Chiral primary amino alcohol organobase catalyst for the asymmetric Diels-Alder reaction of anthrones with maleimides

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Chiral primary amino alcohol organobase catalyst for the asymmetric Diels-Alder reaction of anthrones with maleimides

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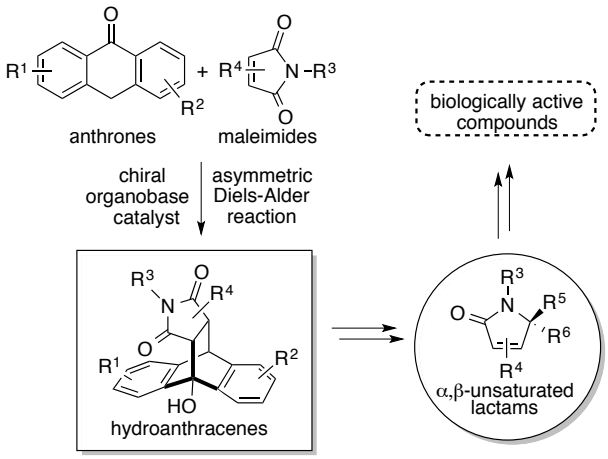
ABSTRACT - Simple chiral TES-amino alcohol organocatalysts containing a bulky silyl [triethylsilyl: TES] group on oxygen atom at γ-position were designed and synthesized as new organocatalysts for the enantioselective Diels-Alder (DA) reaction of anthrones with maleimides to produce chiral hydroanthracene DA adducts (up to 99% yield with up to 94% ee).

Keywords: Organobase catalyst, Diels-Alder reaction, amino alcohol, anthrones, maleimides

1. Introduction

Asymmetric organocatalysis has emerged as an important and rapidly growing area of synthetic organic chemistry, and excellent covalent and non-covalent organocatalysts have been developed for use in a wide range of reactions.[1] The base catalyzed asymmetric Diels-Alder (DA) reaction is one of the most straightforward and atom economical method to construct chiral six-membered carbocyclic compounds in synthetic organic chemistry.[1] Among the dienes, anthrone has been considered as one of the powerful diene component



Scheme 1. The asymmetric Diels-Alder reaction of anthrones with maleimides and its application.

and can react with a variety of dienophiles.[2] Particularly, the DA reaction of anthrone with *N*-substituted maleimide[3] to construct a cage anthrone derivatives, which are key intermediates for the preparations of some unsaturated lactams with antipsoriatic and antiproliferative biological activities, have been studied extensively.[4] Several efficient chiral organobases such as cinchona alkaloids,[5] pyrrolidine derivatives,[6] cyclic guanidines,[7] bisoxazolines,[8] and tertiary amine thioureas[9] have been used to promote those reactions (Scheme 1).[10] However, to the best of our knowledge, the effectiveness of primary β-amino alcohol[11] organocatalyst as an organobase in this reaction has not been shown yet.

We designed a series of chiral primary amino alcohols **1a-f, 2a-h,** and **3-5** with several substituent groups at the β-position as an organobase catalyst (Scheme 2). The reaction using these designed amino alcohol catalysts might proceed through the transition state **X** (Figure 1). Thus, anionic anthracene is formed by the reaction with amino alcohol acting

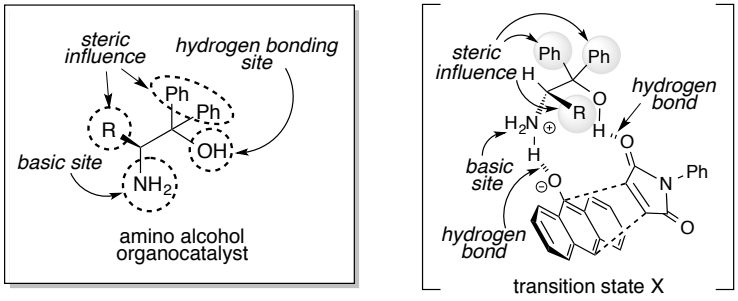


Figure 1. Concept for catalyst design.

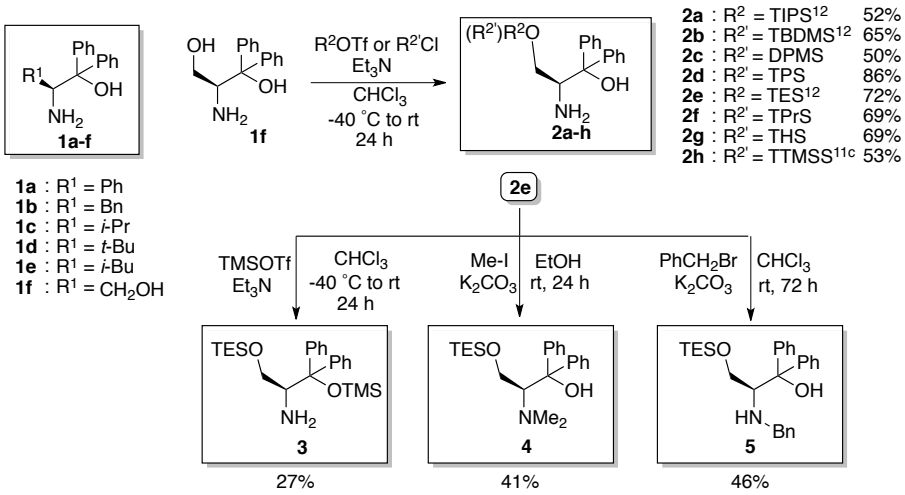
as a base. Then both anionic diene and maleimide dienophile are fixed by the hydrogen bondings with the ammonium alcohol and might react stereoselectively to afford the DA adduct in good chemical yield and enantioselectivity.

We report herein that the newly designed primary amino alcohol containing a bulky silyl group on oxygen atom at γ-position is an efficient organobase catalyst for the asymmetric DA reaction of anthrone with maleimides affording chiral hydroanthracene as a DA adduct with a good chemical yield (up to 99%) and an excellent enantioselectivity (up to 94% ee).

2. Results and Discussion

Primary β-amino alcohol catalysts **1a-f,**[11] **2a-h** and **3-5** containing several substituent groups at the β-position were prepared as follows (Scheme 2). Thus, amino alcohols **1a-f** containing aliphatic or aromatic substituent groups at the β-position were easily prepared by well-known Grignard reactions with the corresponding α-amino acid esters, and the bulkier

β-amino alcohol catalysts **2a-g** containing several silyl groups on oxygen atom at the γ-position were also easily prepared[11b] by the reactions of the amino alcohol **1f** with R^2OTf [R^2 = TIPS (triisopropylsilyl), TES (triethylsilyl)] or $R^{2'}Cl$ [$R^{2'}$ = TBDMS (*tert*-butyldimethylsilyl), DPMS (diphenylmethylsilyl), TPS (triphenylsilyl), TPrS (tripropylsilyl), THS (trihexylsilyl)] in moderate to good yields (50-86%). Furthermore, the bulkiest β-amino alcohol catalyst **2h** containing our explored super silyl [TTMSS: tris(trimethylsilyl)silyl] group[11c] on oxygen atom at the γ-position was also easily obtained



Scheme 2. Preparations of amino alcohol organocatalysts.

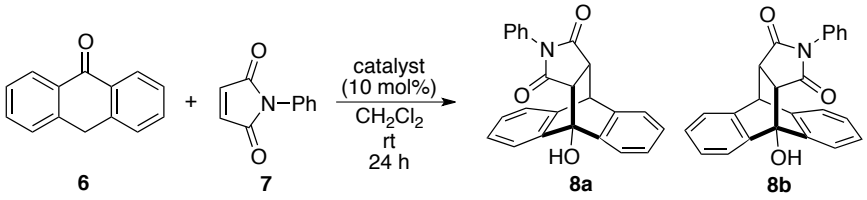
by the reaction of **1f** with TTMSSCl in 53% yield.[11c] In addition, catalyst **3** masked the hydroxy group at α-position by TMS (trimethylsilyl) group was prepared from the reaction of **2e** with TMSOTf in 27% yield. Moreover, the catalyst **4** containing tertiary amino group was obtained by the reaction of **2e** with MeI in moderate yield (41%). The catalyst **5** containing secondary amino group was also prepared by the reaction of **2e** with benzyl bromide in 46% yield.

We first examined the DA reaction of anthrone **6** with *N*-phenylmaleimide **7** using the common amino alcohols **1a-f** as organobase catalyst (Table 1). The reaction of **6** (1 equiv.)

with **7** (1.2 equiv.) was carried out at room temperature in CH_2Cl_2 in the presence of 10 mol% of catalysts **1a-f**, respectively (entries 1-6). The obtained DA adducts **8** (**8a** and/or **8b**) were isolated and those absolute configurations were determined on the basis of both literature values of optical rotation and retention times on HPLC chiral column.[9] Catalysts **1a-e** did not show satisfactory catalytic activity and afforded the DA adduct **8** in only low chemical yields (14-29%) and enantioselectivities (3-23% ee). Furthermore, amino diol catalyst **1f** afforded **8** in good chemical yield (76%), but the enantioselectivity was quite low (9%). Considering with the above results, we next examined the same DA reaction using amino alcohols **2a-h** containing bulkier substituted silyl group on oxygen atom at γ-position in the catalyst. The reaction of **6** (1 equiv.) with **7** (1.2 equiv.) was carried out at room temperature in CH_2Cl_2 in the presence of catalysts **2a-h** (10 mol%), respectively (entries 7-14). As results of these reactions, all catalysts showed a catalytic activity and afforded the DA adduct **8** in moderate to fairly good chemical yields (32-92%). Furthermore, enantioselectivity also increased in the reaction using almost catalysts **2a-c,e-g** (32-43% ee), other than TPS-**2d** (16% ee) and TTMSS-**2h** (25% ee) catalysts, although satisfactory enantioselectivities were not observed under these reaction conditions. The best chemical yield and enantioselectivity were 92% and 42 % ee in the case of using the catalyst **2e** which was bearing TES moiety on oxygen atom at γ-position in the molecule (entry 11). From these results, it was indicated that the use of an amino alcohol catalyst bearing considerably bulky silyl substituent on oxygen atom at γ-position might be not effective for obtaining an satisfactory enantioselectivity in this reaction. The same reaction using TES-amino silyl ether catalyst **3** in which the hydroxyl group was protected by a

trimethylsilyl (TMS) group brought about a great decrease in chemical yield and enantioselectivity (74%, 6% ee, entry 15) in comparison with the result of the reaction using the corresponding amino alcohol catalyst **2e** with free

Table 1
The asymmetric Diels-Alder reaction of anthrone **6** with *N*-phenlmaleimide **7**



6 **7** **8a** **8b**

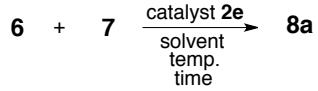
entry	catalyst	yield (%)[a]	ee (%)[b] **8a**	**8b**
1	**1a**	23	12	
2	**1b**	17	23	
3	**1c**	28	17	
4	**1d**	14		7
5	**1e**	29	3	
6	**1f**	76	9	
7	**2a**	68	34	
8	**2b**	69	42	
9	**2c**	32	32	
10	**2d**	40	16	
11	**2e**	92	42	
12	**2f**	65	43	
13	**2g**	57	41	
14	**2h**	66	25	
15	**3**	74		6
16	**4**	84		21
17	**5**	37	11	

[a]Isolated yields. [b]The ee was determined by HPLC using a Daicel AD-H column(*n*-hexane : 2-propanol = 80:20).

hydroxyl group (**2e**: 92%, 42% ee, entry 11). This difference may be due to the loss of the ability for hydrogen bonding to maleimide dienophile **7** or the steric influence of the bulkier TMS group on the molecule, although the reasons are not clear. Furthermore, the catalytic abilities of both catalyst **4** with tertiary amino group and catalyst **5** with secondary amino group in the molecules were also examined (entries 16, 17). However, these catalysts did not afford DA adduct **8a** in satisfactory enantioselectivities in spite of stronger basic property than primary catalyst **2e**.

In order to optimize the reaction conditions using the superior TES-amino alcohol organocatalyst **2e**, we next examined the effect of the molar ratio of catalyst **2e**, the effect of solvent, reaction temperature and reaction time (Table 2). The increase of catalytic loading of **2e** to 20 mol% resulted in a slight increase in both the chemical yield (93%) and enantioselectivity (46% ee) (entry 1) than that of the reaction containing 10 mol% of **2e** (Table 1, entry 11). However, the decrease of catalytic loading of **2e** to 5 mol% resulted in a substantial decrease in the chemical yield (50%) with an enantioselectivity (28% ee) (entry 2). To further improve the enantioselectivity, the reactions using **2e** were examined at lower temperatures of both 0 °C and -30 °C (entries 3 and 4). However, satisfactorily results were not observed in chemical yield and enantioselectivity under each temperature. Next, we also examined the solvent effects on this reaction. Commonly used aprotic ($CHCl_3$, $ClCH_2CH_2Cl$, Et_2O, MeCN, benzene, toluene), aprotic polar (DMF, DMSO), and protic (EtOH, MeOH) solvents were screened, respectively (entries 5-14). Only $ClCH_2CH_2Cl$

Table 2
Optimization of the reaction conditions using catalyst **2e**



entry	**2e** (mol%)	solvent	temp. (°C)	time (h)	yield (%)[a]	ee (%)[b]
1	20	CH_2Cl_2	rt	24	93	46
2	5	CH_2Cl_2	rt	24	50	28
3	20	CH_2Cl_2	0	24	65	27
4	20	CH_2Cl_2	-30	24	24	11
5	20	$CHCl_3$	rt	24	76	43
6	20	$ClCH_2CH_2Cl$	rt	24	99	27
7	20	Et_2O	rt	24	81	10
8	20	MeCN	rt	24	60	7
9	20	benzene	rt	24	84	17
10	20	toluene	rt	24	76	18
11	20	DMF	rt	24	--	--
12	20	DMSO	rt	24	--	--
13	20	MeOH	rt	24	--	--
14	20	EtOH	rt	24	--	--
15	20	CH_2Cl_2	rt	48	98	47

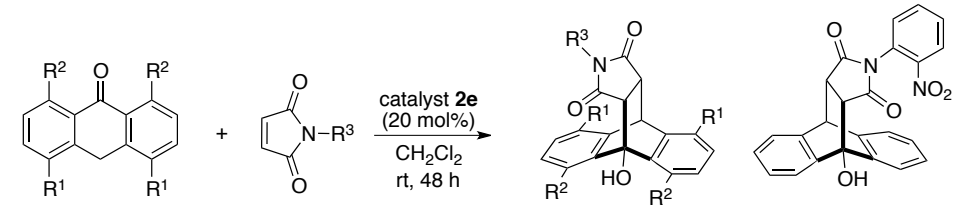
[a]Isolated yields. [b]The ee was determined by HPLC using a Daicel AD-H column(*n*-hexane : 2-propanol = 80:20).

afforded an excellent chemical yield (99%) (entry 6), but other solvents gave chiral DA adduct **8a** in moderate to good yields (60-84%) (entries 5-10). Unfortunately, no improvements in enantioselectivity were observed in these solvents in comparison with the use of CH_2Cl_2 (Table 1, entry 11). Furthermore, the reactions did not proceed in the use of aprotic polar (DMF, DMSO) and protic (EtOH, MeOH) solvents (entries 11-14). In the best reaction condition (CH_2Cl_2, **2e**: 20 mol%, rt), extending the reaction time from 24 to 48 h led to increase the chemical yield (98%) with 47% ee (entry 15).

Under the optimized reaction conditions, a wide range of the DA reactions with anthrones **6, 9a,b**[2] and maleimides **7, 10a-f**[3-9] were investigated using superior TES-catalyst **2e** and the results are shown in Table 3. The obtained DA adducts **11a-h** were isolated and those absolute configurations were determined on the basis of both literature values of optical rotation and retention times on HPLC chiral columns.[7,9,10a] The use of *N*-methylmaleimide **10a** afforded the corresponding DA adduct **11a**[10a] in excellent chemical yield (97%), although enantioselectivity was low (39% ee) (entry 1). The reaction with *N*-(4-methylphenyl)maleimide **10b** also afforded the DA adduct **11b**[10a] in a fairly good chemical yield (91%) and the enantioselectivity also increased to 32% ee (entry 2). Although bulkier *N*-benzylmaleimide **10c** also did not afford the **11c**[9] in a satisfactorily enantioselectivity (46% ee), the chemical yield was fairy good (93%) (entry 3). Based on the results of the reaction using maleimides **7, 10a-c**, the DA reaction of **6** with *N*-(2-nitropheny)lmaleimide **10d** having a polar and bulkier strong electron-withdrawing nitro group at 2-position on phenyl group using TES catalyst-**2e** (20 mol%) was examined at rt for 48 h (entry 4). The reaction was proceeded smoothly and afforded the DA adduct

11d[7] in excellent chemical yield (97%) and with better enantioselectivity (66% ee) in comparison with the result using other maleimides **7, 10a-c** (entry 4). However, the reactions using both *N*-(3-nitrophenyl)maleimide **10e** and *N*-(4-nitrophenyl)maleimide **10f** also afforded the corresponding DA adducts **11e**[10a],**f**[10a] respectively, in excellent chemical

Table 3
The asymmetric Diels-Alder reaction of anthrones **6, 9a,b** with maleimides **7, 10a-f** using catalyst **2e**



6, 9a,b

6 : $R^1 = R^2 = H$
9a : R^1 = Cl, $R^2 = H$
9b : $R^1 = H$, R^2 = Cl

7, 10a-f

7 : R^3 = Ph
10a : R^3 = Me
10b : R^3 = 4-Me-Ph
10c : R^3 = Bn
10d : R^3 = 2-NO_2-Ph
10e : R^3 = 3-NO_2-Ph
10f : R^3 = 4-NO_2-Ph

11a-c,e-h

11a : $R^1 = R^2 = H$, R^3 = Me
11b : $R^1 = R^2 = H$, R^3 = 4-Me-Ph
11c : $R^1 = R^2 = H$, R^3 = Bn
11d : $R^1 = R^2 = H$, R^3 = 2-NO_2-Ph
11e : $R^1 = R^2 = H$, R^3 = 3-NO_2-Ph
11f : $R^1 = R^2 = H$, R^3 = 4-NO_2-Ph
11g : R^1 = Cl, $R^2 = H$, R^3 = Ph
11h : $R^1 = H$, R^2 = Cl, R^3 = Ph

11d

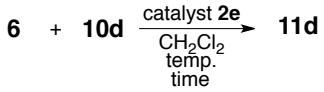
entry	diene	dienophile	DA adduct	yield (%)[a]	ee (%)[b] 11a-c,e-h	ee (%)[b] 11d
1	**6**	**10a**	**11a**	97	39	
2	**6**	**10b**	**11b**	91	32	
3	**6**	**10c**	**11c**	93	46	
4	**6**	**10d**	**11d**	97		66
5	**6**	**10e**	**11e**	97	32	
6	**6**	**10f**	**11f**	95	35	
7	**9a**	**7**	**11g**	98	25	
8	**9b**	**7**	**11h**	98	38	

[a]Isolated yields. [b]The ee was determined by HPLC using a Daicel AD-H column(n-hexane : 2-propanol = 80:20).

yields (**11e**: 97%, **11f**: 95%), but satisfactory enantioselectivities (**11e**: 32% ee, **11f**: 35% ee) were not obtained in the optimized reaction conditions (entries 5,6). Furthermore, the reactions of dichloroanthrones **9a,b** with **7** were also examined in the same reaction conditions (entries 7,8). Although, that reactions also afforded the corresponding DA adducts **11g**[10a],**h**[10a] in excellent chemical yields (**11g**: 98%, **11h**: 98%), satisfactory enantioselectivities were not obtained (**11g**: 25% ee, **11h**: 38% ee).

To further improve the enantioselectivity in the reaction of **6** with **10d** using **2e**, we next examined the effect of the molar ratio of catalyst **2e**, reaction temperature and reaction time (Table 4). The reaction was examined at lower temperatures of both 0 °C and -20 °C (entries 1 and 2). The best enanthioselectivity (94% ee) with good chemical yield (65%)

Table 4
Optimization of the reaction conditions using catalyst **2e**



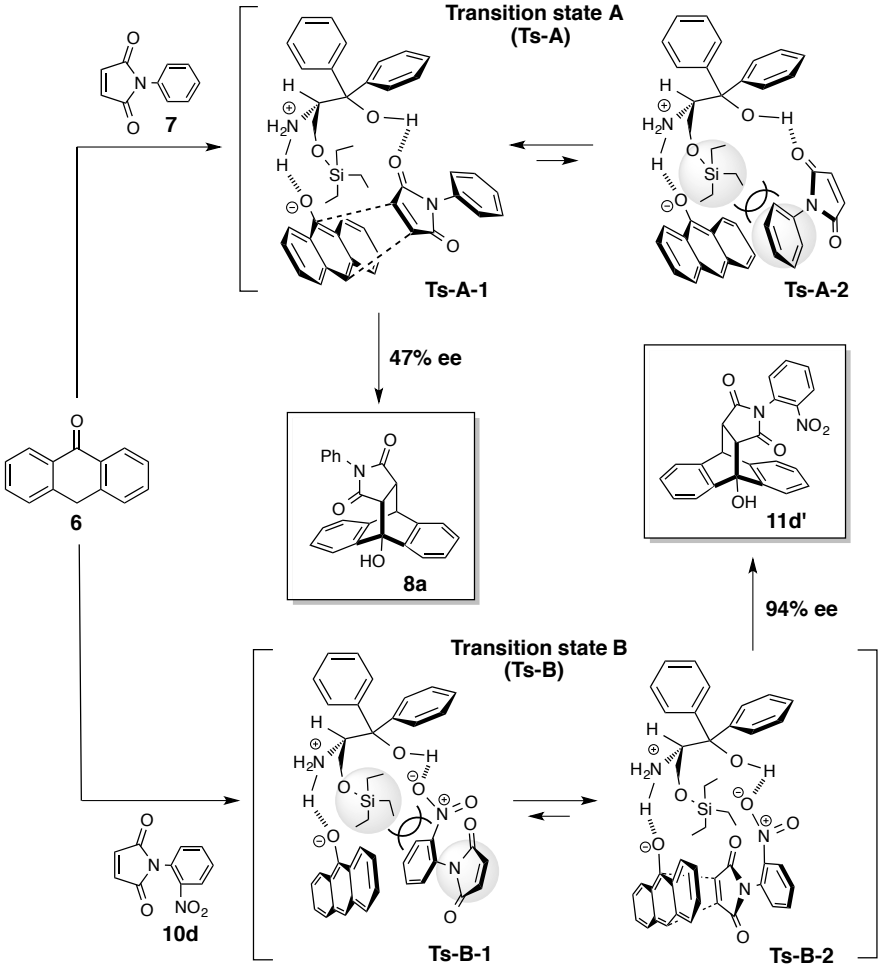
entry	**2e** (mol%)	temp. (°C)	time (h)	yield (%)[a]	ee (%)[b]
1	20	0	48	65	94
2	20	-20	48	21	86
3	10	0	48	39	91
4	5	0	48	24	89
5	20	0	72	83	94

[a]Isolated yields. [b]The ee was determined by HPLC using a Daicel AD-H column(n-hexane : 2-propanol = 80:20).

was obtained when the reaction was carried out at 0 °C (entry 1). However, the reaction at -20 °C brought about a decrease of chemical yield and enantioselectivity (21%, 86% ee)(entry 2). Furthermore, the decrease of catalytic loading of **2e** to 10 mol% and 5 mol%, respectively, resulted in a significant decrease in the chemical yield (10 mol%: 39%, 5 mol%: 24%), respectively, although those enantioselectivities were good (10 mol%: 91% ee, 5 mol%: 89% ee) (entries 3 and 4). In the reaction using catalyst **2e** (20 mol%), extending the reaction time from 48 to 72 h led to increase the chemical yield (83%) with 94% ee (entry 5).

Based on the observed enantiopurities (DA adduct **8a**: 47% ee, Table 2, entry 15, DA adduct **11d**: 94% ee, Table 4, entry 5) of optically active DA adducts **8a** or **11d** that were obtained from the reactions of **6** with **7**, or with **10d**, the models of the enantioselective reaction courses were proposed as follows (Scheme 3). The reaction of **6** with **7** afforded the

DA adduct **8a** might go through the transition state **Ts-A-1** which has a less steric interaction between TES group on the ammonium alcohol and maleimide **7** than that of the transition state **Ts-A-2** in **Ts-A**. Thus, in **Ts-A-1**, the diene and the dienophile are fixed by the two hydrogen bonding interactions between the ammonium site on the ammonium alcohol intermediate and the oxygen atom on the anionic anthracene **6**, and between the hydroxy group on the ammonium alcohol intermediate and the carbonyl group



Scheme 3. Plausible reaction courses.

on maleimide **7**, and then, might react stereoselectively from the one reaction site (i.e.

Ts-A-1). On the other hand, the reaction of **6** with **10d** affording the DA adduct **11d** might go through the different transition state **Ts-B**, based on that both the reaction proceeded with a high enantioselectivity (94% ee) and the obtained DA adduct **11d** have an opposite absolute stereochemistry in comparison with the reactions using other anthrones **6,9a,b** and maleimides **7, 10a-c,e,f** in the manuscript. Thus, reaction proceed through the transition state **Ts-B-2** in which diene and dienophile were fixed by two hydrogen bonding interactions between ammonium site, hydroxy site of ammonium alcohol and anionic oxygen atom on anthrone **6**, strong ionic nitro group on the maleimide **10d**, respectively. Also, **Ts-B-2** shows a less steric interaction between TES group on the ammonium alcohol and the maleimide part in dienophile **10d** when compard with **Ts-B-1**, although the reason is not clear.

3. Conclusions

In conclusion, we have developed new chiral amino alcohols **2a-h, 3-5** bearing silyl groups on oxygen atom at γ-position. The catalysts were easily prepared from the condensation of cheaply and commercially available chiral amino alcohols in two or three steps. The Diels-Alder reactions of anthrones with *N*-substituted maleimides using the explored catalysts were examined. In these catalysts, TES-amino alcohol catalyst **2e** provided the corresponding hydroanthracene DA adducts **11d** in fairly good chemical yield

(up to 97%) and moderate enantioselectivity (up to 94% ee). Further studies, including catalyst design modifications and mechanistic investigations, are in progress.

4. Experimental

4.1. General

All reactions were carried out under an argon atmosphere in flame-dried glassware with magnetic stirring. Thin layer chromatography (TLC) was performed on silica gel 60 F_{254} and analytes were detected using UV light (254 nm) and iodine vapor. Column chromatography was carried out on silica gel 60N (40–100 μm) and preparative TLC was carried out on silica gel 60 F_{254}. Melting points were measured using a micro-melting point apparatus. Infrared (IR) spectra were measured with a FT/IR spectrophotometer (JASCO FT/IR-400). ^{1}H-NMR (500 MHz) and ^{13}C-NMR (125 MHz) spectra were measured in $CDCl_3$ on a JEOL JNM-ECA 500 spectrometer. ^{1}H-NMR data were reported as follows: chemical shifts in ppm from tetramethylsilane (0.0 ppm), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = double-doublet, m = multiplet and br = broad), coupling constants (Hz), and assignment. ^{13}C-NMR spectra were measured with complete proton decoupling. Chemical shifts were reported in ppm from the residual solvent as an internal standard ($CDCl_3$; 77.16 ppm). High performance liquid chromatography (HPLC) was performed using the chiral columns AD-H 4.6 mm x 25 cm column. Optical rotations were measured with JASCO DIP-360 digital polarimeter. HRMS

spectra were measured by EI using sector instruments on Hitachi RMG-6MG and JEOL-JNM-DX 303 spectrometers.

4.2. General procedure for the preparations of amino alcohol organocatalysts 2a-g

A solution of amino alcohol **1f** (1 mmol) in CH_2Cl_2 (15 mL) were added substituted silyl trifluoromethane sulfonates (1 mmol) or substituted silyl chlorides (1 mmol) and Et_3N (1.2 mmol) at -40 $^{\circ}$C under argon. The mixture was stirred for 24 h at room temperature. The reaction mixture was quenched with H_2O and extracted with $CHCl_3$. The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4 and evaporated to give a crude products **2a-g**. The residue was purified by column chromatography on silica gel (*n*-hexane : ethylacetate = 4 : 1) to give products **2a-g** (**2a** : 208 mg, 52%; **2b** : 232 mg, 65%; **2c** : 220 mg, 50%; **2d** : 431 mg, 86%; **2e** : 185 mg, 72%; **2f** : 275 mg, 69%; **2g** : 363 mg, 69%).

4.2.1. (*S*)-2-amino-1,1-diphenyl-3-(triisopropyllsilyloxy)propanol (2a)

Colorless oil; $[\alpha]_D^{24}$ = -57.1 (c 0.63, EtOH); IR (neat) cm^{-1}: 2942, 2889, 1449, 1248; ^{1}H-NMR ($CDCl_3$) δ: 7.60-7.59 (m, 2H), 7.51-7.47 (m, 2H), 7.34-7.14 (m, 6H), 3.95-3.93 (dd, J = 5.8 Hz, J = 3.8 Hz, 1H), 3.71-3.65 (m, 2H), 1.00-0.98 (m, 21H); ^{13}C-NMR ($CDCl_3$) δ: 146.1, 145.0, 128.5, 128.2, 126.7, 126.6, 125.6, 125.1, 79.1, 64.8, 57.4, 17.9, 11.7. EI-MS m/z: 399 (M^+); HRMS (EI) calcd for $C_{24}H_{37}NO_2Si$ (M^+): 399.2594, found:

399.2589.

4.2.2. (*S*)-2-amino-1,1-diphenyl-3-(*tert*-butyldimethylsilyloxy)propanol (2b)

White solid (Et_2O/hexane); mp 49-51 °C; $[\alpha]_D^{22}$ = -51.1 (c 0.45, EtOH); IR (neat) cm^{-1} : 2951, 2882, 1468, 1307; ^{1}H-NMR ($CDCl_3$) δ: 7.59-7.57 (m, 2H), 7.50-7.48 (m, 2H), 7.34-7.15 (m, 6H), 3.92-3.90 (t, *J* = 4.6 Hz, 1H), 3.59-3.58 (d, *J* = 4.6 Hz 2H), 0.86 (s, 9H), -0.02 (s, 3H), -0.05 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ: 146.0, 145.1, 128.5, 128.2, 126.7, 126.6, 125.5, 125.3, 125.1, 79.3, 64.6, 57.1, 25.8, 18.1, -5.6, -5.1; EI-MS m/z: 358 $(M+H)^+$; HRMS (EI) calcd for $C_{21}H_{31}NO_2Si$ $(M+H)^+$: 358.2202, found: 358.2202.

4.2.3. (*S*)-2-amino-1,1-diphenyl-3-(diphenylmethylsilyloxy)propanol (2c)

White solid (Et_2O/hexane); mp 89-90 °C; $[\alpha]_D^{20}$ = -64.8 (c 1.05, $CHCl_3$); IR (neat) cm^{-1} : 2948, 2885, 1428, 1255; ^{1}H-NMR ($CDCl_3$) δ: 7.55-7.12 (m, 20H), 4.00-3.97 (m, 1H), 3.68--3.66 (m, 1H), 0.57 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ: 146.4, 146.3, 146.2, 144.5, 135.3, 135.2, 134.3, 130.1, 129.9, 128.5, 128.2, 128.0, 126.8, 126.6, 125.6, 125.1, 78.5, 64.7, 60.5, 57.6, 55.7, -3.3; EI-MS m/z: 440 $(M + H)^+$; HRMS (EI) calcd for $C_{28}H_{30}NO_2Si$ $(M + H)^+$: 440.2046, found: 440.2054.

4.2.4. (*S*)-2-amino-1,1-diphenyl-3-(triphenylsilyloxy)propanol (2d)

White solid (Et_2O/pentane); mp 91-92 °C; $[\alpha]_D^{22}$ = -55.8 (c 0.52, $CHCl_3$); IR (neat) cm^{-1} : 2951, 2882, 1468, 1307; ^{1}H-NMR ($CDCl_3$) δ: 7.53-7.50 (m, 8H), 7.46-7.43 (m, 3H), 7.37-7.35 (m, 6H), 7.30-7.27 (m, 4H), 7.18-7.14 (m, 3H), 7.11-7.08 (m, 1H), 4.68 (s, 1H), 4.02-3.98 (dd, *J* = 6.5 Hz, *J* = 3.5 Hz, 1H), 3.80-3.75 (m, 2H); ^{13}C-NMR ($CDCl_3$) δ: 146.3, 144.1, 135.3, 133.5, 130.2, 128.4, 128.1, 128.0, 126.7, 126.5, 125.5, 125.0, 78.2, 65.0, 57.7; EI-MS m/z: 501 (M^+); HRMS (EI) calcd for $C_{33}H_{31}NO_2Si$ (M^+): 501.2124, found: 501.2123.

4.2.5. (*S*)-2-amino-1,1-diphenyl-3-(triethylsilyloxy)propanol (2e)

Colorless oil; $[\alpha]_D^{24}$ = -63.4 (c 0.55, EtOH); IR (neat) cm^{-1} : 2911, 2876, 1449, 1269; ^{1}H-NMR ($CDCl_3$) δ: 7.60-7.58 (m, 2H), 7.50-7.49 (m, 2H), 7.34-7.15 (m, 6H), 3.94-3.93 (t, *J* = 4.3 Hz, 1H), 3.60-3.59 (m, 2H), 0.91-0.88 (t, *J* = 8.0 Hz, 9H), 0.56-0.51 (q, *J* = 8.0 Hz, 6H); ^{13}C-NMR ($CDCl_3$) δ: 146.1, 145.0, 128.5, 128.2, 126.7, 126.5, 125.5, 125.1, 79.1, 64.1, 57.2, 6.64, 4.12; EI-MS m/z: 358 $(M + H)^+$; HRMS (EI) calcd for $C_{21}H_{32}NO_2Si$ $(M + H)^+$: 358.2202, found: 358.2202. Anal. Calcd for ($C_{21}H_{31}NO_2Si$): C 70.54, H 8.74, N 3.92, Found: C 70.61, H 8.70, N 3.87.

4.2.6. (*S*)-2-amino-1,1-diphenyl-3-(tripropylsilyloxy)propanol (2f)

Colorless oil; $[\alpha]_D^{22}$ = -77.5 (c 1.02, $CHCl_3$); IR (neat) cm^{-1} : 2953, 2867, 1449, 1204; ^{1}H-NMR ($CDCl_3$) δ: 7.59-7.57 (m, 2H), 7.49-7.48 (m, 2H), 7.33-7.14 (m, 6H), 3.91-3.89 (t,

J = 4.6 Hz, 1H), 3.57-3.56 (m, 2H), 1.32-1.24 (m, 6H), 0.92-0.89 (t, *J* = 7.2 Hz, 9H), 0.52-0.50 (m, 6H); ^{13}C-NMR ($CDCl_3$) δ: 146.2, 145.1, 128.5, 128.2, 126.7, 126.5, 125.6, 125.1, 79.2, 64.2, 57.3, 18.4, 16.7, 16.1; EI-MS m/z: 400 $(M + H)^+$; HRMS (EI) calcd for $C_{24}H_{38}NO_2Si$ $(M + H)^+$: 400.2672, found: 400.2675. Anal. Calcd for ($C_{24}H_{37}NO_2Si$): C 72.13, H 9.33, N 3.50, Found: C 72.19, H 9.24, N 3.42.

4.2.7. (*S*)-2-amino-1,1-diphenyl-3-(trihexylsilyloxy)propanol (2g)

Colorless oil; $[\alpha]_D^{24}$ = -49.6 (c 1.27, $CHCl_3$); IR (neat) cm^{-1} : 2920, 2854, 1449, 1181; ^{1}H-NMR ($CDCl_3$) δ: 7.59-7.57 (m, 2H), 7.49-7.46 (m, 2H), 7.36-7.14 (m, 6H), 3.93-3.90 (m, 1H), 3.55-3.54 (m, 2H), 1.33-1.21 (m, 24H), 0.89-0.86 (t, *J* = 6.9 Hz, 9H), 0.51-0.48 (m, 6H); ^{13}C-NMR ($CDCl_3$) δ: 146.2, 145.0, 128.5, 128.2, 126.7, 126.5, 125.6, 125.1, 79.1, 64.1, 57.3, 33.3, 31.6, 31.5, 23.1, 23.0, 22.6, 15.1, 14.2, 13.3; EI-MS m/z: 526 $(M + H)^+$; HRMS (EI) calcd for $C_{33}H_{56}NO_2Si$ $(M + H)^+$: 526.4080, found: 526.4074.

4.3. Preparation of amino alcohol catalyst 3

A solution of amino alcohol **2e** (358 mg, 1 mmol) in CH_2Cl_2 (15 mL) was cooled down to -40 ^oC. To the solution was added Et_3N (166 μL, 1.2 mmol) and trimethylsilyl trifluoromethanesulfonate (217 μL, 1.2 mmol) and the reaction mixture was stirred at room temperature for 24 h. The solution was quenched with water and extracted with $CHCl_3$. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and filtrated.

The filtrate was concentrated under reduced pressure to give the residue. The residue was purified by column chromatography on silica gel (*n*-hexane : ethylacetate = 4 : 1) to afford **3** (116 mg, 27%).

4.3.1. (*S*)-1,1-diphenyl-3-(triethylsilyloxy)-1-(trimethylsilyloxy)propane-2-amine (3)

Colorless oil; $[\alpha]_D^{19}$ = -43.8 (c 1.05, $CHCl_3$); IR (neat) cm^{-1} : 2953, 2876, 1248; ^{1}H-NMR ($CDCl_3$) δ: 7.43-7.42 (m, 2H), 7.35-7.34 (m, 2H), 7.30-7.21 (m, 6H), 3.88-3.85 (m, 1H), 3.73-3.71 (m, 1H), 3.00-2.96 (t, *J* = 9.5 Hz, 9H), 0.54-0.49 (m, 6H), -0.11 (s, 9H); ^{13}C-NMR ($CDCl_3$) δ: 144.7, 144.2, 128.1, 128.0, 127.8, 127.5, 127.2, 127.0, 82.6, 64.8, 59.2, 6.8, 4.4, 2.1; EI-MS m/z: 430 $(M + H)^+$; HRMS (EI) calcd for $C_{24}H_{40}NO_2Si_2$ $(M + H)^+$: 430.2598, found: 430.2612.

4.4. Preparation of amino alcohol catalyst 4

Amino alcohol **2e** (358 mg, 1 mmol), K_2CO_3 (276 mg, 2 mmol) and iodomethane (120 μL, 2 mmol) were stirred in EtOH (4 mL) at room temperature for 24 h. The reaction mixture was filtered with ethylacetate. The combined organic layer was washed with water, brine, dried over anhydrous Na_2SO_4, and filtrated. The filtrate was concentrated under reduced pressure to give the residue. The residue was purified by column chromatography on silica gel (*n*-hexane : ethylacetate = 4 : 1) to afford **4** (152 mg, 41%).

4.4.1. *N*-dimethyl-(*S*)-2-amino-1,1-diphenyl-3-(triethylsilyloxy)propanol (4)

Colorless oil; $[\alpha]_D^{23}$ = -29.7 (c 0.74, $CHCl_3$); IR (neat) cm^{-1} : 2953, 2875, 1447, 1234; ^{1}H-NMR ($CDCl_3$) δ: 7.46-7.44 (m, 2H), 7.36-7.34 (m, 2H), 7.31-7.18 (m, 6H), 4.03-4.01 (m, 1H), 3.68-3.64 (m, 1H), 3.57-3.55 (m, 1H), 2.37 (s, 6H), 0.94-0.91 (t, *J* = 8.0 Hz, 9H), 0.58-0.53 (m, 6H); ^{13}C-NMR ($CDCl_3$) δ: 146.2, 145.5, 128.0, 127.6, 127.1, 127.0, 77.6, 70.7, 61.1, 44.0, 6.8, 4.3; EI-MS m/z: 386 $(M + H)^+$; HRMS (EI) calcd for $C_{23}H_{36}NO_2Si$ $(M + H)^+$: 386.2515, found: 386.2507.

4.5. Preparation of amino alcohol catalyst 5

Amino alcohol **2e** (358 mg, 1 mmol), K_2CO_3 (332 mg, 2.4 mmol) and benzyl bromide (140 μL, 1.2 mmol) were stirred in $CHCl_3$ (10 mL) at room temperature for 72 h. The reaction mixture was filtered with ethylacetate. The combined organic layer was washed with water, brine, dried over anhydrous Na_2SO_4, and filtrated. The firtrate was concentrated under reduced pressure to give the residue. The residue was purified by column chromatography on silica gel (*n*-hexane : ethylacetate = 4 : 1) to afford **5** (206 mg, 46%).

4.5.1. *N*-benzyl-(*S*)-2-amino-1,1-diphenyl-3-(triethylsilyloxy)propanol (5)

Colorless oil; $[\alpha]_D^{24}$ = -24.8 (c 1.05, $CHCl_3$); IR (neat) cm^{-1} : 2954, 2875, 1449, 1238; ^{1}H-NMR ($CDCl_3$) δ: 7.62-7.57 (m, 2H), 7.53-7.49 (m, 2H), 7.34-7.13 (m, 11H), 3.75-3.60

(m, 3H), 3.50-3.46 (m, 2H), 0.89-0.86 (t, J = 8.0 Hz, 9H), 0.54-0.49 (m, 6H); ^{13}C-NMR ($CDCl_3$) δ: 146.6, 145.6, 128.4, 128.3, 128.1, 127.0, 126.5, 125.9, 125.5, 79.0, 63.2, 62.1, 52.4, 6.7, 4.2; EI-MS m/z: 447 (M^+); HRMS (EI) calcd for $C_{28}H_{37}NO_2Si$ (M^+): 447.2594, found: 447.2589.

4.6. General procedure for the asymmetric Diels-Alder reaction of anthrones 6, with maleimides 7

Anthrone **6** (0.10 mmol), *N*-phenylmaleimide **7** (0.12 mmol) and amino alcohol catalysts **1a-f**, **2a-h**, **3**, **4** and **5** (0.01 mmol) were stirred in CH_2Cl_2 (1 mL) at room temperature for 24 h. The reaction mixture was directly purified by preparative TLC on silica gel ($CHCl_3$) to afford DA adducts **8**. The enantiomeric excess (ee) was determined by HPLC (DAICEL CHIRALPAK AD-H, 1.0 mL/min, *n*-hexane : 2-propanol = 80 : 20). Compounds **8** were known compounds and were identified by spectral data which were in good agreement with those reported.[2-9]

4.7. General procedure for the asymmetric Diels-Alder reaction of anthrones 6,9a,b, with maleimides 7,10a-f

Anthrones **6,9a,b** (0.10 mmol), maleimides **7,10a-f** (0.12 mmol) and amino alcohol catalysts **2e** (0.02 mmol) were stirred in CH_2Cl_2 (1 mL) at room temperature for 48 h. The reaction mixture was directly purified by preparative TLC on silica gel ($CHCl_3$) to afford

DA adducts **11a-h**. The enantiomeric excess (ee) was determined by HPLC (DAICEL CHIRALPAK AD-H, 1.0 mL/min, *n*-hexane : 2-propanol = 80 : 20). Compounds **11a-h** were known compounds and were identified by spectral data which were in good agreement with those reported.[2-9]

References

1. (a) List, B.; *Synlett.* **2001**, 1675-1686; (b) Dalko, P. I.; Moisan, L.; *Angew. Chem. Int. Ed*. **2004**, *43*, 5138-5175; (c) Notz, W.; Tanaka, F.; Barbas Ⅲ, C. F.; *Acc.Chem. Res*. **2004**, *37*, 580-591; (d) Seayad, J.; List, B.; *Org. Biomel. Chem*. **2005**, *3*, 719-724; (e) Yang, H.; Carter, R. G.; *Synlett*. **2010**, 2827-2838.
2. Prinz, H.; Wiegrebe, W.; Müller, K.; *J. Org. Chem.* **1996,** *61,* 2853-2856.
3. (a) Nascimento-Júnior, N. M.; Mendes, T. C. F.; Leal, D. M.; Corrêa, C. M. N.; Sudo, R. T.; Zapata-Sudo, G.; Barreiro, E. J.; Fraga, C. A. M.; *Bioorg. Med. Chem. Lett.* **2010**, *20*, 74-77; (b) Nirogi, R.; Dwarampudi, A.; Kambhampati, R.; Bhatta, V.; Kota, L.; Shinde, A.; Badange, R.; Jayarajan, P.; Bhyrapuneni, G.; Dubey, P. K.; *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4577-4580.
4. Burgess, K. L.; Lajkiewicz, N. J.; Sanyal, A.; Yan, W.; Snyder, J. K.; *Org. Lett.* **2005**, *7*, 31-34.
5. Fache, F.; Piva, O.; *Tetrahedron Lett.* **2001**, *42*, 5655-5657.

6. (a) Tokioka, K.; Masuda, S.; Fujii, T.; Hata, Y.; Yamamoto, Y.; *Tetrahedron Asymmetry* **1997**, *8*, 101-107; (b) Uemae, K.; Masuda, S.; Yamamoto, Y.; *J. Chem. Soc., Perkin Trans. 1* **2001**, 1002-1006.
7. Shen, J.; Nguyen, T. T.; Goh, Y-P.; Ye, W.; Fu, X.; Xu, J.; Tan, C-H.; *J. Am. Chem. Soc.* **2006**, *128*,13692-13693.
8. Akalay, D.; Dürner, G.; Göbel, M. W.; *Eur. J. Org. Chem.* **2008**, 2365-2368.
9. Zea, A.; Alba, A-N. R.; Bravo, N.; Moyano, A.; Rios, R.; *Tetrahedron* **2011**, *67*, 2513-2529.
10. (a) Bai, J-F.; Guo, Y-L.; Peng, L.; Jia, L-N.; Xu, X-Y.; Wang, L-X.; *Tetrahedron* **2013**, *69*, 1229-1233; (b) Alba, A-N.; Bravo, N.; Moyano, A.; Rios, R.; *Tetrahedron Lett.* **2009**, *50*, 3067-3069.
11. (a) Suttibut, C.; Kohari, Y.; Igarashi, K.; Nakano, H.; Hirama, M.; Seki, C.; Matsuyama, H.; Uwai, K.; Takano, N.; Okuyama, Y.; Osone, K.; Takeshita, M.; Kwon, E.; *Tetrahedron Lett.* **2011**, *52*, 4745-4748; (b) Sakuta, Y.; Kohari, Y.; Romauli Hutabarat, N. D. M.; Uwai, K.; Kwon, E.; Okuyama, Y.; Seki, C.; Matsuyama, H.; Takano, N.; Tokiwa, M.; Takeshita, M.; Nakano, H.; *Heterocycles* **2012**, *86*, 1379-1388; (c) Kohari, Y.; Okuyama, Y.; Kwon, E.; Furuyama, T.; Kobayashi, N.; Otuki, T.; Kumagai, J.; Seki, C.; Uwai, K.; Dai, G.; Iwasa, T.; Nakano, H.; *J. Org. Chem.* **2014**, *79*, 9500-9511.
12. A part of the catalyst in this manuscript was used to the enantioselective 1,3-Dipolar cycloaddition of nitrones to α,β-unsaturated aldehydes.; Teppei Otsuki, Jun Kumagai, Yoshihito Kohari, Yuko Okuyama, Eunsang Kwon, Chigusa Seki, Koji Uwai, Yasuteru

Mawatari, Nagao Kobayashi, Tatsuo Iwasa, Michio Tokiwa, Mitsuhiro Takeshita, Atushi Maeda, Akihiko Hashimoto, Kana Turuga, and Hiroto Nakano.; *Eur. J. Org. Chem. in press.*