Simple primary β -amino alcohol catalyzed enantioselective Diels-Alder reaction of 3-hydroxy-2-pyridones

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ABSTRACT

The simple primary β -amino alcohol catalyzed Diels-Alder reaction of 3-hydroxy-2-pyridones as dienes with *N*-substituted maleimides to provide the highly substituted optically active isoquinuclidines as a single diastereomers in excellent enantioselectivities (up to 98%) with excellent chemical yields (up to 95%) was demonstrated. A range of simple β -amino alcohols were synthesized from the corresponding inexpensive amino acids and their catalytic activity was examined for this reaction.

Keywords:

Primary β -amino alcohol

Diels-Alder reaction

3-hydroxy-2-pyridone

Enantioselective organocatalysis

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Introduction

From the last 15 years, enantioselective organocatalysis is emerging as one of the most powerful synthetic paradigm and also as complementary to metal-catalyzed transformations to accelerated the development of new methods to construction of biologically active complex natural products.¹ It is always challenging task for synthetic organic chemists to develop the general method for the enantioselective synthesis of complex natural products. The Diels-Alder (DA) reaction is one of the most important and powerful method as it could provide carbocyclic compounds containing up to four contiguous stereogenic centers in a single step.^{2,3} Usually, chiral Lewis acids are effective in enantioselective Diels-Alder reaction to produce the chiral building blocks.⁴ Recently, the use of optically active organic Brønsted acids or Brønsted bases have also emerged as an effective alternative catalysts for catalytic asymmetric DA reactions.⁵ The DA reaction of 3-hydroxy-2-pyridones as diene provides a direct and versatile access to synthetically valuable multifunctional bicyclic optically active isoquinuclidines containing hydroxyl group at 4-position (4-hydroxy-2-azabicyclo[2.2.2]octanes), which are valuable synthetic

intermediates of biologically active validamines⁶ and pharmacologically important compounds such as oseltamivir phosphate (Tamiflu)⁷ (Scheme 1).

Scheme 1. Efficacy of asymmetric Diels-Alder reaction of 3-hydroxy-2-pyridones.

However, as electron-deficient dienes of aromatic character, 3-hydroxy-2-pyridones are known to be reluctant diene partners for DA reactions. Because of this distinct character of 3-hydroxy-

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2-pyridones, it is challenge for the development of a catalytic asymmetric variant for this synthetically useful class of DA reactions. To the best of our knowledge, till the date there are only few reports for racemic version of this class of DA reaction using 3-hydroxy-2-pyridones as dienes⁸ and only one example for catalytic asymmetric version of this DA reaction reported by Tan and co-workers using indanol-typed tertiary amino alcohol as a Brønsted base organocatalyst (Scheme 2).⁹

Scheme 2. Diels-Alder reaction of 3-hydroxy-2-pyridones with maleimides.

Recently we are developing the simple primary β -amino alcohols and their derivatives as a new class of organocatalysts, since they are easy to synthesize, stable on exposure to air, have the probability of introducing different functional groups and also alter the steric sites.¹⁰ And also, these catalysts could be used as inexpensive alternatives to other primary amino organocatalysts such as the chiral diamines and cinchona derived primary amines. Because of the presence of adjacently positioned bi-functional groups *i.e.* Brønsted acid and base sites, these could be used as iminium precursors and also as hydrogen bond source (Figure 1).

Figure 1. Functionality of β -amino alcohols.

In continuation of our interest to synthesize the different β -amino alcohols and examination of their general applicability in diverse organic transformations as chiral organocatalysts¹⁰ and due to the importance of chiral isoquinuclidines as synthetic intermediates, herein we desire to examine the catalytic efficiency of simple primary β -amino alcohols in DA reaction of 3-hydroxy-2-pyridones with maleimides. The reaction of

Scheme 3. Concept for asymmetry induction using β -amino alcohol organocatalyst.

3-hydroxy-2-pyridones as a diene with maleimides might be afforded the DA adducts through the transition state **Ts-A**, in which the diene could be fixed by the two hydrogen bonding interactions between the ammonium site on the ammonium alcohol intermediate and the hydroxyl group at 3-position on the

2-pyridones and between the hydroxyl group of ammonium alcohol intermediate and the carbonyl group at 2-position on the 2-pyridones, then dienophiles might react stereo selectively from the less steric interaction site of diene to provide the chiral isoquinuclidines (Scheme 3).

Herein, we describe the DA reaction of 3-hydroxy-2-pyridones as dienes with *N*-substituted maleimides to afford the chiral isoquinuclidines in excellent chemical yields (up to 95%) and enantioselectivity (up to 98% ee) using simple β -amino alcohols as Brønsted base organocatalysts (Scheme 2).

Results and Discussion

Primary amino alcohol catalysts **3a-h**, having aliphatic or aromatic substituents at the α -and/or β -positions, respectively, were easily prepared through well-known Grignard reaction.^{10f, 11} Whereas catalyst **3i** was obtained by reduction of the corresponding α -amino acid **2**.^{10f, 12} Moreover, both secondary and tertiary amino alcohols **4a,b**, were prepared by treating **3d** with methyl iodide.^{10f} Furthermore, tertiary amino alcohol **4c** containing pyrrolidiny ring system as an amino group at β -position was prepared by the reaction of **3d** with 1,4-dibromobutane. In addition, amino silyl ether **5** was obtained from **3d** by masking the hydroxyl function with TMS (trimethylsilyl) group by treating with TMSOTf.^{10g} Furthermore, α,β -diamine **6** was prepared by the substitution reaction of the corresponding **3d** with NaN_3 followed by catalytic reduction using Pd/C system.¹³ Primary amine catalyst **8** without hydroxyl group was prepared using the well-known method from the oxazolidinone **7**^{10f} (Scheme 4).

Scheme 4. Preparation of β -amino alcohols.

Initially, the catalytic activity of primary amino alcohol organocatalysts **3a-d** comprising aromatic and aliphatic substituent groups at β -position and diphenyl groups at α -position was examined in the DA reaction of 1-mesitylsulfonyl-3-hydroxy-2-pyridone **9a** with *N*-phenylmaleimide **10a** in CH_2Cl_2 at -50°C following the same reaction condition of Tan *et al.*,⁹ and the results were presented (Table 1). All the used catalysts showed catalytic activities to afforded *endo*-DA adduct **11a** in low to moderate chemical yields (31-60%) but enantioselectivity (*ee*) was differ with substituent group at β -position. Thus, catalyst **3a** bearing phenyl group at β -position afforded the DA adduct **11a** at moderate chemical yield (51%) and a quite poor enantioselectivity (8% ee) (entry 1). The bulkier catalyst **3b** having benzyl group improved enantioselectivity to 25% ee, although the chemical yield was decreased (entry 2). Catalyst **3c**

containing *iso*-propyl group at β -position yield the DA adduct with 37% *ee* and 60% yield (entry 3). Best enantioselectivity (57% *ee*) was obtained by using catalyst **3d** with *tert*-butyl group at β -position, although chemical yield was deeply decreased (entry 4).

Table 1. Diels-Alder reaction of 3-hydroxy-2-pyridone **9a** with *N*-phenylmaleimide **10a** using catalysts **3a-d**.

entry	catalyst	yield (%) ^a	ee (%) ^b
1	3a	51	8
2	3b	42	25
3	3c	60	37
4	3d	31	57

^a Isolated yields. ^bEe's were determined by chiral HPLC using chiralpak AS-H column

By using the superior catalyst **3d** (10 mol%), next we carried out the same reaction at room temperature with various dienes and dienophiles and results were presented (Table 2). Catalyst **3d** furnished the *endo*-DA adduct **11a** at room temperature with enhancement of chemical yield and enantioselectivity (42%, 67% *ee*) (entry 1). Considering of this result, next we examined the reaction of **9a** with *N*-methylmaleimide **10b** and *N*-ethylmaleimide **10c**, respectively (entries 2, 3). However, catalyst **3d** did not yield the **11b** with satisfactory results (entry 2). In contrast, fairly good enantioselectivity (87% *ee*) was obtained when *N*-ethylmaleimide **10c** was used, although chemical yield was low (entry 3). Furthermore, the reactions of *N*-tosyl-3-hydroxy-2-pyridone **9b** with *N*-substituted maleimides **10a-c** were also carried out under the same reaction conditions (entries 4-6). But, *N*-phenyl-maleimide **10a** and *N*-ethyl-maleimide **10c** did not afford the corresponding *endo*-DA adducts **11d,f** with satisfactory results regarding both chemical yield and enantioselectivity (**11d**: 32%, 35% *ee*, **11f**: 38%, 65% *ee*) (entries 4, 6). On the other hand, excellent enantioselectivity (98% *ee*) and good chemical yield (61%) was obtained from the reaction of **9b** with **10b** (entry 5). These results revealed that the use of 3-hydroxy-2-pyridone **9b** and *N*-methylmaleimide **10b** in the presence of **3d** was the best combinations for obtaining chiral DA adduct with the highest optical purity.

Table 2. Diels-Alder reaction of 3-hydroxy-2pyridones **9a,b** with *N*-substituted maleimides **10a-c** using catalyst **3d**.

entry	diene	dienophile	adduct	yield (%) ^a	ee (%) ^b
1	9a	10a	11a	42	67
2	9a	10b	11b	45	29
3	9a	10c	11c	40	87
4	9b	10a	11d	32	35
5	9b	10b	11e	61	98
6	9b	10c	11f	38	65

^a Isolated yields. ^bEe's were determined by chiral HPLC using chiralpak AS-H column

Next, we desire to study the electronic effect of the substituent group on the phenyl group at the α -position of the best catalyst **3d**. So that, the catalytic activities of β -amino alcohols **3e,f** containing *p*-methyl (electron-donating) and *p*-fluoro (electron-withdrawing) groups on the phenyl groups at the α -position were tested under the same reaction conditions (Table 3). Catalyst **3e** afforded the corresponding DA adduct **11e** in low chemical yield and moderate enantioselectivity (37%, 60% *ee*) (entry 1). On the other hand, catalyst **3f** brought about fairly good asymmetric induction (94% *ee*), but chemical yield was low (38%) (entry 2). Furthermore, the catalytic activities of amino alcohols **3g-i** containing dimethyl, diethyl and protons, respectively, at the α -position were also examined under the same reaction conditions (entries 3-5). However, these catalysts afforded the DA adduct **11e** in only low chemical yields and enantioselectivities (**3g**: 46%, 32% *ee*, **3h**: 42%, 40% *ee*, **3i**: 52%, 31% *ee*). Also, the catalytic abilities of secondary and tertiary amino alcohols **4a,b**, respectively were also examined (entries 6, 7). As expected, because of stronger basic property than primary amino alcohols, these catalysts provide the **11e** in good chemical yields with excellent enantioselectivities (**4a**: 72%, 95% *ee*, **4b**: 87%, 97% *ee*). However, they did not afford the better result than the primary amino alcohol catalyst **3d** in respect of enantioselectivity (98% *ee*). Furthermore, the catalytic activity of catalyst **4c** containing pyrrolidinyl ring system also tested in this reaction (entry 8). However, only low enantioselectivity (40% *ee*) was obtained, although chemical yield was considerably good (89%). The catalytic activity of α,β -diamine catalyst **5** was also examined (entry 9). We anticipated that one amino group might act as a base and another amino group might be used for hydrogen bonding with substrate but catalyst **5** yielded the DA adduct **11e** with moderate chemical yield and enantioselectivity (51%, 70% *ee*). Catalyst **6** bearing masked hydroxyl group with trimethylsilyl brought a great decrease in chemical yield (31%), but enantioselectivity was moderate (61% *ee*) (entry 10). We also examined the reaction using catalyst **8** with no substitution for the hydroxyl group at the α -position (entry 11). Although the catalyst **8** afforded **11e** in fairly good enantioselectivity (93% *ee*), but chemical yield (30%) was low in comparison with the results of catalyst **3d** with hydroxyl group (61%, 98% *ee*, entry 5, Table 2).

Table 3. Diels-Alder reaction of **9b** with **10b** using catalysts **3e-i**, **4a-c**, **5**, **6**, **8**.

entry	catalyst	R ¹	R ²	R ³	R ⁴	yield (%) ^a	ee (%) ^b
1	3e	<i>p</i> -Me-Ph	H	H	OH	37	60
2	3f	<i>p</i> -F-Ph	H	H	OH	38	94
3	3g	Me	H	H	OH	46	32
4	3h	Et	H	H	OH	42	40
5	3i	H	H	H	OH	52	31
6	4a	Ph	Me	H	OH	72	95
7	4b	Ph	Me	Me	OH	87	97
8	4c	Ph	(CH ₂) ₄		OH	89	40
9	5	Ph	H	H	NH ₂	51	70
10	6	Ph	H	H	OSiMe ₃	31	61
11	8	Ph	H	H	H	30	93

^a Isolated yields. ^bEe's were determined by chiral HPLC using chiralpak AS-H column

From the study of catalytic efficiency of all synthesized catalysts, we found that catalyst **3d** was superior for this reaction to afford the best enantioselectivity (98% ee) with good chemical yield. In order to optimize the reaction conditions, next we examined the effects of the molar ratio of catalyst **3d**, solvent, reaction temperature and reaction time (Table 4). The increase of catalytic loading of **3d** to 20 mol% did not increase the chemical yield and enantioselectivity (62%, 98% ee) (entry 1). On the other hand, the decrease of catalytic loading of **3d** to 5 and 2.5 mol% resulted in a decrease the chemical yields, but enantioselectivities were maintained at 98% ee and 96% ee, respectively (entries 2, 3). However, 1 and 0.5 mol% of catalyst **3d** brought about a great decrease in both chemical yields and enantioselectivities (1 mol%: 24%, 69% ee, 0.5 mol%: 17%, 37% ee) (entries 4, 5). When the reaction was carried out at 0 °C, both chemical yield and enantioselectivity (60%, 97% ee) were almost similar to the result at room temperature (62, 97% ee) (entry 6). The same reaction at -20 °C and -50 °C results the great decrease of the chemical yields (-20 °C: 46%, -50 °C: 37%) and enantioselectivities were also slightly decreased (-20 °C: 94% ee, -50 °C: 90% ee) (entries 7, 8). Using the best reaction condition (10 mol% of catalyst **3d**, rt), extending the reaction times from 1 to 3 and 6 h led to increase the chemical yields greatly with excellent enantioselectivity (entries 9, 10). Particularly, when the reaction was carried out for 6 h, an excellent chemical yield and enantioselectivity was observed (95%, 98% ee) (entry 10). Next, we also examined the solvent effects on this reaction. Commonly used aprotic polar (DMF, MeCN) and protic (MeOH, 2-propanol) polar solvents were screened (entries 11-14). Unfortunately, no improvement was observed in enantioselectivity in these solvents with comparison the use of CH₂Cl₂.

Table 4. Optimized conditions for Diels-Alder reaction of **9b** with **10b** using catalyst **3d**.

entry	catalyst (mol%)	solvent	temp.	time (h)	yield (%) ^a	ee (%) ^b
1	20	CH ₂ Cl ₂	rt	1	62	98
2	5	CH ₂ Cl ₂	rt	1	57	98
3	2.5	CH ₂ Cl ₂	rt	1	48	96
4	1	CH ₂ Cl ₂	rt	1	24	69
5	0.5	CH ₂ Cl ₂	rt	1	17	37
6	10	CH ₂ Cl ₂	0	1	60	97
7	10	CH ₂ Cl ₂	-20	1	46	94
8	10	CH ₂ Cl ₂	-50	1	37	90
9	10	CH ₂ Cl ₂	rt	3	66	97
10	10	CH ₂ Cl ₂	rt	6	95	98
11	10	DMF	rt	6	61	10
12	10	MeCN	rt	6	41	16
13	10	MeOH	rt	6	84	88
14	10	2-PrOH	rt	6	83	71

^a Isolated yields. ^b Ee's were determined by chiral HPLC using chiralpak AS-H column

The absolute stereochemistry of the obtained DA adduct **11e** was determined by the CD spectroscopy. Thus, the cotton effect pattern of the DA adduct **11e** was showed to be same as that of [1*R*, 4*R*]-**11a** whose structure was confirmed by X-ray diffraction.⁹ DA adduct **11a** with known absolute configuration showed a positive Cotton effect at around 252.5 nm and a negative Cotton effect at around 235.5 nm in CD spectra. On the

other hand, the new DA adduct **11e** showed a positive Cotton effect at around 249.0 nm and a negative Cotton effect at around 232.5 nm. From this experience, the absolute configuration of **11e** was determined as [1*R*, 4*R*] same as **11a** (Scheme 5).

Scheme 5. Determination of absolute stereochemistry of DA adduct **11e** using CD spectra.

Based on the observed enantiopurity (98% ee) (entry 10, Table 4) of the chiral *endo*-DA adduct **11e** that was obtained from the reaction of **9b** with **10b**, the model of the enantioselective reaction course was proposed as follows (Scheme 6). The *endo* DA adduct **11e** might form through the transition state **Ts-A** from the reaction of **9b** with **10b**. In **Ts-A**, the pyridone **9b** could be fixed by the two hydrogen bonding interactions between the ammonium site on the ammonium alcohol intermediate and the hydroxyl function at 3-position on **9b** and between the hydroxyl group on the ammonium alcohol intermediate and the carbonyl group at 2-position on **9b**, and then maleimide **10b** might attack enantioselectively from the one reaction site of **9b**, which shows a less steric interaction between *tert*-butyl and phenyl groups on the ammonium alcohol intermediate and the dienophile **10b**, although the reason is not clear.

Scheme 6. Plausible reaction course.

Conclusion

In conclusion, simple optically active primary β -amino alcohol organocatalysts showed a dramatic asymmetric catalytic activity for affording chiral DA adducts with excellent chemical yields and enantioselectivities (up to 95% yield, up to 98% ee) in the DA reactions of 3-hydroxy-2-pyridones with *N*-substituted maleimides. In particular, catalyst **3d** bearing *tert*-butyl group at β -position afforded the corresponding chiral *endo*-DA adduct **11e** with fairly good chemical yield and an excellent enantioselectivity (95%, 98% ee). These simple β -amino alcohol catalysts might be superior for practical use, because of these catalysts are stable in air and could be synthesized easily from inexpensive commercially available amino acids by means of well-known reactions in few steps. The enantioselective synthesis of DA adducts using 3-hydroxy-2-pyridones as dienes is challenging and important task because of the resulted DA

adducts could be used as synthetic precursors for total synthesis of various biologically active scaffolds. Application of DA adducts in synthesis of biologically active molecules and mechanistic studies of these catalysts for this reaction are now in progress and results will be published in the due course.

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14. Spectral data for new compounds. **(S)-(2-dimethylamino)-3,3-dimethyl-1,1-diphenylbutan-1-ol (4b)**: White solid, m.p.: 110–115 °C; $[\alpha]_D^{25} = -36.3$ (c 0.22, CHCl₃); IR (neat) cm⁻¹: 3626, 3033, 2900, 1660, 1447, 1277, 1050; ¹H NMR (CDCl₃, 500 MHz): δ 7.58–7.55 (m, 5H), 7.24–7.20 (m, 3H), 7.10–7.07 (m, 2H), 3.72 (s, 1H), 2.45 (s, 6H), 0.85 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz): δ 148.6, 128.3, 127.9, 127.5, 127.3, 126.6, 126.5, 126.1, 125.8, 125.6, 125.4, 76.8, 76.2, 40.9, 31.2, 27.8; FAB-MS m/z: 298 [M+H]⁺; HRMS (FAB) calcd for C₂₀H₂₈NO: 298.2170 [M + H]⁺, found: 298.2171. **(S)-3,3-dimethyl-1,1-diphenyl-2-(pyrrolidin-1-yl)buten-1-ol (4c)**: Colorless solid, m.p.: 120–124 °C; $[\alpha]_D^{25} = -28.0$ (c 0.25, CHCl₃); IR (neat) cm⁻¹: 3058, 2955, 2868, 1735, 1717, 1597, 1489, 1364, 1059; ¹H NMR (CDCl₃, 500 MHz): δ 7.63–7.57 (m, 4H), 7.23–7.19 (m, 4H), 7.10–7.04 (m, 2H), 3.98 (s, 1H), 3.07–2.95 (m, 4H), 1.35–1.24 (m, 4H), 0.88 (s, 9H); ¹³C NMR (CDCl₃, 125 MHz): δ 128.9, 128.5, 127.8, 127.7, 127.6, 127.4, 127.2, 125.9, 125.7, 125.5, 125.2, 52.1, 41.1, 31.4, 29.2, 26.7; EI-MS m/z: 323 [M]⁺; HRMS (EI) calcd for C₂₂H₂₉NO: 323.2249 [M]⁺, found: 323.2241. **(4R)-7-hydroxy-9-(mesitylsulfonyl)-2-methyl-3a,4,7,7a-tetrahydro-1H-4,7-(epiminomethano)isoindole-1,3,8(2H)-trione (11b)**: Pale yellow solid, m.p.: 180–182 °C; $[\alpha]_D^{20} = -2.7$ (c 0.33, CHCl₃); The ee was determined by HPLC [DAICEL chiralpak AS-H column, hexane/2-propanol = 10/90, flow rate: 0.2 mL/min, t_r(major) = 47.23 min, t_r(minor) = 116.84 min, ee = 29 %]; IR (neat) cm⁻¹: 3329, 2948, 1779, 1735, 1689, 1439, 1347, 1166, 1106; ¹H NMR (CDCl₃, 500 MHz): δ 6.98 (s, 2H), 6.44 (dd, 1H, J = 8.0, 5.7 Hz), 6.37 (dd, 1H, J = 8.0, 1.0 Hz), 5.81–5.79 (m, 1H), 3.74 (dd, 1H, J = 8.1, 4.3 Hz), 3.11 (d, 1H, J = 7.9 Hz), 2.95 (s, 3H), 2.57 (s, 6H), 2.29 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz): δ 173.5, 173.2, 170.7, 144.9, 141.1, 137.3, 132.3, 131.6, 128.8, 51.3, 48.0, 44.8, 25.4, 22.7, 21.3; FAB-MS m/z: 405 [M + H]⁺; HRMS (FAB) calcd for C₁₉H₂₁N₂O₆S: 405.1120 [M + H]⁺, found: 405.1115. **(4R)-7-hydroxy-2-phenyl-9-tosyl-3a,4,7,7a-tetrahydro-1H-4,7-(epiminomethano)isoindole-1,3,8(2H)-trione (11d)**: Pale yellow solid, m.p.: 190–191 °C; $[\alpha]_D^{20} = -6.7$ (c 0.24, CHCl₃); The ee was determined by HPLC [DAICEL chiralpak AD-H column, hexane/2-propanol = 10/90, flow rate: 0.2 mL/min, t_r(major) = 75.24 min, t_r(minor) = 178.13 min, ee = 35 %]; IR (neat) cm⁻¹: 3449, 3065, 1781, 1712, 1449, 1351, 1240, 1159, 1107; ¹H NMR (CDCl₃, 500 MHz): δ 7.89 (d, 2H, J = 8.4 Hz), 7.46–7.38 (m, 3H), 7.36–7.34 (m, 2H), 7.17–7.15 (m, 2H), 6.48 (dd, 1H, J = 7.9, 5.9 Hz), 6.39 (d, 1H, J = 8.0 Hz), 5.85–5.82 (m, 1H), 4.09 (s, 1H), 3.74 (dd, 1H, J = 8.3, 4.3 Hz), 3.14 (d, 1H, J = 8.3 Hz), 2.57 (s, 3H); ¹³C NMR (CDCl₃, 125 MHz): δ 172.5, 169.7, 146.4, 136.8, 134.5, 131.1, 130.0, 129.4, 129.3, 129.2, 128.2, 126.2, 52.4, 47.3, 21.8; FAB-MS m/z: 439 [M+H]⁺; HRMS (FAB) calcd for C₂₂H₁₈N₂O₆S: 439.0964 [M + H]⁺, found: 439.0970. **(4R)-7-hydroxy-2-methyl-9-tosyl-3a,4,7,7a-tetrahydro-1H-4,7-(epiminomethano)isoindole-1,3,8(2H)-trione (11e)**: White solid, m.p.: 225–227 °C; $[\alpha]_D^{20} = -20.7$ (c 0.34, CHCl₃); The ee was determined by HPLC [DAICEL chiralpak AD-H column, hexane/2-propanol = 10/90, flow rate: 0.2 mL/min, t_r(major) = 49.36 min, t_r(minor) = 110.82 min, ee = 98 %]; IR (neat) cm⁻¹: 3456, 3072, 1778, 1709, 1458, 1360, 1238, 1154, 1112; ¹H NMR (DMSO-d₆, 500 MHz): δ 7.85 (d, 2H, J = 8.5 Hz), 7.33 (d, 2H, J = 8.0 Hz), 6.34 (dd, 1H, J = 6.0, 2.0 Hz), 6.24 (dd, 1H, J = 7.5, 1.0 Hz), 5.76 (m, 1H), 3.58 (dd, 1H, J = 4.5, 3.5 Hz), 3.01 (d, 1H, J = 8.5 Hz), 2.93 (s, 3H), 2.43 (s, 3H); ¹³C NMR (DMSO-d₆, 125 MHz): δ 174.7, 173.6, 170.6, 146.0, 136.6, 135.1, 130.3, 130.1, 128.2, 78.7, 52.1, 47.9, 42.0, 25.1, 21.6; FAB-MS m/z: 377 [M+H]⁺; HRMS (FAB) calcd for C₁₇H₁₆N₂O₆S: 377.0807 [M + H]⁺, found: 377.0813. **(4R)-2-ethyl-7-hydroxy-9-tosyl-3a,4,7,7a-tetrahydro-1H-4,7-(epiminomethano)isoindole-1,3,8(2H)-trione (11f)**: Colorless solid, m.p.: 201–203 °C; $[\alpha]_D^{20} = -8.7$ (c 0.35, CHCl₃); The ee was determined by HPLC [DAICEL chiralpak AD-H column, hexane/2-propanol = 10/90, flow rate: 0.2 mL/min, t_r(major) = 43.25 min, t_r(minor) = 11.73 min, ee = 65 %]; IR (neat) cm⁻¹: 3445, 2938, 1731, 1638, 1596, 1405, 1344, 1227, 1099, 976; ¹H NMR (CDCl₃, 500 MHz): δ 7.86 (d, 2H, J = 8.4 Hz), 7.33 (d, 2H, J = 8.0 Hz), 6.34 (dd, 1H, J = 8.0, 5.9 Hz), 6.24 (d, 1H, J = 7.0 Hz), 5.75–5.73 (m, 1H), 4.06 (s, 1H), 3.54 (dd, 1H, J = 8.0, 4.2 Hz), 3.48 (dd, 1H, J = 14.3, 7.1 Hz), 2.96 (d, 1H, J = 8.2 Hz), 2.43 (s, 3H), 1.07 (t, 3H, J = 7.2 Hz); ¹³C NMR (CDCl₃, 125 MHz): δ 173.5, 173.2, 170.7, 146.3, 136.6, 134.6, 130.0, 129.3, 129.2, 128.9, 128.2, 77.7, 52.3, 47.3, 43.9, 34.3, 21.9; FAB-MS m/z: 391 [M+H]⁺; HRMS (FAB) calcd for C₁₈H₁₉N₂O₆S: 391.0964 [M + H]⁺, found: 396.0963.

Graphical Abstract

Simple primary β -amino alcohol catalyzed enantioselective Diels-Alder reaction of 3-hydroxy-2-pyridones

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