Tetrahedron Letters 49 (2008) 6442–6444

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Dual-reagent organocatalysis with a phosphine and electron-deficient alkene: application to the Henry reaction

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ARTICLE INFO

Article history:
Received 26 June 2008
Revised 25 August 2008
Accepted 26 August 2008
Available online 29 August 2008

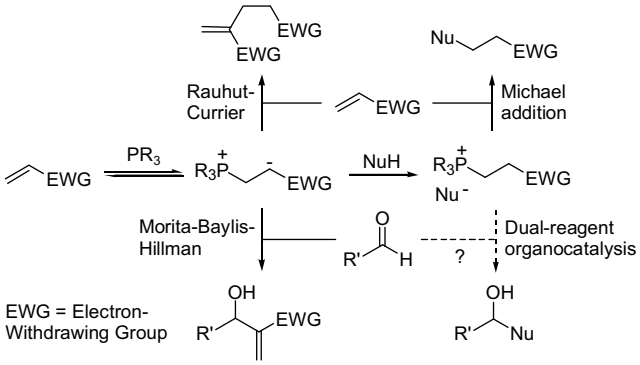
Keywords:
Phosphines
Electron-deficient alkenes
The Henry reaction
Aldehydes
Nitroalkanes

ABSTRACT

Triphenylphosphine in combination with methyl acrylate was found to be able to catalyze the Henry (nitroaldol) reaction of various aldehydes and α-keto esters to give the corresponding β-nitroalkanols in good to excellent yields, and a catalytic cycle involving a zwitterionic phosphine–alkene adduct was proposed for this dual-reagent organocatalysis according to the deuterium-labeling experiments with CD_3NO_2.

The Michael-type additions of phosphines to electron-deficient alkenes readily proceed to generate zwitterions (Scheme 1),[1] which are able to react with electrophiles such as electron-deficient alkenes (the Rauhut–Currier reaction)[1b,2] and aldehydes (the Morita–Baylis–Hillman reaction).[3,4] Such zwitterions can also behave as organic bases to deprotonate protic nucleophiles (NuH) and catalyze the corresponding Michael additions to electron-deficient alkenes.[5,6] Since the deprotonated nucleophiles (Nu^-) are conceivably reactive toward other electrophiles such as aldehydes, it is possible to use a phosphine in combination with electron-deficient alkene to promote other nucleophile–electrophile reactions. In continuation of our program to develop new organocatalysis,[7] we decided to investigate the possibility of such a dual reagent-catalyzed nucleophile–electrophile reaction, which was expected to proceed faster than the corresponding Rauhut–Currier reaction, Morita–Baylis–Hillman reaction, and Michael addition when using an appropriate phosphine and electron-deficient alkene.

The Henry (nitroaldol) reaction was selected to develop such a dual-reagent organocatalysis with a phosphine and electron-deficient alkene. This important carbon–carbon bond-forming reaction is able to produce β-nitroalkanols that are useful intermediates in the synthesis of biologically relevant compounds, and have been demonstrated to be catalyzed by a range of organic bases.[8,9] Although trialkylphosphines and electron-rich triarylphosphines were employed by Chisholm and Weeden as effective catalysts



Scheme 1. Some reactions involving zwitterionic phosphine–alkene adducts.

for the Henry reaction in the presence of 5.0 equiv of nitromethane, triphenylphosphine showed sluggish activity toward the same reaction.[10,11] However, triphenylphosphine was reported to undergo Michael-type addition to electron-deficient alkenes smoothly in the presence of appropriate proton sources,[1a,12] so we decided to use triphenylphosphine in combination with an electron-deficient alkene as a surrogate organic base to catalyze the Henry reaction. The lower nucleophilicity of triphenylphosphine, compared to that of trialkylphosphines and electron-rich triarylphosphines, was expected to reduce the consumption of electron-deficient alkenes by slowing down the corresponding Rauhut–Currier reaction, Morita–Baylis–Hillman reaction, and Michael addition.

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doi:10.1016/j.tetlet.2008.08.092

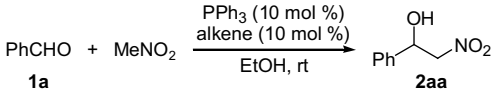
Several inexpensive electron-deficient alkenes (10 mol %) were examined in combination with triphenylphosphine (10 mol %) in the reaction of benzaldehyde (**1a**) with nitromethane (5.0 equiv) in ethanol at room temperature (Table 1), and methyl acrylate was found to be the best one in promoting the reaction to give β-nitroalkanol **2aa** in terms of yield and reaction time (Table 1, entry 5). Interestingly, no desired product was obtained at all when using the corresponding acrylic acid (Table 1, entry 6), and the use of either α-substituted or β-substituted methyl acrylate just led to sluggish reaction (Table 1, entries 7 and 8). Further investigation showed that the reaction proceeded much slower in non-protic solvents such as acetonitrile, ether, tetrahydrofuran, ethyl acetate, dichloromethane, and toluene. Although reducing the loading of triphenylphosphine and methyl acrylate led to extended reaction time and lower yield, the reaction gave the desired product in excellent yield (94%) without extension of reaction time when the amount of nitromethane decreased from 5.0 equiv to 2.0 equiv (Table 1, entry 9).

In the presence of 10 mol % of triphenylphosphine and 10 mol % of methyl acrylate, a wide range of aromatic, heteroaromatic, and aliphatic aldehydes could react well with nitromethane and gave the corresponding β-nitroalkanols in good to excellent yields (Table 2, entries 1–13).[13] Activated ketones such as α-keto esters could also serve as excellent substrates for the catalytic Henry reaction (Table 2, entries 14 and 15). Furthermore, the replacement of nitromethane with nitroethane in the catalytic Henry reaction resulted in formation of the corresponding β-nitroalkanols in excellent yields and with up to 91:9 diastereoselectivity (Table 2, entries 16–18).

In order to gain insights into the reaction mechanism, we carried out the ^{1}H NMR analysis of a solvent-free reaction mixture of CD_3NO_2 with PhCHO (**1a**) in the presence of 10 mol % of triphenylphosphine and 10 mol % of methyl acrylate,[14] and clearly observed H/D exchange at the methylene group of product **2aa** and the dramatic enrichment of deuterium at the α- and β-positions of methyl acrylate and two of its adducts, phosphonium ion **3** and ester **4** (Table 3, entry 1).[15] As indicated by the ratio of methyl acrylate to phosphonium ion **3** and ester **4** (15:32:53), a significant amount of methyl acrylate underwent Michael addition to nitromethane to give ester **4**. Nevertheless, the consumption of methyl acrylate via the Rauhut–Currier reaction and the Morita–Baylis–Hillman reaction was not detected by ^{1}H NMR analysis. While performing this reaction in CD_3OD raised the ratio of deuterium to hydrogen in product **2aa** and phosphonium ion **3**, the use of CH_3OH as the solvent dramatically reduced the ratio of deuterium to hydrogen in product **2aa**, methyl acrylate, and ester **4** (Table 3, entries 2 and 3). In contrast, the use of CD_3OD as the solvent for the reaction of PhCHO (**1a**) with CH_3NO_2 led to significant enrichment of deuterium in product **2aa** and phosphonium ion **3** (Table 3, entry 4). Furthermore, methyl acrylate was clearly observed to undergo transesterification with solvent CD_3OD (Table 3, entries 2 and 4), and it should be noted that rapid H/D exchange of nitromethane took place in all the cases.

On the basis of these deuterium-labeling experiments, we propose a catalytic cycle for the dual reagent-catalyzed Henry reaction (Scheme 2). The Michael-type addition of triphenylphosphine to methyl acrylate generates zwitterion **5**, which serves as an

Table 1
Survey of electron-deficient alkenes[a]

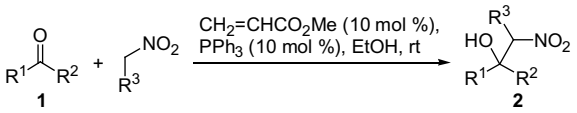


1a 2aa

Entry	Alkenes	Time (h)	Yield[b] (%)
1	None	24	0
2	Benzoquinone	24	65
3	CH_2=CHCONH$_2$	24	75
4	CH_2=CHCOMe	24	88
5	CH_2=CHCO$_2$Me	2	98
6	CH_2=CHCO$_2$H	24	0
7	CH_2=C(Me)CO$_2$Me	24	7
8	*trans*-PhCH=CHCO$_2$Me	24	0
9[c]	CH_2=CHCO$_2$Me	2	94

[a] Reaction conditions: **1a** (1.0 mmol), $MeNO_2$ (5.0 equiv), PPh_3 (10 mol %), alkene (10 mol %), ethanol (0.20 mL), rt.
[b] Isolated yield.
[c] 2.0 equiv of $MeNO_2$ and 0.10 mL of ethanol were used.

Table 2
The Henry reaction catalyzed by triphenylphosphine and methyl acrylate[a]

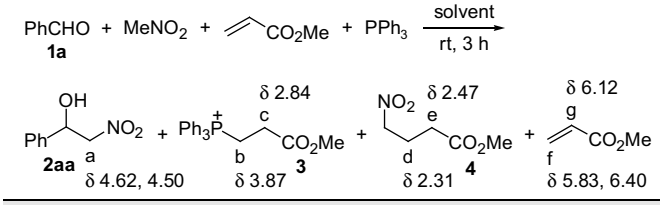


1 2

Entry	1	R^1	R^2	R^3	2	Time (h)	Yield[b] (%)
1	**1a**	Ph	H	H	**2aa**	2	94
2	**1b**	4-$O_2NC_6H_4$	H	H	**2ba**	1	98
3	**1c**	4-ClC_6H_4	H	H	**2ca**	2	90
4	**1d**	4-$MeOC_6H_4$	H	H	**2da**	24	65
5	**1e**	3-$O_2NC_6H_4$	H	H	**2ea**	1	98
6	**1f**	2-$O_2NC_6H_4$	H	H	**2fa**	1	96
7	**1g**	2-ClC_6H_4	H	H	**2ga**	1.5	97
8	**1h**	2-$MeOC_6H_4$	H	H	**2ha**	2	99
9	**1i**	2-Furyl	H	H	**2ia**	1.5	87
10	**1j**	3-Pyridyl	H	H	**2ja**	1.5	99
11	**1k**	*n*-C_6H_{13}	H	H	**2ka**	2	96
12	**11**	*c*-C_6H_{11}	H	H	**2la**	8	90
13	**1m**	Me_3C	H	H	**2ma**	24	87
14	**1n**	Ph	CO_2Et	H	**2na**	9.5	97
15	**1o**	Me	CO_2Et	H	**2oa**	2	85
16[c]	**1a**	Ph	H	Me	**2ab**	2	92
17[d]	**1i**	2-Furyl	H	Me	**2ib**	2	89
18[e]	**11**	*c*-C_6H_{11}	H	Me	**2lb**	8	91

[a] Reaction conditions: **1** (0.50 mmol), $R^3CH_2NO_2$ (2.0 equiv), methyl acrylate (10 mol %), PPh_3 (10 mol %), ethanol (0.050 mL), rt.
[b] Isolated yield.
[c] For **2ab**, *syn*:*anti* = 68:32.
[d] For **2ib**, *syn*:*anti* = 91:9.
[e] For **2lb**, *syn*:*anti* = 50:50.

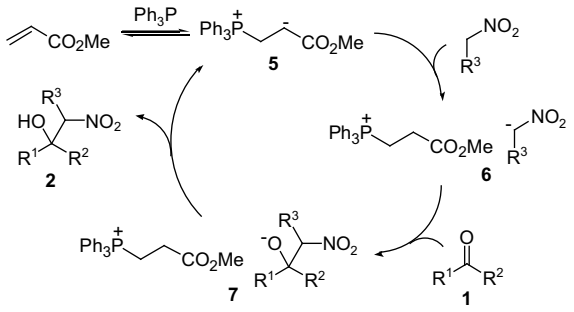
Table 3
Deuterium-labeling experiments[a]



1a 2aa 3 4

Entry	$MeNO_2$	Solvent	Deuterium[b] (%)						
			a	b	c	d	e	f	g
1[c]	CD_3NO_2	None	87	37	>78[d]	12	**55**	42	>95
2	CD_3NO_2	CD_3OD	95	80	95	6	53	ND[e]	>95[f]
3	CD_3NO_2	CH_3OH	75	ND[e]	ND[e]	<5	38	47	76
4	CH_3NO_2	CD_3OD	22	24	24	<5	<5	ND[e]	ND[e]

[a] Reaction conditions: **1a** (0.50 mmol), $MeNO_2$ (2.0 equiv), methyl acrylate (10 mol %), PPh_3 (10 mol %), solvent (if any, 0.050 mL), rt, 3 h.
[b] Determined by ^{1}H NMR analysis.
[c] Methyl acrylate:**3**:**4** = 15:32:53.
[d] Overlapping with a broad signal in the ^{1}H NMR spectrum.
[e] Not determined.
[f] No signal was detected at δ 6.12 by ^{1}H NMR analysis.



Scheme 2. Proposed catalytic cycle.

organic base to deprotonate nitroalkane.[1b,5a] The addition of activated nitroalkane (the anion in ion pair **6**) to carbonyl compound **1** followed by proton transfer releases product **2** and regenerates zwitterion **5**. The reversible formation of zwitterion **5** and the acidity of phosphonium ion **3** (in ion pairs **6** and **7**) can account for the enrichment of deuterium in methyl acrylate and two of its adducts in the deuterium-labeling experiments shown in Table 3. Most importantly, our proposed catalytic cycle is substantially supported by the presence of much greater than 50% deuterium at the α-positions of phosphonium ion **3** and methyl acrylate in the reaction of PhCHO (**1a**) with CD_3NO_2 (Table 3, entries 1–3). In addition, the basic intermediates generated in the catalytic cycle should be responsible for the H/D exchange of nitroalkane, product **2**, and alcoholic solvent (Table 3), and the transesterification of methyl acrylate with CD_3OD (Table 3, entries 2 and 4).

In summary, we have developed an efficient catalytic Henry reaction with a phosphine and electron-deficient alkene. In the presence of 10 mol % of triphenylphosphine and 10 mol % of methyl acrylate, a wide variety of aldehydes and α-keto esters could react with nitroalkanes and gave the corresponding β-nitroalkanols in good to excellent yields. According to the deuterium-labeling experiments with CD_3NO_2, a catalytic cycle involving a zwitterionic phosphine–alkene adduct was proposed for this dual-reagent organocatalysis.

Acknowledgments

We are grateful for the financial support from the National Natural Science Foundation of China (20732006 and 20672105), the Chinese Academy of Sciences, and the University of Science and Technology of China.

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11. Triphenylphosphine (10 mol %) was not able to catalyze the reaction of benzaldehyde with nitromethane in ethanol at room temperature in 24 h (Table 1, entry 1).
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13. *General procedure*: A mixture of carbonyl compound **1** (0.50 mmol), nitroalkane (1.0 mmol), triphenylphosphine (13.1 mg, 0.050 mmol, 10 mol %), and methyl acrylate (4.4 mg, 4.6 μL, 0.050 mmol, 10 mol %) in ethanol (0.050 mL) was allowed to stand in a vial at room temperature for the time as indicated in Table 2. The resulting mixture was concentrated, and the residue was purified by silica gel column chromatography to give β-nitroalkanol **2**. All the products are known and characterized by ^1H and ^{13}C NMR analysis.
14. A small portion (about 5 μL) of the reaction mixture was dissolved in $CDCl_3$ and was subjected to ^1H NMR ($CDCl_3$, 400 M) analysis.
15. The methyl groups in methyl acrylate, phosphonium ion **3**, and ester **4** were chosen as the corresponding references to determine the percentage of deuterium. The signal for the methyl group of phosphonium ion **3** overlaps with that of CH_3OH in the ^1H NMR spectrum (Table 3, entry 3). When CD_3OD was used as the solvent, the percentage of deuterium in methyl acrylate could not be determined as a result of transesterification (Table 3, entries 2 and 4).