Recyclable Asymmetric Cyclization in Ionic Liquid Catalyzed by an Amino Acid, Leading to a Wieland–Miescher Ketone Analogue

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Abstract: A procedure for recyclable asymmetric cyclization leading to optically active Wieland–Miescher ketone analogue has been developed employing D-phenylalanine and D-CSA in [hmim]PF_6 and dimethylimidazolidinone in 81% chemical yield and 74% enantiomeric excess in average after five uses. A Hajos–Wiechert ketone analogue was also synthesized in a similar manner.

Key words: amino acid, asymmetric catalysis, asymmetric synthesis, enones, ionic liquids, supported catalysis

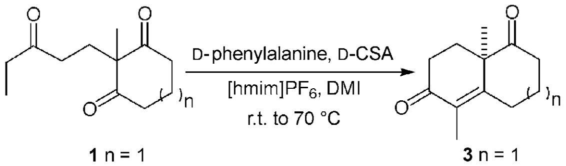
Wieland–Miescher ketone **3** and Hajos–Wiechert ketone **4** analogues are very versatile starting materials for the synthesis of a variety of natural products.[2] Due to the importance of these compounds, there have been several synthetic procedures employing amino acid as a chiral catalyst,[3] which has stimulated recent developments of the chemistry of organomolecular catalysts.[4]

We reported previously a synthetic method toward the Wieland–Miescher ketone analogues **3** employing L/D-phenylalanine (Phe) as a chiral source with D-camphorsulfonic acid (CSA) in DMF, in which the reaction temperature was raised by 10 °C per day to 70 °C.[5] Since that time, the method has been utilized for preparation of compound **3** as a starting material for many natural products not only in our group[6] but also in many other groups.[7]

In reexamining the method, we found that the optimum reaction condition required use of an equivalent amount of L/D-Phe and a half-equivalent amount of D-CSA. This issue should be solved especially in the case that non-natural and expensive D-Phe is used in a large-scale experiment. Gradual warming of the reaction is another issue, which results in longer reaction time.

Room temperature ionic liquid has played key roles as an environmentally benign and recyclable reaction medium.[8] The characteristic nature of the liquid, especially immiscibility with other organic solvents and water, is useful as a support of not only organometallic catalysts but also organomolecular catalysts.[9]

In order to make the cyclization more efficient, economically and environmentally benign, amino acid catalyzed cylization of triketone **1** or **2** leading to Wieland–Miescher ketone **3** or Hajos–Wiechert ketone **4** analogues was reinvestigated in an ionic liquid as a liquid support of amino acid and CSA, which might enable recycle use of the catalysts as well as the reaction medium.



1 n = 1
2 n = 0

3 n = 1
4 n = 0

Scheme 1 Recyclable asymmetric cyclization leading to Wieland–Miescher ketone **3** and Hajos–Wiechert ketone **4** analogues

A recycle experiment of the cyclization of triketone **1** was attempted at first by simply replacing DMF[5] into a common ionic liquid, [bmim]PF_6 (Scheme 1 and Table 1). The reaction was carried out in the presence of an equivalent amount of D-Phe and a half-equivalent amount of D-CSA at room temperature to 70 °C. The reaction temperature was raised by 10 °C per hour. After trituration of the product **3** with Et_2O, the residue was evacuated and reused for subsequent reaction. As shown in entry 3, the third use resulted in decrease of enantiomeric excess (ee) of the enone **3**, probably due to loss of D-Phe during extraction. This result was partially solved by employing more viscous [hmim]PF_6 (entries 4–6), since [hmim]PF_6 was much more separable from Et_2O than [bmim]PF_6. More rapid heating than the original rate (10 °C per day)[5] was not a problem. In order to increase solubility of D-Phe, highly polar co-solvents were tested. Among them, *N*,*N*-dimethylpyrrolidinone (DMI; entries 13–17; 81% yield and 74% ee in average after five uses) and *N*-methyl-2-pyrrolidinone (NMP; entries 18–21; 77% yield and 78% ee after four uses) gave comparable and reproducible results in recycle experiments.

L-Proline provided low chemical yield (entry 12) due to its decomposition. Amberlyst 15 as an alternative of D-CSA gave a comparable result at the first run, though recycle experiments gave discouraging yields. Chiral ionic liquid, tetrabutylphosphonium L-phenylalaninate {[TPP]L-Phe} was not a suitable chiral medium for the present cyclization (entry 22).

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Table 1 Recyclable Asymmetric Cyclization Leading to Wieland–Miescher Ketone Analogue **3**[10]

Entry	Ionic liquid	Cosolvent	Yield (%)	ee (%)[a]
1	[bmim]PF$_6$[d]	–	81	84
2[b]		–	80	68
3		–	68	53
4	[hmim]PF$_6$[e]	–	88	86
5[b]		–	77	70
6[b]		–	85	61
7		formamide	80	84
8[b]			28	8
9		DMF	88	86
10[b]			77	70
11[b]			85	72
12[c]			24	74
13		DMI[f]	87	86
14[b]			85	73
15[b]			81	71
16[b]			73	71
17[b]			79	68
18		NMP[g]	82	90
19[b]			81	79
20[b]			63	70
21[b]			80	72
22	[tbp]L-Phe[h]	–	trace	–

[a] The ee was determined by HPLC analysis with chiral column (Daicel AS-H).
[b] D-Phe, D-CSA and ionic liquid in previous reaction was reused.
[c] L-Proline was used.
[d] Butylmethylimidazolium hexafluorophosphate.
[e] Hexylmethylimidazolium hexafluorophosphate.
[f] *N*,*N*-Dimethylpyrrolidinone.
[g] *N*-Methyl-2-pyrrolidinone.
[h] Tetrabutylphosphonium L-phenylalaninate.

Employing DMI as a co-solvent, asymmetric cyclization of triketone **2** with D-Phe and D-CSA in [hmim]PF$_6$ was recycled and the results are shown in Table 2. The reaction proceeded with similar efficiency (74% yield and 69% ee in average after four uses) as the cyclization of triketone **1** in recycle experiments.

Table 2 Recyclable Asymmetric Cyclization Leading to Hajos–Wiechert Ketone Analogue **4**[10]

Entry	Yield (%)	ee (%)[a]
1	78	84
2[b]	77	70
3[b]	68	63
4[b]	73	58

[a] The ee was determined by HPLC analysis with chiral column (Daicel AS-H).
[b] D-Phe, D-CSA and ionic liquid in previous reaction was reused.

In summary, we have developed a new procedure for the synthesis of Wieland–Miescher ketone **3** and Hajos–Wiechert ketone **4** by recycling the catalysts and the reaction medium, which provided additional efficiency for preparation of important substrates **3** and **4** for natural product synthesis.

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(10) **Typical Experimental Procedure.**
To a solution of the triketone **1** (196 mg, 1 mM) in [hmim]PF_6 (1.8 mL) and DMI (1.2 mL) was added D-Phe (165 mg, 1 mM) and D-CSA (116 mg, 0.5 mM) under nitrogen atmosphere. Reaction temperature was raised from r.t. to 70 °C by 10 °C at 1 h intervals. After being stirred at 70 °C overnight, the product was triturated with Et_2O until the spot of the product **3** in ionic liquid was not observed by TLC monitoring (eluent: EtOAc–*n*-hexane = 1:1). Evaporation of Et_2O followed by column chromatography and subsequent medium pressure LC of the residue (eluent: EtOAc–*n*-hexane = 1:1) afforded the enone **3** (167 mg, 87%). After evacuation of Et_2O under reduced pressure, a mixture of D-Phe and D-CSA in [hmim]PF_6 was reused after addition of DMI (1.2 mL). The ee of the product **3** was determined to be 86% by HPLC analysis using chiral column (Daicel AS-H column, eluent: *n*-hexane–*i*-PrOH = 9:1).