Enantioselective Intramolecular Aldol Reaction Mediated by a Combination of L-Amino Acid and Brønsted Acid to Construct a Bicyclic Enedione Containing a 7-Membered Ring

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Received July 31, 2007; accepted September 10, 2007; published online September 12, 2007

The enantioselectivity of the intramolecular asymmetric aldol reaction of 1,3-cycloheptanedione bearing a C-2 methyl substituent, mediated by a series of combinations of L-amino acid and Brønsted acid, was examined in detail.

Key words intramolecular asymmetric aldol reaction; amino acid; Brønsted acid; organocatalysis

Wieland–Miescher ketone (**3**), which was prepared by L-proline-mediated asymmetric intramolecular aldol reaction of the trione (**1**), has been a highly useful synthon in total syntheses of a variety of natural products.[1—15] This asymmetric aldol reaction has become known as the Hajos–Parrish–Eder–Sauer–Wiechert reaction, and has been widely recognized to involve an enamine-based mechanism.[16—37] Uda and Hagiwara successfully extended the reaction to construct a Wieland–Miescher ketone derivative [(*S*)-**7**] bearing a methyl substituent at C-1.[38—40] However, there has been little development of this reaction for the purpose of constructing new ring systems encompassing a 7-membered or larger carbocycle.[41—44] Recently, we have reported the L-Met (L-methionine)-mediated asymmetric intramolecular aldol reaction of the trione (**5**) to prepare a new bicyclic enedione [(*R*)-**8**] containing a 7-membered ring.[45] Strikingly, the process was characterized by an inversion of enantioselectivity when compared with the similar reaction using the trione (**4**).[45,46] However, the ee value of the reaction to afford (*R*)-**8** was only moderate (Chart 1). In connection with an ongoing synthetic project, we needed to improve this method. We report here new reaction conditions to prepare (*R*)-**8** with higher ee than previously reported.

Results and Discussion

The starting trione (**5**) was prepared from diethyl adipate by the known method.[45] We then screened several commercially available acyclic L-amino acids, especially those bearing a branched or an unbranched alkyl chain, for the aldol reaction of **5**. We had previously found that a Brønsted acid, such as (+)-CSA (camphorsulfonic acid) or PPTS (pyridinium *p*-toluenesulfonate), played a very important role in determining the enantioselectivity,[45] because the reaction without a Brønsted acid afforded (*S*)-**8** with a quite low ee. Therefore, all of the reactions were carried out under the same conditions in the presence of a stoichiometric amount of L-amino acid and 0.5 eq of PPTS in DMSO (dimethylsulfoxide) at 90 °C (Chart 2). Ee (enantiomeric excesses) of the resulting enone [(*R*)-**8**] were determined by HPLC with a chiral stationary phase column (Chiralpak AS-H, Daicel Chemical Corporation, Ltd.). The absolute configuration of the enone (**8**) was assigned to be *R* by comparison of the optical rotation with the reported value.[45] The results are compiled in Table 1.

Although all of the reactions involving L-amino acids bearing alkyl side chains remained incomplete after 24 h, (*R*)-**8** was obtained with almost the same ee values as in the case of

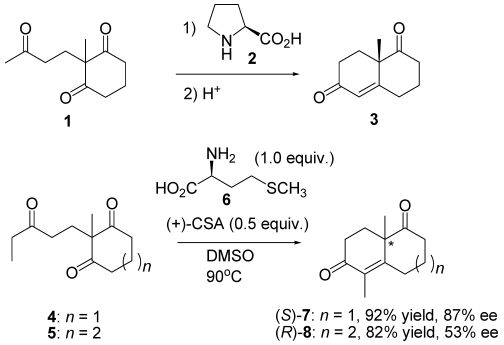

Chart 1. Synthesis of Wieland–Miescher Ketone Analogs by Hajos–Parrish–Eder–Sauer–Wiechert Reaction

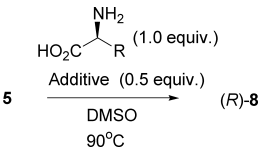

Chart 2. Asymmetric Intramolecular Aldol Reaction of **5** Mediated by an Amino Acid

Table 1. Screening of Several Amino Acids for Asymmetric Aldol Reaction of **5**

Entry	Amino acid	Additive	Time (h)	Yield (%)[a,b]	Ee (%)[c]
1[d]	L-Met (**6**)	(+)-CSA	15	82	53
2[d]	L-Met (**6**)	PPTS	18	67	60
3[d]	L-Phe[e]	PPTS	13	80	50
4	L-Ala[f]	PPTS	24	58 (85)	58
5	L-Val[g]	PPTS	24	74 (89)	61
6	L-Leu[h]	PPTS	24	75 (99)	60
7	L-Norleu[i]	PPTS	24	86 (91)	63
8	L-*tert*-Leu[j]	PPTS	24	73 (78)	46
9	L-Ala	PPTS	42	79	57

a) Isolated yield. *b*) Yields in parentheses were based on the recovery of starting **5**. *c*) Determined by HPLC with a chiral stationary phase. *d*) This result was previously reported in ref. 45. *e*) L-Phenylalanine, R=CH_2Ph. *f*) L-Alanine, R=CH_3. *g*) L-Valine, R=$CH(CH_3)_2$. *h*) L-Leucine, R=$CH_2CH(CH_3)_2$. *i*) L-Norleucine, R=$(CH_2)_3CH_3$. *j*) L-*tert*-Leucine, R=$C(CH_3)_3$.

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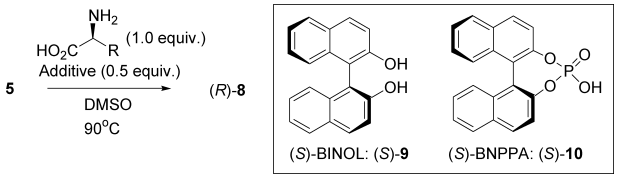

Chart 3. Asymmetric Intramolecular Aldol Reaction of **5** Mediated by a Combination of an Amino Acid and Brønsted Acid

Table 2. Effects of Additives in the Reaction of **5**

Entry	Amino acid	Additive	Time (h)	Yield (%)[a]	Ee (%)[b,c]
1	L-Met	TFA	21	95	61
2	L-Met	TFSA	21	96	60
3	L-Met	(*S*)-BINOL	19	73	−8
4	L-Met	(*R*)-BINOL	32	70	−6
5	L-Met	(*S*)-BNPPA	24	97	62
6	L-Met	(*R*)-BNPPA	26	68	60
7	L-Nor-Leu	TFA	24	80 (92)	61
8	L-Nor-Leu	TFSA	24	79 (90)	60
9	L-Phe	TFA	21	91	58
10	L-Phe	(*S*)-BINOL	12	78	−12
11	L-Phe	(*R*)-BINOL	12	75	−9
12	L-Phe	(*S*)-BNPPA	18	82	57
13	L-Phe	(*R*)-BNPPA	14	78	59
14[d]	—	(*S*)-BNPPA	99	21	−0.6
15[d]	—	(*R*)-BNPPA	96	26	−0.2

a) Yields in parentheses were based on the recovery of starting **5**. *b*) Determined by HPLC with a chiral stationary phase. *c*) Opposite enantioselection is indicated with a minus sign. *d*) No amino acid was added.

L-Met (Table 1). Prolongation of the reaction time resulted in completion of the reaction to afford (*R*)-**8** without decrease of ee (entry 9). Among several amino acids, L-Norleu afforded (*R*)-**8** in high yield with the highest ee. The results showed that the bulkiness of the side chain on the amino acid did not play a very important role in determining the enantioselectivity in the aldol reaction. Finally, L-Met, L-Phe and L-Norleu were selected for further study on the synthesis of (*R*)-**8** *via* the intramolecular asymmetric aldol reaction.

We next examined the effects of the Brønsted acid as an additive on the yield and ee of (*R*)-**8**. All of the reactions were carried out under the same conditions in the presence of a stoichiometric amount of L-amino acid and 0.5 eq of Brønsted acid as shown in Table 2, in DMSO at 90 °C (Chart 3). The results are summarized in Table 2. The reaction mediated by L-Met in the presence of TFA (trifluoroacetic acid) or TFSA (trifluoromethanesulfonic acid) afforded (*R*)-**8** in 95% yield with 61% ee and in 96% yield with 60% ee, respectively (entries 1, 2). Although both reactions required a longer time than that using (+)-CSA or PPTS in Table 1, we obtained (*R*)-**8** with over 60% ee. Entry 9 in Table 2 showed that TFA also afforded a better result in the reaction mediated by L-Phe than entry 3 in Table 1. However, the reaction using L-Norleu in the presence of TFA gave almost the same result as entry 7 in Table 1 (entries 7, 8). We next examined chiral Brønsted acids, such as BINOL (1,1′-binaphthyl-2,2′-diol, **9**)[47] and BNPPA (1,1′-binaphthalene-2,2′-diyl hydrogen phosphate, **10**).[48—53] The L-Met- or L-Phe-mediated reaction in the presence of (*R*)- or (*S*)-BINOL (**9**) having a phenolic proton afforded (*S*)-**8** as a major enantiomer with quite low ee (entries 3, 4, 10, 11). On the other hand, the reaction mediated by L-Met or L-Phe with (*S*)-BNPPA (**10**) as a chiral Brønsted acid gave almost the same result as that using TFA or TFSA (entries 5, 12). (*R*)-BNPPA also afforded (*R*)-**8** in slightly lower yield than (*S*)-BNPPA (entries 6, 13). However, (*R*)- and (*S*)-BNPPA hardly improved the ee value of (*R*)-**8**. The reactions in the presence of (*R*)- or (*S*)-BNPPA without an amino acid also afforded **8** in low yield with no enantioselectivity (entries 14, 15). These results showed that the chirality of the binaphthyl moiety did not influence the enantioselectivity in the aldol reaction of **5**.

Table 3. Solvent and Temperature Effects in the Reaction of **5**

Entry	Amino acid	Solvent	Temp.	Time (h)	Yield (%)	Ee (%)[a,b]
1	L-Met	H_2O	90	24	3 (33)	23
2	L-Met	CH_3OH	50	48	4 (44)	50
3	L-Met	CH_3OH	Reflux	54	18 (100)	56
4	L-Met	CH_3CN	50	48	4 (50)	11
5	L-Met	CH_3CN	75	7	14 (42)	11
6	L-Met	DMF	90	24	78 (91)	49
7	L-Met	DMSO	rt	480	7 (78)	76
8	L-Met	DMSO	50	168	86 (95)	68
9	L-Phe	DMSO	50	168	64 (81)	69

a) Isolated yield. *b*) Yields in parentheses were based on the recovery of starting **5**.

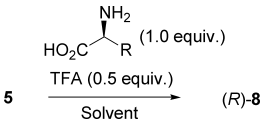

Chart 4. Asymmetric Intramolecular Aldol Reaction of **5** in Several Solvents

Finally, we optimized the reaction conditions for **5**. Table 3 summarizes the solvent and temperature effects in the reaction mediated by the combination of L-Met and TFA (Chart 4). Both protic polar solvents, such as water and MeOH (methanol), and nonprotic polar solvents, such as acetonitrile and DMF (*N*,*N*-dimethylformamide), prolonged the reaction time and afforded (*R*)-**8** in lower yield and ee as compared with the use of DMSO. On this basis, DMSO was selected as the solvent for continued optimization. We next examined the reaction temperature. The reaction in DMSO at room temperature afforded (*R*)-**8** with highest ee (76% ee) in these trials, but the isolated yield of (*R*)-**8** was only 7% even after 20 d. When the reaction was carried out at 50 °C, (*R*)-**8** was obtained in 86% yield (95% yield based on the recovery of starting **5**) with 68% ee after 7 d. A similar tendency was observed in the reaction mediated by L-Phe. Although the best ee value was still only moderate, we could obtain optically pure (*R*)-**8** by fractional recrystallization.

Conclusion

In conclusion, we have improved the intramolecular asymmetric aldol reaction involving the use of a combination of amino acid and Brønsted acid to obtain the 6–7 fused bicyclic enedione [(*R*)-**8**]. The use of **8** as a new chiral synthon to achieve total syntheses of various pharmaceutically important natural products is currently under study.

Experimental

Melting points are uncorrected. IR spectra were recorded on a JASCO-FT-IR-5000 spectrometer. ^{1}H-NMR spectra and ^{13}C-NMR spectra were

recorded on a JEOL-AX-400 (^{1}H 400 MHz, ^{13}C 100 MHz) spectrometer and calibrated using trimethysilane as the internal standard. Mass spectra were recorded on a JEOL-DX-303 or a JEOL-JMS-MS700 spectrometer. Elemental analysis was recorded on a Perkin Elmer CHN-2400 II. Enantiomeric excesses were determined on a Waters-HPLC 600 instrument equipped with a chiral stationary phase. Optical rotations were measured with a JASCO-DIP-370 digital polarimeter.

Typical Procedure for Asymmetric Aldol Reaction of 5 A mixture of **5** (1 g, 4.46 mmol), L-methionine (665 mg, 4.46 mmol), and TFA (166 μl, 2.23 mmol) in DMSO (10 ml) was stirred at 50 °C for 168 h. After cooling, the mixture was poured into saturated $NaHCO_3$ solution and extracted with AcOEt (ethyl acetate). The combined organic layer was washed with brine and dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (hexane/AcOEt, 10/1) to afford (*R*)-**8** (787 mg, 86%) as colorless crystals and starting **5** (93 mg, 9%). The optical purity of (*R*)-**8** was determined to be 68% ee by HPLC with a chiral stationary phase. HPLC conditions: Chiralpak AS-H, ethanol/hexane=10/90 (v/v), flow rate 1.0 ml/min, detected at 254 nM, t_R=10.0 min for (*R*)-**8**, 10.9 min for (*S*)-**8**. Optically pure material was obtained by fractional recrystallization as follows: Compound (*R*)-**8** (787 mg, 68% ee) was recrystallized from hexanes/ether (4/1) twice to afford (*R*)-**8** (156 mg, >99% ee) colorless needles.[54]

For (*R*)-**8**: mp 98—99 °C, lit.[45] 98 °C. $[\alpha]_D^{24}$ −86.1° (c=1.00, $CHCl_3$), lit.[45] $[\alpha]_D^{23}$ −83.4° (c=1.01, $CHCl_3$, >99% ee). IR (KBr) cm^{-1}: 1710, 1664, 1616. ^{1}H-NMR ($CDCl_3$) δ: 2.78—2.65 (2H, m), 2.62—2.46 (2H, m), 2.35—2.28 (1H, m), 2.16 (1H, dt, J=6.0, 13.4 Hz), 2.05—1.95 (2H, m), 1.86 (3H, s), 1.76—1.46 (4H, m), 1.34 (3H, s). ^{13}C-NMR ($CDCl_3$) δ: 213.7, 197.0, 158.9, 132.7, 53.4, 39.9, 32.7, 32.2, 31.2, 28.3, 28.2, 18.2, 10.4. EI-MS: *m*/*z* 206 (M^+), 121 (100%). HR-MS Calcd for $C_{13}H_{18}O_2$: 206.1307. Found: 206.1308.

Acknowledgements We would like to thank Prof. Leo A. Paquette, The Ohio State University, Columbus, OH, for his many useful suggestions.

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