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ASYMMETRIC INDUCTION IN THE INVERSE DIELS-ALDER REACTION OF CHIRAL 2-METHYLENE-IMIDAZOLIDINES

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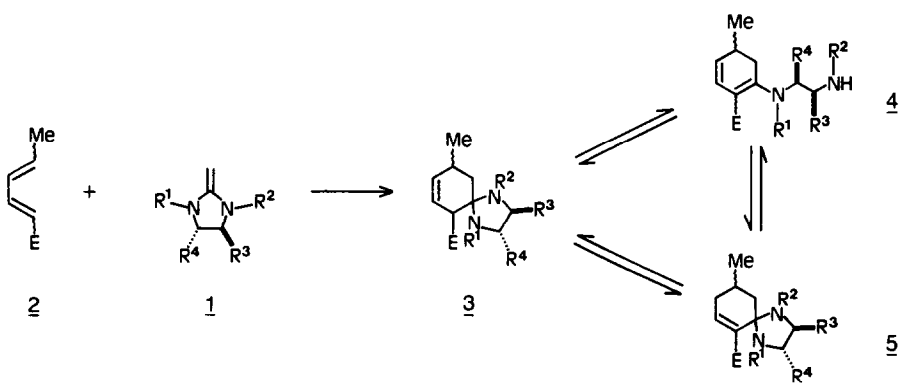
Summary: inverse Diels-Alder reactions of chiral 2-methylene-imidazolidines with 2,4-hexadienoates at ambient temperatures lead to diastereomeric N,N-acetals, which can smoothly be cleaved by dilute acids to optically active cyclohexenones.

Since the first report by Korolev and Mur[1a] asymmetric Diels-Alder cycloadditions have been thoroughly investigated by many groups. These efforts have met with remarkable success in the last years[1]. However, Diels-Alder reactions with normal electron demand[2] were examined, the dienophiles usually being optically active derivatives of acrylic acid[1a-d], in some cases chiral dienes[1b] or catalysts[1b,d] were used. Only one diastereomer was isolated in the inverse Diels-Alder reaction[2] of an optically active enol ether[1e], enantioselective inverse hetero-Diels-Alder reactions[1f] are known. We report here on a rare example of an enantioselective Diels-Alder synthesis with inverse electron demand.

Optically active 2-methylene-imidazolidines 1[3] like their achiral analogues undergo cycloadditions with methyl 2,4-hexadienoates 2[4] in inert solvents at room temperature or below to form diastereomeric mixtures of the N,N-acetals 3, which slowly rearrange to their tautomers 5 and the enamines[5] 4 (eq. 1).



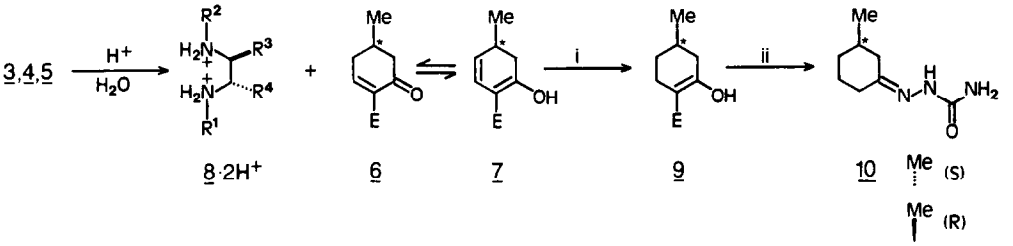
2 1 3 4 5 (eq. 1)

E = CO_2Me, Substituents R^{1-4} see Table 1

Treatment of this mixture in a two phase system with dilute aqueous acids affords the optically active cyclohexenone 6 or enol 7 (eq. 2). Thus, in the whole sequence from 1 to 6/7 the 2-methylene-imidazolidines are used as chiral ketene equivalents.

The chiral amines 8 can easily be isolated from the aqueous phase by treatment with concentrated potassium hydroxide and extraction with ether and can then be converted back to the corresponding 2-methylene-imidazolidines 1[6]. For (S)-1a and (SS)-1l comparison of rotations showed that no racemization had occured during one cycle.

(eq. 2)



i: 10 % Pd/C, H_2; ii: 1) KOH/MeOH, 30 min reflux, 2) H_2N-CO-NH-NH_2;

It was not possible to determine the e.e.'s of the products 6/7 with chiral shift reagents ($Eu(TFC)_3$, $Yb(TFC)_3$). But catalytic reduction of 6/7 with palladium on charcoal to 9[7] and further degradation with potassium hydroxide in refluxing aqueous methanol to 3-methylcyclohexanone and isolation as the semicarbazon 10[8] allowed to determine the optical yield[9] by comparison with the known rotations of the enantiomerically pure compounds. The results are compiled in Table 1.

Some conclusions can be drawn from these first results:

1. the optical yields are kinetically controlled. With thermodynamic control in a reversible, not concerted cycloaddition[10] one particular chiral imidazolidine should yield the same product with methyl hexadienoates of different geometry. However, (S)-1a, (S)-1f, (S)-1g, (R)-1h and (SS)-1l each produce different signs of rotation for the products with (2E,4E)- and (2E,4Z)-hexadienoates 2, respectively. Thus, the reaction is stereospecific with regard to the geometry of the 4-double bond of the hexadienoates 2.

2. the cycloaddition is also stereospecific with regard to the chiral dienophile. As expected, enantiomeric 2-methylene-imidazolidines like (R)- and (S)-1a or (RR)- and (SS)-1l form products with opposite signs of rotation in the reaction with (2E,4E)-2.

3. lower reaction temperatures lead to higher e.e.'s. In the case of (S)-1a, changing from +20°C to -20°C increases the e.e. from 7% to 21%, but this effect can not be further exploited as the reaction rate becomes too slow (two month at -20°C for 85% completion in toluene).

Table 1: Reaction conditions of the cycloadditions of methylene-imidazolidines 1 with dienoates 2 and chemical and optical yields (e.e.; R/S assignment in parenthesis) of the hydrolysis products 6

2-Methylene-imidazolidine	R^1	R^2	R^3	R^4	methyl hexadienoate	solvent	temperature (°C)	yield[a] (%)	e.e. (%)
(S)-1a	Me	Me	iPr	H	2E,4E	toluene	+20	54	7 (S)
					2E,4E	-	+2	45	10 (S)
					2E,4E	toluene	-20	49	21 (S)
					2E,4E	toluene	+30[b]	71	3 (R)
					2E,4Z	benzene	+2	51	16 (R)
					2Z,4E	benzene	+2	39	3 (S)
(R)-1a	Me	Me	iPr	H	2E,4E	toluene	+25	52	8 (R)
(S)-1b	Me	Et	iPr	H	2E,4E	benzene	+25	48	16 (R)
(S)-1c	Me	cHex	iPr	H	2E,4E	benzene	+2	39	18 (R)
(S)-1d	Et	Me	iPr	H	2E,4E	-	+2	35	13 (S)
(S)-1e	Ph	Me	iPr	H	2E,4E	c-hexane	+25	53	38 (S)
(S)-1f	Me	Me	Bz	H	2E,4E	toluene	+2	56	11 (S)
					2E,4Z	toluene	+2	53	46 (R)
(S)-1g	Ph	Me	Bz	H	2E,4E	c-hexane	+25	47	44 (S)
					2E,4Z	c-hexane	+25	50	10 (R)
(R)-1h	Ph	Me	Ph	H	2E,4E	benzene	+25	53	15 (R)
					2E,4Z	c-hexane	+25	54	26 (S)
(S)-1i	Ph	$(CH_2)_3$		H	2E,4E	c-hexane	+25	48	27 (R)
(RR)-1k	Me	Me	$(CH_2)_4$		2E,4E	c-hexane	+25	39	11 (R)
(SS)-1l	Me	Me	Ph	Ph	2E,4E	benzene	+25	51	15 (S)
					2E,4Z	benzene	+25	57	19 (R)
(RR)-1l	Me	Me	Ph	Ph	2E,4E	benzene	+25	48	14 (S)

a) isolated yields after distillation
b) cycloaddition run in a pressure vessel at 3000 bar[11].

4. pressure does not have a positive effect on the optical yields like it did in other Diels-Alder reactions[1g]. The product of (S)-1a and (2E,4E)-2 shows a lower rotation with the opposite sign if the cycloaddition is performed under high (3000 bar) instead of atmospheric pressure.

It was of no avail to introduce bigger substituents on one of the nitrogen atoms to achieve better diastereoselection. With isopropyl, tert-butyl, 2-methylphenyl or 2,6-dimethylphenyl groups on N-1 in different chiral or achiral 2-methylene-imidazolidines no cycloaddition product could be isolated.

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4) (2E,4E)-2: F. D. Lewis, D. K. Howard, S. V. Barancyk, and D. Oxman, J. Am. Chem. Soc. 108, 3016 (1986); (2Z,4E)-2: U. Eisner, J. A. Elvidge, and R. P. Linstead, J. Chem. Soc. 1953, 1372; (2E,4Z)-2: S. Tsuboi, T. Masuda, H. Makino, and A. Takeda, Tetrahedron Lett. 23, 209 (1982), this product was a mixture containing 10% of (2E,4E)-2.

5) 2-Methylenimidazolidines without C_2-axis form additional isomers of 4, where R^1/R^4 and R^2/R^3 are exchanged. 3, 4, and 5 were never isolated. The structures were assigned on the basis of ^1H- and ^{13}C-NMR spectra of the mixtures and by comparison with the cycloaddition products of achiral analogues[3] of 1.

6) Treatment of amines 8 with orthoacetate and HBF_4 leads to dihydroimidazolium-tetrafluoroborates, which can be deprotonated to 1 with sodium hydride in THF.

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9) The stereochemical assignment (R,S) is the same for 6, 9, and 10.

10) Diels-Alder cycloadditions of an achiral analogue of 1 with 2 could be shown[3] to be not concerted and totally reversible at elevated temperatures.

11) We are indebted to Prof. Tiltscher, Erlangen, for his help.

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