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Abstract: New chiral imidazolidinone with an indole group was synthesized and used to catalyze the Diels–Alder reaction of α,β-unsaturated aldehyde with diene. High enantiomeric excesses and good yields were obtained. The reaction media were also surveyed. The best result in terms of enantioselectivity was achieved using acrolein and 2,3-dimethylbutdiene (up to 95% ee) in CH_3OH/H_2O.

Keywords: Catalyst, Diels–Alder reaction, imidazolidinone, α,β-unsaturated aldehyde

INTRODUCTION

The control of absolute stereochemistry in the Diels–Alder reaction, one of the most important methods for construction of cyclohexene derivatives, has been studied extensively.[1] In our previous study, we reported the highly enantioselective Diels–Alder reactions between dienes and 1-phenylsulfonyl-3-alken-2-ones employing chiral Lewis acid catalyst.[2] Our recent interest in asymmetric Diels–Alder reactions has been focused on asymmetric organocatalytic transformations because of the

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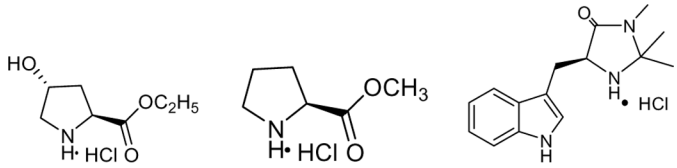


1 **2** **3**

Figure 1. Chiral secondary amine hydrochloride derived from amino acids.

advantages associated with the use of small organic molecules as chiral catalysts.[3]

The first highly enantioselective organocatalyzed Diels–Alder reaction of α,β-unsaturated aldehydes to dienes using chiral secondary amine derived from S-phenylalanine was achieved by Ahrendt et al.[4] The role of neighboring π-electron-rich aromatic groups to channel the Diels–Alder reactions along a specific stereochemical pathway led us to a study of L-tryptophan derivative as a catalyst for enantioselective Diels–Alder reactions because the indole ring has strong π-electron-donating character.[5]

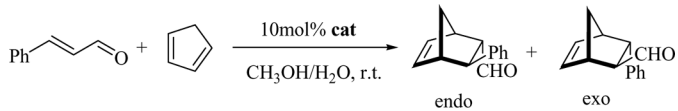
In this work, we report a new organocatalyst **3**. The catalyst synthesized from L-tryptophan was a chiral secondary amine hydrochloride, which can react with aldehydes to generate active iminium ions (Fig. 1).

RESULTS AND DISCUSSION

Our enantioselective catalytic Diels–Alder reaction was first evaluated using cyclopentadiene with (E)-cinnamaldehyde and three kinds of chiral secondary amine hydrochlorides. As revealed in Table 1, the Diels–Alder adduct was obtained in excellent yield but poor stereoselectivity (entry 1, 84%, 2.9:1 exo/endo, exo 30% ee) by using a catalytic quantity of trans-4-hydroxy-L-proline ethyl ester (10 mol%). With the (S)-proline methyl ester, an increase in enantio- control was observed (entry 2, 80% yield, 2.7:1 exo/endo, 48% ee). Importantly, control of iminium ion geometry through the use of steric constraints on the catalyst architecture **3** was found to provide the best levels of enantioselectivity (93% ee) while maintaining reaction efficiency (entry 3, 5.0 mol%). Consequently, amine salt **3** was identified as the optimal catalyst for further exploration.

The reaction media for this organocatalytic Diels–Alder reaction were examined. We selected weak polar solvents such as toluene, dichloromethane (DCM), tetrahydrofuran (THF), and strong ones including water and room temperature ion liquids (RTIL). Interestingly, as

Table 1. Organocatalyzed Diels–Alder reaction between cinnamaldehyde and cyclopentadiene

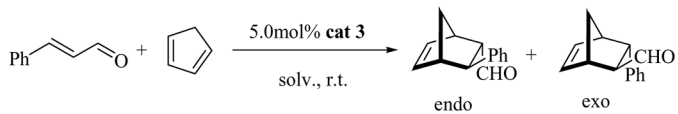


Entry	Catalyst	Time (h)	Yield (%)[a]	Exo/endo	Exo ee (%)[b,c]
1	**1**	24	84	2.9:1	30 (5R,6R)
2	**2**	24	80	2.7:1	48 (5R,6R)
3[d]	**3**	12	99	1:1	93 (5S,6S)

[a]Isolated yield.
[b]Product ratios determined by GLC using an RTX-13100 column.
[c]Absolute and relative configurations were determined by correlation to the literature.[4,6,7].
[d]Using 5.0 mol% catalyst.

revealed in Table 2, the Diels–Alder reaction could be conducted smoothly both in [bmim]BF_4 and [bmim]PF_6 with excellent yield and high stereoselectivity (entry 5: 95%, 1:1 exo/endo, exo 86% ee, endo 88% ee; entry 6: 94%, 1.3:1 exo/endo, exo 66% ee, endo 68% ee). The use of CH_3OH/H_2O provided optimal selectivity and chemical yield

Table 2. Effect of the polarity of solvent on the asymmetric Diels–Alder reaction of cinnamaldehyde and cyclopentadiene



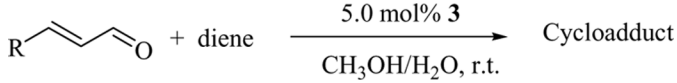
Entry	Solvent	Time (h)	Yield (%)[b]	Exo/endo[a]	Exo/% ee	Endo/% ee
1	THF	48	<10	—	—	—
2	CH_2Cl_2	48	<10	—	—	—
3	Toluene	48	<10	—	—	—
4	H_2O	48	<10	—	—	—
5	[bmim]BF_4	24	95	1:1	86	88
6	[bmim]PF_6	24	94	1.3:1	66	68
7	CH_3OH/H_2O	12	99	1:1	93	90

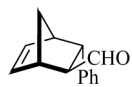
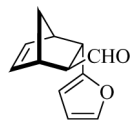
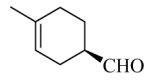
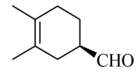
[a]Enantiomeric excess and exo/endo determined by chiral GLC analysis (RTX-13100 column).
[b]Isolated yield.

(entry 7, 99% yield, 1:1 exo/endo, exo 93% ee, endo 90% ee). However, the organocatalytic Diels–Alder reaction of cyclopentadiene with (E)-cinnamaldehyde in weak polar solvents and water was not very efficient with respect to stereoselectivity and yield. The superior levels of asymmetric induction and efficiency exhibited by amine salt **3** in CH_3OH/H_2O at room temperature to afford exo cycloadduct in 93% ee prompted us to select these catalytic conditions for further exploration.

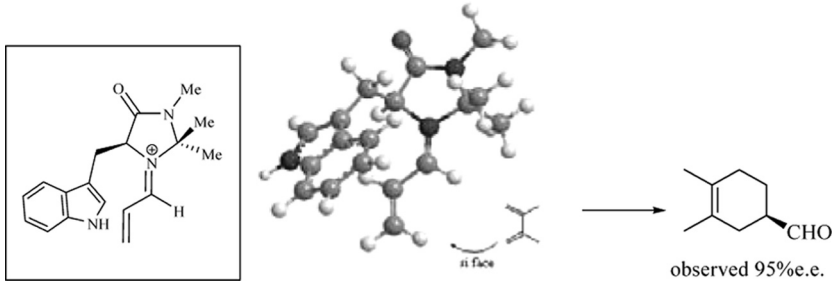
Experiments that probe the scope of the Diels–Alder reaction component are summarized in Table 3. Variation of the olefin substituent (R = Me, Ph. 2-furyl, entries 1–3) is possible without loss in yield or

Table 3. Organocatalyzed Diels–Alder reaction between different dienophiles and representative dienes



Entry	R	Diene	Product	Time (h)	Yield (%)[a]	Dr (exo/endo)	ee[f] (%)
1	Me			18	77	1.3:1[b]	91 (5R,6S)[d]
2	Ph			12	99	1:1[b]	93 (5S,6S)[d]
3	2-Furyl			24	90	1:1.1[b]	89 (5S,6S)[d]
4	H			24	83	—[c]	86 (R)[e]
5	H			24	89	—[c]	95 (R)[e]

[a]Isolated yield.
[b]Product ratios determined by GLC using an RTX-13100 column.
[c]Product ratios determined by HPLC using an AS-H column.
[d]Absolute configuration of exo.
[e]Absolute configuration of para.
[f]Absolute and relative configurations were determined by correlation to the literature.[4,6,7]



Scheme 1. The calculated iminium ion model of MM2.

enantioselectivity (>77% yield, >89% ee). This amine-catalyzed Diels–Alder cycloaddition is also general with respect to diene structure (entries 4 and 5). The acrolein reacted with isoprene and 2,3-dimethylbutdiene to afford the cycloadduct smoothly (entry 4, 83% yield, 86% ee; entry 5, 89% yield, 95% ee). It is noteworthy that the reactions depicted in Tables 2 and 3 were performed under an aerobic atmosphere, using wet solvents and an inexpensive bench-stable catalyst, further illustrating the preparative advantages of organocatalysis.

Regarding the effects of catalyst **3** on the enantioselectivity of the Diels–Alder reaction, we propose the calculated iminium ion model of MM2: the indole group on the catalyst framework effectively shields the *re* face of the dienophile, leaving the *si* face exposed to cycloaddition. [4] See Scheme 1.

CONCLUSION

We have shown that catalyst derived from L-tryptophan can be conveniently employed to promote cycloadditions of α,β-unsaturated aldehydes with dienes. The best reaction medium was CH_3OH/H_2O. This amine-catalyzed Diels–Alder cycloaddition is also general with respect to the structure of dienophile and diene.

EXPERIMENTAL

General Information

All solvents were used as obtained from commercial suppliers unless otherwise indicated. Other commercial reagents were purified prior to use following the guidelines of Huang et al.[8] Reactions were monitored

by thin-layer chromatography (TLC). Organic solutions were concentrated under reduced pressure on a Yarong evaporator.

^{1}H and ^{13}C NMR spectra were recorded on a bruker 400 instrument as noted. Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz), and assignment. Data for ^{13}C NMR are reported in terms of chemical shift. Infrared (IR) spectra were recorded on a Bruker spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Gas liquid chromatography (GLC) was performed on an Agilent 6850 series gas chromatograph using RTX-13100 and AS-H columns (30 m × 0.25 mm). Progress of the Diels–Alder reaction was typically monitored by TLC analysis. Absolute configurations were determined by correlation to the literature.[4,6,7]

(5S)-5-((1H-Indol-3-yl)methyl)-2,2,3-trimethylimidazolidin-4-one hydrochloride (Catalyst 3)

(S)-Tryptophan methyl ester hydrochloride (10 g, 39.3 mmol) was added to a solution of ethanolic $MeNH_2$ (16.3 g, 157 mmol), and the resulting solution was stirred at room temperature until the amino ester was judged to be consumed as determined by TLC (24 h). After removal of the organic solvents in vacuo, the residue was suspended in Et_2O and then concentrated. This Et_2O addition–removal cycle was repeated several times (to remove excess CH_3NH_2) until (S)-tryptophan N-methyl amide hydrochloride was obtained as a white solid. This amide hydrochloride was treated with sat. aq. $NaHCO_3$ (100 ml), and the free amine was extracted with $CHCl_3$ (10 mL × 3), dried with Na_2SO_4, filtered, and concentrated. MeOH (200 ml), acetone (50 ml), and p-TSA (0.2 g) were added to this residue, and the resulting solution was heated to reflux for 10 h, cooled to room temperature, and then concentrated in vacuo. The residue was taken up in Et_2O, and a solution of dioxane–HCl (4.0 M) was added to precipitate **3**. The precipitate was recrystallized from isopropanol to provide (5S)-5-((1H-indol-3-yl)methyl)-2,2,3-trimethylimidazolidin-4-one hydrochloride **3** as colorless crystals in 60% overall yield from (S)-tryptophan methyl ester hydrochloride (6.9 g, 23.6 mmol). IR (KBr) cm^{-1}: 3397, 2975, 1674, 1434, 1405; ^{1}H NMR (400 MHz, d_6-DMSO): 9.00 (s, 1H, NH), 7.57–7.59 (d, $J = 7.6$ Hz, 1H, ArH), 7.28 (d, $J = 0.8$ Hz, 1H, ArH), 7.08–7.12 (t, $J = 6.4$, 8.4 Hz, 1H, ArH), 7.02–7.05 (t, $J = 7.2$ Hz, 1H, ArH), 6.97–6.99 (d, $J = 2.4$ Hz, 1H, ArH), 3.79–3.82 (t, $J = 5.2$ Hz, 1H, CH_2CHCO), 3.24–3.29 (dd, $J = 15.0$, 4.4 Hz, 1H, CHHCH), 3.14–3.19 (dd, $J = 15.2$, 6.0 Hz, 1H, CHHCH), 2.65 (s, 3H, CH_3), 2.13 (s, 1H, NH), 1.19 (s, 3H, CH_3), 0.98

(s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) 174.0, 136.1, 127.7, 123.4, 121.7, 119.2, 118.5, 111.1, 109.8, 75.4, 58.8, 26.7, 26.2, 25.1, 24.9; $[\alpha]D = -87.8^\circ$ ($c = 0.01$, $CHCl_3$).

General Procedure

α,β-Unsaturated aldhyde was added to a solution of (5S)-5-((1H-indol-3-yl)methyl)-2,2,3-trimethyl-imidazolidin-4-one hydrochloride **3** in CH_3OH/H_2O (95/5 v/v). The solution was stirred for 1–2 min before addition of the appropriate diene. Upon consumption of the limiting reagent, the reaction mixture was diluted with Et_2O and washed successively with H_2O and brine. The organic layer was dried with Na_2SO_4, filtered, and concentrated. Hydrolysis of the product dimethyl acetal was performed by stirring the crude product mixture in TFA–H_2O–$CHCl_3$ (1:1:2) for 2 h at room temperature, followed by neutralization with sat. aq. $NaHCO_3$ and extraction with Et_2O. Purification of the Diels–Alder adduct was accomplished by silica-gel chromatography.

Endo-(1S,4R,5S,6S)-6-phenylbicyclo[2.2.1]hex-2-ene-5-carboxaldehyde and Exo-(1R,4S,5S,6S)-6-phenylbicyclo[2.2.1]hex-2-ene-5-carboxaldehyde (Table 1, Entry 3)

The title compound was prepared according to the general procedure with (E)-cinnamaldehyde (0.33 ml, 2.5 mmol), cyclopentadiene (0.75 ml, 7.5 mmol), and **3** (36.69 mg, 0.125 mmol) as a colorless oil in 99% yield after silica-gel chromatography (EtOAc/hex); 1:1 endo/exo, exo 93% ee, and endo 90% ee. Product ratios were determined by gas liquid chromatography (GLC) analysis. Endo isomers $t_r = 30.2$, 30.8 min; exo isomers $t_r = 28.4$, 29.3 min. ^1H NMR (400 MHz, $CDCl_3$) δ 9.92 (1H, d, $J = 2.0$ Hz, CHO), 7.13–7.32 (5H, m, Ar-H), 6.33 (1H, dd, $J = 3.2$, 5.6 Hz, CH=CH), 6.07 (1H, dd, $J = 3.2$, 5.6 Hz, CH=CH), 3.72 (1H, dd, $J = 3.6$, 5.2 Hz, CHPh), 3.23 (1H, br s, CHCH=CH), 3.22 (1H, br s, CHCH=CH), 2.60 (1H, m, CHCHO), 1.56–1.63 (2H, m, CH_2). The absolute configuration was established according to the literature.[4,6]

Endo-(1S,4R,5R,6S)-6-methylbicyclo[2.2.1]hex-2-ene-5-carboxaldehyde and Exo-(1R,4S,5R,6S)-6-methylbicyclo[2.2.1]hex-2-ene-5-carboxaldehyde

The title compound was prepared according to the general procedure with (E)-crotonaldehyde (0.12 ml, 2.5 mmol), cyclopentadiene (0.75 ml,

7.5 mmol), and **3** (36.69 mg, 0.125 mmol) as a colorless oil in 77% yield after silica-gel chromatography (EtOAc/hex); 1:1.3 endo/exo, exo 91% ee, endo 91% ee. Product ratios were determined by GLC analysis. Endo isomers $t_r = 28.9$, 29.5 min; exo isomers $t_r = 27.0$, 27.9 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78–9.79 (d, $J = 2.8$ Hz, 1H, CHO), 6.23–6.25 (dd, $J = 5.7$, 3.1 Hz, 1H, CH=CH), 6.15–6.17 (dd, $J = 5.7$, 3.0 Hz, 1H, CH=CH), 3.02 (br, s, 1H, CHCH=CH), 2.79 (br, s, 1H, CHCH=CH), 2.37–2.45 (m, 1H, CHCHO), 1.70–1.73 (m, 1H, $CHCH_3$), 1.44–1.48 (m, 2H, CH_2), 0.89–0.91 (d, $J = 6.9$ Hz, 3H, $CHCH_3$). The absolute configuration was established according to the literature.[4,6]

Endo-(1S,4R,5S,6S)-6-furan-2-ylbicyclo[2.2.1]hex-2-ene-5-carboxaldehyde and Exo-(1R,4S,5S,6S)-6-furan-2-ylbicyclo[2.2.1]hex-2-ene-5-carboxaldehyde (Table 3, Entry 3)

The title compound was prepared according to the general procedure with (E)-3-furanyl-acrolein (305 mg, 2.5 mmol), cyclopentadiene (0.75 ml, 7.5 mmol), and **3** (36.69 mg, 0.125 mmol) as a colorless oil in 90% yield after silica-gel chromatography (EtOAc/hex); 1.1:1 endo/exo, exo 89% ee; endo 84% ee. Product ratios were determined by GLC analysis. Endo isomers $t_r = 26.0$, 26.7 min; exo isomers $t_r = 23.9$, 24.9 min. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.56 (d, $J = 1.9$ Hz, 1H, CHO), 7.32 (d, $J = 1.0$ Hz, 1H, furyl), 6.35 (dd, $J = 5.6$, 3.1 Hz, 1H, CH=CH), 6.30 (dd, $J = 3.1$, 1.9 Hz, 1H, furyl), 6.13 (dd, $J = 5.6$, 2.7 Hz, 1H, CH=CH), 6.07 (d, $J = 3.2$ Hz, 1H, furyl), 3.33 (br, s, 1H), 3.13–3.09 (m, 1H), 3.18–3.04 (m, 2H), 1.78 (br, d, $J = 8.7$ Hz, 1H), 1.59–1.53 (m, 2H). The absolute configuration was established according to the literature.[4,6]

(R)-4-Methylcyclohex-3-enecarbaldehyde (Table 3, Entry 4)

The title compound was prepared according to the general procedure with acrolein (0.2 ml, 3.0 mmol), isoprene (1.5 ml, 15 mmol), and **3** (44.0 mg, 0.15 mmol) as a colorless oil in 83% yield after silica-gel chromatography (EtOAc/hex). Product ratios were determined by GLC analysis. S isomers $t_r = 4.9$ min; R isomers $t_r = 5.3$ min; R 86% ee. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (s, 1H, CHO), 5.41 (br, 1H, CH=C), 2.44 (m, 1H, CH), 2.21 (br, 2H, CH_2), 2.00 (br, 2H, CH_2), 1.97 (m, 1H, CHH), 1.69 (m, 1H, CHH), 1.65 (s, 3H, CH_3). The absolute configuration was established according to the literature.[4]

(R)-3,4-Dimethylcyclohex-3-enecarbaldehyde (Table 3, Entry 5)

The title compound was prepared according to the general procedure with acrolein (0.2 ml, 3.0 mmol), 2,3-dimethylbutdiene (1.5 ml, 12.5 mmol), and **3** (44.0 mg, 0.15 mmol) as a colorless oil in 89% yield after silica-gel chromatography (EtOAc/hex). Product ratios were determined by GLC analysis. S isomers $t_r = 4.9$ min; R isomers $t_r = 5.4$ min; R 95% ee. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.61 (s, 3H, CH_3), 1.65 (s, 3H, CH_3), 1.90–2.06 (m, 4H, CH_2), 2.09–2.19 (m, 2H, CH_2), 2.42–2.58 (m, 1H, CH), 9.69 (s, 1H, CHO). The absolute configuration was determined according to the literature.[4]

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