

HETEROCYCLES, Vol. 84, No. 2, 2012, pp. 1209 - 1216. © 2012 The Japan Institute of Heterocyclic Chemistry
Received, 11th November, 2010, Accepted, 6th June, 2011, Published online, 8th June, 2011
DOI: 10.3987/COM-10-S(P)2

NEW HYDRAZINE-BASED ORGANOCATALYST FOR ASYMMETRIC DIELS-ALDER REACTION OF 1,2-DIHYDROPYRIDINES

Yuko Okuyama,^a Kenichi Osone,^a Hiroto Nakano,^b and Mitsuhiro
Takeshita*^a

^aTohoku Pharmaceutical University, 4-4-1 Komatsushima, Aoba-ku, Sendai
981-8558, Japan; E-mail: mtake@tohoku-pharm.ac.jp

^bDivision of Applied Chemistry, College of Environmental Technology, Graduate
School of Muroran Institute of Technology, 27-1 Mizumoto, Muroran, Hokkaido
050-8585, Japan; E-mail: catanaka@mmm.muroran-it.ac.jp

Abstract – Chiral hydrazinoalcohol organocatalyst is designed and synthesized as a new organocatalyst for the enantioselective Diels-Alder reaction between 1,2-dihydropyridines and acrolein derivatives to produce an optical active isoquinuclidine derivative (up to 67% ee with up to 96% yield).

The development of the new chiral organocatalysts for use in asymmetric catalytic reactions has drawn considerable interest in the last 10 years. Excellent covalent and non-covalent organocatalysts have been developed for use in a wide range of reactions.¹ Quite recently, we also developed the oxazolidine organocatalyst² **1** that works as the efficient catalyst as with MacMillan's imidazolidone-based catalyst³ in the asymmetric Diels-Alder (DA) reaction of 1,2-dihydropyridines⁴ **3** which is an important reaction for the construction of chiral isoquinuclidines (2-azabicyclo[2.2.2]octanes) **4**. The molecules **4** is valuable synthetic intermediates of biological active iboga-type alkaloids⁵ and oseltamivir phosphate (Tamiflu)⁶ (Scheme 1). Both the oxazolidine and the MacMillan catalysts have only a covalent site in the molecules, and the enantioselectivity in the DA reaction is controlled by the substituents at its both sides of the corresponding covalent site. In the present study, we planned to develop a new organocatalyst that has both covalent and non-covalent sites in the molecule (Figure 1). As the molecule, we paid attention to hydrazinoalcohol **2**. Although the molecule **2** was used to form a chiral diazomethine ylide unit,⁷ the use

*Dedicated to Professor Dr. Albert Padwa on the occasion of his 75th birthday.

of the molecule **2** as an organocatalyst has not been reported yet. Molecule **2** has both hydrazinyl covalent and hydroxyl non-covalent sites (Figure 1). As the advantage point of catalyst **2**, strong nucleophilic hydrazinyl primary amino group might afford higher chemical yield in comparison with the reaction of diene while oxazolidine catalyst **1** having nucleophilic secondary amino group as a covalent site.

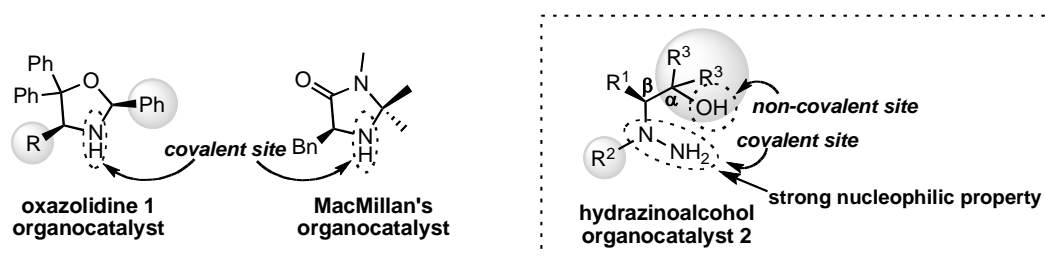
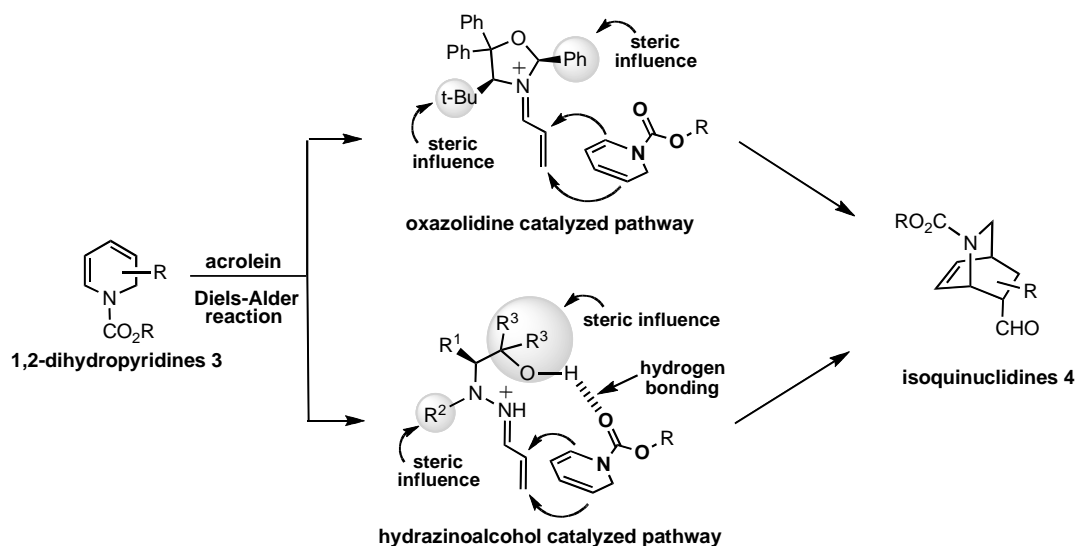


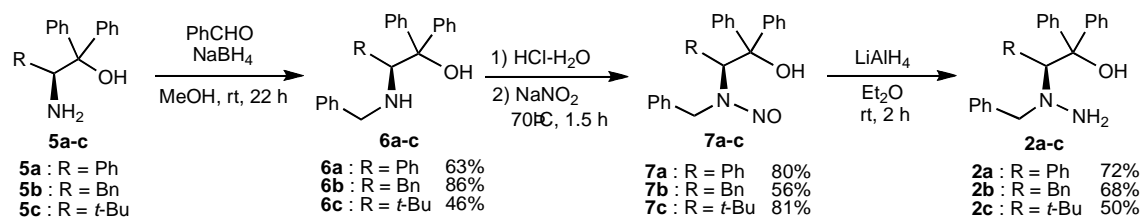
Figure 1. Design of hydrazinoalcohol organocatalyst

Furthermore, it is expected that the catalyst **2** might be able to control the attack of diene by both the hydrogen bonding interactions of the hydroxyl group with the carbonyl group on 1,2-dihydropyridines and the bulky substituent at β -position on **2** to afford high enantioselectivity in the reaction, although oxazolidine catalyst **1** controls the attack of diene only by substituents at its both sides of amino covalent site (Scheme 1). In this paper, we describe the newly designed hydrazinoalcohols in the asymmetric DA reaction of 1,2-dihydropyridines with acroleins as organocatalyst.



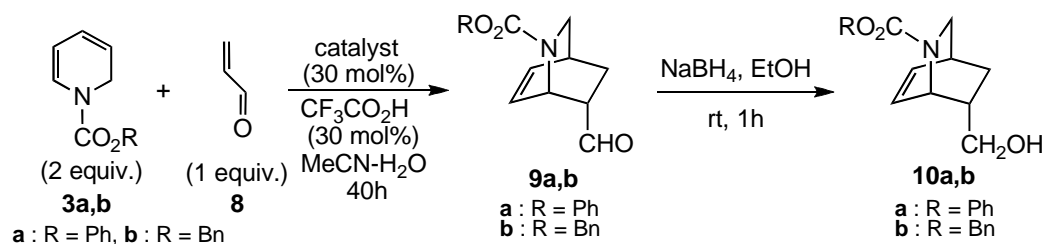
Scheme 1. Function of hydrazinoalcohol organocatalyst

The catalysts **2a-c** were prepared from the corresponding β -amino alcohols⁷ **5a-c** (Scheme 2). Thus, the condensation of **5a-c** with benzaldehyde, followed by the treatment with NaBH_4 afforded *N*-benzyl amino alcohols **6a-c**. The nitrosoation of **6a-c** followed by the reduction of the obtained **7a-c** using LiAlH_4 afforded the desired hydrazinoalcohol catalysts **2a-c** in good to moderate yields (50-72%).



Scheme 2. Synthesis of hydrazine-type organocatalyst

We first examined the DA reaction of common 1-phenoxy-carbonyl-1,2-dihydropyridine **3a** (2 equiv.) with acrolein **8** (1 equiv.). The reaction was carried out at room temperature or 0 °C in MeCN-H₂O in the presence of 30 mol% of catalysts **2a-c** and 30 mol% of CF₃CO₂H as the additive to give the DA adduct **9a**, and its chemical and optical yields were determined by converting to the alcohol **10a** (Scheme 3). The results are summarized in Table 1.



Scheme 3. Enantioselective Diels-Alder reaction of 1,2-dihydropyridines **3a,b** with acrolein **8** using catalysts **2a-c**

The reaction catalyzed by β -Ph-**2a** did not afford satisfactory results for the enantioselectivity and chemical yield (entry 1: 3% ee, 17%). On the other hand, β -benzyl-**2b** gave the corresponding *endo*-DA adduct **10a** in good enantioselectivity and fairly good chemical yield (entry 2: 66% ee, 93%). However, the use of bulkier β -*tert*-butyl-**2c** brought about a decrease in both enantioselectivity and chemical yield (entry 3: 55% ee, 46%).

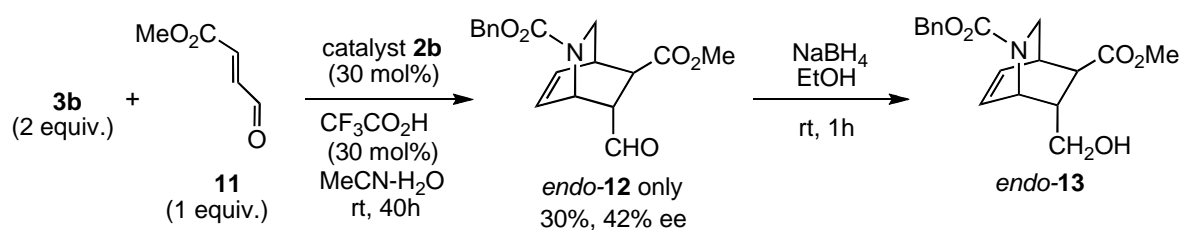
Table 1. Diels-Alder reaction of **3a,b** with **8** using catalysts **2a-c**

Entry	Catalyst	R	Adduct	Temp. (°C)	Yield (%) ^{a)}	<i>Endo/exo</i> ^{b)}	Ee (%) ^{c)}
1	2a	Ph	10a	rt	17	89 : 11	3
2	2b	Ph	10a	rt	93	86 : 14	66
3	2c	Ph	10a	rt	46	94 : 6	55
4	2b	Bn	10b	rt	96	91 : 9	65
5	2b	Bn	10b	0	95	96 : 4	67

^{a)} Isolated yields. ^{b)} The *endo/exo* ratio was determined by ¹H NMR or chiral HPLC. ^{c)} Ee of *endo* isomers were determined by chiral HPLC using a Daicel AS-H column (0.5mL/min, hexane : 2-propanol = 93:7) or AD-H column (0.5mL/min, hexane : 2-propanol = 85:15).

The activity of the most effective catalyst **2b** was then evaluated in the reaction consisting of 30 mol% catalyst with 1-benzyloxycarbonyl-1,2-dihydropyridine **3b** (2 equiv.) and **8** (1 equiv.) (Scheme 3 and Table 1). The chemical and optical yields of the DA adduct was determined by converting to alcohol **10b**. As the results, catalyst **2b** afforded good enantioselectivity (65% ee) with excellent chemical yield (96%) (entry 4). Furthermore, the reaction at 0 °C under the same conditions using catalyst **2b** also gave good enantioselectivity (67% ee) and excellent chemical yield (95%) (entry 5). From the above results, β -benzyl-**2b** is better than catalysts **2a,c** as an organocatalyst for affording higher enantioselectivity in this DA reaction. Although catalyst **2b** showed higher catalytic activity than oxazolidine catalyst for the chemical yield in this reaction, the enantioselectivity was dissatisfaction. This might explain on the base of steric constraints imposed by the catalyst framework. Thus, it might be for less steric constraints of **2a-c** for blocking one iminium face from attacking of diene in the reaction transition state. In addition, the effectiveness of the hydroxyl non-covalent site on catalyst **2** to the enantioselectivity was not also clarified.

We examined the effectiveness of acrolein derivative **11** using superior catalyst **2b** (Scheme 4). The reaction of diene **3b** with dienophile **11** was carried out at room temperature in the presence of 30 mol% of catalyst **2b** to give only the *endo*-DA adduct **12** and those chemical and optical yields were determined by converting to the alcohol **13**. Unfortunately, catalyst **2b** did not show satisfactory asymmetric catalytic activity to afford only the corresponding *endo*-DA adduct **12** (42% ee, 30%).



Scheme 4. Enantioselective reaction of **3b** with **11** using organocatalyst **2b**

In conclusion, new chiral hydrazinoalcohol organocatalysts **2a-c** were explored. The catalysts were prepared from the corresponding β -amino alcohols in three steps. The DA reaction of 1,2-dihydropyridine **3b** with acrolein **8** using the explored catalyst **2b** provided the corresponding DA adduct **9b** in good enantioselectivity (67% ee) and excellent chemical yield (95%). Further optimizations of the structure of the catalyst **2** for increasing enantioselectivity in this reaction are now in progress.

EXPERIMENTAL

IR spectra were measured with PERKIN ELMER 1725X spectrophotometer. ¹H-NMR spectra were

recorded on JEOL JNM-GSX 400 spectrometers with TMS as an internal standard. MS were taken on Hitachi RMG-6MG and JEOL-JNM-DX 303 spectrometers. Optical rotations were measured with JASCO-DIP-370 digital polarimeter.

General procedure for the preparation of hydrazinoalcohol organocatalysts **2a-c**

To a solution of amino alcohols **5a-c** (2.0 mmol) in MeOH (16 mL) was added benzaldehyde (0.20 mL, 2.0 mmol) and the mixture was stirred for 30 min. The solution was then cooled to at $-10\text{ }^{\circ}\text{C}$ and NaBH_4 (113.5 mg, 3.0 mmol) was added over 1h. The mixture was stirred for 22h at rt. Water (10 mL) was added, the aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL) and organic phases were dried over MgSO_4 and evaporated to give a crude products **6a-c**. The residue was purified by column chromatography (SiO_2 , CHCl_3) to give a pure products **6a-c** (**a**: 478 mg, 63%, **b**: 677 mg, 86%, **c**: 331 mg, 46%). An aqueous solution of NaNO_2 (276 mg, 4 mmol in 3 mL H_2O) was added dropwise over 1 h at $70\text{ }^{\circ}\text{C}$ to a solution of **6** and conc. HCl (1.0 mmol) in H_2O (10 mL). The mixture was stirred at $70\text{ }^{\circ}\text{C}$ for 1.5 h, cooled and extracted with Et_2O (60 mL). The organic phases was washed H_2O (10 mL), dried over MgSO_4 , and the solvent was evaporated under a reduced pressure. The residue was purified by column chromatography (SiO_2 , CHCl_3) to give a pure product **7a-c** (**a**: 327 mg, 80%, **b**: 237 mg, 56%, **c**: 291 mg, 81%). LiAlH_4 (420 mg, 11 mmol) was slowly added under Ar to a cooled solution of **7a-c** (1 mmol) in anhydrous Et_2O (30 mL) keeping the temperature under $-10\text{ }^{\circ}\text{C}$. The mixture was stirred two additional hours at this temperature, cooled to $-78\text{ }^{\circ}\text{C}$, quenched with H_2O (0.42 mL), 15% aq NaOH (0.42 mL) and H_2O (1.26 mL) filtered by Celite[®] and evaporated to give white crystals of **2a-c** (**a**: 294 mg, 72%, **b**: 268 mg, 68%, **c**: 187 mg, 50%).

(S)-2-(N-Benzylamino)-1,1,3-triphenylpropan-1-ol (6b): White crystal (AcOEt), mp $75\text{-}77\text{ }^{\circ}\text{C}$, $[\alpha]_{\text{D}}^{22}$ -28.84 (c1.04, CHCl_3). IR (KBr) cm^{-1} : 697, 749, 1651, 3448. $^1\text{H-NMR}$ (CD_3OD) δ : 7.73 (d, $J = 7.7$ Hz, 2H), 7.65 (d, $J = 7.7$ Hz, 2H), 7.10-7.35 (m, 14H), 6.59 (d, $J = 7.3$ Hz, 2H), 4.86 (brs, 1H), 3.94 (dd, $J = 10.6$ Hz, 2.9 Hz, 1H), 2.92-3.02 (m, 3H), 2.35 (dd, $J = 14.5$ Hz, 10.6 Hz, 1H), 1.43 (brs, 1H). $^{13}\text{C-NMR}$ (CD_3OD) δ : 147.59, 145.0, 139.6, 139.3, 129.05, 128.68, 128.21, 128.18, 128.16, 128.03, 126.85, 126.65, 126.48, 126.45, 126.02, 125.65, 78.09, 65.68, 53.75, 37.63. Ms m/z : 394. HRMS (EI) calcd for ($\text{C}_{28}\text{H}_{27}\text{NO}$): 393.2093, found: 393.2096.

(S)-2-(N-Benzylamino)-3,3-dimethyl-1,1-diphenylbutan-1-ol (6c): White crystal (ether), mp $117\text{ }^{\circ}\text{C}$, $[\alpha]_{\text{D}}^{20}$ -98.57 (c 0.70, CHCl_3). IR (KBr) cm^{-1} : 708, 746, 1599, 1651, 3358. $^1\text{H-NMR}$ (CD_3OD) δ : 7.84 (dd, $J = 8.5$ Hz, 1.2 Hz, 2H), 7.70 (dd, $J = 8.5$ Hz, 1.2 Hz, 2H), 7.32 (t, $J = 7.7$ Hz, 2H), 7.09-7.23 (m, 7H),

6.88 (dd, $J = 7.2$ Hz, 1.9 Hz, 2H), 4.76 (s, 1H), 3.57 (d, $J = 11.6$ Hz, 1H), 3.53 (s, 1H), 3.26 (d, $J = 11.1$ Hz, 1H), 0.79 (s, 9H). $^{13}\text{C-NMR}(\text{CD}_3\text{OD})$ δ : 150.03, 144.89, 140.23, 128.31, 128.26, 127.80, 127.51, 127.08, 126.83, 126.39, 126.25, 126.19, 79.82, 72.72, 56.12, 37.55, 29.20. Ms m/z : 360 $[\text{M}+\text{H}]^+$. HRMS (FAB $^+$) calcd for $(\text{C}_{25}\text{H}_{29}\text{NO} + \text{H})^+$: 360.2249, found: 360.2330.

(S)-2-(N-Benzyl-N-nitrosoamino)-1,1,2-triphenylethanol (7a): Amorphous, $[\alpha]_{\text{D}}^{22} -574.74$ (c1.94, CHCl_3). IR (film) cm^{-1} : 697, 751, 1599, 1658, 3489. $^1\text{H-NMR}(\text{CD}_3\text{OD})$ δ : 7.36-7.41 (m, 3H), 7.06-7.25 (m, 15H), 6.89-6.91 (m, 2H), 5.72 (d, $J = 14.0$ Hz, 1H), 5.64 (s, 1H), 4.43 (s, 1H), 3.53 (d, $J = 14.0$ Hz, 1H). $^{13}\text{C-NMR}(\text{CD}_3\text{OD})$ δ : 145.03, 143.19, 134.03, 132.96, 130.03, 129.56, 128.92, 128.53, 128.24, 128.18, 127.90, 127.79, 127.56, 126.98, 126.76, 126.15, 125.44, 80.44, 71.64, 47.47. Ms m/z : 409 $[\text{M}+\text{H}]^+$. HRMS (FAB $^+$) calcd for $(\text{C}_{27}\text{H}_{24}\text{N}_2\text{O}_2 + \text{H})^+$: 409.1838, found: 409.1916.

(S)-2-(N-Benzyl-N-nitrosoamino)-1,1,3-triphenylpropan-1-ol (7b): Amorphous, $[\alpha]_{\text{D}}^{22} +84.61$ (c1.04, CHCl_3). IR (film) cm^{-1} : 697, 750, 1599, 1701, 3489. $^1\text{H-NMR}(\text{CD}_3\text{OD})$ δ : 7.66 (d, $J = 8.2$ Hz, 2H), 7.40 (t, $J = 7.7$ Hz, 2H), 7.09-7.29 (m, 10H), 6.95-7.00 (m, 4H), 6.37 (d, $J = 7.2$ Hz, 2H), 5.29 (d, $J = 10.6$ Hz, 1H), 4.16 (d, $J = 15.0$ Hz, 1H), 3.93 (d, $J = 15.0$ Hz, 1H), 3.43 (dd, $J = 14.5$ Hz, 11.6 Hz, 1H), 3.22 (dd, $J = 14.5$ Hz, 2.9 Hz, 1H), 1.58 (s, 1H). $^{13}\text{C-NMR}(\text{CD}_3\text{OD})$ δ : 144.31, 143.99, 137.59, 132.77, 129.06, 128.85, 128.66, 128.43, 128.29, 127.42, 127.28, 126.97, 126.75, 125.41, 125.38, 80.58, 71.68, 50.21, 36.77. Ms m/z : 423 $[\text{M}+\text{H}]^+$. HRMS (FAB $^+$) calcd for $(\text{C}_{28}\text{H}_{26}\text{N}_2\text{O}_2 + \text{H})^+$: 423.1994, found: 423.2073.

(S)-2-(N-Benzyl-N-nitrosoamino)-3,3-dimethyl-1,1-diphenylbutan-1-ol (7c): White crystal (ether), mp 154-156 °C, $[\alpha]_{\text{D}}^{20} +80.99$ (c1.21, CHCl_3). IR (KBr) cm^{-1} : 694, 742, 1597, 1650, 3447. $^1\text{H-NMR}(\text{CD}_3\text{OD})$ δ : 7.75 (d, $J = 7.7$ Hz, 2H), 7.39 (t, $J = 8.2$ Hz, 2H), 6.87-7.30 (m, 11H), 4.98 (d, $J = 1.9$ Hz, 1H), 4.68 (d, $J = 14.5$ Hz, 1H), 4.43 (s, 1H), 4.31 (d, $J = 15.5$ Hz, 1H), 0.88 (s, 9H). $^{13}\text{C-NMR}(\text{CD}_3\text{OD})$ δ : 147.21, 145.05, 134.09, 128.92, 128.43, 128.36, 128.31, 128.03, 127.49, 126.62, 126.36, 125.33, 124.68, 82.57, 79.31, 56.14, 39.13, 30.82. Ms m/z : 389 $[\text{M}+\text{H}]^+$. HRMS (FAB $^+$) calcd for $(\text{C}_{25}\text{H}_{28}\text{N}_2\text{O}_2 + \text{H})^+$: 389.2151, found: 389.2228.

(S)-2-(1-Benzylhydrazinyl)-1,1,2-triphenylethanol (2a): Pale yellow solid, mp 95-97 °C, $[\alpha]_{\text{D}}^{20} -70.58$ (c 1.19, CHCl_3). IR (KBr) cm^{-1} : 698, 744, 1588, 3334. $^1\text{H-NMR}(\text{CDCl}_3)$ δ : 7.69 (dd, $J = 8.2$ Hz, 1.0 Hz, 2H), 7.52 (dd, $J = 8.2$ Hz, 1.5 Hz, 2H), 6.69-7.37 (m, 16H), 4.63 (s, 1H), 3.92 (d, $J = 13.5$ Hz, 1H), 3.13 (d, $J = 13.0$ Hz, 1H), 2.93 (brs, 2H). $^{13}\text{C-NMR}(\text{CD}_3\text{OD})$ δ : 148.96, 145.47, 136.92, 134.10, 131.17,

129.11, 128.89, 128.48, 128.45, 128.40, 127.77, 127.54, 127.52, 127.51, 127.37, 127.26, 126.64, 126.50, 125.99, 125.93, 125.71, 82.18, 71.51, 65.32. Ms m/z : 395 $[M+H]^+$. HRMS (FAB⁺) calcd for (C₂₈H₂₈N₂O +H)⁺: 395.2045, found: 395.2130.

(S)-2-(1-Benzylhydrazinyl)-1,1,3-triphenylpropan-1-ol (2b): White crystal (ether), mp 79-81 °C, $[\alpha]_D^{20}$ -76.63 (c 2.14, CHCl₃). IR (KBr) cm⁻¹: 697, 746, 1601, 1656, 3332. ¹H-NMR (CDCl₃) δ: 7.65 (m, 4H), 7.10-7.33 (m, 14H), 6.67 (m, 2H), 4.20 (dd, $J = 9.2$ Hz, 2.9 Hz, 1H), 3.72 (d, $J = 14.0$ Hz, 1H), 3.22 (dd, $J = 15.0$ Hz, 11.8 Hz, 1H), 3.11 (d, $J = 13.5$ Hz, 1H), 2.92-2.96 (m, 3H). ¹³C-NMR(CD₃OD) δ: 148.98, 146.10, 141.77, 137.83, 129.10, 128.50, 128.46, 128.42, 128.36, 128.27, 128.20, 127.67, 127.22, 126.27, 126.11, 126.02, 125.98, 125.76, 125.38, 82.47, 70.70, 66.13, 30.53. Ms m/z : 409 $[M+H]^+$. HRMS (FAB⁺) calcd for (C₂₈H₂₈N₂O +H)⁺: 409.2202, found: 409.2272.

(S)-2-(1-Benzylhydrazinyl)-3,3-dimethyl-1,1-diphenylbutan-1-ol (2c): White crystal (ether), mp 115 °C, $[\alpha]_D^{20}$ +5.35 (c 0.56, CHCl₃). IR (KBr) cm⁻¹: 702, 746, 1604, 1656, 3326. ¹H-NMR (CD₃OD) δ: 7.80 (d, $J = 7.7$ Hz, 2H), 7.01-7.32 (m, 13H), 4.22 (d, $J = 14.0$ Hz, 1H), 3.92 (s, 1H), 3.58 (d, $J = 14.0$ Hz, 1H), 2.66 (brs, 2H), 1.00 (s, 9H). ¹³C-NMR(CD₃OD) δ: 150.83, 147.98, 138.71, 128.26, 127.95, 127.88, 127.18, 126.01, 125.83, 125.71, 83.28, 75.78, 68.81, 40.51, 30.97. Ms m/z : 375 $[M+H]^+$. HRMS (FAB⁺) calcd for (C₂₅H₃₀N₂O +H)⁺: 375.2358, found: 375.2433.

General procedure for the enantioselective Diels-Alder reaction of **3a,b** with **8** or **11**

A solution of catalysts **2a-c** (0.03 mmol) and CF₃CO₂H (0.03 mmol) in MeCN/H₂O (95/5 v/v, 0.5 mL) was added distilled acroleins **8** or **11** (0.3 mmol) and under argon. To the reaction solution, 1,2-dihydropyridines **3a** or **3b** (0.6 mmol) was added, and stirred at rt or 0 °C for 40 h. The reaction was quenched by water. The aqueous layer was extracted with AcOEt and organic phases were dried over MgSO₄. After the solution was evaporated, EtOH (1.0 mL) and NaBH₄ (2.0 mg, 0.05 mmol) was added and the mixture was stirred at rt for 1 h. The reaction mixture was diluted with water and extracted with AcOEt. The combined organic extracts were washed with brine, dried over MgSO₄, removed under reduced pressure to give a crude DA adduct **10a**, **10b** or **13**. The residue was purified by preparative TLC (SiO₂, *n*-hexane : AcOEt = 1 : 1) to afford the DA adduct **10a**, **10b** or **13** in quantitative yield. The enantiomeric excess (ee) was determined by HPLC [DAICEL Chiralcel AD-H, 0.5 mL/min, *n*-hexane : 2-propanol = 85 : 15, t_r (major) = 21.64 min, t_r (minor) = 23.09 min for *endo*-**10a**, DAICEL Chiralcel AS-H, 0.5mL/min, *n*-hexane : 2-propanol = 93 : 7, t_r (major) = 43.94 min, t_r (minor) = 54.67 min for

endo-**10b**, AD-H, 0.5 mL/min, *n*-hexane : 2-propanol = 85 : 15, t_r (major) = 37.50 min, t_r (minor) = 40.02 min for *endo*-**13**].

REFERENCES

- (a) J. Seayad and B. List, *Org. Biomol. Chem.*, 2005, **3**, 719; (b) P. I. Dalko and L. Moisan, *Angew. Chem. Int. Ed.*, 2004, **43**, 5138; (c) W. Notz, F. Tanaka, and C. F. Barbas, III, *Acc. Chem. Res.*, 2004, **37**, 580; (d) B. List, *Synlett*, 2001, 1675; (e) H. Yang and R. G. Carter, *Synlett*, 2010, 2827.
- H. Nakano, K. Osone, M. Takeshita, E. Kwon, C. Seki, H. Matsuyama, N. Takano, and Y. Kohari, *Chem. Commun.*, 2010, **46**, 4827.
- K. A. Ahrendt, C. J. Borths, and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2000, **122**, 4243.
- (a) N. Takenaka, Y. Huang, and V. H. Rawal, *Tetrahedron*, 2002, **58**, 8299; (b) H. Nakano, N. Tsugawa, and R. Fujita, *Tetrahedron Lett.*, 2005, **46**, 5677; (c) H. Nakano, N. Tsugawa, K. Takahashi, and Y. Okuyama, R. Fujita, *Tetrahedron*, 2006, **62**, 10879.
- (a) M. E. Kuehne and I. Marko, in *Syntheses of Vinblastine-type Alkaloids. The Alkaloids. Antitumor Bisindole Alkaloids from Catharanthus roseus (L.)*, ed. by A. Brossi and M. Suffness, Academic: San Diego, 1990, Vol. 37, pp. 77-131; (b) P. Popik and P. Skolnick, in *Pharmacology of Ibogaine and Ibogaine-related Alkaloids. The Alkaloids. Chemistry and Biology*, ed. by G. A. Cordell, Academic: San Diego, 1999, Vol. 52, pp. 197-231; (c) S. D. Glick, I. M. Maisonneuve, and K. K. Szumlinski, in *Mechanisms of Action of Ibogaine: Relevance to Putative Therapeutic Effects and Development of a Safer Iboga Alkaloid Congener. The Alkaloids*, ed. by K. R. Alper, S. D. Glick, and G. A. Cordell, Academic: San Diego, 2001, Vol. 56, pp. 39-53; (d) G. Buchi, D. L. Coffen, K. Kocsis, P. E. Sonnet, and F. E. Ziegler, *J. Am. Chem. Soc.*, 1996, **88**, 3099; (e) C. Marazano, M. LeGoff, J. Fourrey, and B. C. Das, *J. Chem. Soc., Chem. Commun.*, 1981, 389; (f) S. Raucher and B. L. Bray, *J. Org. Chem.*, 1987, **109**, 442; (g) M. T. Reding and T. Fukuyama, *Org. Lett.*, 1999, **1**, 973.
- (a) N. Satoh, T. Akiba, S. Yokoshima, and T. Fukuyama, *Angew. Chem. Int. Ed.*, 2007, **46**, 5734; (b) N. Satoh, T. Akiba, S. Yokoshima, and T. Fukuyama, *Tetrahedron*, 2009, **65**, 3239.
- F. Roussi, A. Chauveau, M. Bonin, L. Micouin, and H.-P. Husson, *Synthesis*, 2000, **8**, 1170.