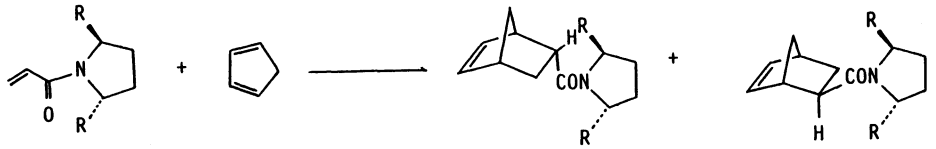
Asymmetric Diels-Alder Reaction of Acrylamides Having *trans*-2,5-Disubstituted Pyrrolidines as Chiral Auxiliaries

Yasuhiro KAWANAMI,* Tsutomu KATSUKI,† and Masaru YAMAGUCHI†
Department of Chemistry, Faculty of Education, Kagawa University, Takamatsu, Kagawa 760
†Department of Chemistry, Faculty of Science, Kyushu University 33,
Higashi-ku, Fukuoka 812
(Received June 2, 1987)

Synopsis. The asymmetric Diels-lder reaction between chiral acrylamides derived from (2R,5R)-2,5-disubstituted pyrrolidines and cyclopentadiene gave (1*R*,2*R*,4*R*)-5-norbornene-2-carboxylic acid amides **3a—c** with excellent diastereoface selectivity. The amides **3a—c** were converted into the corresponding carboxylic acid by an iodolactonization-reduction sequence and 2,5-disubstituted pyrrolidines were recovered intact.

The Diels–Alder reaction[1] provides one of the useful methods of creating new chiral centers and some highly diastereoselective examples employing different types of optically active dienophiles have been reported in the last few years.[2-4] Recently, we have developed chiral auxiliaries, *trans*-2,5-disubstituted pyrrolidines,[5] which were quite effective for asymmetric α-alkylations,[5] α-acylation,[6] aldol reaction,[7] and [2,3]-Wittig rearrangement[8] of carboxylic acids through their amides. In this note, we wish to describe the asymmetric Diels–Alder reaction of acrylamides **1a—c** bearing the same chiral auxiliaries with cyclopentadiene under Lewis acid catalyzed and uncatalyzed conditions.



1a; R=COOMe
1b; R=CH_2OMe
1c; R=CH_2OCH_2OMe

2 endo-3 exo-4

The dienophiles **1a—c** were prepared by the acylation of the corresponding (2R,5R)-2,5-disubstituted pyrrolidines[5] with acryloyl chloride and Et_3N in CH_2Cl_2 at 0 °C. Then, **1a—c** were submitted to Diels–Alder reaction with cyclopentadiene in toluene under various conditions. The reaction proceeded smoothly to give (1*R*,2*R*,4*R*)-5-norbornene-2-carboxylic acid amides **3a—c** as major isomers. The results obtained were summarized in Table 1. Aluminum trichloride among Lewis acids examined afforded the highest *endo*- and almost quantitative diastereoface selectivity (Entries 5 and 8). Diethylaluminum chloride also gave the same degree of diastereomeric excess as aluminum trichloride but the *endo*

Table 1. Asymmetric Diels-Alder Reaction of **1a—d** with **2**[a]

Entry	Dienophile R	Catalyst	Temp °C	Time h	Yield[b] %	endo : exo[c] (**3** : **4**)	%de of *endo*-**3**[d,e]
1	**1a**(R=COOMe)	none	rt	48	81	68 : 32	67
2	**1a**	BF_3-OEt_2	−10	4	65	87 : 13	90
3	**1a**	$AlCl_3$	0	2	85	87 : 13	94
4	**1b**(R=CH_2OMe)	none	rt	24	80	68 : 32	85
5	**1b**	$AlCl_3$	0	1	71	89 : 11	98
6	**1c**(R=CH_2OMOM)[f]	none	rt	42	75	69 : 31	90
7	**1c**	BF_3-OEt_2	−10	1	76	92 : 8	94
8	**1c**	$AlCl_3$	0	1	76	95 : 5	98
9	**1c**	Et_2AlCl	0	1	73	86 : 14	98
10	**1d**[g]	$AlCl_3$	0	1	76	91 : 9	73[h]

a) Reactions were carried out in 0.2—0.5 mol dm^{-3} toluene solution of **1**. b) Isolated yield. c) Ratios were determined after column chromatography separation. Each compound gave satisfactory ^1H NMR analysis. d) Determined by ^1H NMR spectra in the presence of Eu(fod)$_3$ and/or ^{13}C NMR spectra. e) Configurations of the adducts were deduced to be 2'R from the configuration of (+)-(1*R*,2*R*,4*R*)-5-norbornene-2-carboxylic acid. f) MOM=CH_2OMe. g) Acrylamide derived from (*S*)-*O*-methoxymethylprolinol. h) Absolute configuration was determined to be 2'S.

selectivity suffered a small loss (Entry 9). In the reactions in the absence of catalyst, the diastereoface selectivity depended on the substituent on the pyrrolidine ring and the best result (90% de) was obtained when the amide **1c** was used (Entry 6). This result is noteworthy because highly diastereoselective Diels–Alder reactions with one exception[2] have usually been attained in the presence of Lewis acid catalysts.[1] An acrylamide **1d** derived from (*S*)-*O*-methoxymethylprolinol, was examined for comparison and only moderate diastereoface selectivity (73% de) was obtained under aluminum trichloride-catalyzed conditions, though high *endo* selectivity was also observed (Entry 10).

The major *endo*-adducts **3** were converted to (+)-(1*R*,2*R*,4*R*)-5-norbornene-2-carboxylic acid[2,9] by the sequence, i) iodolactonization to a iodo lactone using iodine in H_2O–DME[10] and ii) reduction of the iodo lactone by zinc in methanol. Chiral auxiliaries were also recovered by this iodolactonization process.

Although the exact steric cource of the reaction is not clear at present, absolute configurations of cycloaddition products and a CPK-model examination suggest that the acrylamide exists as a cisoid conformer due to the severe repulsion between the *cis*-vinylic hydrogen on the β-carbon atom and one of the C_2-symmetrically placed substituents on the pyrrolidine ring and that the amide is attacked by cyclopentadiene on its less hindered side (*si*-face). Further work on the reaction of other combinations of dienophiles and dienes is under way.

Experimental

Melting points were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were obtained at 90 MHz in $CDCl_3$ with TMS as an internal standard.

(2*R*,5*R*)-*N*-Acryloyl-*trans*-2,5-bis(methoxycarbonyl)pyrrolidine (1a). Acryloyl chloride (0.21 ml, 2.58 mmol) was added to a solution of (2*R*,5*R*)-*trans*-2,5-bis(methoxycarbonyl)pyrrolidine (242 mg, 1.29 mmol) and triethylamine (0.36 ml, 2.58 mmol) in dichloromethane (4 ml) at 0 °C and the mixture was stirred for 1 h. The reaction mixture was diluted with ether and filtered through Celite. The filtrate was concentrated and chromatographed on silica gel (hexane–acetone, 10:3) to give **1a** (172 mg, 58%): $[\alpha]_D^{23}$ +118° (*c* 1.14, EtOH); UV (EtOH) 206 nm (ε 4065); IR (neat) 1740, 1650, and 1615 cm^{-1}; ^{1}H NMR δ=1.92—2.63 (4H, m), 3.73 (3H, s), 3.75 (3H, s), 4.6—4.8 (2H, m), 5.70 (1H, dd, *J*=9.5 and 4.0 Hz), 6.06—6.55 (2H, m); Found: C, 54.98; H, 6.16; N, 5.54%. Calcd for $C_{11}H_{15}NO_5$: C, 54.77; H, 6.27; N, 5.81%.

(2*R*,5*R*)-*N*-Acryloyl-*trans*-2,5-bis(methoxymethyl)pyrrolidine (1b): Yield, 72%; $[\alpha]_D^{23}$ +70.6° (*c* 1.36, EtOH); UV (EtOH) 206 nm (ε 7890); IR (neat) 1640 and 1610 cm^{-1}, ^{1}H NMR δ=1.8—2.2 (4H, m), 3.06—3.08 (4H, m), 3.30 (6H, s), 3.9—4.4 (2H, m), 5.66 (1H, dd, *J*=8.4 and 4.2 Hz), 6.25—6.68 (2H, m); Found: C, 61.70; H, 9.26; N, 6.39%. Calcd for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; N, 6.57%.

(2*R*,5*R*)-*N*-Acryloyl-*trans*-2,5-bis(methoxymethoxymethyl)-pyrrolidine (1c): Yield, 79%; $[\alpha]_D^{23}$ +50.0° (*c* 0.72, EtOH); UV (EtOH) 206 nm (ε 7500); IR (neat) 1640 and 1608 cm^{-1}; ^{1}H NMR δ=1.8—2.4 (4H, m), 3.25—3.86 (4H, m), 3.35 (6H, s), 4.12 (1H, m), 4.30 (1H, m), 4.59 (4H, s), 5.66 (1H, dd, *J*=4.2 and 8.4 Hz), 6.26—6.70 (2H, m); Found: C, 56.86; H, 8.75; N, 5.27%. Calcd for $C_{13}H_{23}NO_5$; C, 57.13; H, 8.48; N, 5.12%.

Representative Procedure for Diels-Alder Reaction of Acrylamides with Cyclopentadiene. Aluminum trichloride (122 mg, 0.904 mmol) was added to a solution of **1c** (206 mg, 0.753 mmol) in toluene (3.7 ml) at 0 °C. After 5 min, freshly distilled cyclopentadiene (0.5 ml, 6 mmol) was added to the solution. The mixture was stirred for 1 h, quenched with saturated aqueous $NaHCO_3$ solution, and extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The concentrate was chromatographed on silica gel (hexane–acetone, 5:2) to give the less polar *exo*-isomer (**4c**, 10 mg, 4%) and the more polar *endo*-isomer (**3c**, 185 mg, 72%).

4c: IR (neat) 1635 cm^{-1}; ^{1}H NMR δ=1.1—1.4 (2H, m), 1.78—2.50 (7H, m), 2.75 (1H, m), 2.92 (1H, m), 3.32 (3H, s), 3.35 (3H, s), 3.2—3.8 (4H, m), 3.93—4.32 (2H, m), 4.56 (2H, s), 4.60 (2H, s), 6.15 (2H, m).

3c: $[\alpha]_D^{23}$ +161.8° (*c* 1.23, EtOH); IR (neat) 1640 cm^{-1}; ^{1}H NMR δ=1.15—2.40 (8H, m), 2.82—3.72 (7H, m), 3.35 (6H, s), 4.20 (2H, m), 4.60 (4H, s), 5.76 (1H, dd, *J*=2.6 and 5.6 Hz), 6.25 (1H, dd, *J*=3.1 and 5.6 Hz); ^{13}C NMR δ=25.1, 27.5, 29.2, 42.0, 43.2, 46.6, 50.2, 55.1, 55.2, 56.8, 57.3, 67.0, 69.4, 96.5, 96.6, 130.3, 137.3, 173.0; Found: C, 63.49; H, 8.79; N, 4.17%. Calcd for $C_{18}H_{29}NO_5$: C, 63.69; H, 8.61; N, 4.13%.

(2*R*,5*R*)-*N*-[(1*R*,2*R*,4*R*)-5-Norbornene-2-carbonyl]-*trans*-2,5-bis(methoxycarbonyl)pyrrolidine (3a): $[\alpha]_D^{23}$ +212.6° (*c* 1.98, EtOH); IR (neat) 1735 and 1650 cm^{-1}; ^{1}H NMR δ=1.16—2.98 (10H, m), 3.17 (1H, m), 3.70 (3H, s), 3.77 (3H, s), 4.61 (1H, m) 4.79 (1H, d, *J*=7.4 Hz), 5.89 (1H, dd, *J*=6.0 and 3.0 Hz), 6.19 (1H, dd, *J*=6.0 and 3.0 Hz); ^{13}C NMR δ=26.9, 29.6, 30.1, 42.3, 42.8, 45.9, 49.8, 52.0, 52.6, 59.3, 131.5, 136.7, 172.3, 172.5, 173.0; Found: C, 62.52; H, 6.93; N, 4.58%. Calcd for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N, 4.56%.

(2*R*,5*R*)-*N*-[(1*R*,2*R*,4*R*)-5-Norbornene-2-carbonyl]-*trans*-2,5-bis(methoxymethyl)pyrrolidine (3b): $[\alpha]_D^{23}$ +213° (*c* 1.0, EtOH); IR (neat) 1640 cm^{-1}; ^{1}H NMR δ=1.15—2.55 (9H, m), 2.82—3.68 (6H, m), 3.32 (3H, s), 3.35 (3H, s), 4.15 (2H, m), 5.74 (1H, m), 6.24 (1H, m); ^{13}C NMR δ=25.0, 27.3, 29.0, 42.0, 43.0, 46.6, 50.2, 56.5, 57.1, 58.6, 59.0, 71.4, 74.5, 130.3, 137.4, 173.0; Found: C, 68.54; H, 9.27; N, 5.00%. Calcd for $C_{16}H_{25}NO_3$: C, 68.79; H, 9.02; N, 5.01%.

Conversion of (+)-3c to (+)-(1*R*,2*R*,4*R*)-5-Norbornene-2-carboxylic Acid. Iodine (57.8 mg, 0.228 mmol) was added to a solution of **3c** (70.3 mg, 0.207 mmol) in H_2O–DME (1:1, 0.6 ml) at room temperature and the mixture was stirred for 1 day. The resultant solution was diluted with ethyl acetate and washed with saturated $Na_2S_2O_3$ and with 0.5 mol dm^{-3} HCl. The organic layer was further washed with saturated $NaHCO_3$ and with brine, dried over $MgSO_4$, and concentrated. The residue was subjected to preparative TLC (hexane–acetone, 10:3) to give the iodo lactone (**5**, 34.6 mg, 63%): ^{1}H NMR δ=1.59—2.80 (6H, m), 3.20 (1H, m), 3.89 (1H, d, *J*=2.6 Hz), 5.13 (1H, d, *J*=5.3 Hz). The whole aqueous solution was made basic with $NaHCO_3$ and extracted with chloroform–ethanol (3:1). The extract was dried over $MgSO_4$ and concentrated to recover (2*R*,5*R*)-2,5-bis(methoxymethoxymethyl)pyrrolidine (63%). The iodo lactone **5** was then treated with zinc (120 mg, 1.84 mmol) and CuBr (40 mg, 0.279 mmol) in methanol at room temperature for 2 h. The mixture was filtered through Celite and concentrated. The residue was submitted to bulb-to-bulb distillation (130—140 °C/2133 Pa, bath temperature) to give (+)-5-norbornene-2-carboxylic acid (12.3 mg, 68%); $[\alpha]_D^{23}$ +146° (*c* 0.615, EtOH) [lit,[2] $[\alpha]_D^{23}$ −147.14° (*c* 0.49, EtOH) for (*S*)-acid].

The compounds [(+)-**3a** and (+)-**3b**] were also converted into the same (+)-norbornene-2-carboxylic acid in a similar manner.

The present work was partially supported by a Grant-in-Aid for Scientific Research No. 61740306 from the Ministry of Education, Science and Culture.

References

1) For a review, see; L. A. Paquette, "Asymmetric Synthesis" ed by J. D. Morrison, Vol. 3, Academic Press, New York (1984), p. 455. See, also; K. Narasaka, M. Inoue, and N. Okada, *Chem. Lett.*, **1986**, 1109; K. Narasaka, M. Inoue, and T. Yamada, *ibid.*, **1986**, 1967.

2) W. Choy, L. A. Reed, III, and S. Masamune, *J. Org. Chem.*, **48**, 1137 (1983); S. Masamune, L. A. Reed, III, J. T. Davis, and W. Choy, *ibid*, **48**, 4441 (1983).

3) W. Oppolzer, C. Chapuis, G. M. Dao, D. Reichlin, and T. Godel, *Tetrahedron Lett.*, **23**, 4781 (1982).

4) D. A. Evans, K. T. Chapman, and J. Bisaha, *J. Am. Chem. Soc.*, **106**, 4261 (1984).

5) Y. Kawanami, Y. Ito, T. Kitagawa, Y. Taniguchi, T. Katsuki, and M. Yamaguchi, *Tetrahedron Lett.*, **25**, 857 (1984); M. Enomoto, Y. Ito, T. Katsuki, and M. Yamaguchi, *ibid.*, **26**, 1343 (1985); S. Ikegami, T. Hayama, T. Katsuki, M. Yamaguchi, *ibid.*, **27**, 3403 (1986); T. Hanamoto, T. Katsuki, and M. Yamaguchi, *ibid.*, **27**, 2463 (1986).

6) Y. Ito, T. Katsuki, and M. Yamaguchi, *Tetrahedron Lett.*, **25**, 6015 (1984); **26**, 4643 (1985).

7) T. Katsuki and M. Yamaguchi, *Tetrahedron Lett.*, **26**, 5807 (1985).

8) M. Uchikawa, T. Hanamoto, T. Katsuki, and M. Yamaguchi, *Tetrahedron Lett.*, **27**, 4577 (1986).

9) The acid could not be obtained by ordinary hydrolysis of **3** (1 mol dm^{-3} HCl, reflux) because of the lability of the acid under the conditions.

10) Y. Tamaru, M. Mizutani, Y. Furukawa, S. Kawamura, Z. Yoshida, K. Yanagi, and M. Minobe, *J. Am. Chem. Soc.*, **106**, 1079 (1984).