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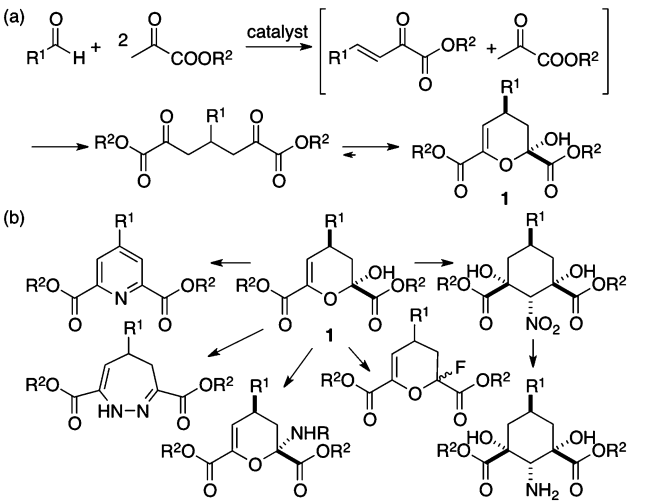
Reactions of pyruvates: organocatalytic synthesis of functionalized dihydropyrans in one pot and further transformations to functionalized carbocycles and heterocycles†‡

Pandurang V. Chouthaiwale and Fujie Tanaka*

Concise cascade reactions of pyruvates with aldehydes that generate functionalized dihydropyran derivatives in one pot have been developed. The products, dihydropyrans, were further concisely transformed to various molecules.

The development of synthetic methods that allow access to a series of functionalized small molecules in concise routes under mild conditions is important in the search for bioactive molecules.[1] Here we report the development of reactions that use pyruvates as key reactants to provide a set of functionalized molecules.

Pyruvates can act as nucleophiles and electrophiles, and thus are expected to be useful synthons.[2,3] For example, pyruvates have been used for enzyme-catalyzed aldol reactions to generate *N*-acetylneuraminic acid and related molecules.[2] In non-enzymatic reactions of pyruvates, however, the dual reactivties of pyruvates are difficult to control.[3–6] Reactions of simple pyruvates (such as ethyl pyruvate and methyl pyruvate) as nucleophiles are especially difficult and have been very limited.[3a–e,4] We hypothesized that with the use of appropriate catalysts and conditions, the dual reactivities of pyruvates could be managed for the formation of more than two-bonds in one pot to generate functionalized molecules in non-enzymatic reactions. Here we report the development of a concise, one-pot cascade reaction system to generate functionalized dihydropyran derivatives **1** using pyruvates and aldehydes as starting materials (Scheme 1a).[7–9] Dihydropyran is an important core structure as often found in bioactive natural products and pharmaceuticals.[7] Formation of **1** is distinct from previously reported reactions of pyruvates that yield the self-aldol product[3a,b] or cross aldol products.[3c,d] We also report the utility of dihydropyrans **1** as synthons to concisely synthesize a wide range of functionalized molecules, including molecules relevant to the search of biofunctional molecules, such as amino group-substituted and fluoro group-substituted dihydropyrans, cyclohexanes, dihydrodiazepines, and pyridines (Scheme 1b).



Scheme 1 (a) One-pot cascade reaction of pyruvates that afford functionalized dihydropyran derivatives **1** reporting here; (b) various functionalized molecules synthesized from **1**, reporting here.

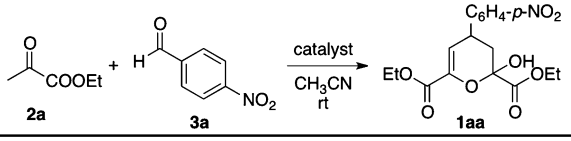
First, catalysts and reaction conditions were evaluated in the reaction of ethyl pyruvate (**2a**) and *p*-nitrobenzaldehyde (**3a**) to afford dihydro-2*H*-pyran derivative **1aa** (Table 1). Pyruvate-dependent aldolases often use an enamine-based mechanism,[10] and we tested the use of amine-based catalysts for the formation of **1** *via* an enamine-mechanism. It has been reported that proline forms an oxazolidine derivative with pyruvates and thus cannot act as a catalyst in the reaction of pyruvates.[3a] Therefore, amines other than proline, including pyrrolidine, pyrrolidine bearing acid functional groups at either 2- or 3-position, and primary amines

Chemistry and Chemical Bioengineeing Unit, Okinawa Institute of Science and Technology Graduate University, 1919-1 Tancha, Onna, Okinawa 904-0495, Japan. E-mail: ftanaka@oist.jp

† This article is dedicated to Prof. Carlos F. Barbas, III, The Scripps Research Institute, in memoriam, who died in June 2014.

‡ Electronic supplementary information (ESI) available: Synthesis and characterization of compounds, X-ray crystal structures of **1ab** and **7aa**. CCDC 1012430 (compound **1ab**) and 1012431 (compound **7aa**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4cc06035k

Table 1 Screening of catalysts in the reaction of ethyl pyruvate (**2a**) and aldehyde **3a** to form **1aa**[a]



Entry	Catalyst	Time (h)	Yield[b] (%)
1	Pyrrolidine	48	4
2	Pyrrolidine–CH_3COOH (1 : 1)	48	27
3	CH_3COOH	48	nd
4	(*S*)-5-Pyrrolidin-2-yl-1*H*-tetrazole	48	2
5	(*S*)-Prolinamide	48	nd
6	3-(Trifluoromethanesulfonylamino)pyrrolidine	48	9
7	(*S*)-β-Proline	24	49
8[c]	(*S*)-β-Proline	24	72
9[c]	(*S*)-β-Prolinamide	24	46
10	(*S*)-β-Proline-Et_3N	48	nd
11	β-Alanine	48	nd
12[d]	(*S*)-L-Alanine, valine, histidine, or tryptophan	48	nd
13	O-*t*Bu-(*S*)-L-threonine	48	nd
14[d]	Et_3N, DBU, or DMAP	48	nd

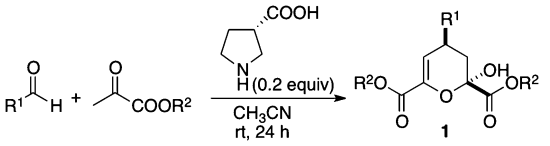
[a] Reaction was performed using **2a** (2.2 mmol) and **3a** (1.0 mmol) in the presence of catalyst (0.1 mmol) in CH_3CN (1.0 mL) at 25 °C except where indicated. [b] Isolated yield (the cyclic form and the linear form were combined[11]); nd = formation of **1aa** was not detected by TLC analyses. [c] Reaction using **2a** (3.0 mmol) and **3a** (1.0 mmol) in the presence of catalyst (0.2 mmol). [d] Each catalyst was tested in a separate reaction.

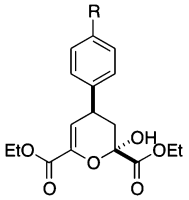
such as α-amino acids, were tested as catalysts for the formation of **1aa**. We found that pyrrolidine-3-carboxylic acid (β-proline) was the best catalyst of those tested (entries 7 and 8).[11,12] Reactions using non-enamine-forming bases, such as DBU,[13] as catalysts were also tested, but did not afford **1aa** (entry 14). With optimization, when the reaction was performed using ethyl pyruvate (**2a**) (3 equiv.), aldehyde **3a** (1 equiv.), and β-proline (0.2 equiv.) in CH_3CN at 25 °C for 24 h, **1aa** (including the linear form) was obtained in 72% yield (entry 8).[14]

Next, the scope of the β-proline-catalyzed reaction was examined under the optimized conditions to afford **1aa**, and various dihydropyran derivatives were synthesized (Table 2).[11] The use of β-proline catalysis efficiently provided various dihydropyrans **1**; the main product was **1** for all cases. In the reactions to generate **1na** and **1oa**, aldol condensation products **4na** and **4oa**, respectively, were also obtained. In most cases, however, significant formation of the aldol condensation product was not detected during the reaction. The generated dihydropyran product (*i.e.*, the cyclic form) was mostly a single diastereomer (dr > 10 : 1). The relative stereochemistry of **1ab** was determined to be as drawn in Table 2 by X-ray crystal structural analysis (see ESI‡).

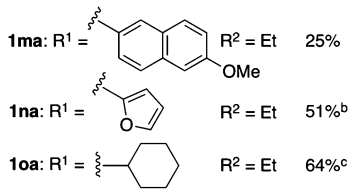
To understand the mechanism of the formation of dihydropyrans **1** from pyruvates and aldehydes, reactions using a possible intermediate β,γ-unsaturated α-ketoester and pyruvates were examined. When the reaction began with preformed β,γ-unsaturated α-keto methyl ester **4ab** with ethyl pyruvate (**2a**) or benzyl pyruvate (**2c**), a mixture of dihydropyran derivatives in which the methyl ester group was either at the

Table 2 Scope of the β-proline-catalyzed reaction to form dihydropyrans[a]

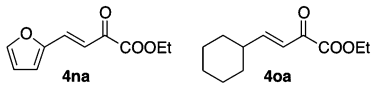


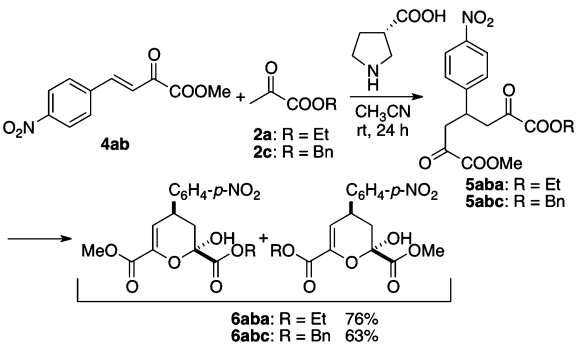


1aa: R = NO_2 72%
1ba: R = CN 72%
1ca: R = CF_3 66%
1da: R = F 55%
1ea: R = Cl 64%
1fa: R = Br 65%
1ga: R = H 58%
1ha: R = Me 39%
1ia: R = C≡CH 55%
1ja: R = COOH 47%
1ka: R = OMe 26%
1la: R = OH 32%



[a] Reaction conditions: pyruvate (3.0 mmol), aldehyde (1.0 mmol), and (*S*)-β-proline (0.2 mmol) in CH_3CN (1.0 mL) at 25 °C for 24 h. Yields were the isolated yields; the cyclic form and the linear form were combined. The main product was **1** for all cases. The reaction time was not optimized for each aldehyde substrate. [b] **4na** (30%) was obtained with **1na**. [c] **4oa** (11%) was obtained with **1oa**.





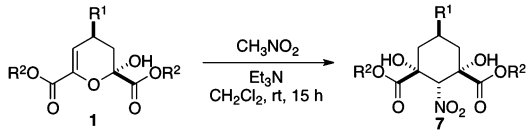
Scheme 2 Reactions using preformed intermediate **4ab**.

sp^2 or sp^3 carbon of the dihydropyran ring was obtained (Scheme 2). That is, no significant discrimination between the two ketoester groups was observed in the reaction to form the dihydropyran ring. This result suggests that the formation of **6** is likely *via* a Michael addition–cyclization, *i.e.*, *via* the formation of acyclic intermediate **5** or its iminium ion with β-proline, rather than a [4+2] reaction[15] between **4ab** and an enol of the pyruvate.

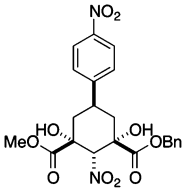
It is expected that the synthesized dihydropyran derivatives **1** have features of α-ketoesters and thus are useful for further transformations to synthesize various functionalized molecules.[16]

Reactions of **1** with nitromethane gave functionalized cyclohexanes **7** in high yields (Table 3). In all cases, the isolated

Table 3 Transformation of the dihydropyrans **1** to functionalized cyclohexanes **7**[a]

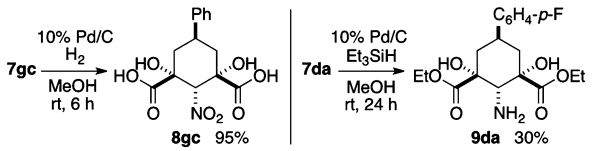


7aa: R^1 = C_6H_4-*p*-NO_2	R^2 = Et	89%	
7ba: R^1 = C_6H_4-*p*-CN	R^2 = Et	94%	
7ca: R^1 = C_6H_4-*p*-CF_3	R^2 = Et	88%	
7da: R^1 = C_6H_4-*p*-F	R^2 = Et	83%	
7ea: R^1 = C_6H_4-*p*-Cl	R^2 = Et	85%	
7ha: R^1 = C_6H_4-*p*-Me	R^2 = Et	87%	
7ia: R^1 = C_6H_4-*p*-C≡CH	R^2 = Et	89%	
7na: R^1 = 	R^2 = Et	92%	
7qa: R^1 = $CH(OMe)_2$	R^2 = Et	87%	
7ra: R^1 = 	R^2 = Et	89%	
7gc: R^1 = Ph	R^2 = Bn	95%	



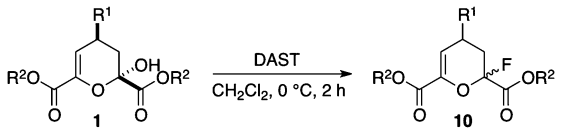
7abc 91%[b]

[a] Reaction conditions: **1** (0.1 mmol), CH_3NO_2 (1.0 mmol), and Et_3N (0.15 mmol) in CH_2Cl_2 (0.5 mL) at 25 °C. [b] **7abc** was synthesized from **6abc**.



Scheme 3 Transformations of **7**.

Table 4 Transformations of **1** to fluorodihydropyrans



10aa: R^1 = C_6H_4-*p*-NO_2	R^2 = Et	96%, dr 3:1	
10ea: R^1 = C_6H_4-*p*-Cl	R^2 = Et	95%, dr 3:1	
10fa: R^1 = C_6H_4-*p*-Me	R^2 = Et	88%, dr 3:1	
10oa: R^1 = cyclohexyl	R^2 = Et	92%, dr 1:1	
10qa: R^1 = $CH(OMe)_2$	R^2 = Et	63%, dr 1:1	

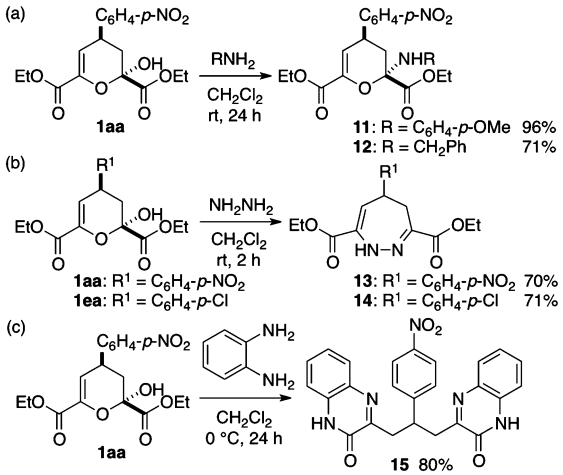
cyclohexane product was a single diastereomer. The relative stereochemistry of **7aa** was determined to be as shown in Table 3 by X-ray crystal structural analysis (see ESI‡).

Debenzylation of **7gc** gave diacid **8gc** and reduction of the nitro group of **7da** gave amino acid derivative **9da** (Scheme 3). A highly functionalized amino acid derivative was obtained in a concise route *via* the use of the cascade reaction of pyruvates.

Reactions of **1** with diethylaminosulfur trifluoride (DAST) afforded fluorinated pyran derivatives **10** (Table 4).[17,18]

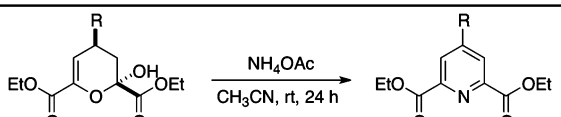
Reactions of **1** with amines afforded amino group substituted dihydropyrans **11** and **12**, dihydrodiazepines **13** and **14**, and quinoxalinone derivative **15** depending on the amine under mild conditions (Scheme 4).[19]

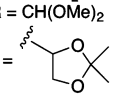
Reactions of **1** with ammonium acetate afforded pyridine derivatives **16** (Table 5). Pyridine-2,6-dicarboxilic acids and their derivatives are important as ligands for metals, small organic molecules, and biomolecules, and have been used as building blocks in the synthesis of bioactive and biofunctional



Scheme 4 Reactions of **1** with amines.

Table 5 Transformation of **1** to pyridines



16aa: R = C_6H_4-*p*-NO_2	78%	**16oa**: R = cyclohexyl	72%
16ea: R = C_6H_4-*p*-Cl	69%	**16pa**: R = $CHMe_2$	72%
16fa: R = C_6H_4-*p*-Br	75%	**16qa**: R = $CH(OMe)_2$	67%
16ja: R = C_6H_4-*p*-COOH	68%	**16ra**: R = 	50%
16la: R = C_6H_4-*p*-OH	64%		
16na: R = 	79%		

molecules.[20] Previously reported synthesis of substituted pyridine-2,6-dicarboxylic acids often requires long routes including steps that require severe conditions.[20] Here, starting from pyruvates and aldehydes, pyridine-2,6-dicarboxylic acid derivatives bearing various substitutions at the 4-position of the pyridine were concisely synthesized under mild conditions.

In conclusion, we have developed concise cascade reactions of pyruvates that provide various functionalized dihydropyrans in one pot under mild conditions. We have demonstrated that the use of β-proline catalysis can provide the dihydropyrans that were not obtained in previously reported reactions of pyruvates. Our strategy enabled harnessing of the reactivity of the pyruvates to synthesize complex, functionalized products in one pot. Furthermore, we have demonstrated that the cascade reaction products, dihydropyrans, can be readily transformed to various molecules under mild conditions, which can be used as bioactive candidates.

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11 Product **1aa** obtained in Table 1 was mainly (>70%) the cyclic forms after initial isolation/purification. The ratio of the cyclic form to the corresponding acyclic, C_2 symmetric, achiral linear form varied depending on the aldehyde used in the reaction and on other factors such as time kept after isolation. (See ESI‡). Cyclic hemiacetals are often in equilibrium with the corresponding open chain, linear forms.

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13 D. Zhang, S. Johnson, H.-L. Cui and F. Tanaka, *Asian J. Org. Chem.*, 2014, **3**, 391.

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