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# Asymmetric Organocatalytic Tandem Reaction to Chiral Pyrimidinone Derivatives using Urea as Dinitrogen Source

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**Abstract:** A facile method for the asymmetric synthesis of pyrimidinone derivatives was developed *via* an organocatalytic tandem aza-Michael addition–hemiaminal formation–dehydroxylation reaction, using *N,N′*-dialkyloxyurea as dinitrogen source (up to 97% *ee*). The transformations of hemiaminal intermediates to pyrimidinones with more complex structures have been also investigated.

**Keywords:** amines; asymmetric catalysis; organic catalysis; pyrimidinones; tandem reactions

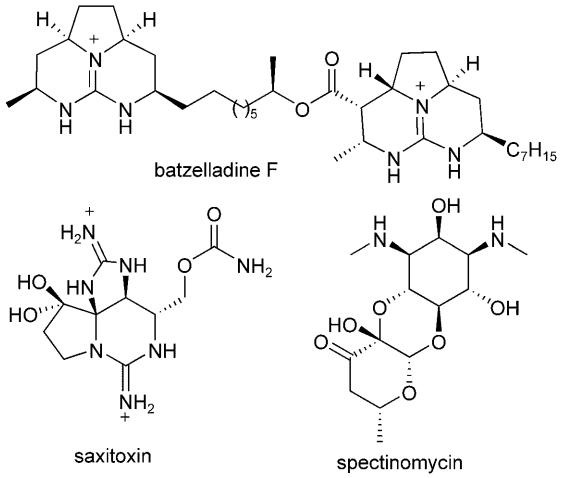


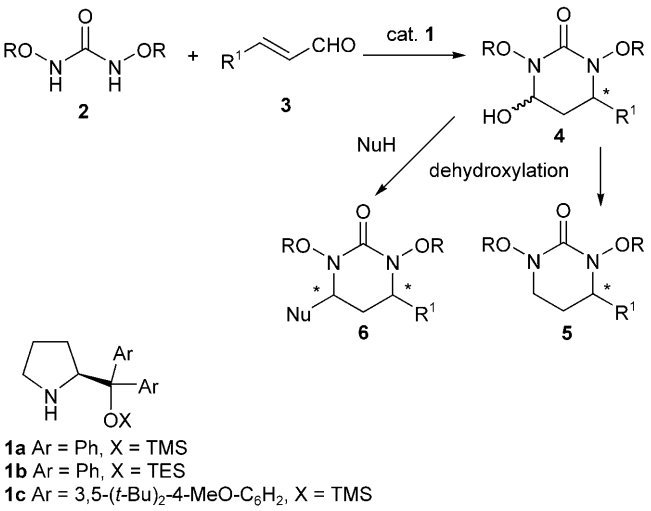

**Figure 1.** Some natural products containing 1,3-diamine structure.

Enantiomerically enriched 1,3-diamines are key structural units in a number of natural products or pharmacologically active molecules. For example, the batzelladine alkaloids containing 1,3-diamine skeletons are members of a growing class of guanidine alkaloids that exhibit a broad spectrum of biological activity. Most of them could be used to treat autoimmune disorders and, therefore, are potential leads for AIDS therapy. It is worthy of note that chiral 1,3-diamines are important intermediates in the total synthesis of batzelladines A, B and F.[1] Saxitoxin (Figure 1), the paralytic agent of the Alaska butter clam *Saxidomas giganteus,* is one of the most toxic non-protein poisons known and has also found widespread applications in the studies of various nerve disorders.[2] In addition, 1,3-diamine structures are always key moieties of some aminoglycosides, most of which are important antibiotics with a broad antibacterial spectrum, particularly against Gram-negative bacteria.[3] 1,3-Diamines, especially chiral ones, are of great interest in medicinal chemistry, for example, in cancer research.[4] On the other hand, these compounds have also been efficiently applied as ligands in asymmetric catalysis.[5]

Consequently, the significance of 1,3-diamine compounds has attracted increasing attention in the development of a number of protocols to access such motifs. However, most of these processes are functional group transformations of optically active compounds to prepare 1,3-diamines.[6] Only a few direct asymmetric syntheses of 1,3-diamines have been described[7] in comparison with the analogous 1,2-diamines.[8] It remains indispensable to find new effective approaches to prepare structurally diverse chiral 1,3-diamines. We envisaged that an tandem asymmetric aza-Michael addition[9]–intramolecular hemiaminal formation from readily available *N,N′*-dialkyloxyureas **2** and α,β-unsaturated aldehydes **3** would afford chiral heterocyclic intermediates **4** under the catalysis of a chiral secondary amine **1**, which could be smoothly converted to 1,3-diamine derivatives, pyrimidinones **5**, after a simple dehydroxylation. Moreover, the electrophilic hemiaminal functionality should be further attacked by some nucleophiles under suitable condi-

tions, thus pyrimidinones **6** with more molecular complexity would be generated (Scheme 1).

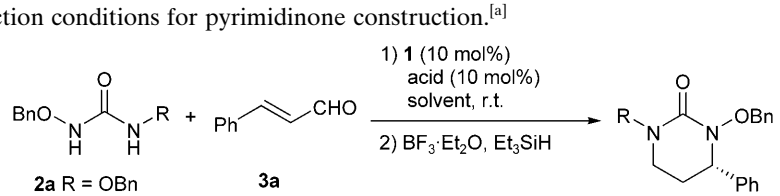
We first investigated the reaction of *N,N′*-dibenzyloxyurea **2a** and cinnamaldehyde **3a** in toluene at ambient temperature catalyzed by chiral α,α-diphenylprolinol *O*-TMS ether **1a** (10 mol%) and benzoic acid (BA, 10 mol%).[10] The reaction proceeded very slowly and poor conversion was observed after 72 h (Table 1, entry 1). Urea substrate **2a** could be consumed at 40 °C but a long reaction time (140 h) was still required. $Et_3SiH/BF_3{\cdot}OEt_2$ could be directly added to the reaction mixture to afford the dehydroxylated product **5a** in good yield (81%) and moderate enantioselectivity (65% *ee*, entry 2).[11,12] Fortunately, the reaction could be greatly accelerated when the stronger *o*-fluorobenzoic acid (OFBA) or *p*-nitrobenzoic acid (PNBA) were used even at ambient temperature, and both yield and stereoselectivity were remarkable (entries 3 and 4). Moreover, the reaction time could be further shortened by the combined catalysis of **1a** and AcOH (entry 5). Subsequently, some solvents were screened (entries 6–9), and the best results were delivered in $PhCF_3$ (entry 9). The bulkier catalysts **1b** and **1c** could not give superior data under the optimal reaction conditions (entries 10 and 11). It should be noted that much inferior results were obtained when an unsymmetrical urea **2b** was applied, indicating that both alkyloxy substituents in the urea structure were crucial (entry 12).




**Scheme 1.** Proposed organocatalytic reaction sequence to chiral pyrimidinones.

Having established the optimal reaction conditions, the substrate scope of the tandem aza-Michael addition–hemiaminal formation–dehydroxylation sequence to access pyrimidinones **5** was investigated with urea **2a** and a number of α,β-unsaturated alde-

**Table 1.** A survey of reaction conditions for pyrimidinone construction.[a]




| Entry | **1** | Acid | Solvent | *t* [h] | Yield[b] [%] | ee[c] [%] |
|---|---|---|---|---|---|---|
| 1 | **1a** | BA | toluene | 72 | <10 | – |
| 2[d] | **1a** | BA | toluene | 140 | 81 | 65 |
| 3 | **1a** | OFBA | toluene | 59 | 93 | 95 |
| 4 | **1a** | PNBA | toluene | 60 | 90 | 93 |
| 5 | **1a** | AcOH | toluene | 35 | 93 | 94 |
| 6 | **1a** | AcOH | THF | 72 | <10 | – |
| 7 | **1a** | AcOH | MeCN | 72 | <10 | – |
| 8 | **1a** | AcOH | DCM | 44 | 93 | 94 |
| 9 | **1a** | **AcOH** | **$PhCF_3$** | **16** | **95** | **95** |
| 10 | **1b** | AcOH | $PhCF_3$ | 22 | 85 | 94 |
| 11 | **1c** | AcOH | $PhCF_3$ | 96 | 60 | 92 |
| 12[e] | **1a** | AcOH | $PhCF_3$ | 144 | 59 | 71 |

[a] Unless otherwise noted, reactions were performed with 0.1 mmol of **2a**, 0.15 mmol of **3a**, 0.01 mmol of catalyst **1** and acid in 1 mL solvent at room temperature. Then $Et_3SiH/BF_3{\cdot}Et_2O$ (0.3 mmol/0.3 mmol) were directly added to conduct the dehydroxylation reaction at 0 °C.
[b] Isolated yield for two steps.
[c] Determined by chiral HPLC analysis.
[d] At 40 °C.
[e] **2b** was used, *ee* for **5b**.

**Table 2.** Tandem aza-Michael addition–hemiaminal formation–dehydroxylation to access pyrimidinones.[a]


| Entry | R | *t* [h] | Product | Yield[b] [%] | *ee*[c] [%] |
|---|---|---|---|---|---|
| 1 | Ph | 16 | **5a** | 95 | 95 |
| 2 | *p*-Cl-$C_6H_4$ | 10 | **5c** | 92 | 93 |
| 3 | *m*-Cl-$C_6H_4$ | 10 | **5d** | 90 | 94 |
| 4 | *p*-Br-$C_6H_4$ | 9 | **5e** | 83 | 95 |
| 5 | *o*-Br-$C_6H_4$ | 19 | **5f** | 86 | 97 |
| 6 | *p*-$CF_3$-$C_6H_4$ | 15 | **5g** | 90 | 95 |
| 7 | *m*-Me-$C_6H_4$ | 18 | **5h** | 85 | 94 |
| 8 | *p*-MeO-$C_6H_4$ | 34 | **5i** | 83 | 93 |
| 9 | 2-thienyl | 13 | **5j** | 82 | 93 |
| 10[d,e] | Me | 6 | **5k** | 95 | 83 |
| 11[d] | *n*-Pr | 8 | **5l** | 93 | 86 |
| 12[d] | *i*-Pr | 88 | **5m** | 82 | 95 |

[a] Unless otherwise noted, reactions were performed with 0.1 mmol of **2a**, 0.15 mmol of **3a**, 0.01 mmol of **1a** and AcOH in 1 mL $PhCF_3$ at room temperature. Then $Et_3SiH/BF_3{\cdot}Et_2O$ (0.3 mmol/0.3 mmol) were directly added to conduct the dehydroxylation reaction at 0 °C.

[b] Isolated yield for two steps.

[c] Determined by chiral HPLC analysis.

[d] 0.2 mmol of enal was used.

[e] The absolute configuration of **5k** was determined after conversion to a known compound, see the Supporting Information. The other products were assigned by analogy.

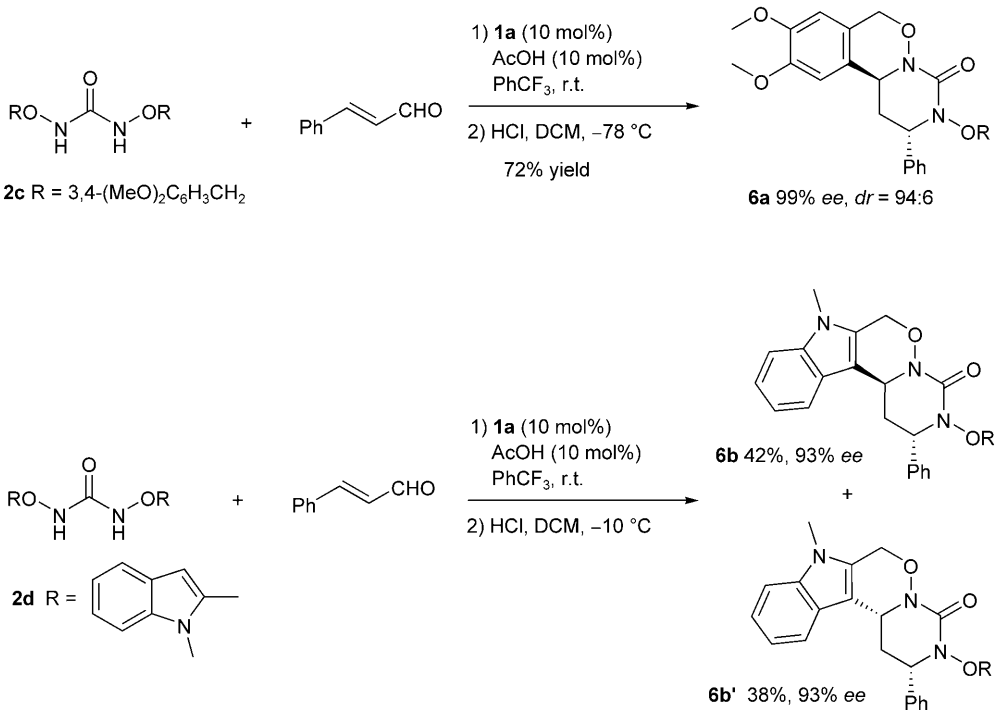
hydes **3**. The results are summarized in Table 2. The electronic characteristics of aryl-substituted α,β-unsaturated aldehydes seemed to have limited effects on the enantioselectivity. Excellent *ee* values were obtained for a diversity of α,β-unsaturated aldehydes bearing electron-withdrawing or electron-donating aryl groups, and good to excellent isolated yields were obtained (Table 2, entries 1–8). In addition, a heteroaryl-substituted enal could be successfully utilized, and excellent enantioselectivity was also attained (entry 9). Linear alkyl-substituted α,β-unsaturated aldehydes exhibited high reactivity while the enantioselectivity was slightly lower (entries 10 and 11). The reaction of an α,β-unsaturated aldehyde bearing a branched β-isopropyl group was quite sluggish, but good yield and excellent enantioselectivity could be provided by extending the reaction time (entry 12).

Since the attempted intramolecular Friedel–Crafts reaction of **4a** was unsuccessful under various conditions, we designed two new ureas **2c** and **2d** with more electron-rich 3,4-dimethoxybenzyl and (1-methyl-1*H*-indol-2-yl)methyl group, respectively. After the aminocatalytic domino aza-Michael addition–hemiaminal formation of **2c** and cinnamaldehyde finished, the solvent was removed and a catalytic amount of HCl in ethyl acetate (20 mol%) was added in DCM at −78 °C.[13] After an additional 30 min, the tricyclic product **6a** was gratifyingly isolated in excellent enantio- and diastereoselectivity. A similar tandem sequence could be applied for the reaction of urea **2d** and cinnamaldehyde. Although a poor *dr* ratio was observed, both diastereomers **6b** and **6b′** could fortunately be separated by a simple flash column chromatography, also with high *ee* values (Scheme 2).

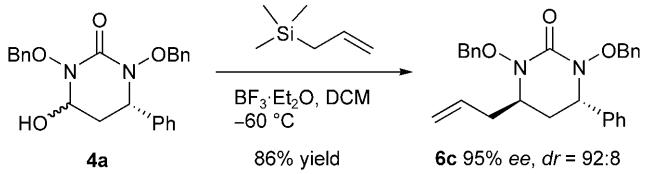
In addition, we were pleased to find that the diastereoselective allylation of hemiaminal **4a** could be smoothly performed with allyltrimethylsilane under the catalysis of $BF_3{\cdot}Et_2O$ at −60 °C.[14] As outlined in Scheme 3, a pyrimidinone compound **6c** bearing a versatile terminal olefinic functionality was attained in high yield with a good *dr*.

In conclusion, we have presented a facile protocol to access chiral pyrimidinones *via* an aminocatalytic tandem aza-Michael addition–intramolecular hemiaminal formation–dehydroxylation reaction from readily available *N,N′*-dialkyloxyureas and α,β-unsaturated aldehydes. This process exhibited good efficiency and excellent enantiocontrol under environmentally friendly and mild conditions. In addition, some synthetic transformations with chiral hemiaminal intermediates could be conducted to afford pyrimidinone derivatives with more molecular complexity,[15] which might be useful for further applications in




**Scheme 2.** Tandem aza-Michael addition–hemiaminal formation–intramolecular Friedel–Crafts reaction to access polycyclic frameworks.




**Scheme 3.** Diastereoselective allylation of hemiaminal intermediate **4a**.

medicinal chemistry or other fields. More investigation is underway in our laboratory and the results will be reported in due course.

## Experimental Section

### General Procedure for the One-Pot, Tandem Aza-Michael Addition–Intramolecular Hemiaminal Formation–Dehydroxylation Reaction

Urea **2a** (27.2 mg, 0.1 mmol) was added to a mixture of catalyst **1a** (3.2 mg, 0.01 mmol), acetic acid (0.6 μL, 0.01 mmol) and cinnamaldehyde **3a** (19.8 mg, 0.15 mmol) in $PhCF_3$ (1 mL) at room temperature. The reaction mixture was stirred until complete consumption of **2a** (monitored by TLC). Then the solution was cooled to 0 °C and $Et_3SiH$ (48 μL, 0.3 mmol) and $BF_3{\cdot}OEt_2$ (38 μL, 0.3 mmol) were added. After 5 min, the mixture was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate, 15:1–10:1) to give pyrimidinone **5a**; yield: 36.8 mg (95%). 95% *ee*, determined by chiral HPLC analysis (Daicel chiralpak IC, 30% 2-propanol/*n*-hexane, 1 mL min$^{-1}$, UV 220 nm): $t_{minor}$ = 19.91 min, $t_{major}$ = 22.43 min; $[\alpha]_D^{20}$: +6.2 (*c* 1.81 in $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.50–7.48 (m, 2H), 7.39–7.32 (m, 6H), 7.29–7.25 (m, 5H), 7.13–7.12 (m, 2H), 5.05–5.00 (m, 3H), 4.58 (d, $J$ = 9.6 Hz, 1H), 4.44 (dd, $J$ = 4.8 Hz, $J$ = 7.2 Hz, 1H), 3.32–3.20 (m, 2H), 2.18–2.05 (m, 2H); $^{13}$C NMR (50 MHz, $CDCl_3$): $\delta$ = 159.8, 139.7, 136.0, 135.6, 129.5, 128.6, 128.5, 128.4, 128.2, 128.0, 126.9, 77.8, 77.2, 63.8, 47.2, 29.2; ESI-HR-MS: $m/z$ = 411.1684, calcd. for $[C_{24}H_{24}N_2O_3+Na]$: 411.1685.

### Deprotection Procedure

The *N*-benzyloxy moeity of **5a** could be easily removed (see also the Supporting Information). To a solution of **5a** (46 mg, 012 mmol) in methanol (4 mL) was added Raney Ni (30 mol%) at room temperature. The reaction mixture was kept under a hydrogen atmosphere (1 bar) for 8 h. Then the mixture was filtered through celite. The celite was washed with methanol and the filtrate was concentrated under vacuum. The residue was washed with petroleum ether/ethyl acetate (10:1, 20 mL) to afford the debenzyloxylated pyrimidone **6d**; yield: 72%; $[\alpha]_D^{20}$: −22.2 ( *c* 0.46, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.38–7.34 (m, 5H), 4.97–4.91 (m, 2 H), 4.58 (brs, 1 H), 3.36–3.28 (m, 2H), 2.16–2.14 (m, 1H), 1.94–1.91 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 166.0, 128.9, 128.0, 126.1, 55.1, 38.5, 30.4; ESI-HR-MS: $m/z$ = 177.1022, calcd. for $[C_{10}H_{12}N_2O+H]$: 177.1028.

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