Asymmetric Diels–Alder Reaction: Comparison of Menthoxyaluminium and Lanthanide Chiral Catalysts

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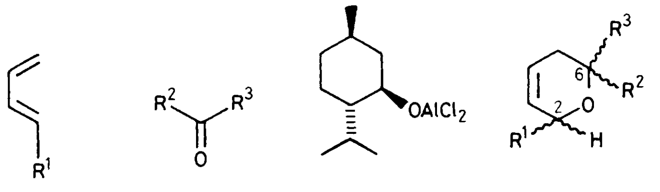
Some dihydropyran carboxylates synthesized *via* the Diels–Alder reaction with chiral catalysts display an enantiomeric excess of up to 16% for menthoxyaluminium and up to 64% for chiral lanthanide catalysts.

Apart from the use of chiral dienes or chiral dienophiles as starting materials, the asymmetric Diels–Alder reaction may be realised by using a chiral catalyst. Although the enantiomeric excess (e.e.) is not particularly high, this method has led Koga[1] and Valenta[2] to asymmetric adducts on cyclopentadienes. In both studies, terpenyloxyaluminium dichlorides (Koga catalysts) were used. More recently Danishefsky[3] has achieved an interesting increase of e.e. by using the lanthanide n.m.r. chiral shift reagent tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III) [Eu(hfc)$_3$] as catalyst on more functionalised dienes. We have treated 1-methoxybuta-1,3-diene (**1a**) and penta-1,3-diene (**1b**) with two carbonyl dienophiles, diethyl mesoxalate (**2a**) and n-butyl glyoxalate (**2d**), using as catalysts both menthoxyaluminium

Table 1. Asymmetric Diels–Alder reactions using catalysts (**3**) and (**4**).

Diene (**1**)	Dienophile (**2**)	Catalyst[a]	Adduct (**5**) Yield, %	% E.e.[c]	Configuration of major adduct
(**1a**)	(**2a**)	None[b]	(**5a**) (99)	–	–
		(**3**)	(30)	9	(*S*)
		(**4**)	(100)	15	(*R*)
(**1b**)	(**2a**)	None	(**5b**) (60)	–	–
		(**3**)	(15)	4	(*R*)
		(**4**)	(traces)		
(**1a**)	(**2d**)	None	(**5c**) *cis* (58)	–	–
			trans (32)	–	–
		(**3**)	*cis* (17)	16	(2*R*,6*S*)
			trans (9)	3	(2*R*,6*R*)
		(**4**)	*cis* (19)	64	(2*R*,6*S*)
			trans (79)	39	(2*R*,6*R*)
(**1b**)	(**2d**)	None	(**5d**) *cis* (25)	–	–
			trans (25)	–	–
		(**3**)	*cis* (6)	5	(2*R*,6*R*)
			trans (6)	5	(2*R*,6*S*)
		(**4**)	(traces)		

[a] (**3**), Koga catalyst, 0.25 M, −78 °C; (**4**), lanthanide catalyst, 0.05 M, room temp. [b] *I.e.*, thermal reaction. [c] Observed at *ca.* 20% Eu(hfc)$_3$.



(**1**) (**2**) (**3**) (**5**)

a; R^1 = OMe, R^2 = R^3 = CO$_2$Et
b; R^1 = Me, R^2 = R^3 = CO$_2$Et
c; R^1 = OMe, R^2 = H, R^3 = CO$_2$Bu
d; R^1 = Me, R^2 = H, R^3 = CO$_2$Bu

Scheme 1

dichloride (**3**) and Eu(hfc)$_3$ (**4**) in order to compare their utility in asymmetric Diels–Alder reactions leading to the total synthesis of sugars. The dihydropyran carboxylate adducts (**5a,b**) formed using dienophile (**2a**) contain one asymmetric centre at C-2, while those formed using (**2d**) [(**5c,d**)] contain such centres at C-2 and C-6. The latter two adducts exist in two forms, *cis* and *trans*, both observed in the Diels–Alder condensation (Table 1, Scheme 1).

The determination of optical yield was performed using the chiral shift reagent Eu(hfc)$_3$.[4] The series of uncatalysed thermal condensations leading to racemic adducts allowed the assignment of spectra[5,6] and the calculation of e.e. by comparison with these racemates. The configuration of the stereoisomeric adducts was tentatively assigned by using the difference in the induced chemical shifts of the 2-methoxy or 2-methyl protons observed at 200 MHz (Varian XL200).[4] This difference for, *e.g.*, adduct (**5a**) obtained with the Koga catalyst shows that the (*S*)-isomer is present in 9% e.e. over its (*R*)-epimer. For the *trans*-(**5c**) adduct of diene (**1a**) and dienophile (**2d**) obtained with the lanthanide catalyst, the (2*R*,6*R*)-enantiomer displays a 39% e.e. over its (2*S*,6*S*)-enantiomer.

As shown in Table 1, the largest overall e.e. was observed during the formation of the *cis*-(**5c**) adduct from the activated diene (**1a**) and glyoxalate (**2d**) using the lanthanide chiral catalyst. Comparison with the Koga catalyst shows that the major adduct bears the inverted configuration.[7] The same condensation of diene (**1a**) performed in the presence of the nonchiral lanthanide catalyst tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyloctane-3,5-dionato)europium [Eu(fod)$_3$] yields 100% adduct (**5a**) for dienophile (**2a**) and 96% adduct (**5c**) for dienophile (**2d**). However, the lanthanide catalysts are of little help for the non-activated diene (**1b**), where only traces of adducts have been observed.

The Koga catalyst, which failed to perform well toward the activated dienes, works much better with an alkylated diene. Two other dienes, 1-acetoxybuta-1,3-diene and 1-trimethylsilyloxybuta-1,3-diene, display a very low reactivity (1—3% yield) toward both dienophiles with the Koga catalyst. Both trimethylsilyloxy adducts from the expected reaction with either dienophile (15—25%) easily undergo deblocking and glycal–pseudoglycal rearrangement in the presence of lanthanide catalysts.[6,8]

The application of Koga catalysts remains essentially limited because of their difficult preparation and instability. In spite of the laborious separation of the catalyst and the decomposition of the complex formed, the chiral lanthanide catalysts seem to be more promising in the asymmetric Diels–Alder reaction.

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