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Cinchona-derived ammonium salts-catalyzed aza Diels–Alder reaction of Danishefsky's diene with imines

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ABSTRACT

Described is the efficiency of *cinchona*-derived quaternary ammonium salts as Lewis acid organocatalysts in aza Diels–Alder reaction of Danishefsky's diene **1** with imines **2** and **16**, providing 1,2-dialkyl-2,3-dihydro-4-pyridinones **3** and cyclic dihydropyridones **17**, respectively. Among the nine of *cinchonidine*-derived quaternary ammonium catalysts prepared, *N*-2′,3′,4′-trifluorobenzyl-*O*-benzylcinchonidinum bromide (**6**) exhibited the highest chemical yield (up to 99%). Systematic study on structure-catalytic efficiency relationship revealed that 2′,3′,4′-trifluorobenzyl, quinuclidine, and quinoline moieties are essential.

1. Introduction

Since the late of 1970′s, lots of *cinchona*-derived catalysts have been developed as practical catalysts and utilized in various useful chemical reactions.[1] Among them, *cinchona*-derived quaternary ammonium salts, diversely modified by N-alkylation of *cinchona* alkaloids, have successfully been applied to phase-transfer catalytic reactions.[2] During the last decade, we also have developed polymeric or hydrogen bonding inducible functional group incorporated *cinchona*-derived quaternary ammonium catalysts and successfully applied them to various useful synthetic reactions.[3] In continuation of our studies on broadening the scope of reactions and the usefulness of *cinchona*-derived catalysts, we attempted to apply them to the aza Diels–Alder reaction of Danishefsky's diene **1** with imines **2**, which is the most powerful methodology for the construction of nitrogen-containing six membered ring compounds.[4] Recent advances in these reactions have been made by a number of Lewis acid-catalyzed versions in organic solvents or aqueous media, including asymmetric versions using chiral catalysts.[5] In this article, we report a new synthetic method of the aza Diels–Alder reaction in the presence of *cinchona*-derived ammonium salts as Lewis acid organocatalysts.

2. Results and discussion

As a preliminary study, we performed the aza Diels–Alder reaction of Danishefsky's diene **1** with *N*-benzylideneaniline (**2a**) under CH_3CN at room temperature in the presence of tetrabutyl ammonium salts as facile quaternary ammonium salts to optimize the reaction conditions of solvents and the counter anions of the ammonium catalysts.

As shown in Table 1, only 10% of the cyclized product **3a** was obtained with no catalyst, which was in accordance with previous results (entry 1).[5j] Interestingly, the chemical yields were quite variable depending on the counter anions of the *n*-tetrabutyl ammonium salts. TBAF, expected to facilitate the reaction by the removal of the TMS group of **1**, did not afford **3a** (entry 2), but rather unidentified products. The same results were obtained with other solvents (H_2O, THF; data are not shown). However, there was a significant increase of chemical yield (entry 2–4) by changing of the counter anion from fluoride to iodide, and TBAI exhibited the best chemical yield (entry 4, 92%). It was speculated that a softer counter anion could be more easily displaced by imine **2a** to form an activated transition state, which could give higher chemical yields. The polarity of the solvents was also important (entry 4–7). The more polar solvents showed the higher chemical yields (entry 4, CH_3CN 92%; entry 7, CH_2Cl_2 22%), but aqueous solvents afforded lower chemical yields than aprotic polar solvents (entry 5, H_2O 80%; entry 6, H_2O/CH_2Cl_2 (1:1) 39%), which was in accordance with previous results.[6]

The reaction was monitored by ^1H NMR for the determination of the reaction mechanism, and it revealed that there was a Mannich addition intermediate in addition to the further cyclized final product **3a**. After quenching the reaction mixture with 1.0 M HCl during the work-up process, only the aza Diels–Alder type cyclized product **3a** could be isolated. Based on these NMR studies, this reaction seemed to be gone through the Mannich type

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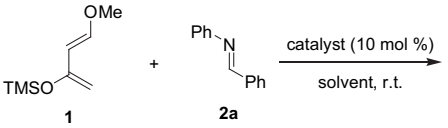
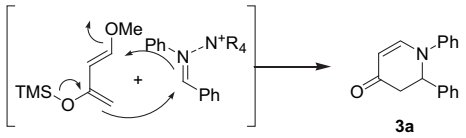
Table 1
Optimization with the *n*-tetrabutyl ammoniums salts

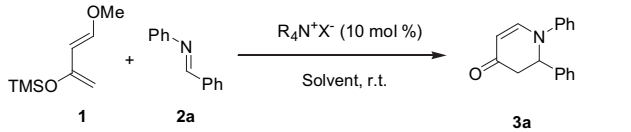




Entry	Catalyst	Solvent	Time(h)	Yield[a](%)
1	—	MeCN	72	10
2	TBAF	MeCN	72	—
3	TBAB	MeCN	24	23
4	TBAI	MeCN	24	92
5	TBAI	H_2O	24	80
6	TBAI	H_2O/CH_2Cl_2 (1:1)	24	39
7	TBAI	CH_2Cl_2	72	22

[a] Isolated yield after acidic work-up.

Table 2
Aza Diels–Alder reaction with quaternary ammonium salts



Entry	Catalyst	Solvent	Time(h)	Yield[a](%)
1	**4**	MeCN	8	97
2	**5**	MeCN	8	98
3	**6**	MeCN	3	99
4	**6**	H_2O	3	83
5	**6**	CH_2Cl_2	4.5	93
6	**7**	MeCN	24	72
7	**8**	MeCN	72	—
8	**9**	MeCN	24	14
9	**10**	MeCN	5	85
10	**11**	MeCN	24	64
11	**12**	MeCN	24	29
12	**13**	MeCN	24	36
13	**14**	MeCN	24	58
14	**15**	MeCN	72	10

[a] Isolated yield after acidic work-up.

intermediate via the transition state by the chelation of the *N*-lone pair on imine **2a** with an ammonium cation (Table 1).

Next we examined cinchonidinum quaternary ammonium salts. Aza Diels–Alder reaction of Danishefsky's diene **1** with *N*-benzylideneaniline (**2a**) was performed in the presence of various cinchonidinum quaternary ammonium salts (10 mol %) (Fig. 1, **4**[6]–**12**) under CH_3CN at room temperature. As shown in Table 2, the chemical yields were quite variable depending on the structure of the catalysts. A significant increase of chemical yield resulted from the change of the counter anion from fluoride to bromide, which is similar to the preliminary results (Table 1).[7] The solvent also greatly affected the chemical yields (entry 3–5) as well. Notably, the chemical yields were dramatically dependent on the functional groups on the *N*-benzyl group. The electron withdrawing group (entry 3, 2,3,4-F_3 99%; entry 10, 4-F 85%) yielded a higher chemical yield than that of the electron donating group (entry 10, 4-Me 64%; entry 11, 4-MeO 29%). Very high chemical yields were observed with catalysts **4**–**6** and catalyst **6** (entry 3, 99%) exhibited the best yield with a lower reaction time. To confirm the electronic effect of the 2,3,4-F_3 group and what part of the cinchonidine moiety is

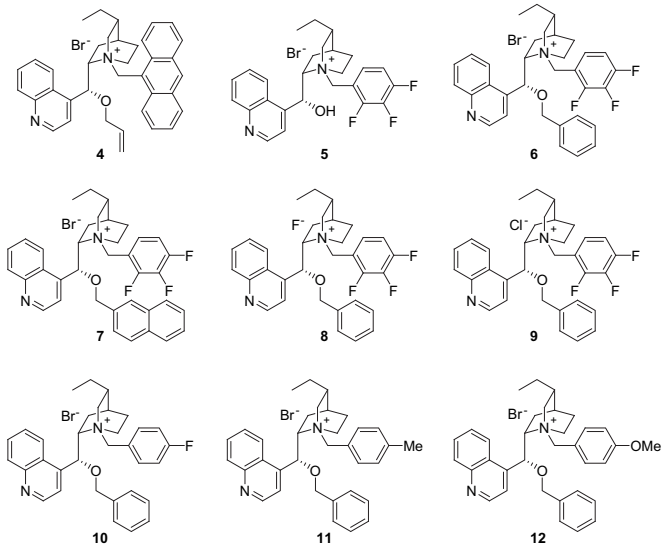


Fig. 1. *Cinchona*-derived ammonium catalysts.

responsible for high chemical yield, non-cinchona type ammonium salts (Fig. 2, **13**–**15**[8]) were prepared and evaluated for their catalytic efficiency. *N*-2′,3′,4′-trifluorobenzyl-*N*-tri-*n*-butylquternary ammonium bromide (**13**, 36%) gave 1.6 times higher efficiency than that of *n*-tetrabutyl ammonium bromide (TBAB, 23%), and even higher catalytic efficiency was observed with *N*-2′,3′,4′-trifluorobenzylquinuclidine ammonium bromide (**14**, 58%). The higher efficiency of **6** over that of **14** may indicate that the quinoline ring contributes to form a more rigid conformation of the transition state by a π–π stacking interaction. Steric hindrance might lead to lower chemical yields (**13**, 36%; **14**, 58%; **15**, 10%). The cumulative results revealed that 2′,3′,4′-trifluorobenzyl, quinuclidine, and quinoline moieties play integral roles for the catalytic efficiency of **6**.

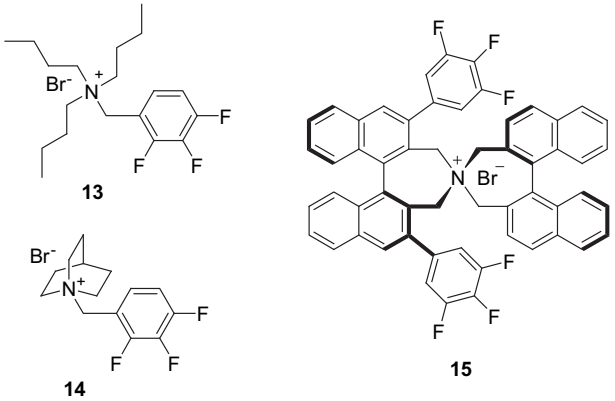
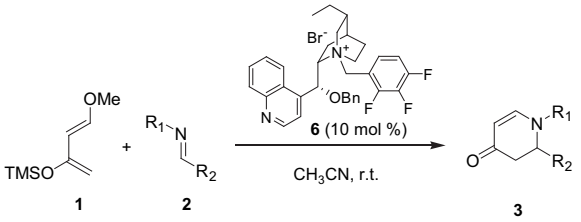


Fig. 2. Non-*Cinchona*-derived ammonium catalysts.

Catalyst **6** was chosen for further investigation for scope and limitation in aza Diels–Alder reaction of Danishefsky's diene with various *trans*-imines. As shown in Table 3, very high chemical yields (80–99%) were observed. Much to our disappointment, no enantioselectivity (<5% ee) was observed in **3**. The low affinity of *cinchona*-derived catalysts with imines in the transition state is not effective enough for the induction of enantioselectivity.

The substrate scope was extended to cyclic arylimines. Aza Diels–Alder reaction of **1** with 3,4-dihydroisoquinoline (**16a**[9])in the

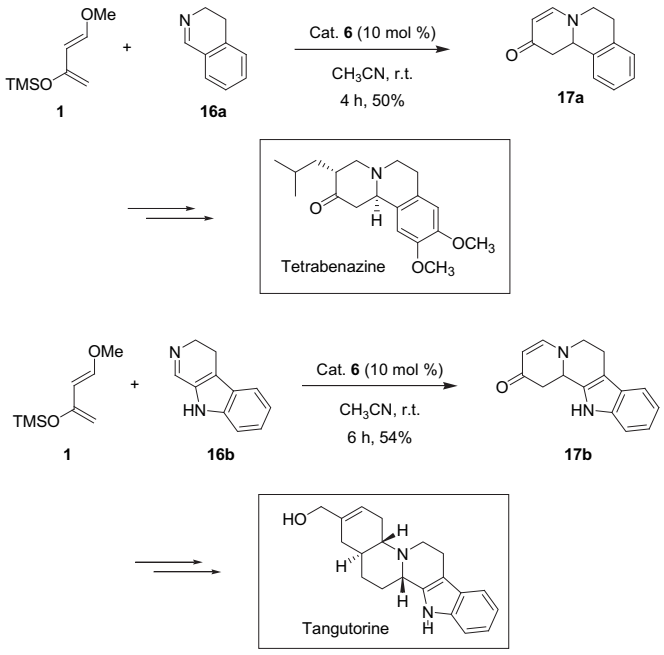
Table 3
Scope of imine substrates in aza Diels–Alder reaction



Entry	R_1	R_2	Time(h)	Yield[a](%)
1	Ph	Ph	3	99
2	Ph	4-CH_3OPh	5	99
3	Ph	4-Br–Ph	8	98
4	4-CH_3OPh	Ph	8	97
5	4-Br–Ph	Ph	5	99
6	4-NO_2–Ph	Ph	5	99
7	2-Furyl	Ph	5	95
8	2-Pyridyl	Ph	3	99
9	Ph–CH=CH	Ph	4	99
10	*c*-C_6H_{11}	Ph	8	80

[a] Isolated yield after acidic work-up.

presence of catalyst **6** afforded dihydropyridone **17a**[10] in 50% yield (Scheme 1). In addition, 4,9-dihydro-3*H*-β-carboline (**16b**[11]) provided the corresponding dihydropyridone **17b**[12] in 54% yield. In our knowledge, it was the first application to construct polycyclicdihydropyridone system by aza Diels–Alder reaction. The dihydropyridones **17a** and **17b** are essential skeleton of tetrabenazine[13a] and tangutorine,[13b] respectively.



Scheme 1. Cyclic imines (**16**) in aza Diels–Alder reaction.

3. Conclusion

Cinchona-derived ammonium catalysts were prepared and applied to aza Diels–Alder reaction of Danishefsky's diene **1** with various imines (**2**), providing 1,2-dialkyl-2,3-dihydro-4-pyridinones (**3**). Catalyst **6** showed the highest chemical yield (up to 99%). Although the reaction did not exhibit enantioselectivity, catalyst **6** successfully applied to the synthesis of polycyclicdihydropyridones via aza Diels–Alder reaction of **1** with cyclic imines, which can be applied to the synthesis of biologically active aza polycyclic natural products.

4. Experimental

4.1. General

Infrared (IR) spectra were recorded on a JASCO FT/IR-300E and Perkin–Elmer 1710 FT spectrometer. Nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR) spectra were measured on a JEOL JNM-LA 300 [300 MHz (^{1}H), 75 MHz (^{13}C)] spectrometer and JEOL JNM-GSX 400 [400 MHz (^{1}H), 100 MHz (^{13}C)] spectrometer, using $CHCl_3$-*d* or DMSO-*d* as a solvent, and were reported in parts per million relative to $CHCl_3$-*d* (δ 7.24) or DMSO-d_6 (δ 2.50) for ^{1}H NMR and relative to the $CHCl_3$-*d* (δ 77.23) or DMSO-d_6 (δ 39.50) resonance for ^{13}C NMR. Coupling constants (*J*) in ^{1}H NMR are in Hz. Low-resolution mass spectra (MS) were recorded on a VG Trio-2 GC–MS spectrometer. High-resolution mass spectra (HRMS) were measured on a JEOL JMS-AX 505wA, JEOL JMS-HX/HX 110A spectrometer. Melting points were measured on a Büchi B-540 melting point apparatus. For thin layer chromatography (TLC) analysis, a Merck precoated TLC plate (silica gel 60 GF_{254}, 0.25 mm) was used. For column chromatography, a Merck Kieselgel 60 (70–230 mesh) was used.

4.2. General procedure for ammonium salts-catalyzed aza Diel–Alder reaction in acetonitrile

Danishfsky's diene (**1**) (90 μL) was added to *N*-benzylidieneaniline (**2a**) (54 mg) with ammonium catalyst (10 mol %) in anhydrous acetonitrile (1 mL) and stirred at room temperature for 3 h. The reaction mixture was quenched with 1.0 M HCl and diluted with dichloromethane and (10 mL), washed with brine (2×10 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexanes/EtOAc=4:1) to afford 1,2-diphenyl-2,3-dihydro-4-pyridinone (**3a**) as a yellow solid. Spectral data of **3** and **17** were consistent with literature values.[5g,10,12]

*4.2.1. 1,6,7,11b-Tetrahydro-pyrido[2,1-α]isoquinolin-2-one (**17a**[10]).* ^{1}H NMR (300 MHz, $CHCl_3$-*d*) δ 7.28–7.14 (m, 5H), 5.06 (d, *J*=7.5 Hz, 1H), 4.74 (dd, J_1=16.1 Hz, J_2=4.3 Hz, 1H), 3.65–3.59 (m, 1H), 3.43 (t×d, J_1=12.0 Hz, J_2=3.1 Hz, 1H), 3.14 (t×d, J_1=15.9 Hz, J_2=5.1 Hz, 1H), 2.86–2.79 (m, 2H), 2.59–2.46 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CHCl_3$-*d*) δ 192.7, 154.1, 134.9, 133.3, 129.0, 127.1, 127.0, 125.6, 98.5, 56.6, 49.7, 43.9, 30.3 ppm.

*4.2.2. 6,7,12,12b-Tetrahydro-1H-indolo[2,3-α]quinolizin-2-one (**17b**[12]).* ^{1}H NMR (300 MHz, $CHCl_3$-*d*) δ 9.15 (s, 1H), 7.48 (d, *J*=7.5 Hz, 1H), 7.38 (d, *J*=8.0 Hz, 1H), 7.23–7.08 (m, 3H), 5.08 (d, *J*=7.3 Hz, 1H), 4.83 (br d, *J*=14.4 Hz, 1H), 3.70 (dd, J_1=11.9 Hz, J_2=4.5 Hz, 1H), 3.49 (t×d, J_1=11.9 Hz, J_2=4.2 Hz, 1H), 3.02–2.97 (m, 2H), 2.96–2.89 (m, 1H), 2.59 (dd, J_1=15.7 Hz, J_2=15.7 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CHCl_3$-*d*) δ 192.5, 155.0, 136.7, 131.5, 126.4, 122.3, 119.7, 118.1, 111.5, 107.8, 98.2, 54.0, 50.9, 41.6, 22.1 ppm.

4.3. General procedure for anion exchange of cinchonidinium catalyst[7b]

After 1.0 M HF was added to amberlyst-A26 (OH^-) in a column, the resin was rinsed with water three times for neutralization. 95% aqueous EtOH and benzene was added and then it was dried at

40 °C in a vacuum oven (4 h). When the amberlyst-A26 (F^-) was generated and it was packed in the column, the catalyst **6** (100 mg) was loaded and spilled by MeOH in the column. After evaporation of the gained mixtures, the brown caramel was afforded (99%). In the MS (FAB^-) analysis, the peak of Br^- (79) disappeared and the F^- peak (19) appeared. For the chloride anion exchange, the same procedure was used with 1.0 M HCl, a yellow solid was obtained, and in MS (FAB^-) analysis, the peak of Br^- (79) was disappeared and the Cl^- peak (35) was appeared.

4.4. Representative procedure of N-benzylation to hydrocinchonidine: catalyst 5

Hydrocinchonidine (3.0 g, 10.1 mmol) with 2′,3′,4′-trifluorobenzyl bromide (2.5 g, 11.1 mmol) in dichloromethane was stirred at room temperature for 4 h. After evaporating dichloromethane, the reaction mixture was columned by dichloromethane and methanol in a 40:1 mixture. After column chromatography, the solid was diluted with methanol (50 mL) and then added to ether (400 mL) dropwise with stirring. The precipitated solid was filtered and washed with ether (600 mL). The desired product was 4.8 g (91% yield) as a light yellow solid. Spectral data were consistent with literature values.[3d]

4.5. Representative procedure of O-benzylation to hydrocinchonidinium: catalyst 6

To a suspension of *N*-(2′,3′,4′-Trifluoro)benzylhydro-cinchonidinium bromide (1.0 g, 1.92 mmol) in dichloromethane (4 mL) was added benzyl bromide (0.25 mL, 2.11 mmol) and 50% aqueous KOH (0.65 mL, 5.76 mmol). The resulting mixture was stirred vigorously at room temperature for 4 h, during, which time all of solids dissolved. The mixture was diluted with water (3 mL) and was extracted with dichloromethane (3×10 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, CH_2Cl_2/MeOH=40:1) and diluted with methanol (20 mL), which was added to ether (200 mL) by dropwise with stirring. The precipitated solid was filtered and washed with ether (600 mL). The desired product was afforded (1.06 g, 90% yield) as a light yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.05 (d, J=4.5 Hz, 1H), 8.33 (d, J=8.2 Hz, 1H), 8.18 (d, J=8.4 Hz, 1H), 7.92–7.70 (m, 4H), 7.64–7.36 (m, 5H), 6.55 (s, 1H), 5.29 (d, J=12.9 Hz, 1H), 4.96 (d, J=13.2 Hz, 1H), 4.85 (d, J=10.7 Hz, 1H), 4.53(d, J=10.8 Hz, 1H), 4.12–4.08 (m, 1H), 3.97–3.93 (m, 1H), 3.43–3.36 (m, 2H), 3.26–3.22 (m, 1H), 2.28–2.26 (m, 1H), 1.95 (s, 2H), 1.73–1.65 (m, 2H), 1.47–1.43 (m, 1H), 1.25–1.06 (m, 3H), 0.71 (t, J=7.2 Hz, 3H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 150.2, 148.0, 140.8, 136.9, 130.5, 129.8, 129.6, 129.0, 128.5, 128.2, 128.1, 127.5, 125.1, 124.1, 119.9, 113.6, 113.5, 113.4, 113.1, 70.4, 67.3, 64.8, 61.1, 56.0, 51.0, 35.1, 25.2, 24.8, 23.5, 20.7, 11.1 ppm; IR (KBr) 3402, 2929, 1622, 1510, 1311, 1240, 1128, 1066, 818, 754, 698 cm^{-1}; mp 152 °C; HRMS (FAB) calculated for $[C_{33}H_{34}F_3N_2O]^+$: 531.2623, found: 531.2616.

4.6. Spectroscopic characterization of the ammonium catalysts

4.6.1. Catalyst ***7***. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.08 (d, J=4.4 Hz, 1H), 8.45 (d, J=8.0 Hz, 1H), 8.18 (d, J=8.4 Hz, 1H), 8.05–7.91 (m, 4H), 7.88–7.74 (m, 4H), 7.71–7.68 (m, 1H), 7.59–7.56 (m, 1H), 7.54–7.53 (m, 3H), 6.69 (s, 1H), 5.39 (d, J=12.6 Hz, 1H), 5.12 (m, 2H), 4.71 (d, J=10.8 Hz, 1H), 4.18–4.02 (m, 2H), 3.57–3.10 (m, 2H), 2.33–2.31 (m, 1H), 1.92 (s, 2H), 1.73–1.64 (m, 2H), 1.44–1.41 (m, 1H), 1.21–1.04 (m, 2H), 0.69 (t, J=7.1 Hz, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 150.3, 148.1, 140.8, 134.5, 132.8, 132.6, 130.3, 129.9, 129.7, 128.2, 127.9, 127.6, 127.5, 126.9, 126.4, 126.3, 126.2, 125.2, 123.8, 120.0, 113.5, 113.3, 113.2, 70.5, 67.6, 61.2, 56.3, 51.0, 35.1, 25.2, 24.8, 23.5, 20.6, 11.2 ppm; IR (KBr) 2931, 1628, 1508, 1311, 1240, 1128, 1068, 818, 754 cm^{-1}; mp 155 °C; HRMS (FAB) calculated for $[C_{37}H_{36}F_3N_2O]^+$: 581.2780, found: 581.2789.

4.6.2. Catalyst ***10***. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.04 (d, J=4.4 Hz, 1H), 8.30 (d, J=8.3 Hz, 1H), 8.17 (d, J=8.24 Hz, 1H), 7.90–7.86 (m, 1H), 7.82–7.79 (m, 2H), 7.73–7.71 (m, 2H), 7.58–7.54 (m, 2H), 7.48–7.37 (m, 5H), 6.52 (s, 1H), 5.10–5.02 (m, 1H), 4.89–4.86 (m, 2H), 4.60–4.52 (m, 1H) 3.99–3.94 (m, 2H), 3.40–3.38 (m, 1H), 3.29–3.16 (m, 2H), 2.35–2.28 (m, 1H), 1.98–1.91 (m, 2H), 1.76–1.70 (m, 2H), 1.53–1.47 (m, 1H), 1.27–1.07 (m, 2H), 0.70 (t, J=7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 150.2, 148.1, 141.1, 137.0, 136.2, 136.1, 129.9, 129.6, 128.6, 128.3, 128.1, 127.5, 125.2, 124.1, 123.6, 119.8, 116.0, 115.7, 70.2, 67.7, 62.3, 61.0, 50.7, 34.8, 25.1, 24.6, 23.7, 20.4, 11.1 ppm; IR (KBr) 3400, 2925, 1603, 1512, 1460, 1230, 1065, 843, 754 cm^{-1}; mp 148 °C; HRMS (FAB) calculated for $[C_{33}H_{36}FN_2O]^+$: 495.2812, found: 495.2820.

4.6.3. Catalyst ***11***. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.04 (d, J=4.4 Hz, 1H), 8.28 (d, J=8.2 Hz, 1H), 8.17 (d, J=8.1 Hz, 1H), 7.90–7.87 (m, 1H), 7.81–7.78 (m, 2H), 7.58–7.53 (m, 2H), 7.50–7.40 (m, 5H), 7.38–7.36 (m, 2H), 6.51 (s, 1H), 4.99–4.93 (m, 1H), 4.84–4.69 (m, 2H), 4.57 (d, J=11.1 Hz, 1H), 3.99–3.91 (m, 2H), 3.27–3.13 (m, 2H), 2.39 (s, 3H), 2.31–2.23 (m, 1H), 1.97–1.91 (m, 3H), 1.75–1.67 (m, 2H), 1.51–1.45 (m, 1H), 1.25–1.06 (m, 2H), 0.71 (t, J=7.3 Hz, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 150.3, 148.1, 141.2, 139.9, 137.0, 133.6, 129.9, 129.7, 129.5, 129.1, 128.7, 128.4, 128.2, 127.5, 125.2, 124.6, 123.6, 119.9, 70.3, 67.6, 63.2, 61.1, 50.7, 34.8, 25.2, 24.7, 23.8, 20.9, 20.5, 11.2 ppm; IR (KBr) 3396, 2925, 1736, 1603, 1512, 1458, 1375, 1240, 1122, 1065, 816, 752 cm^{-1}; mp 145 °C; HRMS (FAB) calculated for $[C_{34}H_{39}N_2O]^+$: 491.3062, found: 491.3056.

4.6.4. Catalyst ***12***. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.04 (d, J=4.4 Hz, 1H), 8.27 (d, J=8.3 Hz, 1H), 8.17 (d, J=8.2 Hz, 1H), 7.91–7.87 (m, 1H), 7.82–7.78 (m, 2H), 7.58–7.44 (m, 5H), 7.40–7.37 (m, 1H), 7.34–7.20 (m, 2H), 7.12 (d, J=8.6 Hz, 2H), 6.50 (s, 1H), 5.04–5.01 (m, 1H), 4.88–4.84 (m, 1H), 4.81–4.75 (m, 1H), 4.56 (d, J=11.1 Hz, 1H), 4.01–3.93 (m, 2H), 3.84 (s, 3H), 3.15–3.12 (m, 1H), 2.30–2.26 (m, 1H), 1.97–1.90 (m, 2H), 1.75–1.67 (m, 3H), 1.51–1.45 (m, 1H), 1.28–1.08 (m, 2H), 0.69 (t, J=7.3 Hz, 3H) ppm; ^{13}C NMR (100 MHz, DMSO- d_6) δ 160.5, 150.3, 148.1, 141.2, 137.0, 135.1, 129.9, 129.6, 128.7, 128.4, 128.2, 128.0, 127.5, 125.2, 123.5, 119.9, 119.3, 114.3, 70.3, 67.4, 62.9, 60.9, 55.3, 50.5, 34.8, 25.2, 24.6, 23.8, 20.5, 11.2 ppm; IR (KBr) 3398, 2925, 1606, 1512, 1458, 1254, 1028, 827, 752 cm^{-1}; mp 143 °C; HRMS (FAB) calculated for $[C_{34}H_{39}N_2O_2]^+$: 507.3012, found: 507.3012.

4.6.5. Catalyst ***13***. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.54–7.46 (m, 2H), 4.63 (s, 2H), 3.33–3.12 (m, 6H), 1.71 (m, 6H), 1.35–1.24 (m, 6H), 0.96–0.92 (m, 9H) ppm; ^{13}C NMR (75 MHz, $CHCl_3$-d) δ 153.9, 151.5, 150.1, 141.1, 138.6, 129.7, 113.62, 113.59, 113.44, 113.41, 113.00, 112.96, 112.90, 59.5, 56.8, 30.1, 24.6, 19.7, 13.5 ppm; IR (KBr) 3755, 3460, 2962, 1626, 1510, 1383, 1309, 1163, 1065, 870, 750 cm^{-1}; mp 120 °C; HRMS (FAB) calculated for $[C_{19}H_{31}F_3N]^+$: 330.2409, found: 330.2399.

4.6.6. Catalyst ***14***. ^{1}H NMR (300 MHz, $CHCl_3$-d) δ 7.94–7.86 (m, 1H), 7.14–7.05 (m, 1H), 5.07 (s, 2H), 3.78 (t, J=7.8 Hz, 6H), 2.23–2.19 (m, 1H), 2.03–1.97 (m, 6H) ppm; ^{13}C NMR (75 MHz, $CHCl_3$-d) δ 153.8, 152.2, 151.3, 149.6, 141.1, 138.6, 129.7, 113.4, 113.2, 112.5, 59.3, 54.4, 23.9, 19.5 ppm; IR (KBr) 3408, 2949, 1626, 1506, 1389, 1309, 1255, 1167, 1072, 1009, 960, 831, 756, 681 cm^{-1}; mp 291 °C; HRMS (FAB) calculated for $[C_{14}H_{17}F_3N]^+$: 256.1313, found: 256.1324.

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.12.002.

References and notes

1. For the multiple roles of *Cinchona* alkaloid and their derivatives in chemical reactions, see: (a) Kacprzak, K.; Gawronski, J. *Synthesis* **2001**, 961; (b) Taggi, A. E.; Hafez, A. M.; Lectka, T. *Acc. Chem. Res.* **2003**, *36*, 10.
2. For recent reviews on phase-transfer catalysis, see: (a) Maruoka, K.; Ooi, T. *Chem. Rev.* **2003**, *103*, 3013; (b) O'Donnell, M. J. *Acc. Chem. Res.* **2004**, *37*, 506; (c) Lygo, B.; Andrews, B. I. *Acc. Chem. Res.* **2004**, *37*, 518; (d) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2007**, *107*, 5656; (e) Jew, S.-s.; Park, H.-g. *Chem. Commun.* **2009**, 7090.
3. For our recent reports on asymmetric phase-transfer catalysis with *Cinchona* derivatives, see: (a) Jew, S.-s.; Jeong, B.-S.; Yoo, M.-S.; Huh, H.; Park, H.-g. *Chem. Commun.* **2001**, 1244; (b) Park, H.-g.; Jeong, B.-S.; Yoo, M.-S.; Park, M.-k.; Huh, H.; Jew, S.-s. *Tetrahedron Lett.* **2001**, *42*, 4645; (c) Park, H.-g.; Jeong, B.-S.; Yoo, M.-S.; Lee, J.-H.; Park, M.-k.; Lee, Y.-J.; Kim, M.-J.; Jew, S.-s. *Angew. Chem., Int. Ed.* **2002**, *41*, 3036; (d) Jew, S.-s.; Yoo, M.-S.; Jeong, B.-S.; Park, I. Y.; Park, H.-g. *Org. Lett.* **2002**, *4*, 4245; (e) Yoo, M.-S.; Jeong, B.-S.; Lee, J.-H.; Park, H.-g.; Jew, S.-s *Org. Lett.* **2005**, *7*, 1129; (f) *Angew. Chem., Int. Ed.*; Jew, S.-s., Lee, J.-H., Jeong, B.-S., Yoo, M.-S., Kim, M.-J., Lee, Y.-J., Lee, J., Choi, S.-h., Lee, K., Lah, M. S., Park, H.-g., Eds.; 2005; 44, p 1383.
4. (a) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon: Oxford, 1990; (b) Oppolazer, W. In *Comprehensive Organic Synthesis*; Paquette, L. A., Ed.; Pergamon: Oxford, 1991; Vol. 5; p 315; (c) Weinreb, S. M. Hetero dienophile additions to dienes In. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5; p 401; (d) Waldmann, H. *Synthesis* **1994**, 535.
5. For aza-Diels–Alder reactions with Danishefsky's diene: (a) Collin, J.; Jaber, N.; Lannou, M. I. *Tetrahedron Lett.* **2001**, *42*, 7405; (b) Laurent-Robert, H.; Garrigues, B.; Dubac, J. *Synlett* **2000**, 1160; (c) Ali, T.; Chauhan, K. K.; Frost, C. G. *Tetrahedron Lett.* **1999**, *40*, 5621; (d) Kobayashi, S.; Ishitani, H.; Nagayama, S. *Synthesis* **1995**, 1195; (e) Kobayashi, S.; Ishitani, H.; Nagayama, S. *Chem. Lett.* **1995**, 423; (f) Kobayashi, S.; Manabe, K.; Mori, Y. *Tetrahedron* **2001**, *57*, 2537; (g) Yuan, Y.; Li, X.; Ding, K. *Org. Lett.* **2002**, *4*, 3309; (h) Kobayashi, S.; Loncaric, C.; Manabe, K. *Chem. Commun.* **2003**, *5*, 574; (i) Kobayashi, S.; Loncaric, C.; Manabe, K. *Adv. Synth. Catal.* **2003**, *345*, 475; (j) Wilhelm, R.; Jurčík, V. *Org. Biomol. Chem.* **2005**, *3*, 239.
6. Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414.
7. (a) Colonna, S.; Re, A.; Gelbard, G.; Cesarotti, E. *J. Chem. Soc. Perkin Trans.* **1979**, 2248; (b) Shioiri, T.; Ando, A.; Miura, T.; Tatematsu, T. *Tetrahedron Lett.* **1993**, *34*, 1507.
8. Ooi, T.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 5139.
9. Mohamed, M. A.; Yamada, K.-i.; Tomioka, K. *Tetrahedron Lett.* **2009**, *50*, 3436.
10. (a) Cicchi, S.; Revuelta, J.; Zanobini, A.; Betti, M.; Brandi, A. *Synlett* **2003**, 2305; (b) Revuelta, J.; Cicchi, S.; Brandi, A. *J. Org. Chem.* **2005**, *70*, 5636.
11. (a) Nicolaou, K. C.; Mathison, C. J. N.; Montagnon, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 4077; (b) Nicolaou, K. C.; Mathison, C. J. N.; Montagnon, T. *J. Am. Chem. Soc.* **2004**, *126*, 5192.
12. Wolter, M.; Borm, C.; Merten, E.; Wartchow, R.; Winterfeldt, E. *Eur. J. Org. Chem.* **2001**, 4051.
13. (a) Paek, S.-M.; Kim, N.-J.; Shin, D.; Jung, J.-K.; Jung, J.-W.; Chang, D.-J.; Moon, H.; Suh, Y.-G. *Chem.—Eur. J.* **2010**, *16*, 4623; (b) Nemoto, T.; Yamamoto, E.; Franzén, R.; Fukuyama, T.; Wu, R.; Fukamachi, T.; Kobayashi, H.; Hamada, Y. *Org. Lett.* **2010**, *12*, 872.