Asymmetric Diels–Alder Reaction with use of (*S*)-5-(Trityloxymethyl)pyrrolidin-2-one as a Chiral Auxiliary

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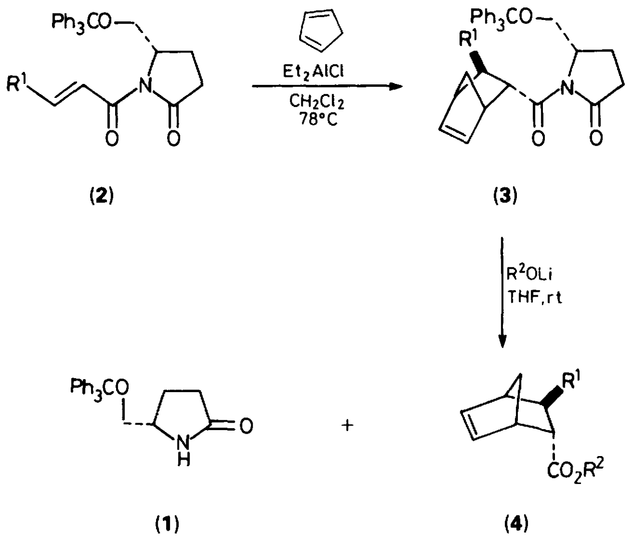
(*S*)-5-(Trityloxymethyl)pyrrolidin-2-one (**1**) is an efficient and recyclable chiral auxiliary in the asymmetric Diels–Alder reaction of the imide (**2**) with dienes, affording cycloadducts (**3**) with excellent diastereofacial selectivity.

The asymmetric Diels–Alder reaction has been a focus in recent synthetic organic chemistry.[1] We report herein an efficient asymmetric Diels–Alder reaction with use of (*S*)-5-(trityloxymethyl)pyrrolidin-2-one (**1**) as a chiral auxiliary which has been proven to induce high diastereofacial differentiation in conjugate additions.[2] The chiral lactam (**1**) is quite unique in its

Table. Asymmetric Diels–Alder reaction of the chiral imides (**2**).

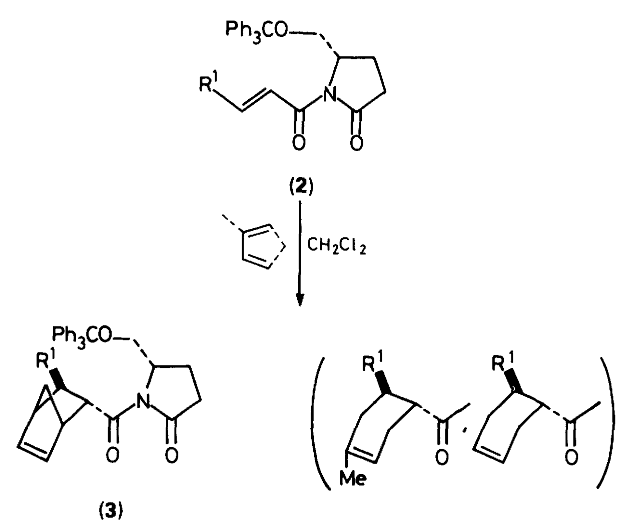
	(**2**)				Cycloadduct (**3**)			
Run	R^1	Diene	Lewis acid[a]	Temp/°C	Yield/%[b]	*endo*/*exo*[c]	Ratio[d]	d.e./%[e]
1	Me	Cyclopentadiene	None	15	44	80:20	42:58	16
2	Me		BF_3OEt_2	−78	0			
3	Me		$EtAlCl_2$	−78	70	93:7	79:21	58
4	Me		Et_2AlCl	−78	98	>99:1	99:1	98
5	Me		*i*-Bu_2AlCl	−78	85	>99:1	99:1	98
6	Ph		Et_2AlCl	−78	92	>99:1	>99:1	>99
7	CO_2Me		Et_2AlCl	−78	95	96:4	99:1	98
8	Me	2-Methylbutadiene	*i*-Bu_2AlCl	−23	91		>99:1	>99
9	CO_2M2		Et_2AlCl	−78	80		97:3	94
10	Me	Butadiene	Et_2AlCl	−23	36		>99:1	>99
11	CO_2Me		$TiCl_4$	−45	52		98:2	96
12	CO_2Me		$TiCl_2(Oi\text{-}Pr)_2$	0	92		93:7	86

[a] 1.0 ~ 2.5 equiv of Lewis acid was used. [b] Combined yield. [c] Determined by HPLC and/or NMR analyses. [d] Ratio of *endo* product. [e] Diastereoisomeric excess of *endo* product.



(**2**) (**3**) (**1**) (**4**)

Scheme.



(**2**)

(**3**)

ability to control reaction stereochemistry by its characteristic conformation.[3]

The results of Diels–Alder reactions of the imide (**2**) with various dienes are summarized in the Table. As we expected, almost complete diastereoface selection was observed in reaction of (**2**; R^1 = Ph) with cyclopentadiene to afford (**3**), arising from the least hindered approach (run 6).[2,3] The stereochemistry of (**3**) was confirmed by its conversion to (**4**).[4]

Recycling of the chiral auxiliary (**1**) is possible. Treatment of the cycloadduct (**3**; R^1 = Ph) with $PhCH_2OLi$ in THF at room temperature for 18 h provided, after work-up, the benzyl ester (**4**; R^1 = Ph, R^2 = CH_2Ph) and (**1**) in 93 and 92% yields, respectively.† The optical purity of (**4**) {$[\alpha]_D^{25}$ −120.5° (*c* 1.41, $CHCl_3$)} was confirmed to be over 99% e.e. by comparison of the optical rotation with that reported {$[\alpha]_D$ −121° (*c* 1.33, $CHCl_3$)}.[4] The absolute configuration of (**3**) and (**4**) was unambiguously determined by converting (**3**; R^1 = Ph) to (1*S*,2*R*,3*R*,4*R*)-bicyclo[2.2.1]heptane-2,3-dimethanol.[5]

We have also found that an exceptionally stereoselective reaction occurs between the fumarate derivative (**2**; R^1 = CO_2Me) and cyclopentadiene to afford the cycloadduct (**3**; R^1 = CO_2Me) in 98% d.e. and in 95% yield (Table, run 7). Treatment of (**3**; R^1 = CO_2Me) with MeOLi in THF also provided (**1**) (81%) for recycling and the dimethyl ester (**4**; R^1 = CO_2Me, R^2 = Me) (72%) which was then reduced with $LiAlH_4$ to (1*S*,4*R*,5*R*,6*R*)-bicyclo[2.2.1]hept-2-ene-5,6-dimethanol {$[\alpha]_D^{22}$ +22.5° (*c* 1.03, $CHCl_3$); lit,[5] $[\alpha]_D^{22}$ +23° (*c* 0.6, $CHCl_3$)}, confirming the absolute configuration as well as an optical purity of 98%.

The stereochemical course of the Diels–Alder reaction generally takes place on the front face of (**2**), avoiding steric interference with the trityloxymethyl group.[2,3] To gain more insight into the stereochemistry, reactions of (**2**; R^1 = Me) with cyclopentadiene were studied with regard to the effect of Lewis acids.

In the absence of Lewis acid, the reaction proceeded at 15 °C to afford the cycloadducts in 16% d.e. and the major product was the diastereoisomer of (**3**) (Table, run 1). Among those Lewis acids tested, *i*-Bu_2AlCl and Et_2AlCl were superior to others (runs 2–5).

Dienes other than cyclopentadiene were also applicable in the present asymmetric Diels–Alder reaction to provide various types of cycloadducts. The reaction of (**2**) with isoprene provided (**3**) in excellent d.e. and yields (run 8–9). However, reactions with butadiene were sluggish under catalysis by dialkylaluminium chlorides; in this case, $TiCl_4$ or $TiCl_2(Oi\text{-}Pr)_2$

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† The acyclic amide-ester initially formed by ring-opening of the lactam is converted to (**4**) and (**1**). See also reference 6.

are the Lewis acids of choice, affording efficiently cycloadduct (**3**) (see runs 10–11).

As has been reported by Dr. I. Fleming in the case of asymmetric conjugate addition reactions,[6] the trityl-lactam (**1**) is also a potentially useful chiral auxiliary in an asymmetric Diels–Alder reaction. Further studies using (**1**) are in progress in our laboratories.

Experimental

Typical procedure is exemplified by the following reaction (Scheme 1, Table, run 6): to a cooled (−78 °C) solution of the imide (**2**; R^1 = Ph) (1.22 g, 2.50 mmol)[2] and cyclopentadiene (10 ml, 12.5 mmol) in CH_2Cl_2 25 ml was added Et_2AlCl (1M in hexane; 3.5 ml, 3.50 mmol). The mixture was stirred at −78 °C for 1 h and quenched with saturated aqueous NH_4Cl (15 ml) and 10% HCl (15 ml). The product was extracted with CH_2Cl_2 repeatedly. The combined extracts were washed with saturated aqueous $NaHCO_3$ and brine, then dried and concentrated. Column chromatography (SiO_2, hexane–benzene–AcOEt, 25:25:1) afforded the adduct (**3**; R^1 = Ph) in 92% yield, m.p. 186–187 °C (Found: C, 82.18; H, 6.43; N, 2.71%. $C_{38}H_{35}NO_3$ requires C, 82.42; H, 6.38; N, 2.53%; M^+, 553); $[\alpha]_D^{20}$ −118.4° (*c* 1.01, $CHCl_3$); ν_{max}(KBr) 1 730 and 1 687 cm^{-1}; δ($CDCl_3$) 1.4–3.6 (11 H, m), 4.30 (1 H, dd, *J* 3.4 and 5.4 Hz), 4.5 (1 H, m), 5.61 (1 H, dd, *J* 2.7 and 5.6 Hz), 6.42 (1 H, dd, *J* 3.2 and 5.6 Hz), and 7.0–7.5 (20 H, m).

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References

1 Review: G. Helmchen, R. Karge, and J. Weetman, 'Modern Synthetic Methods,' ed. by R. Scheffold, Springer-Verlag, Berlin, 1986, Vol. IV, p. 262; Leading references: M. E. Jung, W. D. Vaccaro, and K. R. Buszek, *Tetrahedron Lett.*, 1989, 1893, and references cited therein.
2 K. Tomioka, T. Suenaga, and K. Koga, *Tetrahedron Lett.*, 1986, 369.
3 K. Tomioka, Y.-S. Cho, F. Sato, and K. Koga, *J. Org. Chem.*, 1988, **53**, 4094.
4 D. A. Evans, K. T. Chapman, and J. Bisaha, *J. Am. Chem. Soc.*, 1988, **110**, 1238.
5 D. Horton, T. Machinami, and Y. Takagi, *Carbohydr. Res.*, 1983, **121**, 135.
6 I. Fleming and N. D. Kindon, *J. Chem. Soc., Chem. Commun.*, 1987, 1177.

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