JOC Article

Organocatalyst-Mediated Enantioselective Intramolecular Aldol Reaction Featuring the Rare Combination of Aldehyde as Nucleophile and Ketone as Electrophile

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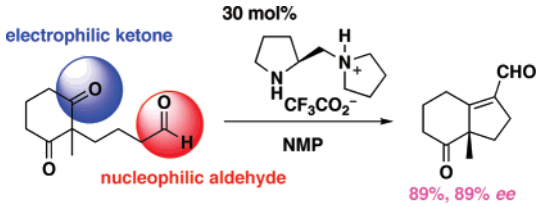
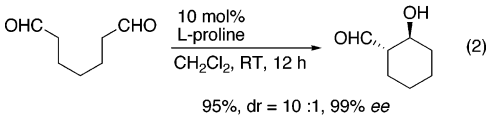


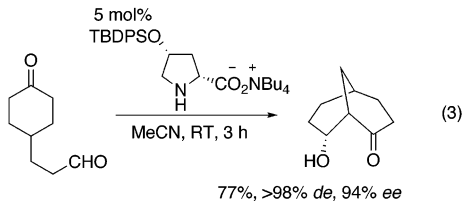
The trifluoroacetic acid salt of 2-(pyrrolidinylmethyl)pyrrolidine was found to be an effective organocatalyst of an asymmetric intramolecular aldol reaction, affording bicyclo[4.3.0]nonane derivatives with a high enantioselectivity, in which the rare combination of aldehyde as a nucleophile and ketone as an electrophile was realized.

Introduction

The intramolecular aldol reaction is a powerful method for the synthesis of cyclic carbocycles. In the early 1970s, Hajos and Parrish and Eder et al. discovered a proline-catalyzed asymmetric intramolecular aldol reaction of triketones, which afforded synthetically useful bicyclic compounds in good yield with excellent enantioselectivity (eq 1).[1]

In 2000, List et al. disclosed a proline-mediated asymmetric and direct intermolecular aldol reaction.[2] Since this discovery, many kinds of organocatalysts have been developed for intermolecular aldol reactions.[3,4] Regarding intramolecular aldol reactions, List and co-workers reported a dienal system for the synthesis of chiral cyclohexanecarbaldehydes catalyzed by proline in excellent enantioselectivity (eq 2).[5] Iwabuchi and co-workers reported an intramolecular aldol reaction catalyzed by siloxyproline ammonium salt for the synthesis of bicyclo[3.3.1]-alkanones (eq 3)[6a] and applied this reaction to the total synthesis of (−)-CP55,940.[6b]





In general, aldehydes are more reactive than ketones as electrophiles. Thus, in most direct asymmetric aldol reactions catalyzed by organocatalysts, an aldehyde or ketone is used as the donor, and an aldehyde is used as the acceptor. The reverse combination, in which an aldehyde is used as the donor and a ketone is employed as the acceptor, is very rare. One example is the aldol reaction of aldehyde and activated ketones such as

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(1) (a) Hajos, Z. G.; Parrish, D. R. German Patent 2,102,623, 1971. (b) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615. (c) Eder, U.; Sauer, G.; Wiechert, R. German Patent 2,014,757, 1971. (d) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed.* **1971**, *10*, 496. (e) Barbas and Bui reported that amine **25** promoted Robinson annulation, but the enantioselectivity is not reported, see: Bui, T.; Barbas, C. F., III. *Tetrahedron Lett.* **2000**, *41*, 6951.

(2) (a) List, B.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2000**, *122*, 2395. (b) Sakthivel, K.; Notz, W.; Bui, T.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2001**, *123*, 5260.

(3) (a) List, B. *Tetrahedron* **2002**, *58*, 5573. (b) Alcaide, B.; Almendros, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 858. (c) List, B. *Modern Aldol Reactions*; Mahrwald, R., Ed.; Wiley-VCH: Weinheim, 2004; Vol. 1, Ch. 4, pp 161−201. (d) List, B. *Acc. Chem. Res.* **2004**, *37*, 548.

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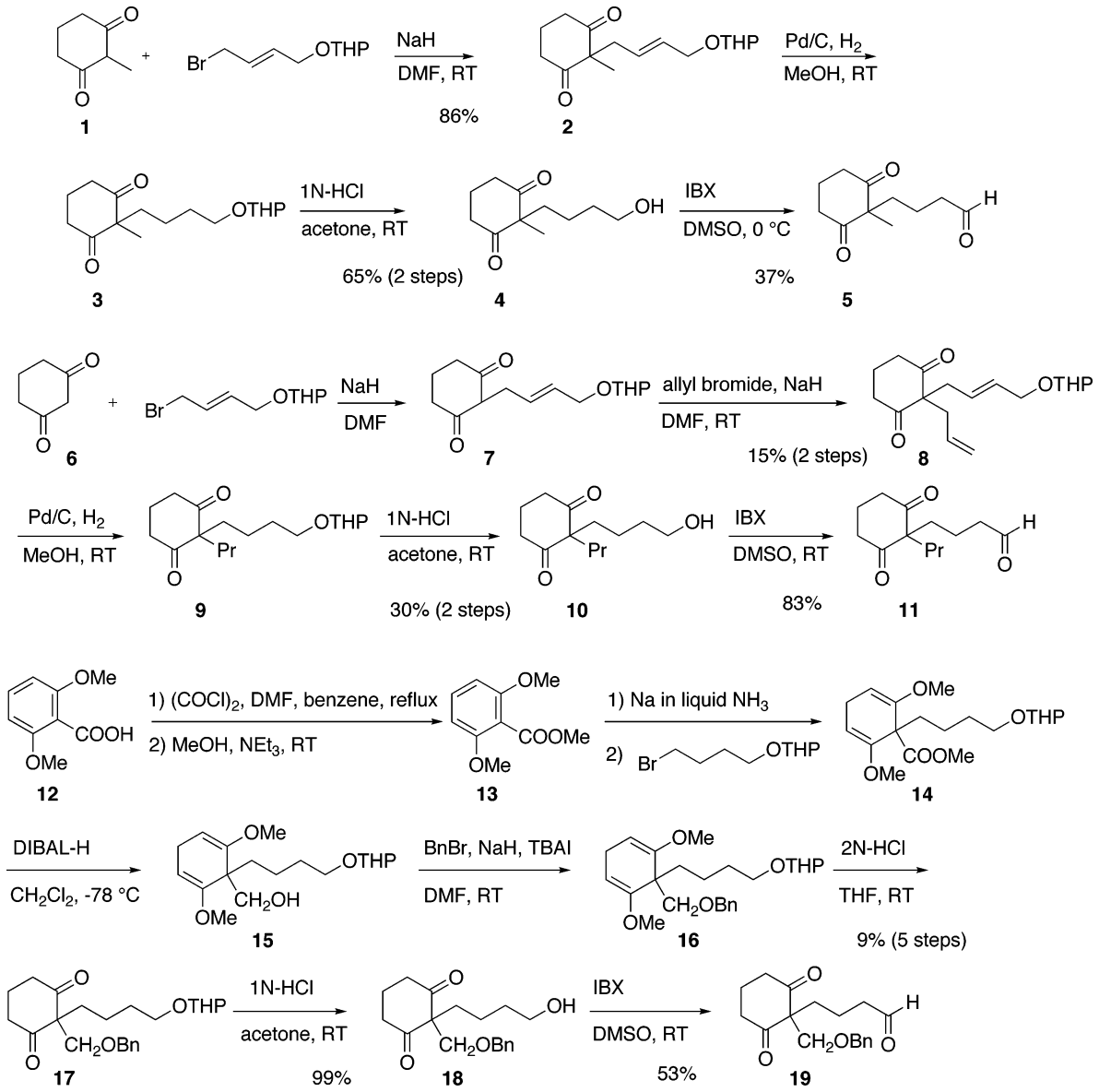
SCHEME 1. Synthetic Scheme of Compounds 5, 11, and 19



diethyl ketomalonate.[7] Even among previously described intramolecular aldol reactions using organocatalysts, the combinations of donor and acceptor that have been used are almost exclusively ketone−ketone, aldehyde−aldehyde, or ketone−aldehyde. The one exception is the proline-catalyzed reaction of 2-oxo-octanal, which proceeds with excellent enantioselectivity but low diastereoselectivity.[5] In this paper, we disclose an intramolecular, enantioselective, and direct aldol reaction, in which the aldehyde and ketone act as donor and acceptor, respectively.

Results and Discussion

Syntheses of the Starting Materials. 2-(3-Formylpropyl)-2-methylcyclohexan-1,3-dione (**5**) was synthesized as follows: 2-methylcyclohexan-1,3-dione (**1**) was treated with 2-(4-bromo-2-butenyloxy)tetrahydropyran and NaH in DMF, affording **2** in 86% yield. Hydrogenolysis using Pd/C in MeOH, followed by removal of the THP group with 1 N HCl and oxidation of the resulting alcohol **4** with IBX (*o*-iodoxybenzoic acid) gave tricarbonyl compound **5**.

Similarly, 2-(3-formylpropyl)-2-propylcyclohexan-1,3-dione (**11**) was synthesized from cyclohexan-1,3-dione (**6**) by successive alkylation with 2-(4-bromo-2-butenyloxy)tetrahydropyran and allyl bromide, followed by hydrolgenolysis, deprotection, and oxidation using IBX.

2-Benzyloxymethyl-2-(3-formylpropyl)cyclohexan-1,3-dione (**19**) was prepared from 2,6-dimethoxybenzoic acid (**12**). Acid **12** was converted into its methyl ester **13**. Birch reduction

(4) For reviews on organocatalysis, see: (a) Berkessel, A.; Groger, H. *Asymmetric Organocatalysis*; Wiley-VCH: Weinheim, 2005. (b) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (c) Hayashi, Y. *J. Synth. Org. Chem. Jpn.* **2005**, *63*, 464. (d) List, B. *Chem. Commun*. **2006**, 819. (e) Marigo, M.; Jørgensen, K. A. *Chem. Commun*. **2006**, 2001. (f) Gaunt, M. J.; Johnsson, C. C. C.; McNally, A.; Vo, N. T. *Drug Discovery Today* **2007**, *12*, 8.

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(6) (a) Itagaki, N.; Kimura, M.; Sugahara, T.; Iwabuchi, Y. *Org. Lett*. **2005**, *7*, 4185. (b) Itagaki, N.; Sugahara, T.; Iwabuchi, Y. *Org. Lett*. **2005**, *7*, 4181.

(7) Bogevig, A.; Kumaragurubaran, N.; Jørgensen, K. A. *Chem. Commun.* **2002**, 620.

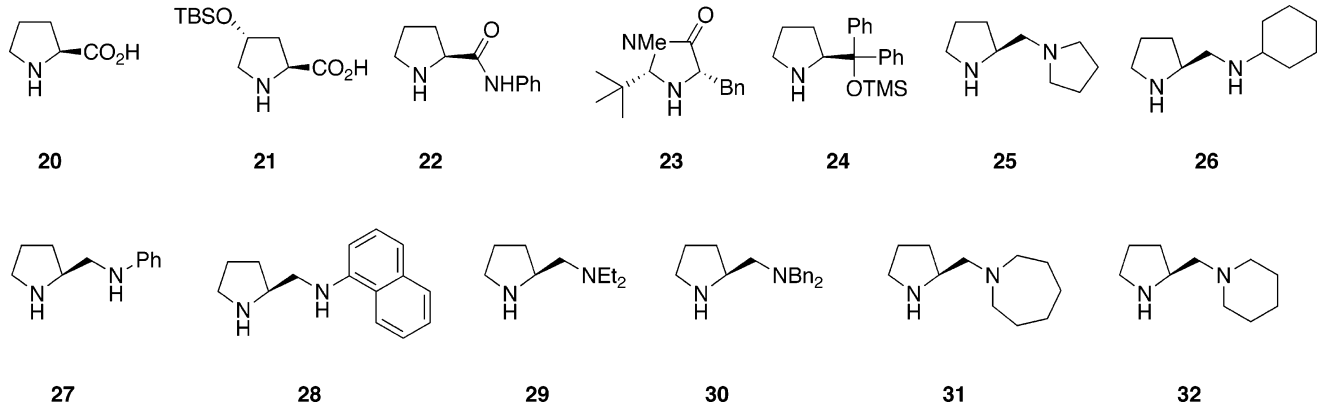
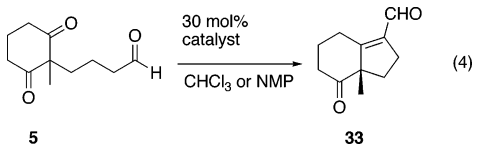


FIGURE 1. Organocatalysts examined in this study.

TABLE 1. Effect of Catalyst in Intramolecular Aldol Reaction of 5[a]



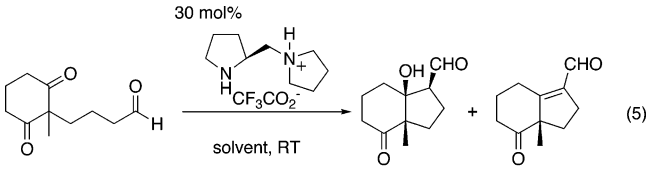
entry	catalyst	solvent	*T* (°C)	time (h)	yield (%)[b]	ee (%)[c]
1	**20**	$CHCl_3$	23	8	94	−43
2	**21**	$CHCl_3$	23	4	80	−6
3	**22**	$CHCl_3$	23	9	97	5
4	**23**	$CHCl_3$	23	63	quant.[d]	34
5	**24**	$CHCl_3$	23	4	quant.[d]	37
6	**25**	$CHCl_3$	23	1	67	3
7	**25**	NMP	0	6	62	44
8	**25**·HCl	NMP	0	3	65	52
9	**25**·HOTf	NMP	0	19	95	45
10	**25**·TFA	NMP	0	56	89	89
11	**26**·TFA	NMP	0	40	53	16
12	**27**·TFA	NMP	0	24	53	21
13	**28**·TFA	NMP	0	24	57	11
14	**29**·TFA	NMP	0	24	56	47
15	**30**·TFA	NMP	0	24	64	24
16	**31**·TFA	NMP	0	24	54	13
17	**32**·TFA	NMP	0	24	56	76

[a] Reaction was performed employing **5** on a 0.1 to ∼0.15 mmol scale at 0.1 M in each solvent at room temperature or 0 °C. [b] Isolated yield. [c] Optical yield was determined by HPLC on a chiral phase (chiralcel OB-H). [d] Quant. = quantitatively.

followed by alkylation with 2-(4-bromobutoxy)tetrahydropyran afforded **14**. Reduction with DIBAL-H and benzyl ether formation afforded **16**. Acid treatment, followed by oxidation, gave tricarbonyl compound **19**.

Screening of the Reaction Conditions. With the starting materials in hand, the reaction conditions were screened using tricarbonyl **5** as a model substrate. First, the organocatalyst was investigated. Tricarbonyl **5** was treated with 30 mol % organocatalyst in $CHCl_3$ at room temperature. When proline (**20**) was used as a catalyst, the aldol reaction proceeded, followed by the dehydration, affording bicyclo[4.3.0]nonene derivative **33** in 94% yield with 43% ee after 8 h. Several organocatalysts were employed with the results summarized in Table 1. Siloxyproline **21**, which is an effective catalyst in the α-aminoxylation reaction,[8] Mannich reaction,[8] and aldol reaction in the presence of water,[9] gave a nearly racemic product. MacMillan et al.'s catalyst **23**[10,11] and diphenylprolinol silyl ether **24**[12−14] gave the product **33** quantitatively but with low enantioselectivity. As NMP (*N*-methyl-2-pyrrolidinone) was found to be a suitable solvent (vide infra), the following experiments were conducted in NMP at 0 °C. Although (*S*)-2-(pyrrolidinylmethyl)-pyrrolidine **25** is not an effective catalyst, its acid salt was found to give good results. Using its HCl salt improves the enantioselectivity to 52% (Table 1, entry 8). Although the HOTf salt did not give a better result (45% ee, Table 1, entry 9), the CF_3CO_2H salt afforded good enantioselectivity (89% ee, Table 1, entry 10).

TABLE 2. Solvent Effect in Intramolecular Aldol Reaction[a]



			34		33	
entry	solvent	time (h)	yield (%)[b]	ee (%)[c]	yield (%)[b]	ee (%)[d]
1	Et_2O	3	42	66	32	61
2	MeOH	4	34	55	38	63
3	CH_2Cl_2	24	18	57	63	61
4	CH_3CN	0.1	33	63	38	78
5	DMF	1	48	77	44	82
6[e]	NMP	1.5	35	76	42	85
7	NMP	48	<5	nd	96	85

[a] Reaction was performed employing **5** on a 0.1 to ∼0.15 mmol scale at 0.1 M in each solvent at room temperature. [b] Isolated yield. [c] Optical yield was determined by HPLC on a chiral phase (chiralcel OB-H) after conversion into dehydrated product **33**. [d] Optical yield was determined by HPLC on a chiral phase (chiralcel OB-H).

As a diamine salt containing a pyrrolidine core had been found to be an effective catalyst, the effect of altering the "right-hand" moiety of the diamine as drawn was investigated in detail as described in Table 1, entries 11−17. Catalysts containing a secondary amine group (**26**−**28**) are not suitable, and neither are those with a diethyl or dibenzyl amine moiety **29** or **30** effective. The hexamethylene amine **31** is not suitable, while the catalyst containing a piperidine group **32** gave a good result (76% ee). It should be noted that Barbas'[15] group first reported that diamine **25** in combined use with CF_3CO_2H was an effective organocatalyst of the enantioselective intermolecular aldol reaction and Michael reaction, while Yamamoto's[16] group

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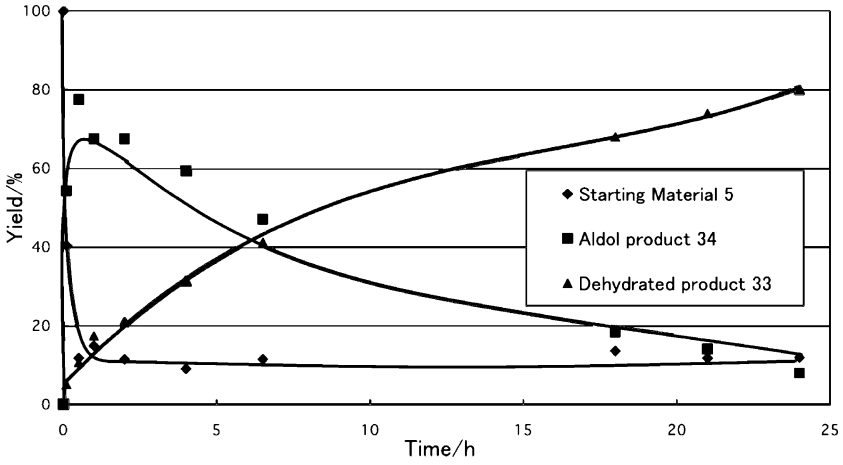

FIGURE 2. Yields of **5**, **33**, and **34** vs reaction time.

reported that diamine **25** in combined use with 2,4-dinitrobenzenesulfonic acid is an effective organocatalyst of the enantioselective intermolecular aldol reaction.

Next, the effect of solvent was investigated. As the dehydration reaction is not so fast when the CF_3CO_2H salt of **25** is employed, the aldol product could be isolated. For this screening, we quenched the reaction after a predetermined time and isolated both aldol **34** and dehydrated product **33**. Their yields and enantioselectivities were determined with the results summarized in Table 2. The aldol product **34** was isolated as a single isomer (vide infra). The enantiomeric excess of aldol product **34** is a little lower than that of dehydrated product **33** except for the reaction in Et_2O. When Et_2O, MeOH, and CH_2Cl_2 were used as solvents, the enantioselectivity was moderate. In polar solvents such as DMF and NMP, better enantioselectivity was achieved. Especially good results were obtained in NMP. The aldol reaction is fast, and within 1.5 h, the aldol product **34** and dehydrated product **33** were obtained in 35 and 42% yield with 76 and 85% ee, respectively (Table 2, entry 6). When the reaction was performed for a long time (48 h), dehydration proceeded completely, affording **33** in excellent yield (96%) with good enantioselectivity (85% ee, Table 2, entry 7).

The relationship between yield and reaction time was investigated by monitoring the yield and enantiomeric excess of aldol **34** and dehydrated product **33** at 0.5, 1, 2, 4, 6.5, 18, 21, and 24 h with the results summarized in Figure 2.

The yield of aldol product **34** increases at first and then gradually decreases as the amount of dehydrated product increases. The optical purities of the aldol product **34** and dehydrated product **33** remained almost the same throughout the reaction. These results indicate that it is probably not the case that the other diastereomer of the aldol reaction is also formed but dehydrated instantly but rather that the aldol product **34** was obtained selectively and that this dehydrated to give **33**. No kinetic discrimination occurs at the dehydration stage.

Determination of the Absolute Configuration. The absolute configuration was determined by chiral HPLC comparison with an authentic sample prepared as shown in Scheme 2.

The Wieland−Miecher ketone **35** of 73% ee was reduced with $NaBH_4$ in the presence of $CeCl_3$,[17] followed by treatment with BnBr and NaH, to afford dibenzyl ether **37**. Ozonolysis and then reduction with SmI_2[18] gave keto aldehyde **39**. Removal of the Bn protecting group, followed by an intramolecular aldol reaction using pyrrolidine, gave bicyclo[4.3.0]nonene derivative **41**. Oxidation of alcohol **41** gave ketone **33**. HPLC comparison of this authentic sample with the dehydrated product **33** prepared using diamine **25**·TFA showed that the two compounds have the same absolute stereochemistry.

The relative stereochemistry of the aldol product **34** was determined by the NOEs observed in the compounds **43** (Figure

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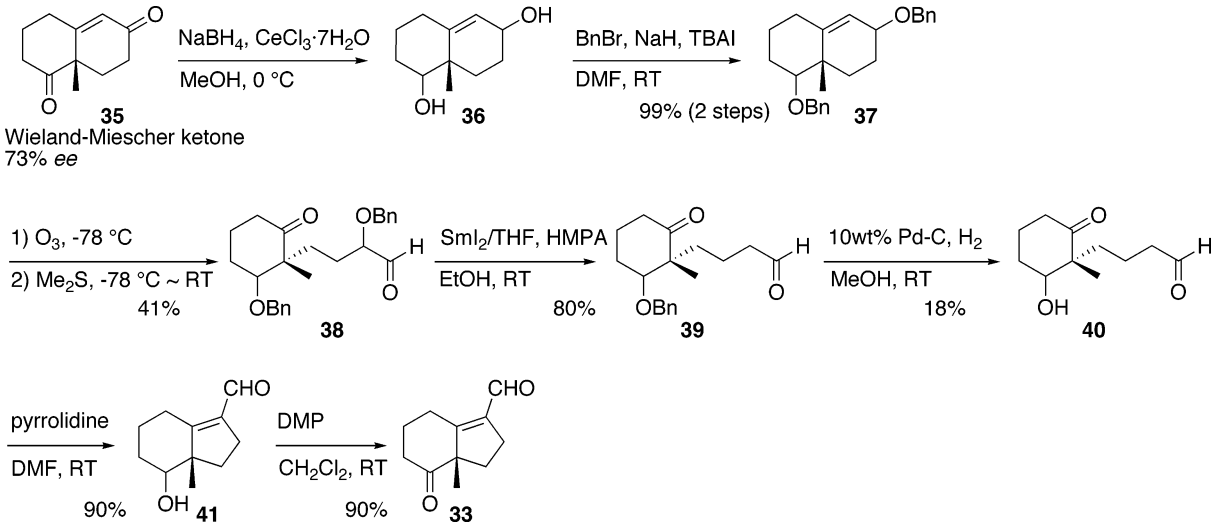
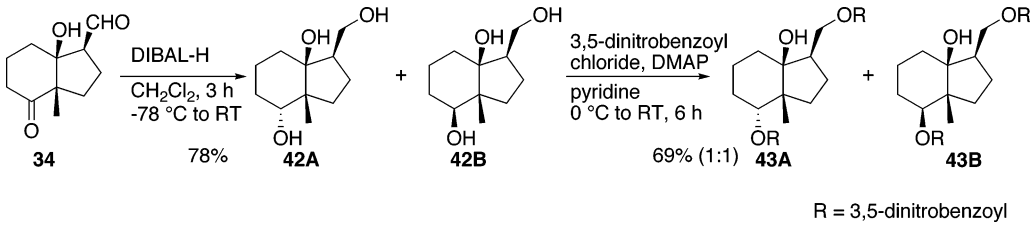
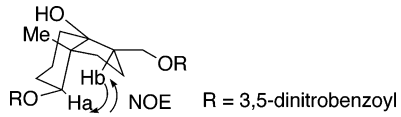
SCHEME 2. Synthetic Scheme for 33 from the Wieland−Miescher Ketone to Determine the Absolute Configuration of the Aldol Product



SCHEME 3. Synthetic Scheme of 43



3), which were synthesized as shown in Scheme 3: reduction of **34** with DIBAL-H afforded a diastereomer mixture of triols **42**. Treatment of **42** with 3,5-dinitrobenzoyl chloride in pyridine afforded bis(3,5-dinitrobenzoyl)ester **43**, and the diastereomers were separated.



43B

FIGURE 3. NOE observed for **43B**.

Intramolecular Aldol Reaction of 5, 11, and 19. This intramolecular aldol reaction, in which the aldehyde and ketone act as nucleophile and electrophile, respectively, was applied to two other substrates (**11** and **19**), with the results summarized in Table 3. With regard to the substituent at the 2 position of cyclohexadione, not only a methyl group but also propyl and benzyloxymethyl groups can be successfully utilized to afford bicyclo[4.3.0]nonene derivatives with good yield and high enantioselectivities. In the reactions of **11** and **19**, the dehydration reaction was slow, which was performed at room temperature for 1 day.

Reaction Mechanism. The reaction is thought to proceed as follows: organocatalyst **25**·TFA reacts with the aldehyde moiety of tricarbonyl **5** to generate enamine **46**, which reacts with one of the carbonyl groups intramolecularly to generate **47**. Hydrolysis of the iminium ion **47** generates the aldol product **34** with regeneration of the organocatalyst **25**·TFA. The aldol product **34** was dehydrated to **33** under the reaction conditions without compromising the enantioselectivity.

In the transition state, a proton coordinated to the nitrogen of the pyrrolidine ring activates one of the carbonyl groups, which can occur in the two major conformations **A** and **B** shown in Scheme 4. Although there is considerable steric hindrance in the case of **B**, this is avoided in transition state **A**. Thus, the reaction proceeds from **A** to afford **47** stereoselectively.

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SCHEME 4. Reaction Mechanism and Transition State

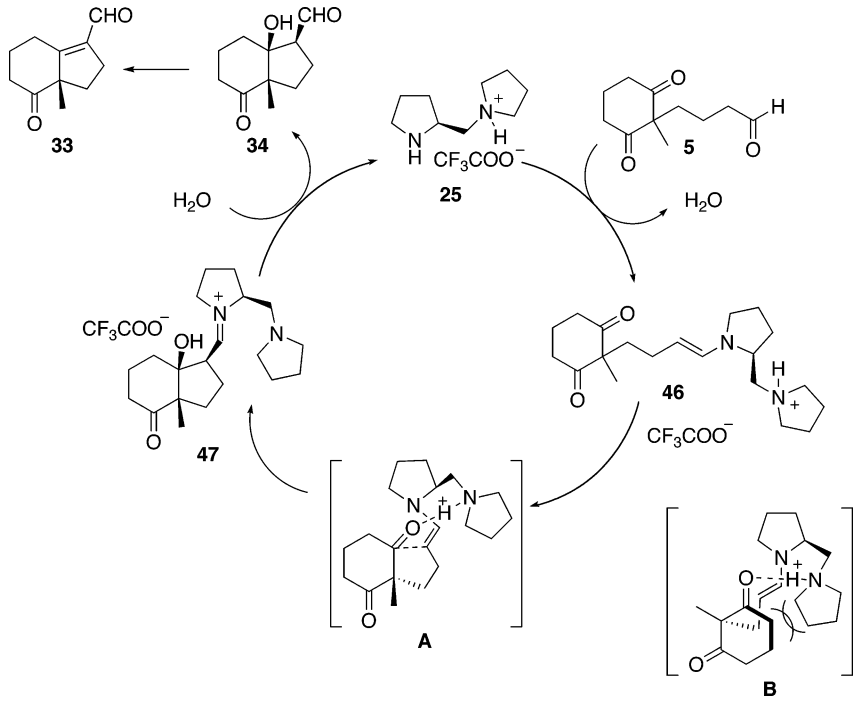
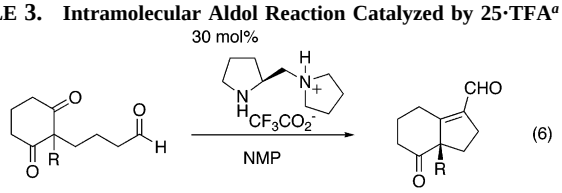
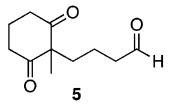
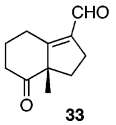
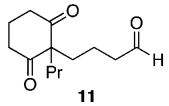
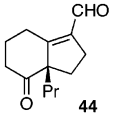
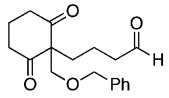
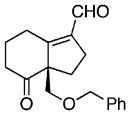


TABLE 3. Intramolecular Aldol Reaction Catalyzed by 25·TFA[a]



entry	starting material	product	conditions	yield (%)[b]	ee (%)
1	 5	 33	0 °C, 56 h	89	89[c]
2	 11	 44	0 °C, 40 h then RT, 24 h	81	83[d]
3	 19	 45	0 °C, 40 h then RT, 24 h	79	81[e]

[a] Reaction was performed employing **11** on a 0.1 mmol scale or **19** on a 0.05 mmol scale at 0.1 M in NMP. [b] Isolated yield. [c] Optical yield was determined by HPLC on a chiral phase (chiralcel OB-H). [d] Optical yield was determined by HPLC on a chiral phase (chiralcel OD-H). [e] Optical yield was determined by HPLC on a chiral phase (chiralpak AS-H).

Conclusion

In summary, we have found that the trifluoroacetic acid salt of 2-(pyrrolidinylmethyl)pyrrolidine (**25**) is an effective organocatalyst of the intramolecular aldol reaction of tricarbonyl compounds **5**, **11**, and **19** to afford bicyclo[4.3.0]nonene derivatives **33**, **44**, and **45** with the creation of a quaternary carbon center with high enantioselectivity. In this reaction, the aldehyde and ketone act as nucleophile and electrophile, respectively, a rare reversal of their normal roles.

Experimental Section

2-Methyl-2-[4-(2-tetrahydropyranyloxy)-2-butenyl]-1,3-cyclohexanedione (2). To a DMF (11.7 mL) solution of 2-methyl-1,3-cyclohexanedione (393 mg, 3.1 mmol) was added NaH (60% in oil, 128 mg, 3.2 mmol) at 0 °C, and the reaction mixture was stirred for 1 h at room temperature. To this reaction mixture was added a DMF (3 mL) solution of 2-(4-bromobut-2-enyloxy)tetrahydropyran (1.1 g, 4.1 mmol) over 10 min, and the reaction mixture was stirred for 5 h at room temperature. The reaction was quenched with a saturated aqueous NH_4Cl solution, the organic materials were extracted with AcOEt 3 times, and the combined organic phase was washed with brine 3 times, dried over anhydrous Na_2SO_4, and concentrated in vacuo after filtration. Purification by flash column chromatography (ethyl acetate/hexane = 1:10) gave 753 mg (86%) of **2**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (3H, s), 1.43−1.64 (4H, m), 1.65−2.10 (4H, m), 2.58 (2H, d, J = 7.5 Hz), 2.64 (4H, t, J = 6.5 Hz), 3.42−3.60 (1H, m), 3.78−3.94 (1H, m), 4.06 (1H, dd, J = 12.6, 7.1 Hz), 4.23 (1H, dd, J = 6.0, 12.5 Hz), 4.61 (1H, s), 5.24−5.38 (1H, m), 5.55−5.75 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.5, 19.5, 20.1, 25.5, 30.7, 34.7, 38.1 (2C), 62.3, 62.7, 64.8, 98.1, 126.3, 129.9, 209.8 (2C); IR (neat) ν 2942, 1726, 1696, 1119, 1026 cm^{-1}; HRMS (ESI): [M + Na]$^+$: calcd for $C_{16}H_{24}O_4Na$: 303.1567, found: 303.1579.

2-(4-Hydroxybutyl)-2-methyl-1,3-cyclohexanedione (4). To a MeOH (270 mL) solution of **2** (8.0 g, 28.5 mmol) was added 10 wt % Pd−C (800 mg) at room temperature, and the reaction mixture was stirred for 1.5 h under H_2 atmosphere. The reaction mixture was filtrated through a pad of Celite and concentrated in vacuo. The crude materials of 2-methyl-2-[4-(2-tetrahydropyranyloxy)-butyl]-1,3-cyclohexanedione were used directly in the next reaction.

To an acetone (70 mL) solution of crude **3** was added 1 N HCl (28 mL) at room temperature, and the reaction mixture was stirred for 24 h. The reaction was quenched with pH 7 phosphate buffer, the organic materials were extracted with AcOEt 3 times, and the combined organic phase was washed with brine 3 times, dried over

anhydrous Na_2SO_4, and then concentrated in vacuo after filtration. Purification by flash column chromatography (ethyl acetate/hexane = 1:10) gave 3.7 g (65% over two steps) of **4**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10−1.24 (2H, m), 1.20 (3H, s), 1.42−1.58 (2H, m), 1.72−1.81 (2H, m), 1.81−2.04 (2H, m), 2.21−2.40 (1H, bs), 2.54−2.75 (4H, m), 3.57 (2H, t, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.5, 19.7, 21.0, 32.5, 36.6, 37.9 (2C), 62.1, 65.5, 210.6 (2C); IR (neat) ν 3403, 2941, 1724, 1694, 1462, 1027 cm^{-1}; HRMS (ESI): $[M + Na]^+$: calcd for $C_{11}H_{18}O_3Na$: 221.1148, found: 221.1141.

(3-Formylpropyl)-2-methyl-1,3-cyclohexanedione (5). To a DMSO (8 mL) solution of **4** (400 mg, 2.0 mmol) was added IBX (*o*-iodoxybenzoic acid, 1.6 g, 6.0 mmol) at room temperature, and the reaction mixture was stirred for 1.5 h at the same temperature. The reaction was quenched with a saturated aqueous $NaHCO_3$ solution, the organic materials were extracted with AcOEt 3 times, and the combined organic phase was washed with additional saturated aqueous $NaHCO_3$ solution 3 times, dried over anhydrous Na_2SO_4, and concentrated in vacuo after filtration. Purification by flash column chromatography (ethyl acetate/hexane = 1:3) gave 144 mg (37%) of **5**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (3H, s), 1.45 (2H, dtt, J = 4.4, 7.2, 14.4 Hz), 1.76−1.84 (2H, m), 1.87−2.04 (2H, m), 2.42 (2H, dt, J = 1.2, 7.2 Hz), 2.61−2.75 (4H, m), 9.72 (1H, t, J = 0.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.5, 17.6, 20.4, 35.7, 38.0 (2C), 43.7, 65.4, 201.5, 210.0 (2C); IR (neat) ν 2943, 2730, 1723, 1694, 1459, 1027 cm^{-1}; HRMS (ESI): $[M + Na]^+$: calcd for $C_{11}H_{16}O_3Na$: 219.0992, found: 219.0997.

Typical Procedure for the Intramolecular Aldol Reaction (Table 3, entry 1). To a NMP (*N*-methyl-2-pyrrolidinone, 2.7 mL, 0.1 M) solution of aldehyde **5** (54.5 mg, 0.27 mmol) was added a TFA salt of **25** (21.7 mg, 30 mol %) at 0 °C, and the reaction mixture was stirred for 56 h at the same temperature. The reaction was quenched with pH 7 phosphate buffer solution, the organic materials were extracted with AcOEt 3 times, and the combined organic phase was washed with brine solution 3 times, dried over anhydrous Na_2SO_4, and concentrated in vacuo after filtration. Purification by preparative thin layer chromatography (ethyl acetate/hexane = 1:1) gave 42.6 mg (89%) of **33**.

(*S*)-7-(1-Methyl-2-oxo-bicyclo[4.3.0]non-6-ene)carbaldehyde (33). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (3H, s), 1.56−1.70 (1H, m), 1.72−1.81 (1H, m), 2.18−2.33 (2H, m), 2.40−2.56 (4H, m), 2.65−2.78 (1H, m), 3.26−3.36 (1H, m), 9.98 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.8, 23.8, 24.0, 26.4, 30.4, 37.8, 63.8, 136.1, 165.2, 187.8, 211.4; IR (neat) ν 2960, 2869, 1713, 1665, 1635, 1346, 1190 cm^{-1}; HRMS (ESI): $[M + Na]^+$: calcd for $C_{11}H_{14}O_2Na$: 201.0886, found: 201.0890; $[\alpha]_D^{22.6}$ +83.2 (c = 0.16, MeOH).

Enantiomeric excess was determined by HPLC with a Chiralcel OB−H column (10:1 = hexane/2-propanol), 1.0 mL/min; major enantiomer tr = 18.9 min, minor enantiomer tr = 26.4 min.

(1*S*,6*S*,9*S*)-9-(1-Hydroxy-6-methyl-5-oxo-bicyclo[4.3.0]nonane)-carbaldehyde (34). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (3H, s), 1.54−1.70 (3H, m), 1.83−2.13 (4H, m), 2.15−2.23 (1H, m), 2.26−2.33 (1H, m), 2.50−2.68 (3H, m), 9.74 (1H, d, J = 1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.9, 20.4, 20.7, 30.0, 31.3, 36.7, 55.0, 62.4, 85.4, 204.1, 212.2; IR (neat) 3483, 2944, 1704, 1463, 991 cm^{-1}; HRMS (ESI): $[M + Na]^+$: calcd for $C_{11}H_{16}O_3Na$: 219.0992, found: 219.0984; $[\alpha]_D^{22.0}$ −19.6 (c = 0.18, MeOH).

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

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