaldol reactions

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Abstract—Trialkyl phosphines and electron-rich triaryl phosphines are excellent catalysts for the nitroaldol (Henry) reaction. Aryl and alkyl aldehydes participate well in the reaction with nitromethane providing good yields of product. Care should be exercised in the use of phosphine-metal complexes as catalysts for the nitroaldol reaction, as the phosphine can alone function as the catalyst.

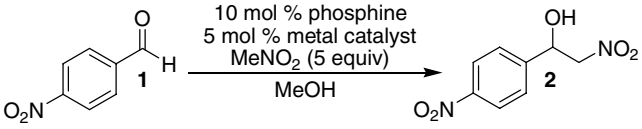
The addition of nitroalkanes to aldehydes and ketones is a significant transformation as the products, β-nitroalkanols, are important intermediates in the synthesis of biologically relevant compounds.[1] Historically, this reaction has been mediated by ionic bases such as metal hydroxides or alkoxides.[2] More recently catalysis of this transformation has been demonstrated using enzymes[3] and Cinchona alkaloids.[4,5] Despite their similarity to amine bases, phosphines have not been explored as catalysts for the Henry reaction. Precedent for such a nitroaldol reaction has been presented by Verkade and Kisanga in their use of proazaphosphatranes.[6] Phosphonium salts have also been reported to catalyze the addition of nitromethane to aldehydes.[7]

In our recent studies on transition-metal catalyzed nucleophilic addition reactions, we considered expanding the substrate scope to nitroalkanes based upon a report made by Milstein,[8] where several metal complexes were shown to be excellent catalysts for the nitroaldol reaction. Kiyooka has also demonstrated that cyclopentadienyl rhodium complexes are good catalysts for the Henry reaction.[9] These transformations appeared to be easily modified into asymmetric processes, and therefore a reinvestigation of this work was undertaken.

To facilitate ligand screening studies, attempts were made to generate the catalytically active species in situ. A combination of $[Rh(nbd)Cl]_2$ (nbd = norbornadiene) and tri-*n*-butyl phosphine (**3**) provided the desired nitroaldol product in a 46% conversion as judged by ^1H NMR (Table 1, entry 1). While this result appeared promising, control experiments proved even more enlightening. The use of the rhodium complex with no phosphine ligand provided only 26% of the nitroaldol product, while tri-*n*-butyl phosphine (**3**) alone gave an excellent conversion, implicating phosphine as the primary active catalyst (Table 1, entries 2 and 3, respectively).

The solvent used in the phosphine-catalyzed Henry reaction was found to have a significant effect on the conversion of the aldehyde to the β-nitroalkanol using tri-*n*-butyl phosphine (**3**) as the catalyst. The use of nonpolar solvents such as dichloromethane proved to have a detrimental effect on the reaction. In contrast, polar protic solvents such as methanol gave an excellent conversion to the alcohol product. Polar aprotic solvents, like acetonitrile, were also inferior to polar protic solvents.

Table 1. Investigation of rhodium–phosphine catalysis for the Henry reaction



Entry	Metal catalyst	Phosphine	Conversion[a] (%)
1	$[Rh(nbd)Cl]_2$[b]	PBu_3 (**3**)	46
2	$[Rh(nbd)Cl]_2$	None	26
3	None	PBu_3 (**3**)	93

[a] Conversion was determined by ^1H NMR.
[b] nbd = norbornadiene.

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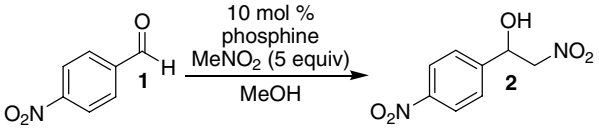
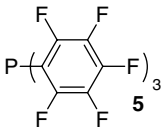
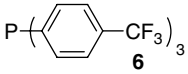
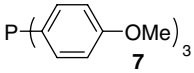
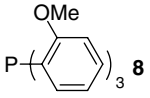
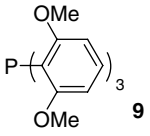
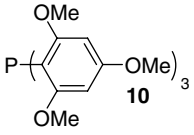
Table 2. Screen of phosphine catalysts



Entry	Phosphine	Conversion[a] (%)	Yield (%)
1	PPh_3 (**4**)	16	nd[b]
2	 **5**	0	nd
3	 **6**	0	nd
4	 **7**	15	nd
5	 **8**	8	nd
6	 **9**	93	92
7	 **10**	95	91
8	PBu_3 (**3**)	93	91
9	$PPhCy_2$ (**11**)	83	59

[a] Conversion was determined by ^1H NMR.
[b] nd = not determined.

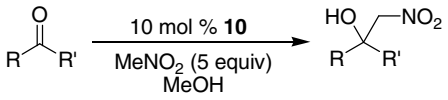
An investigation into the effect of phosphine structure on catalytic activity was then undertaken. To define the limits of this new class of catalysts, a number of phosphines were tested for catalysis (Table 2). Unlike tri-*n*-butyl phosphine (**3**), triphenylphosphine gave a poor conversion in the addition of nitromethane to 4-nitrobenzaldehyde **1** (Table 2, entry 1). This appears to be the result of the reduced basicity of triarylphosphines compared to trialkyl phosphines. This is confirmed by the use of substituted triaryl phosphines. Incorporation of electron-withdrawing groups on the phenyl substituents (Table 2, entries 2 and 3) resulted in no formation of nitroaldol products. The use of electron-rich aromatic rings on the phosphines provided better results, but at least two electron-donating methoxy groups were necessary to obtain high yields (Table 2, entries 6 and 7).

Because of its amenable nature tris(2,4,6-trimethoxyphenyl)phosphine **10** was then chosen as the catalyst of choice for further studies. A number of aldehydes were then tested to determine their propensity to undergo this transformation using the phosphine catalyst.

Aryl aldehydes possessing an electron-withdrawing or an electron-donating substituent were shown to be effective acceptors for the reaction (Table 3, entries 1–4). Alkyl aldehydes and diketones also gave acceptable yields (Table 3, entries 6–10). Alternatively, ketoesters gave lower yields, which can be rationalized by their lower electrophilicity (Table 3, entry 11). Pyruvic acid gave no product, likely because the acid protonated the phosphine catalyst (Table 3, entry 12).

From the results presented in Tables 1 and 2 the role of the phosphine catalyst appears to be that of a base which deprotonates the nitromethane, facilitating the nitroaldol reaction (Fig. 1). A similar mechanism has

Table 3. Phosphine catalyzed nitroaldols[10]



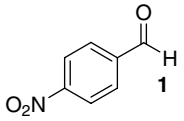
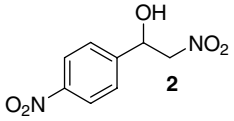
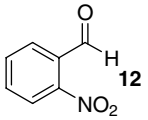
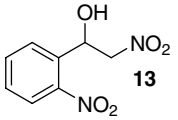
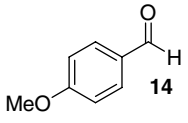
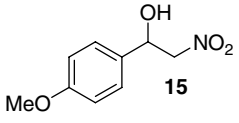
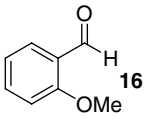
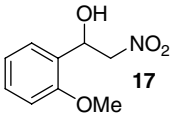
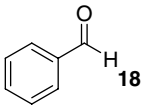
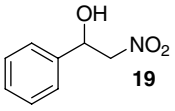
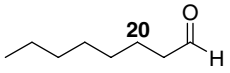
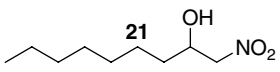
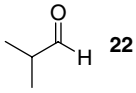
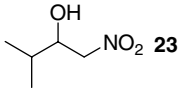
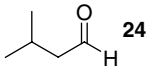
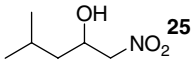
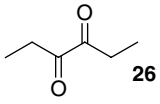
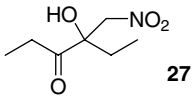
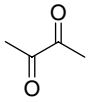
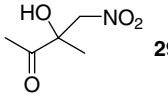
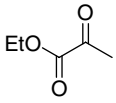
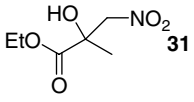
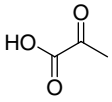
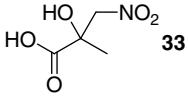
Entry	Electrophile	Product	Yield (%)
1	 **1**	 **2**	91
2	 **12**	 **13**	84
3	 **14**	 **15**	60

Table 3 (*continued*)

Entry	Electrophile	Product	Yield (%)
4	 **16**	 **17**	79
5	 **18**	 **19**	57
6	 **20**	 **21**	69
7	 **22**	 **23**	56
8	 **24**	 **25**	68
9	 **26**	 **27**	67
10	 **28**	 **29**	65
11	 **30**	 **31**	39
12	 **32**	 **33**	0

been proposed for other amine catalysts of the Henry reaction.[2] The failure of pyruvic acid (Table 3, entry 12) to provide nitroaldol product supports this catalytic cycle, as the acid protonates the phosphine deactivating the catalyst. This mechanism requires a basic phosphine, which explains the failure of electron-deficient phosphines to perform the catalysis (Table 1).

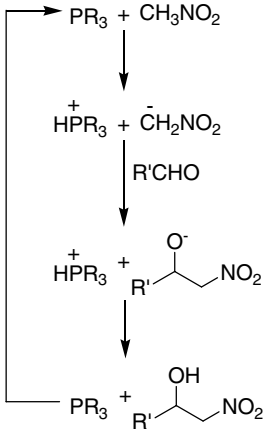
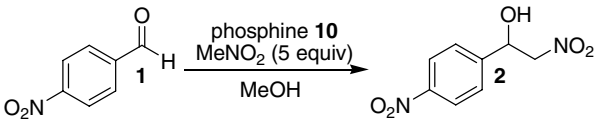


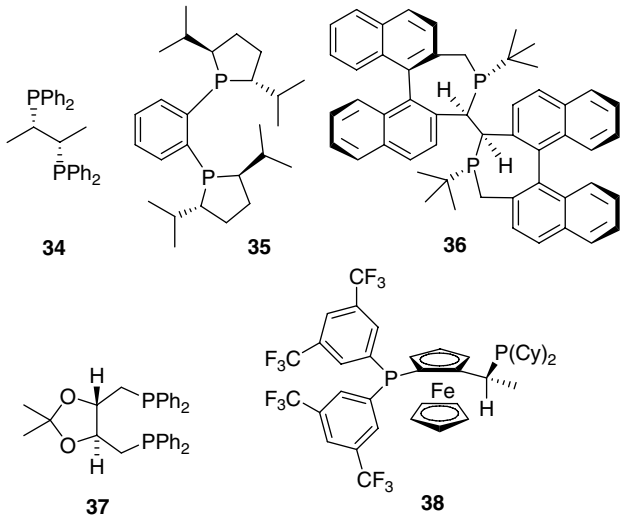
Figure 1. Catalytic cycle for the phosphine catalyzed nitroaldol.

The effect of catalyst loading on the reaction was also briefly investigated. Catalyst loadings as low as 0.05% were found to generate the nitroaldol products using phosphine **10** (Table 4, entry 4). This demonstrates that

Table 4. Catalyst loading study



Entry	Phosphine (mol %)	Yield (%)
1	10	91
2	5	86
3	2	94
4	0.5	87



Scheme 1.

even trace contamination of an electron-rich phosphine leads to excellent conversions of the nitroaldol products.

A number of chiral phosphines were also used to catalyze the reaction of nitromethane with 4-nitrobenzaldehyde (**1**) in order to determine if they could engender enantioselectivity. Phosphines **34**–**36** provided trace amounts of nitroaldol products (<5%). Phosphines **37** and **38** provided improved yields of 25% and 21%, respectively. In all cases no enantioselectivity was observed using chiral HPLC (Scheme 1).

Trialkyl phosphines and electron-rich triaryl phosphines are effective catalysts for the addition of nitromethane to aldehydes and activated ketones. Care should be exercised in using metal–phosphine complexes as catalysts for this transformation, as even small amounts of phosphine can lead to excellent yields of the nitroalcohol product.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.10.107.

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10. *Representative experimental procedure*: 4-Nitrobenzaldehyde (115 mg, 0.764 mmol) was dissolved in 0.5 mL of methanol. Nitromethane (200 μL, 3.82 mmol, 5 equiv) was then added followed by tris(2,4,6-trimethoxyphenyl)phosphine (41 mg, 0.0764 mmol, 10 mol %). The reaction was stirred at room temperature for 24 h. The reaction was then preabsorbed on silica gel and purified by silica gel chromatography providing 161 mg (91%) of 1-(4-nitrophenyl)-2-nitroethanol as a clear yellow oil. TLC $R_f = 0.34$ (30% EtOAc/70% Hex); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (t, $J = 8.8$ Hz, 1H), 8.27 (t, $J = 9.0$ Hz, 1H), 7.65 (t, $J = 1.0$ Hz, 1H), 7.63 (t, $J = 1.2$ Hz, 1H), 5.62 (p, $J = 8.21$, 4.29 Hz, 1H), 4.62–4.59 (m, 2H) 3.12 (d, $J = 4.0$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.3, 146.7, 128.2, 125.3, 81.6, 70.8.