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Organocatalytic Sequential α-Amination/Corey–Chaykovsky Reaction of Aldehydes: A High Yield Synthesis of 4-Hydroxypyrazolidine Derivatives

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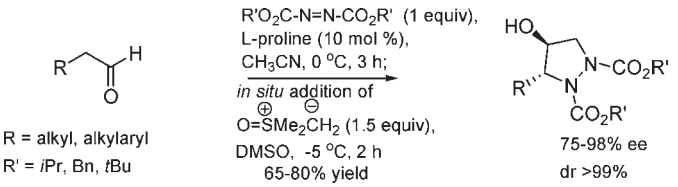
ABSTRACT



A tandem reaction of *in situ* generated α-amino aldehydes with dimethyloxosulfonium methylide under Corey–Chaykovsky reaction conditions proceeds efficiently to give 4-hydroxypyrazolidine derivatives in high yields with excellent enantio- and diastereoselectivities. This organocatalytic sequential method provides for the efficient synthesis of *anti*-1,2-aminoalcohols, structural subunits present in several bioactive molecules as well.

Pyrazolidines (**1**), pyrazolines (**2**), and pyrazoles are an interesting class of heterocyclic units found in many complex bioactive natural products.[1] Among them chiral hydroxypyrazolidine derivatives represent not only useful building blocks in the pharmaceutical industry[2] but also powerful intermediates in the preparation of enantiopure 1,3-diamines (**3**) (Figure 1).[3] More importantly, the derivatives of densely functionalized pyrazolidines exhibit a wide variety of biological acitivities including anticonvulsant,[4] antidepressant,[5] and antitumor[6] properties along with other minor uses (e.g., as brightening agent).[7] Generally, these nitrogen-containing heterocyclic rings are constructed by [3 + 2]-cycloaddition strategies under strongly acidic ($AcOH/H_2SO_4$)[8a–c] as well as thermal conditions (≥150 °C).[8d–g] Their asymmetric versions are reported employing chiral $Zr(OTf)_4$/BINOL,[9] Si-based Lewis acid derivatives,[10] and transition metal (Pd, Ni, Au)-catalyzed intramolecular annulations.[11] However, these methods are limited because of harsh reaction conditions, complex

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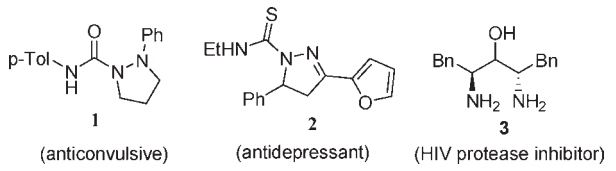
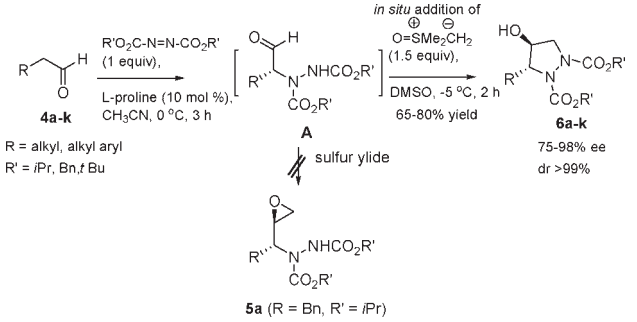


Figure 1. Some bioactive molecules.

chiral pool resources, expensive chiral ligands, and metal catalysts often involving multistep reaction sequences.

In recent years, proline-catalyzed direct α-amination of aldehydes has emerged as a reliable method for the enantioselective synthesis of α-amino acid derivatives.[12] In this regard, the *in situ* generated amino aldehyde **A** was readily transformed into several functionalized organic derivatives: e.g., 1,2-aminoalcohols,[12a] 3,6-dihydropyridazines,[13a] functionalized β-aminoalcohols,[13b] and γ-amino-α,β-unsaturated esters.[13c] As part of our program directed toward asymmetric synthesis of bioactive molecules employing organocatalysts,[13c,14] we envisaged that *in situ* trapping of amino aldehyde **A** with Corey's sulfur ylide (dimethyloxosulfonium methylide)[15,17a] under basic conditions should provide the corresponding highly functionalized terminal amino epoxides **5a**. Surprisingly, the reaction took a different course to furnish the corresponding 4- hydroxypyrazolidine derivatives **6a**−**k** in high yields (Scheme 1). In this communication, we describe a one-pot procedure for a tandem α-amination/Corey−Chaykovsky reaction of aldehydes **4a**−**k** that proceeds to give 4-hydroxypyrazolidine derivatives **6a**−**k** in a highly enantio- and diastereoselective manner (Scheme 1).

Scheme 1. In Situ Trapping of α-Amino Aldehydes **A** with Dimethyloxosulfonium Methylide



As a model substrate, the amination of hydrocinnamaldehyde **4a** was carried out following the List protocol[12a] that produced the corresponding α-amino aldehyde **A** *in situ*. As intermediate **A** is prone to racemization[16] under basic conditions, several experiments were conducted to identify the most effective and suitable condition for the Corey−Chaykovsky reaction; the results are presented in Table 1. First, a solution of dimethyloxosulfonium methylide in DMSO [sulfur ylide (1.5 equiv), prepared *in situ* from O=SMe_3I/NaH in DMSO][17a] was added to intermediate **A** at 25 °C which gave **6a** as a single diastereomer in 80% yield with 5% ee (low % ee is probably due to racemization) (entry 1). A dramatic improvement in enantioselectivity (75% ee) was however realized by performing the reaction at 10 °C for 2 h. Finally, the best results could be obtained when the addition of ylide was conducted at −5 °C (91% ee with 73% yield). However, further lowering of the temperature to

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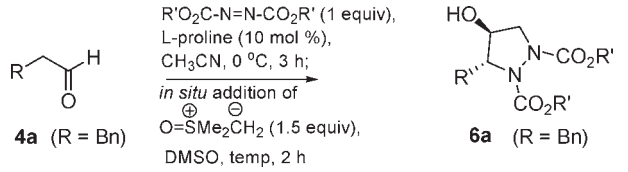
(17) **General Experimental Procedure:** (a) **Preparation of sulfur ylide**: 0.18 g (7.5 mmol) of NaH (previously washed with petroleum ether to remove oil) was added to an oven-dried three-necked flask, followed by the addition of dry DMSO (10 mL) through a septum to it, and the whole slurry was stirred at 25 °C under a N_2 atmosphere. Then trimethyloxosulfonium iodide (1.67g, 7.5 mmol) was added to the slurry over a period of 5 min *via* a solid addition funnel until it became a homogenous solution. (b) **Sequential α-Amination/Corey−Chaykovsky Reaction of Aldehydes**: To a cooled solution of azadicarboxylate (5.0 mmol) and L-proline (10 mol%) in dry CH_3CN (20 mL) at 0 °C was added α-unsubstituted aldehyde (**4a**−**k**, 5 mmol), and the mixture was stirred for 3 h at 0 °C. This was followed by the addition of a solution of dimethyloxosulfonium methylide in DMSO at −5 °C and allowed to stir for 2 h at the same temperature. The progress of the reaction can be monitored by TLC. It was then quenched by the addition of an aq. NH_4Cl solution. The mixture was concentrated in vacuum to remove acetonitrile and concentrate extracted with diethyl ether (3 × 40 mL). The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4, and concentrated under reduced pressure to give the crude products, which were then purified by flash column chromatography (100−200 mesh) using petroleum ether and ethyl acetate as eluents to afford the pure products **6a**−**k**.

either −20 or −40 °C had a deleterious effect on both the yield and enantioselectivity.

Table 1. Proline-Catalyzed α-Amination/Corey−Chaykovsky Reaction of Hydrocinnamaldehyde[a]



no.	amine (R′)	temp (°C)	yield of **6a** (%)[b]	ee (%)[c]	de (%)[d]
1	*i*Pr	25	80	5	99
		10	75	75	99
		−5	73	91	99
			(45)[e]	(79)[e]	
		−20	52	88	99
		−40	48	84	99
2	Bn	−5	71	90	100
3	*t*Bu	−5	60	80	100

[a] Aldehyde (5 mmol), amine ($R'O_2C—N=N—CO_2R'$) (5 mmol), L-proline (10 mol %), dimethyloxosulfonium methylide (7.5 mmol). [b] Isolated yield after column chromatographic purification. [c] Determined from chiral HPLC analysis (Chiracel OD-H, Whelk-01 columns; *n*-hexane/2-propanol). [d] Product is obtained as a single diastereomer as determined from ^1H, ^{13}C NMR and HPLC analysis. [e] Refers to 2-[bis-(3,5-bistrifluoromethylphenyl)trimethylsilanyloxymethyl]pyrrolidine is used as catalyst.

Also (*S*)-α,α-diarylprolinol silyl ether as a modified proline catalyst was found to be less effective for the reaction (Table 1, footnote e). We then turned our attention to briefly investigate the scope of amine sources and the results of which indicated that diisopropyl- and dibenzylazadicarbxylates were found to be better candidates (entries 1 and 2). Use of other solvents such as THF and CH_2Cl_2 for the tandem protocol resulted in a sluggish reaction with poor yields (~30%).

With the optimized reaction conditions in hand,[17b] we next examined the scope of the reaction. Aldehydes bearing bromo, cyano, nitro, methoxy, and methylene-dioxy groups on the aromatic nucleus and azide and benzyl ether substitutions in aliphatic compounds were well-tolerated under the reaction conditions. For all the cases studied, the products **6a**−**k** were indeed obtained in high yields (65−80%) and excellent enantioselectivities (75−98% ee) with dr > 99% (Table 2).

(18) The relative stereochemistry of **6a** (R = Bu^t) was confirmed by COSY and NOESY studies. A significant NOESY correlation was observed between H_{5a} and H_4. There was no observed correlation between H_3−H_4 confirming the *anti* relationship between H_3 and H_4 (see below).

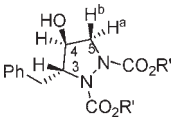


Table 2. Proline-Catalyzed Asymmetric Tandem α-Amination/Corey−Chaykovsky Reaction[a]

			products[a] **6a**−**k**	
no.	substrates **4a**−**k** (R)	amine (R′)	yield (%)[b]	ee (%)[c]
1	benzyl (**4a**)	*i*Pr	73	91
2	3,4-dimethylbenzyl (**4b**)	*i*Pr	71	94
3	3,4-methylenedioxybenzyl (**4c**)	Bn	80	90
4	2-Br-4,5-methylenedioxybenzyl (**4d**)	*i*Pr	74	95
5	2-CN-4,5-methylenedioxybenzyl (**4e**)	*i*Pr	75	75
6	naphthalene-1-yl-methyl (**4f**)	*i*Pr	70	90
7	2-NO_2-4,5-dimethoxybenzyl (**4g**)	*i*Pr	68	90
8	*n*-butyl (**4h**)	Bn	65	92
9	4-azidopropyl (**4i**)	Bn	66	91
10	3-benzyloxymethyl (**4j**)	Bn	70	90
11	3-benzyloxypropyl (**4k**)	*i*Pr	72	98

[a] Aldehyde (5 mmol), amine source ($R'O_2C—N=N—CO_2R'$) (5 mmol), L-proline (10 mol %), dimethyloxosulfonium methylide (7.5 mmol). [b] Isolated yield after column chromatographic purification. [c] Determined from chiral HPLC analysis (Chiracel OD-H, Whelk-01 column; *n*-hexane/2-propanol).

The absolute configuration of the newly generated amine center was assigned on the basis of the previously established configuration of α-amino aldehydes.[12a] The *anti*-stereochemistry in pyrazolidines **6a**−**k** is proven unambiguously from COSY and NOESY NMR studies as well as [18] X-ray crystallographic analysis (Figure 2) and is also in conformity with the Felkin−Ahn model.[19]

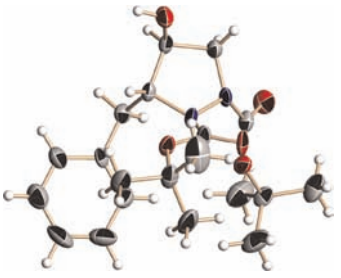


Figure 2. ORTEP diagram of **6a** (R′ = *t*Bu).

A probable mechanistic pathway is shown in Scheme 2. This pathway is supported by the following experimental facts: (a) no aminoepoxide **5a** was detected (GC and ^1H NMR) even at −40 °C when the reaction was monitored every 10 min; (b) alternatively, **5a** was prepared separately in two steps from aldehyde **A** *via* a Wittig reaction ($Ph_3P^+MeI^-$, KOBu^t, THF, 0−25 °C, 90%) followed by epoxidation (MCPBA, CH_2Cl_2, 25 °C, 92%) and found to be quite stable under the reaction conditions. This leads us

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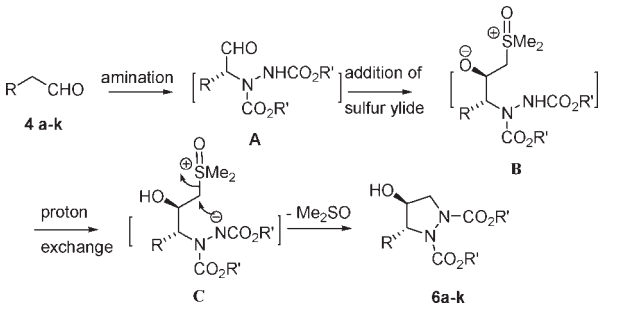
Scheme 2. Probable Mechanistic Pathway



to believe that addition of sulfur ylide onto aldehyde **A** generates the intermediate **B**. This in turn is followed by a facile proton exchange[20] from the carbamate nitrogen to the basic oxide ion to give the stable species **C**, which then subsequently undergoes intramolecular cyclization with the removal of DMSO to afford the products **6a**–**k**. A single step transformation of **6a** under catalytic hydrogenation conditions [Raney Ni, H_2, (80 psig)] gave the corresponding *anti*-1,2-aminoalcohol **7**, which are common structural subunits present in phytospingosines[21a,b]

(20) Attempts to deuterate the NH proton of carbamate **A** under various reaction conditions to ascertain the proton exchange phenomena were unsuccessful.

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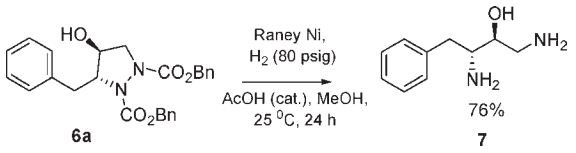
Scheme 3. Synthesis of *anti*-1,2-Aminoalcohol (**6**)



and HIV protease inhibitors,[21c,d] thus constituting an important application of this methodology (Scheme 3).

In summary, we have described, for the first time, a novel one-pot procedure for a sequential amination/Corey–Chaykovsky reaction of aldehydes that leads to the synthesis of 4-hydroxypyrazolidine derivatives **6a**–**k** with good yields and excellent enantio- and diastereoselectivities. The salient features of the methodology are as follows: (1) metal-free synthesis, (2) milder reaction conditions, (3) functional group tolerance, and (4) high yields with excellent enantio- and diastereoselectivity.

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Supporting Information Available. Detailed experimental procedures, ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.