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Inverse-Electron-Demand Hetero-Diels–Alder Reaction of β,γ-Unsaturated α-Ketophosphonates Catalyzed by Prolinal Dithioacetals†

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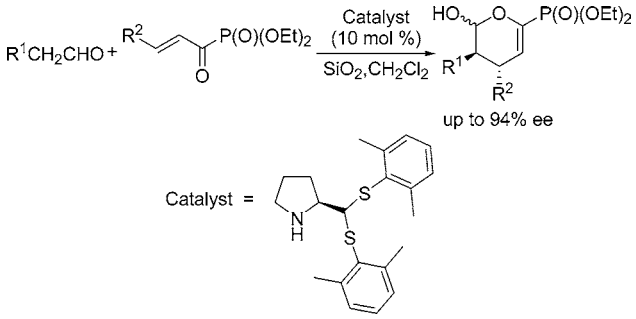
ABSTRACT



Some novel prolinal dithioacetal derivatives were studied as catalysts for the inverse-electron-demand hetero-Diels–Alder reaction of enolizable aldehydes and β,γ-unsaturated α-ketophosphonates. The corresponding 5,6-dihydro-4*H*-pyran-2-ylphosphonates were obtained in good ee values (up to 94% ee).

Recently we reported a highly enantioselective method for the synthesis of α-hydroxyphosphonates by using a proline derivative-catalyzed aldol reaction of ketones and α-ketophosphonates.[1] In view that the aldol reaction works through an enamine intermediate formed by the reaction of the ketone and the proline derivative[1] and that aldehydes readily form enamine intermediates with proline derivatives,[2] it is quite reasonable to assume that aldehydes are also good substrates for this reaction. On the basis of this assumption, we tried to react aldehydes with α-ketophosphonates by using L-proline (**3**)[1a] as the catalyst. Surprisingly enough, most of our attempts failed to produce any useful product, except for the reaction of propanal (**1a**) and diethyl *trans*-1-oxo-2-butenylphosphonate (**2a**, a β,γ-unsaturated α-ketophosphonate, Scheme 1), which indeed yielded a definite product. Nevertheless, after purification, the product isolated was not the expected aldol product **4** (Scheme 1, top equation). Instead, a careful analysis of the spectroscopic data of this compound revealed that it is the cyclic product **5a** (Scheme 1, bottom equation). This result is in striking contrast to that of acetone, which under similar conditions reacts with **2a** to give exclusively the expected aldol product in high yield.[1a]

Compound **5a** may be regarded as a glycal phosphonate derivative. Similar compounds have been shown to have multiple biological activities.[3] The formation of **5** may be explained by an inverse-electron-demand hetero-Diels−Alder

† Dedicated to Professor Waldemar Adam on the occasion of his 70th birthday.

‡ Undergraduate student.

(1) (a) Samanta, S.; Zhao, C.-G. *J. Am. Chem. Soc.* **2004**, *126*, 7442−7443. (b) Dodda, R.; Zhao, C.-G. *Org. Lett.* **2006**, *8*, 4911−4914.

(2) For reviews, see: (a) Notz, W.; Tanaka, F.; Barbas, C. F., III *Acc. Chem. Res.* **2004**, *37*, 580−591. (b) Houk, K. N.; List, B. *Acc. Chem. Res.* **2004**, *37*, 548−557. (c) List, B. *Tetrahedron* **2002**, *58*, 5573−5590.

(3) Pachamuthu, K.; Figueroa-Perez, I.; Ali, I. A. I.; Schmidt, R. R. *Eur. J. Org. Chem.* **2004**, 3959−3961.

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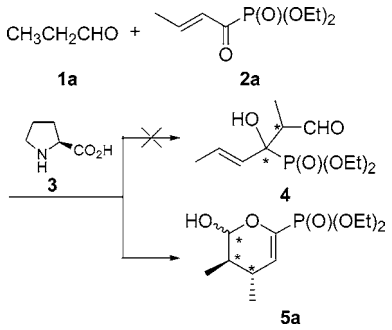
Scheme 1



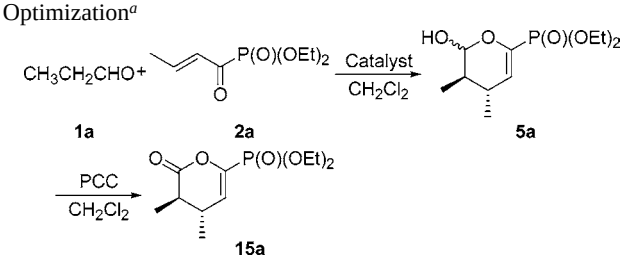
reaction[4] between the enamine, generated in situ from propanal (**1a**) and proline, and the α,β-unsaturated ketone **2a**. Examples of such an organocatalytic hetero-Diels−Alder reaction are very scarce in the literature. To the best of our knowledge, only Jørgensen and co-workers have reported a similar reaction of β,γ-unsaturated α-ketoesters.[5]

Three new stereogenic centers are generated during the formation of product **5a** out of the L-proline catalysis, but only two diastereomers were obtained in an 80/20 ratio as determined by ^{1}HNMR analysis of the crude product. This mixture of diastereomers is difficult to separate on HPLC columns and makes it impossible to determine the ee value of the product directly and, therefore, product **5a** was further oxidized to the corresponding lactone derivative **15a** (Table 1). After oxidation, the two diastereomers give the same product, which indicates that the diastereomerism was due to the stereochemistry of the hydroxy group, whereas the formation of the two carbon stereogenic centers is completely diastereoselective. The stereochemistry of the two alkyl groups was determined to be in trans configuration through the NMR study of the oxidized product **15a**.[6] A similar phenomenon was also observed by Jørgensen and co-workers in the reaction of β,γ-unsaturated α-ketoesters.[5]

The ee value of product **15a** was determined to be 38%, and the major enantiomer is dextrorotatory (Table 1, entry 1). To improve the enantioselectivity of this reaction, several proline derivatives (Figure 1) were screened. The results are summarized in Table 1.

Besides L-proline, L-prolinamide (**6**), L-proline tetrazole (**7**),[7] and an L-proline-derived dipeptide (**8**)[8] all were found to catalyze the same reaction; however, the enantioselectivities obtained were unsatisfactory (≤50% ee, entries 2−4). The reaction catalyzed by a 2-piperidinyl monophosphonic acid (**9**)[9] also led to poor results (26% ee, entry 5). While all these catalysts do lead to the desired product, the MacMillan catalyst (**10**)[10] gives almost no conversion of the substrate (entry 6). In the presence of benzoic acid, (*S*)-2-(pyrrolidin-1-ylmethyl)pyrrolidine (**11**) also produces the desired Diels−Alder product, but again in poor ee value (46%, entry 7). The diphenylmethylpyrrolidine catalyst **12** has been studied by Jørgensen and co-workers in the reaction of β,γ-unsaturated α-ketoesters.[5] We also applied this catalyst in our reaction, and a much improved enantioselectivity (79% ee) was obtained in the presence of silica gel (entry 8). Without silica gel, the reaction was very slow and poor yield was obtained with this catalyst (data not shown). It is our conviction that acidic silica gel catalyzes the cleavage of

Table 1. Catalyst Screening and Reaction Condition Optimization[a]



entry	solvent	catalyst	time (h)	yield (%)[b]	anomeric ratio[c]	ee (%)[d]
1	CH_2Cl_2	**3**	18	92	80:20	38 (+)
2	CH_2Cl_2	**6**	20	87	80:20	14 (+)
3	CH_2Cl_2	**7**	15	92	78:22	50 (+)
4	CH_2Cl_2	**8**	25	78	83:17	16 (+)
5	CH_2Cl_2	**9**	24	43	80:20	26 (+)
6	CH_2Cl_2	**10**	24	<5	nd[e]	nd[e]
7[f]	CH_2Cl_2	**11**	30	87	76:24	46 (+)
8[g]	CH_2Cl_2	**12**	30	82	81:19	79 (−)
9[g]	CH_2Cl_2	**13**	30	83	81:19	40 (+)
10[g]	CH_2Cl_2	**14**	30	79	80:20	87 (−)
11[g]	hexane	**14**	40	82	83:17	80 (−)
12[g]	toluene	**14**	48	82	80:20	80 (−)
13[g]	THF	**14**	48	85	82:18	62 (−)
14[g]	$CHCl_3$	**14**	36	73	78:22	63 (−)

[a] Unless otherwise indicated, all reactions were carried out with diethyl *trans*-1-oxo-2-butenylphosphonate (**2a**, 0.25 mmol), propanal (**1a**, 2.0 mmol), and the catalyst (0.025 mmol, 10 mol %) in the specified solvent (1.0 mL) at room temperature. [b] Yield of the isolated product **5a** after column chromatography. [c] Only the trans product (refers to R^1 and R^2 groups) was obtained according to the ^{1}H NMR of the crude product; the anomeric ratio was determined by ^{1}H NMR analysis of the crude product. [d] The ee values were determined by HPLC analyses of the oxidized product **15a**; the absolute configuration was not determined. [e] Not determined. [f] $PhCO_2H$ (10 mol %) was added. [g] The reaction was carried out with added silica gel (100 mg).

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(6) For details, see the Supporting Inforamtion.

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(8) Martin, H. J.; List, B. *Synlett* **2003**, 1901−1902.

(9) Catalyst **9** is a known compound, although it has never been used in organocatalysis; see: Maury, C.; Wang, Q.; Gharbaoui, T.; Chiadmi, M.; Tomas, A.; Royer, J.; Husson, H.-P. *Tetrahedron* **1997**, *53*, 3627−3636.

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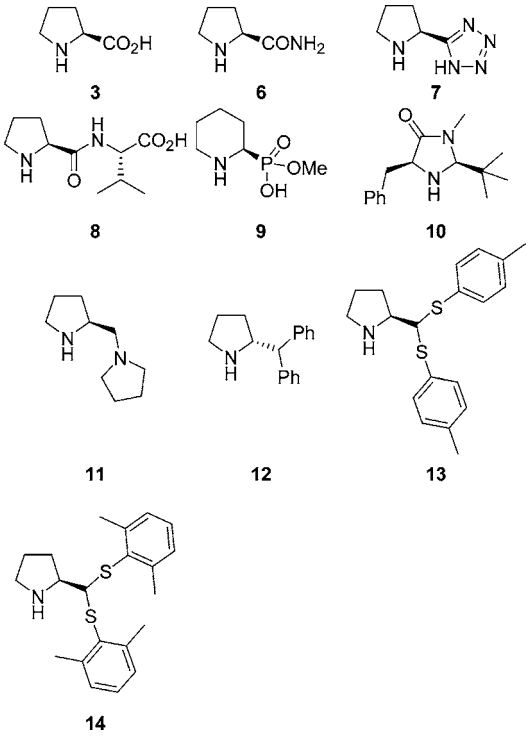


Figure 1. Catalysts screened for the hetero-Diels−Alder reaction.

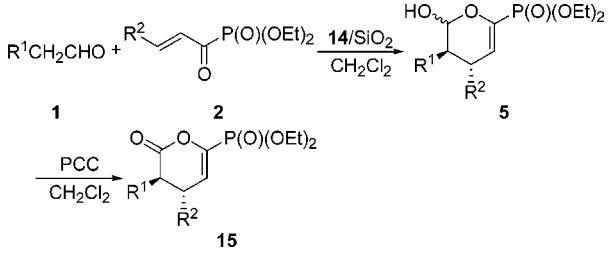
catalyst **12** from the primary Diels−Alder product of the enamine and, therefore, improves the catalytic efficiency of **12**. It should be pointed out that catalyst **12** is *R*-configured and the formation of the levorotary enantiomer as the major product (entry 8) is in line with the other *S*-configured proline-derived catalysts.

Catalyst **12** is the best one among these screened catalysts, but the enantioselectivity is still below 80% ee. To further improve the asymmetric induction, modification of the structure of **12** is desirable. Nevertheless, because the side chain of **12** consists of C−C σ bonds, the modification of **12** is not easy. Because dithioacetal bonds are much easier to form (as compared with C−C σ bonds) and there are a variety of thiol structures available, we became interested in replacing the C−C σ bonds in **12** with dithioacetal bonds. Thus, catalysts **13** and **14** were designed. Both catalysts[11] may be synthesized in just one step from the commercially available *N*-Boc-prolinal in high yields.[6]

These two catalysts were then applied in the above Diels−Alder reaction. Both catalysts were found to process similar reactivities as that of **12**. While a lower ee value of 40% (entry 9) was obtained with catalyst **13**, the more hindered catalyst **14** did lead to a better ee value than catalyst **12** (87% ee, entry 10). Most surprisingly, however, is the finding that these two catalysts led to opposite enantiomers as the major products, although they have the same absolute configuration: catalyst **13** yields dextrorotary enantiomer as the major product (entry 13), whereas catalyst **14** produces levorotary enantiomer (entry 14). The fact that all the products obtained in this study (including those in Table 2, vide infra) are

(11) These catalysts are stable under both acidic and basic conditions.

Table 2. Enantioselective Hetero-Diels−Alder Reaction[a]



entry	R^1	R^2	time (h)	yield (%)[b]	anomeric ratio[c]	ee (%)
1	Me	Me	30	79	81:19	87[d]
2	Et	Me	28	87	83:17	82[d]
3	$CH_3(CH_2)_3$	Me	30	88	76:24	83[d]
4	$CH_3(CH_2)_4$	Me	36	87	79:21	89[d]
5	$CH_3(CH_2)_7$	Me	30	91	72:28	85[e]
6	*i*-Pr	Me	40	69	59:41	89[e]
7	Ph	Me	36	82	71:29	68[e]
8[f]	$PhCH_2$	Me	72	69	77:23	94[e]
9	Me	Et	48	72	71:29	80[d]
10	Et	Et	48	71	68:32	89[d]
11	Me	Ph	29	41	78:22	19[e]

[a] Unless otherwise indicated, all reactions were carried out with unsaturated ketophosphonate **2** (0.25 mmol), aldehyde **1** (2.0 mmol), catalyst **14** (0.025 mmol, 10 mol %), and silica gel (100 mg) in CH_2Cl_2 (1.0 mL) at room temperature. [b] Yield of isolated product after column chromatography. [c] Only the trans product (refers to R^1 and R^2 groups) was obtained according to the ^{1}H NMR of the crude product; the anomeric ratio was determined by ^{1}H NMR analysis of the crude product. [d] Determined by HPLC analysis of the oxidized product **15**; the absolute configuration was not determined. [e] Determined by direct HPLC analysis of product **5**. [f] The reaction was carried out at 0 °C.

liquids hampers the determination of the absolute configurations of the stereogenic centers in the products (**5** and **15**) and, therefore, the reason for this enantiofacial selectivity switch is not clear at this moment.

For catalyst **14**, further screening of solvents revealed that normal organic solvents, such as hexane (entry 11), toluene (entry 12), THF (entry 13), and $CHCl_3$ (entry 14), all led to inferior results than CH_2Cl_2 (entry 10). Thus, CH_2Cl_2 was identified as the best solvent for this reaction.

As is evident from Table 1, the ratio of the two anomers of the trans product remains almost unchanged even though the catalysts or the reaction conditions are changed.

To understand the scope of this reaction, we studied reactions of several enolizable aldehydes and β,γ-unsaturated α-ketophosphonates under the optimized conditions. The results are collected in Table 2.

As is evident from Table 2, enolizable aliphatic aldehydes are good substrates for the reaction with diethyl *trans*-1-oxo-2-butenylphosphonate (**2a**). Regardless of the chain lengths (C_2−C_9), the enantioselectivities obtained were very similar for straight-chain aldehydes (ca. 85% ee, entries 1−5). A good ee value (89%) was also obtained for the

branched isovaleraldehyde (entry 6). In contrast, a big drop in the enantioselectivity was observed for phenylacetaldehyde (to 68% ee, entry 7). Such a selectivity drop is most likely due to some electronic effects, because good enantioselectivity has been obtained with the hindered isovaleraldehyde (entry 6). When the phenyl group moves further away from the reaction center, i.e., as in dihydrocinnamaldehye, high enantioselectivity was obtained once again (94% ee, entry 7). Besides diethyl *trans*-1-oxo-2-butenylphosphonate, diethyl *trans*-1-oxo-2-pentenylphosphonate reacts similarly, and gives the expected products in similar enantioselectivities (entries 9 and 10). However, the reaction of *trans*-1-oxo-3-phenyl-2-propenylphosphonate leads to a very low ee value of the product (entry 11), probably also due to electronic effects.

In all cases only the trans (refers to the alkyl groups R^1 and R^2) stereoisomers were formed, while the anomeric ratios are dependent on the nature of these two substituents. Nevertheless, after PCC oxidation, both anomers should give the same product **15**. However, a simple α,β-unsaturated ketone, such as chalcone, does not participate in this reaction (data not shown). On the basis of these results and those reported by Jørgensen and co-workers,[4] the presence of a strong electron-withdrawing group (such as phophonate or carboxylate) adjacent to the carbonyl group is crucial for this reaction.

In summary, we have found that β,γ-unsaturated α-ketophosphonates, like β,γ-unsaturated α-ketoesters, undergo inverse-electron-demand hetero-Diels−Alder reaction under the catalysis of proline derivatives. Readily available and highly tunable L-prolinal dithiolacetal catalysts have been shown to be promising catalysts for this reaction and good ee values of the Diels−Alder products were obtained (up to 94% ee).

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Supporting Information Available: Experimental procedures, NMR spectra for new compounds, and HPLC analysis data. This material is available free of charge via the Internet at http://pubs.acs.org.

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