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2-Azanorbornane-Based Amino Alcohol Organocatalysts for Asymmetric Michael Reaction of β-Keto Esters with Nitroolefins

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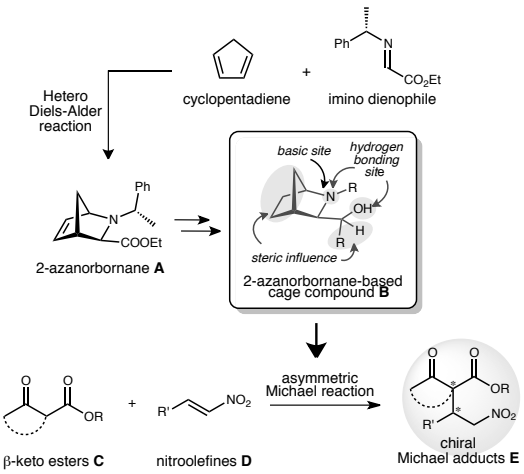
Abstract: New optically active 2-azanorbornane-based amino alcohol organocatalysts were designed and synthesized, and these catalysts were successfully employed in the asymmetric Michael reaction of β-keto esters with nitroolefins to obtain the corresponding chiral Michael adducts with both high chemical yields (up to 99%) and high stereoselectivities (up to dr = 91:9, up to 91% ee).

Introduction

The development of new organocatalysts has attracted considerable interest in the field of synthetic organic chemistry over the past 10 years. Efficient covalent and non-covalent organocatalysts have been explored for proceeding successfully a wide range of reactions.[1] 2-Azanorbornane **A** having cage structure is prepared by the hetero Diels-Alder (HDA) reaction of cyclopentadiene with chiral imino dienophile, and the cage compound works as useful synthetic intermediate for converting to various biologically active compounds such as *anti*-tumor drugs (Scheme 1).[2] 2-Azanorbornane-based amino alcohol **B**, that is derived from the DA adduct **A**, has bulky 2-azanorbornane backbone and the cage structure contains nitrogen atom acting as a Brønsted basic site. Furthermore, the compound **B** has the side chain at 3-position on the 2-azanorbornane skeleton, which might show strong electronic and steric effects for controlling stereoselectivity in the course of reaction. Considering these structurally properties, it is expected that the cage type amino alcohol **B** might show an efficient functionality as an organocatalyst for enantioselective reactions. However, till now only a few successful studies were reported by using the compound **B** containing with *di*-phenylmethanol moiety at 3-position and thiourea derived azanorbornanes as organocatalyst for asymmetric aldol and Michael reactions respectively.[2a,e] Especially, to the best of our knowledge, the successfully use of 2-azanorbornanes **B** with *mono*-phenylmethanol moiety at 3-position as organocatalyst has not been reported until now.

The Michael reaction is widely used as one of the most well-known versatile carbon-carbon bond-forming reactions. This reaction is especially useful for the construction of chiral building blocks containing quaternary stereocenters, which are key chiral intermediates for the synthesis of biologically active complex compounds and synthetic drug candidates.[3] Therefore, intensive efforts have been made in recent years to develop an efficient organocatalyst for this reaction. However, despite its great synthetic potential, only a few successful catalysts that show satisfactory activity to substrates in a wide range of applications have been reported.[5]



Scheme 1. Functional of 2-azanorbornanes and its use in Michael addition

Against this background, we explore the optically active 2-azanorbornane organocatalysts **B** for this reaction using β-keto esters **C** with nitroolefins **D** (Scheme 1).

We describe that the 2-azanorbornane-based amino alcohol organocatalysts **B** prepared here showed efficient catalytic activity in the Michael addition of β-keto esters **C** with various nitroolefins **D** to obtain chiral Michael adducts **E** at satisfactory chemical yields and stereoselectivities (up to 99%, dr = 91:9, 91% ee).

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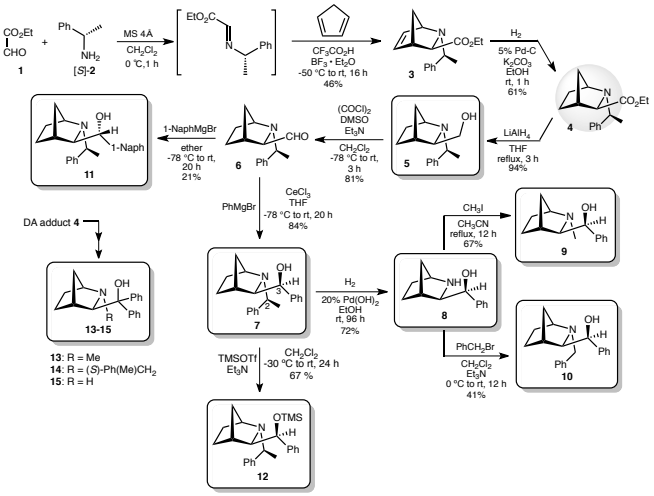
Results and Discussion

2-Azanorbornanes with a phenylmethanol moiety as the side chain organocatalyst **5, 7–15** were derived from the DA adduct **3** by the following reactions (Scheme 2).[4] First, 2-azanorbornanes **3** having an ethoxycarbonyl group as the side chain at the 3-position were prepared by the HDA reaction of cyclopentadiene with a chiral imino dienophile, which was afforded



Scheme 2. Preparations of 2-azanorbornane-based organocatalysts

by the condensation of aldehydes **1** with chiral amines **2**. The catalytic hydrogenation of the DA adduct **3** resulted in the hydrogenated compound **4**. Furthermore, the reduction using $LiAlH_4$ of **4** afforded 2-azanorbornylmethanol **5** and then the alcohol **5** was converted to aldehyde **6** by Swern oxidation. The Grignard reaction of the obtained product **6** with phenyl magnesium bromide gave 2-azanorbornane with *mono*-(*S*)-phenylmethanol **7** at the side chain, followed by catalytic reduction with palladium hydroxide in an H_2 stream of **7** affording the *N*-unsubstituted compound **8** at good yield. Compound **8** was also converted to *N*-methylated **9** and *N*-benzylated **10** products. In addition, the Grignard reaction of aldehyde **6** with 1-naphthyl magnesium bromide gave the bulkier 2-azanorbornane **11** with a *mono*-(*S*)-1-naphthylmethanol moiety as the side chain. 2-Azanorbornyl-trimethylsilylphenylether **12** having a TMS (trimethylsilyl)-protected hydroxyl group was obtained by the reaction of **7** with TMSOTf at moderate yield. Moreover, 2-azanorbornanes **13–15** with a *di*-phenylmethanol moiety as the side chain were also easily prepared by our previously reported method,[4f] along with 2-azanorbornanes with a *mono*-(*S*)-phenylmethanol moiety. The (*S*)-absolute configuration of the secondary chiral center at the side chain in 2-azanorbornane with *mono*-phenylmethanol **7** was confirmed, in accordance with previous reports.[4d,f] Thus, when the Grignard reaction of aldehyde **6** with PhMgBr proceeds, a phenyl nucleophile may attack from the less sterically hindered side, which is not influenced by the bulky phenyl ethyl group on the amino nitrogen atom in the 2-azanorbornane backbone to afford compound **7** having the (*S*)-configuration on a side chain (Fig. 1).

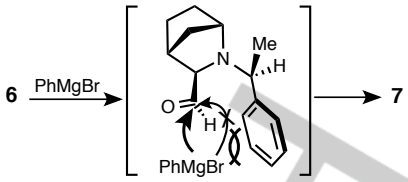
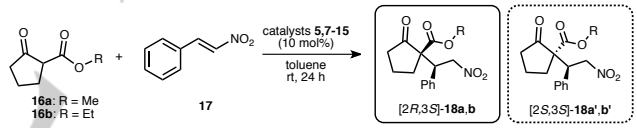


Fig. 1. Direction of attack of PhMgBr on aldehyde **6**

First, we carried out the Michael addition of methyl 2-oxo-cyclopentanecarboxylate **16a** as a Michael donor and nitro-styrene **17** as a Michael acceptor with 10 mol% of our explored 2-azanorbornanes with *mono*-(*S*)-phenylmethanol moiety organocatalysts **5, 7–12** in toluene at room temperature (entries 1–4, Table 1). All catalysts **5, 7–12** showed catalytic activities in this reaction and afforded the Michael adduct **18a**. In particular, the bulkiest *N*-(*S*)-phenylethylated 2-azanorbornanes **7** with a *mono*-(*S*)-phenylmethanol moiety afforded the adduct **18a** at good chemical yield and stereoselectivities (70%, dr = 82:18, 86% ee, entry 2). In addition, the catalytic activities of our previously explored 2-azanorbornanes **13–15** with a *di*-phenylmethanol moiety were also examined (entries 8–10). However, these catalysts did not show satisfactory catalytic activities in this reaction, in contrast to 2-azanorbornane with a *mono*-phenylmethanol moiety. The absolute configuration and diastereoselectivity of **18a** were identified based on a comparison with literature data.[5]

Table 1. Asymmetric Michael additions of β-keto esters **16a,b** with *trans*-β-nitrostyrene **17** using organocatalysts **5,7-15**



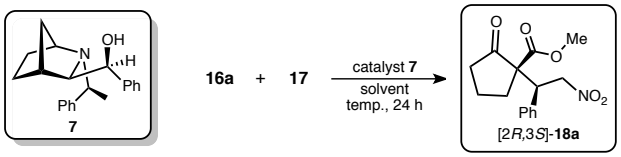
entry	**16**	product	catalyst	yield (%)[a]	dr (**18**:**18'**)[b]	ee (%)[c] **18**	**18'**
1	**16a**	**18a**	**5**	60	63:37	55	*rac*
2	**16a**	**18a**	**7**	70	82:18	86	8
3	**16a**	**18a**	**8**	37	63:37	-56	-16
4	**16a**	**18a**	**9**	38	58:42	58	5
5	**16a**	**18a**	**10**	27	50:50	*rac*	16
6	**16a**	**18a**	**11**	54	84:16	33	*rac*
7	**16a**	**18a**	**12**	99	88:12	4	*rac*
8	**16a**	**18a**	**13**	42	57:43	7	17
9	**16a**	**18a**	**14**	71	88:12	*rac*	*rac*
10	**16a**	**18a**	**15**	42	55:45	-44	-33
11	**16b**	**18b**	**7**	90	91:9	23	*rac*

[a]Isolated yield. [b]Diastereoselectivity was determined by ^{1}H-NMR.
[c]The ee of isomer was determined by HPLC using CHIRALCEL OD-H column (hexane:2-propanol = 90:10).

To further improve the enantioselectivity of this organocatalytic reaction, we evaluated the effects of various solvents, molar ratios, temperatures, and reaction times using superior catalyst **7** (entries 1–24, Table 2). First, we examined the solvent screening in different non-polar aromatic (entries 1, 2), aliphatic (entry 3), ethereal (entries 4–7), chlorinated (entry 8), polar protic (entries 9–13), and special hexafluorobenzene (entry 14) solvents in the presence of 10 mol% of catalyst **7** for 24 h. As a result, toluene, *i*-Pr_2O, and CH_2Cl_2 afforded the Michael adduct **18a** at good chemical yields and stereoselectivities. Based on these results, the reactions were carried out at 0, −30, and −50 °C in these solvents, respectively (entries 15–21). The best

results for the chemical yield (80%) and enantioselectivity (91% ee) were obtained in *i*-Pr_2O at 0 °C with good diastereoselectivity (84:16) (entry 16). Furthermore, the effects of catalyst loading (20 mol% and 5 mol%, entries 22–24) were examined in superior *i*-Pr_2O solvent. However, the reactions under both catalytic loadings did not afford better results than the use of 10 mol%. These results showed that catalyst loading at 10 mol% in *i*-Pr_2O as a solvent at 0 °C was the best reaction conditions to afford product **18a** at satisfactory chemical yield, diastereoselectivity, and enantioselectivity as the optimized conditions (entry 16).

Table 2. Asymmetric Michael additions of β-keto ester **16a** with *trans*-β-nitrostyrene **17** using organocatalyst **7**

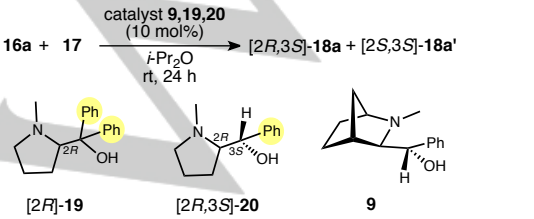


entry	solvent	catalyst (mol%)	temp. (°C)	yield (%)[a]	dr[b] (**18a**:**18a'**)	ee (%)[c] **18a**	ee (%)[c] **18a'**
1	toluene	10	rt	70	82:12	86	8
2	benzene	10	rt	78	84:16	79	11
3	hexane	10	rt	22	74:26	82	*rac*
4	Et_2O	10	rt	77	82:18	64	9
5	THF	10	rt	53	63:37	71	4
6	*i*-Pr_2O	10	rt	82	81:19	85	8
7	1,4-dioxane	10	rt	35	75:25	36	7
8	CH_2Cl_2	10	rt	62	81:19	79	11
9	CH_3CN	10	rt	21	53:47	53	12
10	MeOH	10	rt	36	50:50	8	*rac*
11	acetone	10	rt	68	77:23	51	34
12	C_6F_6	10	rt	68	79:21	34	*rac*
13	water	10	rt	51	64:36	50	*rac*
14	brine	10	rt	41	71:29	54	8
15	toluene	10	0	65	76:24	63	23
16	*i*-Pr_2O	10	0	80	84:16	91	*rac*
17	CH_2Cl_2	10	0	85	86:14	59	5
18	toluene	10	-30	70	84:16	88	5
19	*i*-Pr_2O	10	-30	75	86:14	75	4
20	toluene	10	-50	70	88:12	44	*rac*
21	*i*-Pr_2O	10	-50	82	88:12	40	*rac*
22	*i*-Pr_2O	20	0	68	84:16	86	27
23	*i*-Pr_2O	15	0	70	77:23	86	17
24	*i*-Pr_2O	5	0	70	78:22	57	6

[a]Isolated yield. [b]Diastereoselectivity was determined by ^{1}H-NMR.
[c]The ee of isomer was determined by HPLC using CHIRALCEL OD-H column (hexane:2-propanol = 90:10).

It is well known that proline-based amino alcohol organocatalyst **19** showed excellent catalytic activity to the reaction of **16a** with **17** in special hexafluorobenzene as a solvent.[5g] However, the use of this solvent might be limited by its higher cost than other typical organic solvents, and it also shows toxicity such as serious eye damage. We thus examined this reaction using catalyst **19**[6] with a *di*-phenylmethanol moiety and related catalyst **20**[6] with a *mono*-phenylmethanol moiety,

Table 3. Asymmetric Michael additions of β-keto ester **16a** with **17** using organocatalysts **9,19,20**



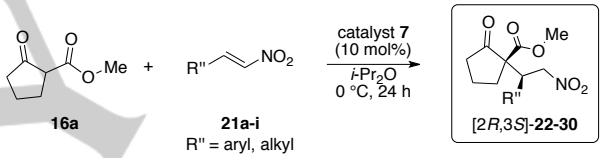
entry	catalyst	yield (%)[a]	dr (**18a**:**18a'**)[b]	ee (%)[c] **18a**	ee (%)[c] **18a'**
1	**19**	39	54:46	11	30
2	**20**	68	82:18	21	10
3	**9**	29	62:38	85	14

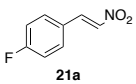
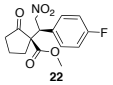
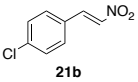
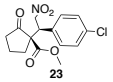
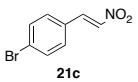
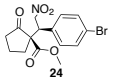
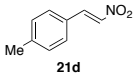
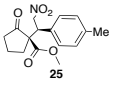
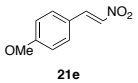
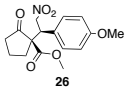
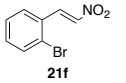
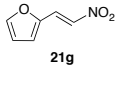
[a]Isolated yield. [b]Diastereoselectivity was determined by ^{1}H-NMR.
[c]The ee of isomer was determined by HPLC using CHIRALCEL OD-H column (hexane:2-propanol = 90:10).

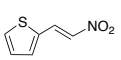
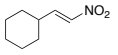
in our identified superior *i*-Pr_2O solvent (entries 1 and 2, Table 3). However, neither catalyst **19** nor catalyst **20** showed better catalytic activities than our 2-azanorbornane catalyst **7**. In addition, not only *N*-(*S*)-phenylethylated **7** but also *N*-methylated 2-azanorbornane **9** with a *mono*-phenylmethanol moiety showed better catalytic activity than both catalysts **19** and **20** in *i*-Pr_2O (entry 3). In contrast with proline-based **19**, 2-azanorbornanes **7** did not work well in hexafluorobenzene (entry 12, Table 2).

After optimization of the reaction conditions, the asymmetric Michael addition was extended to various nitroolefins **21a–i** with β-keto ester **16a** using catalyst **7** (Table 4).[5][7]

Table 4. Asymmetric Michael additions of β-keto ester **16a** with *trans*-β-nitroolefins **21a-i** using organocatalyst **7**

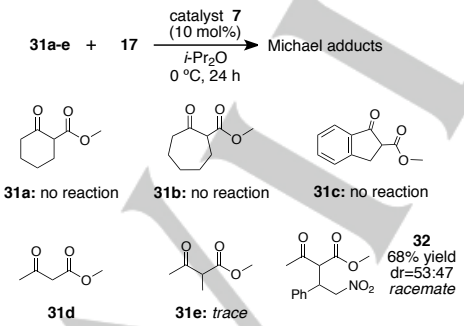


entry	**21a-i**	products	yield (%)[a]	dr[b]	ee (%)[c]
1	 **21a**	 **22**	97	91:9	35
2	 **21b**	 **23**	99	90:10	35
3	 **21c**	 **24**	99	89:11	49
4	 **21d**	 **25**	74	89:11	20
5	 **21e**	 **26**	83	89:11	31
6	 **21f**	 **27**	93	88:12	59
7	 **21g**	 **28**	94	89:11	30

8	 **21h**	 **29**	86	91:9	70
9	 **21i**	 **30**	-	-	-

[a]Isolated yield. [b]Diastereoselectivity was determined by ^{1}H-NMR. [c]The ee of isomer was determined by HPLC using CHIRALCEL OD-H, CHIRALPAK IC (hexane:2-propanol = 90:10, hexane:EtOH = 90:10).

As summarized in Table 4, in most cases, the desired Michael adducts **22–29** were obtained at good yields and stereoselectivities. The reactions of substrate **16a** with *p*-halogenated nitrostyrenes **21a–c** also proceeded at good chemical yields and diastereoselectivities, but with low to moderate enantioselectivities (**22**: 97%, dr = 91:9, 35% ee; **23**: 99%, dr 90:10, 35% ee; **24**: 99%, dr = 89:11, 49% ee) (entries 1–3). Although the reaction using *p*-methylated nitrostyrene **21d** also afforded the corresponding Michael adduct **25**, the enantioselectivity was substantially reduced (74%, dr = 89:11, 20% ee) (entry 4). Similarly, the use of *p*-methoxynitrostyrene **21e** also afforded the corresponding adduct **25** at good chemical yield and diastereoselectivity, but with low enantioselectivity (83%, dr = 89:11, 31% ee) (entry 5). When bulkier *o*-bromonitrostyrene **21f** was used as a Michael acceptor, enantioselectivity was increased to a moderate level with good chemical yield and diastereoselectivity (93%, dr = 88:12, 59% ee) to afford the corresponding adduct **27** (entry 6). Furthermore, the reaction using heterocyclic 2-1-(2-furyl)-2-nitroethylene **21g** was also carried out and adduct **28** was obtained at good chemical yield with low enantioselectivity (94%, dr = 89:11, 30% ee) (entry 7). On the other hand, the use of similar heterocyclic 2-[(*E*)-2-nitrovinyl]thiophene **21h** afforded the adduct **29** at good chemical yield and stereoselectivity (86%, dr = 91:9, 70% ee) (entry 8). In a similar manner, the reaction is also examined with aliphatic nitroolefin **21i** with **16a** in superior reaction conditions (*i*-Pr_2O, 0 °C, 24 h). However, the reaction did not proceed under these conditions (entry 9).



Scheme 3. Asymmetric Michael additions of cyclic or acyclic β-keto esters **31a-e** with **17** using organocatalyst **7**

Moreover, we also examined the reactions of six membered 2-methoxycarbonylcyclohexanone **31a**, seven membered 2-methoxy-carbonylcycloheptanone **31b** and 2-methoxycarbonyl-indanone **31c** with **17**, respectively, in the superior reaction conditions (*i*-Pr_2O, 0 °C, 24 h)(Scheme 3). However, catalyst **7** did not show catalytic activity in their reactions to afford the corresponding Michael adducts. And also, the uses of acyclic β-keto esters **31d** or **31e** instead of cyclic β-keto esters were examined (Scheme 3). The reaction of **17** with simple **31d** afforded the corresponding Michael adduct **32** with good chemical yield and diastereoselectivity (68%, dr = 53:47), but racemate. On the other hand, the use of bulkier **31e** gave only trace amount of the corresponding adduct. Unfortunately, catalyst **7** did not show catalytic activity to some substrates **21i** and **31a-c,e**. It might be that substrates do not coordinate with catalyst **7** due to steric interaction between them, given the bulkiness of this catalyst, although the actual reason remains unclear.

Considering both the good enantioselectivity (91% ee) of the chiral Michael adduct [2*R*,3*S*]-**18a** that was obtained in the reaction of **16a** with **17** using catalyst **7** and the results of its calculation studies (Fig. 2–5), an enantioselective reaction course is proposed as follows (Scheme 3).

First, the frontier orbital DFT calculation between **16a** and **17** was examined for consideration of the regioselectivity of the reaction between **16a** and **17** (Fig. 2). For the DFT calculation,

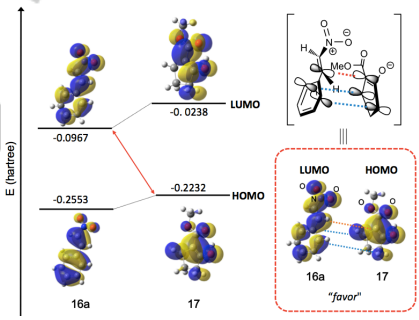


Fig. 2. The frontier orbitals between **16a** and **17** obtained by DFT calculations at the 6-31 G(d) level using a B3LYP exchange-correction functional (the blue and red dotted lines in the square expressed an interactions between the molecular orbitals of 1**6a** and **17**).

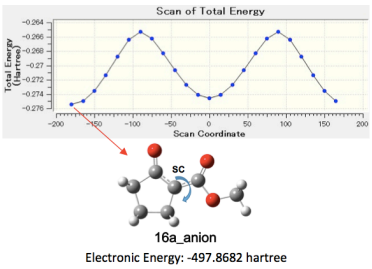


Fig. 3. The scan of total energies for **16a**-anion

the conformation of **16a-anion** moiety was assumed by using the scan of total energy analysis (Fig. 3). The energy levels of the orbitals indicated the dominant interaction between the HOMO of **16a** and the LUMO of **17**, and their orbital phase and the coefficient of the orbital clearly showed matching in favor of overlapping to afford the observed configuration of major adduct **18a** (Fig. 2).

Moreover, the conformational analysis of catalyst **7** was carried out using the scan of total energy of catalyst **7-cation** for estimation of the enantioselective reaction course (Fig. 4).

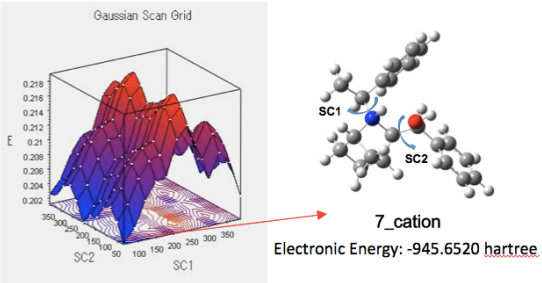


Fig. 4. The scan of total energies for **7**

Based on the calculation results, the structure of catalyst **7-cation** might be fixed by the intramolecular hydrogen bonding interaction between amino nitrogen atom and the hydroxyl hydrogen atom at the side chain; thereby, **7-cation** might have a conformation with less steric interaction between the bulky 2-azanorbornane skeleton and the phenyl group on the (*S*)-phenylethyl substituent at the nitrogen atom.

In addition, in the electrostatic potential maps of **7-cation**, **16a-anion**, and **17** based on the Mulliken charge distribution, the positive charges were observed around both the amino nitrogen atom and the hydroxyl hydrogen atom in the catalyst **7-cation**, and the negative charges were observed around both the nitro oxygen atoms in nitrostyrene **17** and the ester oxygen atoms in the β-keto ester moiety **16a-anion** (Fig. 5).

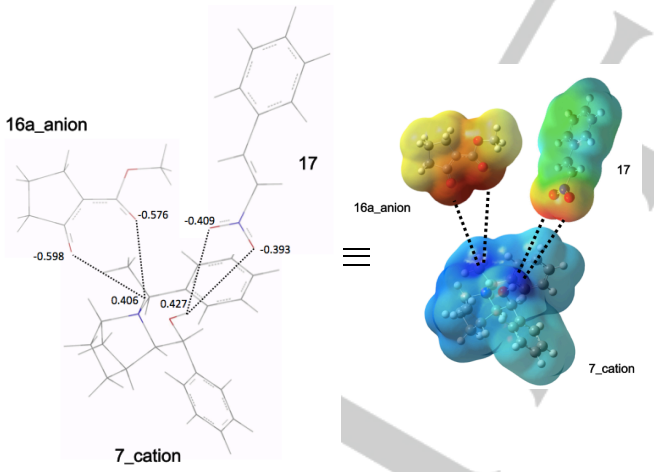
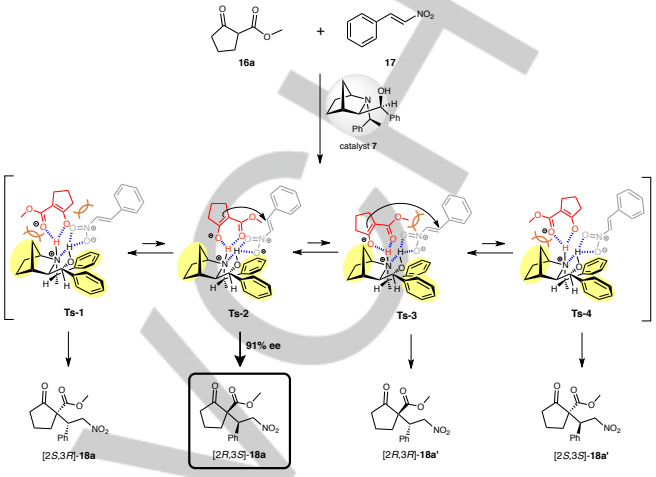


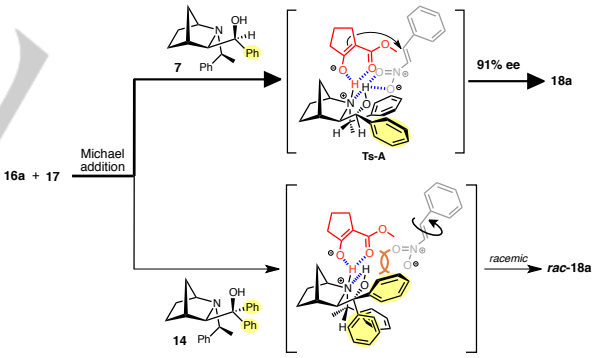
Fig. 5. The electrostatic potential maps of **7-cation**, **16a-anion** and **17**

Considering the above calculation results, the reaction might proceed through any proposed **Ts-1-4**, in which substrate **16a** fixes with the ammonium hydrogen atom and **17** fixes with the hydrogen atom that is formed by the intramolecular hydrogen bonding interaction between amino nitrogen atom and the hydroxyl hydrogen atom on the ammonium catalyst species. In the proposed **Ts-1-4**, the reaction might proceed through **Ts-2**, which has smaller steric interactions both between substrates **16a** and **17** and between **16a** and the ammonium catalyst species than those of **Ts-2-4**, which have a larger steric interaction among substrates **16a**, **17,** and the ammonium catalyst species (Scheme 4).



Scheme 4. Plausible reaction course

In this reaction, 2-azanorbornane **7** with a *mono*-phenylmethanol moiety and 2-azanorbornane **14** with a *di*-phenylmethanol moiety showed a great difference in catalytic activities; namely, the reaction using catalyst **7** afforded the chiral Michael adduct **18a** at good enantioselectivity (91% ee) (entry 16, Table 2), while that using catalyst **14** only afforded racemate **18a** (entry 9, Table 1). This might depend on the steric influences of the bulky structures of catalysts **7** and **14** (Scheme 5).



Scheme 5. Differences of enantioselectivities by catalysts **7** and **14**

Thus, less bulky catalyst **7** might fix both substrates **16a** and **17** by the hydrogen bonding interaction to afford high enantioselectivity (91% ee). On the other hand, catalyst **14** that is bulkier than catalyst **7** might be difficult to fix with substrate **17** for the steric influence of the phenyl group on the side chain.

Conclusions

Newly designed optically active 2-azanorbornane-based amino alcohol organocatalysts were developed based on a new design

concept and their catalytic activities were examined in the asymmetric Michael addition of various β-keto esters with nitroolefins. All catalysts showed activities as catalysts in this reaction. In particular, *N*-(*S*)-phenylethylated 2-azanorbornane **7** with a *mono*-phenylmethanol moiety showed the best catalytic performance and the corresponding chiral Michael adducts having a quaternary chiral carbon center were obtained with good to excellent chemical yields (up to 99%), diastereoselectivities (up to 91:9), and enantioselectivities (up to 91% ee). The modification of 2-azanorbornane-based amino alcohol organocatalysts, the application to other substrates, and detailed mechanistic study are underway.

Experimental Section

General

All reactions were performed under argon atmosphere in flame dried glassware. Thin layer chromatography was performed on silica gel 60 F254, and the analytes were detected under UV light and coloration of TLC performed in ninhydrin and iodine vapor. Column chromatography was performed on silica gel 60N (40-100 μm), and PLC was performed on silica gel 60 F254. Infrared (IR) spectra were measured with a FT-IR Spectro-photometer (JASCO FT/IR-400). Optical rotations were measured on JASCO DIP-360 digital polarimeter. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were measured using JEOL JNM-ECS 500 instrument and chemical shifts (δ) are expressed in ppm down-field from internal TMS. Diastereomeric ratio was determined by ^{1}H-NMR of crude reaction mixture and enantiomeric excess was determined by high performance liquid chromatography (HPLC) with DAICEL CHIRALPAK OD-H and CHIRALPAK IC columns. HRMS data were collected in electron impact (EI) mode using Hitachi RMG-GMG sector instrument.

(1*S*,3*R*,4*R*)-2-Methyl-2-azabicyclo[2.2.1]hepane-3-*exo*-phenylmethanol (9)

To the stirred solution of **8** (0.100g, 1.0 mmol) in acetonitrile (5 mL) were added methyl Iodide (0.33 mL, 1.1 mmol) and reaction mixture was allowed to reflux for 12 hours. After completion of the reaction indicated by TLC, the solvent was evaporated under reduced pressure and residue was purified by flash chromatography on silica gel (EtOAc/MeOH = 10/1) to give **9** (36 mg, 67%). $[\alpha]_D^{22}$ = 15.00 (c = 0.2, CH_2Cl_2); IR (neat) cm^{-1}: 3510, 3315, 2975, 1450. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.40-7.21 (m, 5H), 4.60 (d, *J* = 4.9 Hz, 1H), 3.29 (s, 1H), 2.28 (s, 3H), 2.03 (m, 2H), 1.92-1.79 (m, 3H), 1.76 (br s, 1H), 1.43 (m, 4.4 Hz, 1H), 1.35-1.23 (m, 1H), 1.16-1.01 (m, 2H). ^{13}C-NMR (500 MHz, $CDCl_3$) δ 142.04, 128.23, 127.00, 126.12, 75.03, 72.59, 62.64, 38.42, 36.96, 36.37, 30.20, 21.61. Ms m/z: 110 [M+H]. HRMS (EI) calcd for ($C_{14}H_{19}NO$): 217.1467, found: 217.1460.

(1*S*,3*R*,4*R*)-[(*S*)-α-Phebylethyl]-2-azabicyclo[2.2.1]hepane-3-*exo*-phenyl(trimethylsilyoxy)methane (12)

To the stirred solution (6 mL) of trimethylsiliyl triflate (0.07 mL, 0.39 mmol) and Et_3N (0.54 mL, 0.39 mmol) in DCM the compound **7** (0.100g, 0.325 mmol) was added at -30 ℃ under argon. After stirring for 10 min, the solution was allowed to stir at room temperature for 24 h. After completion of reaction indicated by TLC, the reaction mixture was quenched with H_2O. The resulting mixture was extracted with DCM (3×10 mL), and the combined organic layers were washed with brine. After drying over Na_2SO_4, the solvent was removed under reduced pressure. The residue was purified by using flash chromatography on silica gel (*n*-hexanes/EtOAc = 5/1) to give **12** (0.82, 67%) as a colourless liquid. $[\alpha]_D^{24}$ = -54.00 (c = 0.5, CH_2Cl_2); IR (neat) cm^{-1}: 3026, 1248, 1360, 1350. ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.51-7.45 (m, 2H), 7.42-7.35 (m, 2H), 7.33-7.27 (m, 1H), 7.16-7.02 (m, 3H), 6.73-6.66 (m, 2H), 3.67 (s, 1H), 3.59 (s, 1H), 3.47 (q, *J* = 6.5 Hz, 1H), 2.28-2.19 (m, 2H), 2.00 (s, 1H), 1.97-1.88 (m, 1H), 1.43 (m, 1H), 1.37 (d, *J* = 6.6 Hz, 3H), 1.33-1.24 (m, 1H), 1.09 (d, *J* = 8.6 Hz, 1H), 0.97-0.91 (m, 1H), -0.01-0.04 (m, 9H). ^{13}C-NMR (500 MHz, $CDCl_3$) δ 146.76, 144.9, 129.08, 128.32, 127.55, 127.45, 126.14, 125.93, 76.74, 76.02, 62.01, 58.27, 37.02, 36.42, 29.76, 23.12, 22.79, 0.62. Ms m/z: 380 [M+H]. HRMS (EI) calcd for ($C_{24}H_{34}NOSi$): 379.6104, found: 380.2405.

General Procedure for Catalytic Asymmetric Michael addition of β-Keto Ester 16a to Nitroolefins 21a-i

To the solution of catalyst **7** (10 mol%) in dry *i*-Pr_2O (2 mL) were added nitroolefines **21a-i** (0.2 mmol) and β-keto ester **16a** (0.4 mmol) and the solution was stirred at 0 °C for 24 h, after completion of the reaction the solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (*n*-hexane/AcOEt = 10/1) to give the chiral Michael adducts **22-30**. The compounds **18a** and **23-32** are the known compounds and the structures were identified by spectral data which were in good agreement with those reported.[5]

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Keywords: organocatalyst・amino alcohol・2-azanorbornane・Michael addition・asymmetric reaction

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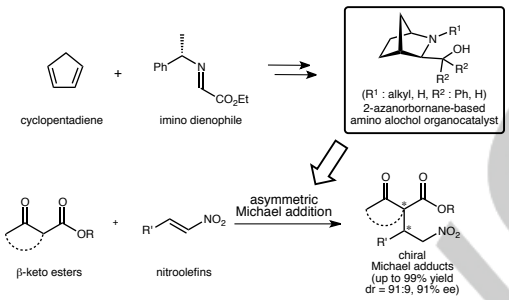
Entry for the Table of Contents (Please choose one layout)

Layout 1:

A highly enantioselective Michael addition of β-keto esters to nitroolefins was carried out using newly designed optically active 2-azanorbornane-based amino alcohol organocatalysts to produce the corresponding chiral Michael adducts in good chemical yields (up to 99%) and stereoselectivities (up to dr = 91:9, up to 91% ee).



Key Topic *Asymmetric Organocatalysis

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2-Azanorbornane-Based Amino Alcohol Organocatalysts for Asymmetric Michael Reaction of β-Keto Esters with Nitroolefins

*Organocatalyst, 2-Azanorbornane-based amino alcohols, Asymmetric Michael Addition