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One-Pot Synthesis of Optically Enriched 2-Piperidinones from Aliphatic Aldehydes and Cyanoacrylamides

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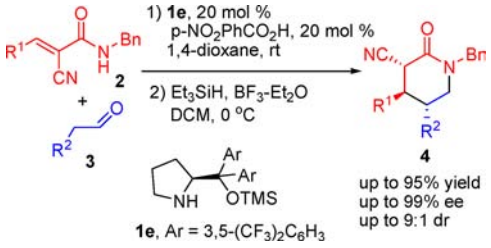
ABSTRACT



A highly stereoselective one-pot reaction of aliphatic aldehydes and cyanoacrylamides has been developed. The one-pot reaction includes an organocatalytic Michael addition followed by an intramolecular hemiaminalization. After reduction, optically enriched 2-piperidinones with three contiguous chiral centers were obtained in up to 95% yield and 9:1 dr with 99% *ee*.

The rapid construction of C−C and C−N bonds has recently received great attention and significant progress has been achieved over the past few years.[1] Formation of several bonds in a one-pot reaction is highly desirable since the laborious purification procedures and protection/deprotection protocols may thus be avoided.[2] 2-Piperidinones, nitrogen-containing six-membered heterocycles, have especially attracted much attention from many synthetic

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chemists because they are key structural motifs prevalent in numerous natural compounds and in biologically active synthetic drugs as exemplified by the molecules shown in Figure 1.[3] Moreover, they also served as the chiral building blocks or intermediates in the synthesis of polysubstituted piperidines and medicinally relevant compounds.[3,4] Thus numerous ingenious approaches for the synthesis of substituted 2-piperidinones have been reported,[5] including the Diels–Alder reaction,[5a–c] ring-closing metathesis,[5d,e] amination reaction[5f–h] and the general cyclization of amino acids or esters.[5i,j] Due to most approaches having their own disadvantages and the versatility of 2-piperidinone derivatives in both pharmaceuticals and organic synthesis, the development of efficient methods to access optically pure multifunctionalized 2-piperidinones is still an attractive goal in organic synthesis.[6]

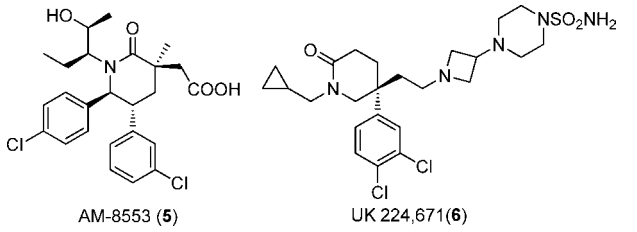

Figure 1. Examples of bioactive 2-piperidinones.

Recently, the organocatalytic cascade reactions were widely employed in the synthesis of structurally diverse molecules.[7] Conjugate addition of aliphatic aldehydes to unsaturated systems such as nitroolefins,[8] vinyl sulfones,[9] and unsaturated ketone or ester[10] is likewise applied in the synthesis of complicated molecules. To our knowledge, however, α,β-unsaturated amides have been seldom employed in the conjugate addition probably due to the low reactivity of amides compared to other systems.[1h] In connection with our interest in the synthesis of nitrogen-containing heterocycle compounds[11] and the wide range of biological activities associated with the 2-piperidinones moiety, herein we wish to report the one-pot synthesis of functionalized 3,4,5-trisubstituted 2-piperidinones by the reaction of aliphatic aldehydes with cyanoacrylamide.

Initially, the reaction of (*E*)-*N*-benzyl-3-phenylacrylamide and propionaldehyde **3a** was investigated using proline as the catalyst. Unfortunately, the reaction did not proceed at all (see Supporting Information (SI)). We thought that this may be attributed to the inherent low reactivity of acrylamide resulting in the failed reaction. To solve the problem, we introduced a cyano functionality to the α-position of the acrylamide and investigated whether (*E*)-cyanoacrylamide **2a** would be more amenable to this reaction.[12] To our delight, the reaction led to desired hemiaminalization product **7a** in 94% yield, but in a disappointing mixture of diastereoisomers by using 20 mol % proline **1a** in THF at rt.[13] After reduction of **7a** using $Et_3SiH/BF_3 \cdot Et_2O$ at 0 °C for 0.5 h, all *trans* 2-piperidinone derivative **4a** as the major isomer resulted. The enantioselectivity of **4a** was determined to be 25% *ee* (Table 1, entry 1). This promising result encouraged us to further improve the enantioselectivity of the reaction.

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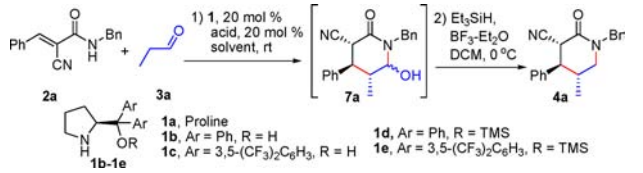
(13) **7a** as a mixture of 1.3/1 dr.

Catalyst diarylprolinol and silyl ether studies showed that silyl has a considerable effect on the stereochemistry (entry 2 vs 4 and 3 vs 5). A significant increase of *ee* was observed when prolinol **1b** or **1c** (20 mol %) was employed as the catalyst in the presence of 20 mol % 4-nitrobenzoic acid (entries 2–3). We were pleased to observe that the *ee* of **4a** further increased to 86% when the chiral diphenylprolinol silyl ether **1d** was used (entry 4). The most optimal catalyst turned out to be diarylprolinol silyl ether **1e**, affording a 94% yield and 93% *ee* after 48 h (entry 5). All catalysts afforded similar diastereoselectivities for the reaction. A screening of different acids revealed that the yield and enantioselectivity are both dependent on the acid employed (entries 6–9). The screening of different solvents

Table 1. Optimization of the Michael Addition–Hemiaminalization Reaction of the (*E*)-*N*-Benzyl-2-cyano-3-phenylacrylamide **2a** and Propionaldehyde **3a**[a]



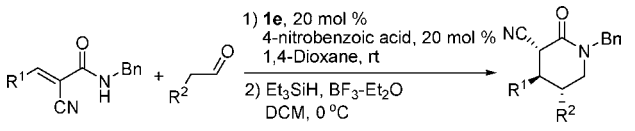
entry	cat.	solvent	time (h)[b]	yield (%)[c]	dr[d]	*ee*[e]
1[f]	**1a**	THF	48	93	5:1	25
2	**1b**	THF	48	73	5:1	60
3	**1c**	THF	48	67	5:1	61
4	**1d**	THF	48	90	6:1	86
5	**1e**	THF	48	94	6:1	93
6[g]	**1e**	THF	48	90	6:1	83
7[h]	**1e**	THF	48	97	6:1	87
8[i]	**1e**	THF	48	<10	nd	nd
9[j]	**1e**	THF	48	<10	nd	nd
10	**1e**	CH_2Cl_2	36	90	5:1	89
11	**1e**	$CHCl_3$	36	94	3:1	93
12	**1e**	MeOH	48	55	3:1	85
13	**1e**	DMF	48	<10	nd	nd
14	**1e**	DMSO	48	<10	nd	nd
15	**1e**	dioxane	12	94	6:1	94

[a] Unless otherwise noted, reactions were carried out with **2a** (0.1 mmol), propionaldehyde **3a** (0.2 mmol), and catalyst **1** (0.02 mmol, 20 mol %) and 20 mol % of 4-nitrobenzoic acid in 0.5 mL of solvent indicated. [b] The time required for the first-step reaction. [c] Isolated yield of **4a**. [d] Determined by crude ^{1}H NMR. [e] ee of major diastereomer determined by chiral HPLC analysis. [f] No additives used. [g] Benzoic acid (20 mol %) used. [h] 20 mol % acetic acid used. [i] Trifluoroacetic acid (20 mol %) used. [j] Triflic acid (20 mol %) used.

indicated that 1,4-dioxane was the optimal choice (entries 10–15). To the best of our knowledge, this result presents the first highly stereoselective reaction initiated by a Michael addition of aliphatic aldehydes to cyanoacrylamides.

With the optimal conditions for the reaction established above, we next examined the generality of the protocol for various cyanoacrylamides **2** and aliphatic aldehydes **3**. As summarized in Table 2, the electronic nature of the aromatic ring attached to the β-position of cyanoacrylamides had little effect on the reaction. Various cyanoacrylamides

Table 2. Scope of the Reaction[a]



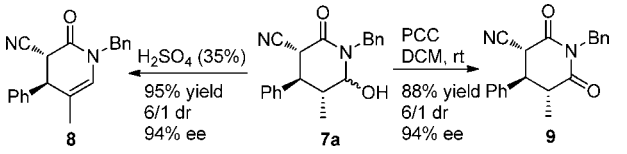
entry	R^1/R^2	time (h)[b]	4	yield (%)[c]	dr[d]	*ee*[e]
1	Ph/Me	12	**4a**	94	6:1	94/97
2	4-MeC_6H_4/Me	12	**4b**	90	6:1	99/99
3	4-$MeOC_6H_4$/Me	72	**4c**	88	6:1	98/99
4	4-ClC_6H_4/Me	12	**4d**	92	9:1	98/–
5	4-BrC_6H_4/Me	12	**4e**	92	6:1	99/99
6	4-$CF_3C_6H_4$/Me	12	**4f**	91	6:1	97/99
7	4-FC_6H_4/Me	12	**4g**	89	6:1	99/99
8	3-MeC_6H_4/Me	24	**4h**	95	6:1	96/99
9	3-$MeOC_6H_4$/Me	48	**4i**	94	6:1	96/99
10	3-ClC_6H_4/Me	12	**4j**	90	8:1	96/–
11	3-BrC_6H_4/Me	12	**4k**	90	6:1	96/–
12	2-$MeOC_6H_4$/Me	36	**4l**	91	6:1	96/99
13	2-ClC_6H_4/Me	12	**4m**	83	6:1	92/–
14	3,4,5-$(MeO)_3$-C_6H_2/Me	96	–	trace	–	–
15	2-furyl/Me	12	**4n**	80	6:1	93/–
16[f]	4-BrC_6H_4/H	48	**4o**	80	3:1	68/73
17	C_6H_5/Et	48	**4p**	85	6:1	94/–
18	C_6H_5/^{n}C_3H_7	48	**4q**	65	5:1	94/–
19	C_6H_5/^{n}C_4H_9	48	**4r**	62	5:1	95/–
20	C_6H_5/Bn	48	**4s**	60	5:1	92/–
21	C_6H_5/^{i}Pr	96	–	trace	–	–

[a] Reaction conditions: 0.1 mmol of **2**, 0.2 mmol of **3**. [b] The time required for the first step. [c] Isolated yields of **4**. [d] Determined by crude ^{1}H NMR. [e] Determined by chiral HPLC analysis, and the second ee is for the minor diastereomer. [f] At 0 °C, 4 mmol of **3**.

were tolerated under the present conditions affording the desired 3,4,5-trisubstituted 2-piperidinone derivatives (**4a**–**m**) in good yields and diastereoselectivities with excellent enantioselectivities (entries 2–13, 88–99% ee, Table 2). However, cyanoacrylamide bearing the highly electron-rich 3,4,5-trimethoxylphenyl substitutent was not reactive, providing only a trace amount of product after a long reaction time (entry 14). This may have resulted from the electronic effect. It should be mentioned that the heteroaromatic furan substituted cyanoacrylamide was tolerated under the present catalytic system, likewise with excellent stereoselectivity (entry 15). The current protocol can also be applied to other linear aliphatic aldehydes. Acetaldehyde was able to participate in this reaction in 80% yield, but with moderate 3/1 diastereoselectivity and 68% *ee* (entry 16). When butyraldehyde was surveyed, the 2-piperidinone derivative **4p** was isolated in 85% yield and 6:1 dr with 94% *ee*, although a long reaction time was required (entry 17). The longer chain valeraldehyde and hexaldehyde were also investigated, affording 2-piperidinone **4q** and **4r** in moderate yield with 94% and 95% *ee*, respectively (entries 18–19). The 3-phenylpropanal worked in this transformation giving **4s** in 60% yield and 5:1 dr with 92% *ee* (entry 20). Unfortunately, no desired

product was isolated when the branched isovaleraldehyde was used (entry 21).

Scheme 1. Synthetic Transformations of **7a**



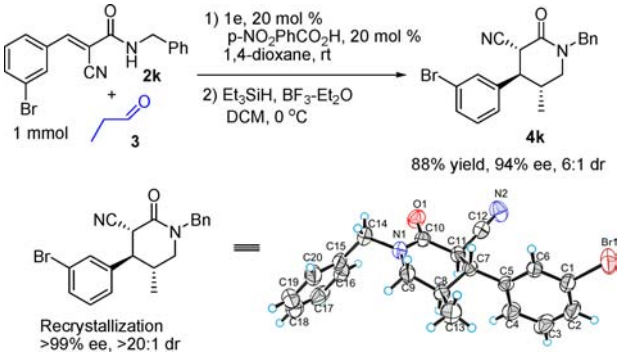
The unreduced hemiaminal **7a** could be converted smoothly into other valuable compounds[14] (Scheme 1). Upon oxidation with PCC (pyridinium chlorochromate), piperidine-2,6-dione **9** was produced in 88% yield, 6/1 dr and with 94% *ee*. When **7a** was treated with H_2SO_4 (35%, 2 equiv) in water for 24 h, the corresponding dehydration product **8** was formed in 95% yield and 6/1 dr with 94% *ee* with the cyano functionality unaffected (Scheme 1).

The present protocol could be scaled up to a millimole scale with almost no reduction in yield and with very subtle erosion in enantioselectivity (Scheme 2). For example, the reaction between 1 mmol of 3-bromophenyl substituted cyanoacrylamide **2k** with propionaldehyde proceeded smoothly to afford 2-piperidinone **4k** in 88% yield with 94% *ee* and 5:1 dr. The compound **4k** could be grown to a crystal suitable for X-analysis after a simple recrystallization from the mixture solvent of hexane/ethyl acetate. The absolute configuration of **4k** was thus assigned to be 3*R*, 4*R* and 5*R* by single crystal X-ray diffraction analysis[15] (see Supporting Informaition). The absolute configurations of other products were tentatively assigned by analogy.

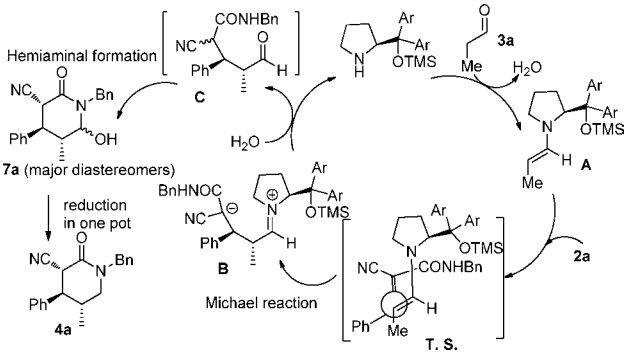
Based on the absolute configuration observed in the experiment and previous literature,[7e,f] a plausible mechanism for the one-pot reaction was proposed (Scheme 3). Propionaldehyde first reacts with catalyst **1e** to form a stereodefined enamine intermediate **A**, which would react with **2a** to generate **B** by a Michael reaction, to afford a mixture of diastereomers **C** after hydration and diastereoselective protonation.[7e,f] Then **C** undergoes an intramolecular hemiaminalization in which C_3-epimerization could occur, thereby generating **7a** as major diastereomers. Removal of the 6-hydroxy group of **7a** using $Et_3SiH/BF_3 \cdot Et_2O$ affords the desired product **4a**.

In summary, we have developed a highly stereoselective organocatalytic one-pot reaction of linear aliphatic aldehydes and cyanoacrylamides, which proceeds through a Michael addition followed by an intramolecular hemiaminalization, and after reduction of the products, the corresponding highly functionalized 2-piperidinones were obtained in high yield and moderate diastereoselectivity with excellent enantioselectivity. The one-pot reaction can lead to rapid access to 2-piperidinone derivatives with three new stereocenters under mild reaction conditions. Studies toward the application of this methodology in the synthesis of structurally diversified molecules are ongoing.

Scheme 2. A Millimole-Scale Synthesis and Absolute Configuration of **4k**



Scheme 3. A Plausible Mechanism for the One-Pot Reaction



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Supporting Information Available. Experimental procedures and full spectroscopic data 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.

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(15) CCDC 936011 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.can.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Center, 12 Union Road, Cambridge, CB21EZ, U.K.; Fax: (+44)1223-336033; or deposit@ccdc.cam.ac.uk).