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HIGH ASYMMETRIC INDUCTION IN DIELS-ALDER ADDITIONS OF CYCLOPENTADIENE TO ACRYLATES DERIVED FROM ISOBORNEOL

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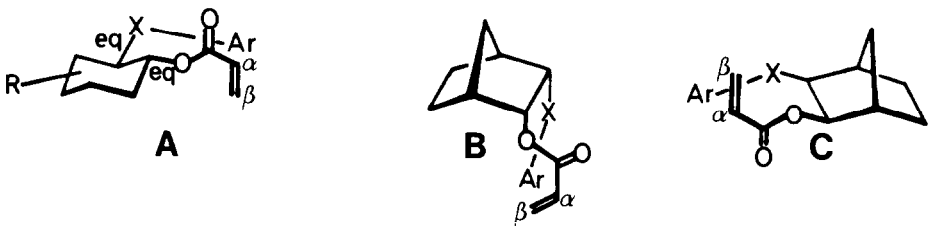
Abstract: Starting from (R)-(+)- and from (S)-(-)-camphor the chiral alcohols 1, 2 and 3 have been prepared; their acrylates II underwent $TiCl_2(OR)_2$-promoted Diels-Alder additions to cyclopentadiene giving efficiently in a predictable manner either the (2R)- or the (2S)-adducts III with up to virtually quantitative asymmetric induction.

The Diels-Alder addition of 1,3-dienes to olefins is a reaction of pre-eminent importance in organic synthesis. Consequently, considerable efforts have been expended to enantioselective versions of this process which may create two pairs of new chiral centers at the binding sites. Despite encouraging progress in this field, employing either chiral dienophiles[1], dienes[2] or Lewis acid catalysts[3], much remains to be done. Recently a host of *si*-face directing acrylates A, B and C (Scheme 1) and their *re*-face directing counterparts have been added to cyclopentadiene in the presence of $TiCl_4$ with ≤90% predictable enantioselection[1i].

Scheme 1

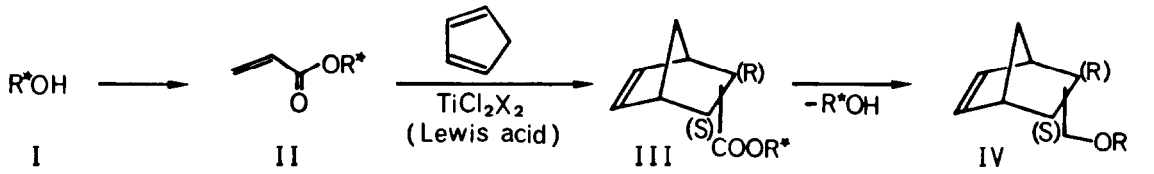


We attribute this induction to a transition state where the ester-carbonyl group is antiplanar with the C_α=C_β- and synplanar with the alkoxy-C,H bonds which causes the aryl group to shield either the C_α*re*-face or the C_α*si*-face, respectively.

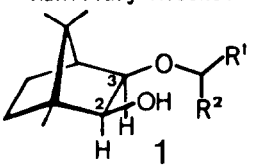
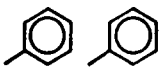
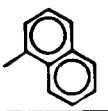
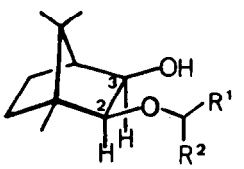
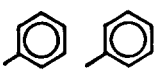
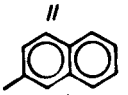
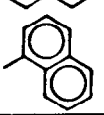
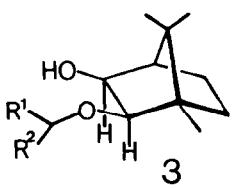
This communication reports the first virtually quantitative asymmetric induction in the [4+2]-cycloaddition of cyclopentadiene to acrylates (II → III). Reduction of III with $LiAlH_4$ refurnished the auxiliary alcohol to give the *endo*-product IV, R=H, which was isolated and analysed as previously described[1h]. Our results are summarised in Scheme 2 and the Table.

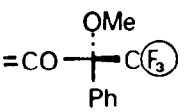
Our starting point was the $TiCl_4$-mediated addition of the *cis*-3-benzyloxyisobornyl acrylate (entry a) yielding the (S)-cycloadduct III in 88% d.e.[1i]. Pursuing this lead *cis*-3-diphenylmethoxy- (entries c, d), 3-α-naphthylmethoxy- (entries e, f) and 3-β-naphthylmethoxy- (entry g) isoborneols 1[4] were prepared either from (1R)-(-)-*cis*-3-hydroxyisoborneol[5] (Method A, 34 - 48%)[6] or, regioselectively, from (1R)-(+)-3-*exo*-hydroxycamphor[7] (Method B, 44%)[6]. Although these alcohols are nicely crystalline their acrylates suffered from rapid ether-cleavage on exposure

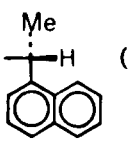
Scheme 2 and Table



I II III IV

Entry	Auxiliary Alcohol	R^1	R^2	m.p.	X Lewis acid	Reaction Temp. °C	Yield %	endo/exo	Endo-Adduct Config.	d.e.%
a	 1		H	oil	Cl	0	46	92/8	S	88
b		"	H	oil	OiPr	0	91	86/14	S	46
c				74	OiPr	0	94	86/14	S	64
d		"	"	74	OiPr	-20	94	90/10	S	72
e			H	73-74	OiPr	-20	98	90/10	S	69
f		"	H	73-74	OEt	-40	72	94/6	S	77
g			H	74-75	OiPr	0	97	85/15	S	54
h		tBu	H	oil	OiPr	-20	95	96/4	S	97
i	 2			57	OiPr	-20	74	95/5	R	91
j		//	//	57	OiPr	-40	36	97/3	R	92
k			H	70-71	OiPr	-20	98	95/5	R	92
l			H	69/70	OiPr	0	97	93/7	R	88
m		tBu	H	4-5	OiPr	-20	96	96/4	R	99.4[a] 99.2[b]
n	 3	tBu	H	4-5	OiPr	-20	98	95/5	S	99.4[a] 99.1[b]

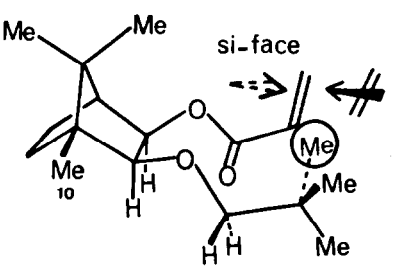
a) IV, R = CO– 

b) IV, R = CONH–  (HPLC)

to $TiCl_4$. Furthermore, the use of $TiCl_4$ generally required painstaking care to exclude traces of water which may decrease the efficiency of the addition II → III due to polymerisation. On the other hand, high chemical yields of cycloadducts III were safely obtained at -20° to 0° using the mild Lewis acid $TiCl_2(OiPr)_2$ [8]. Thus, entry b shows compared to entry a an improved yield (46 → 91%) but some loss of *endo*-selectivity (92 → 86%) and a much more severe drop of asymmetric induction (88 → 46% d.e.). Nevertheless, according to our expectations an increase of the aromatic surface enhanced the shielding and therefore the induction up to 77% (entries c - g). Lowering of the reaction temperature improved the *endo*- as well as the enantio-selectivity of the cycloaddition (entries c/d and e/f). Entry f indicates the advantageous use of $TiCl_2(OEt)_2$ [9] which even at -40°C led to the (2S)-adduct in 72% yield (as compared to entry j) with 77% d.e. More promising are the optical yields obtained on $TiCl_2(OiPr)_2$-promoted [4+2]-cycloadditions of the acrylates derived from the crystalline *cis*-3-hydroxyisobornyl-methylaryl ethers 2[4] which in turn are accessible from (1R)-(-)-*cis*-3-hydroxyisoborneol[5] (Method A, 22 - 36%)[6]. Thus, entries i - l demonstrate the efficient conversion II → III with 88 to 92% induction of (2R)-chirality.

We then wondered to what extent the observed shielding depends on π-π-aryl/acrylate-orbital overlap or on mere steric crowding. In fact, we were pleased to find that the neopentyl ethers 1h[4] and 2m[4] exert a chirality directing ability dramatically superior to the examples listed above. Notably, 2m, selectively prepared from (1R)-3,3-ethylenedioxycamphor[10] (Method C, 65%)[6] gave after esterification and acrylate cycloaddition the (2R)-adduct III in 99.4 to 99.2 d.e. as determined by ^{19}F-NMR and HPLC [11] analyses of IVa and IVb, respectively. Crystallisation of 2m (pentane, -30°C) permits its facile purification and purity control despite the low melting point. Its antipode 3n, readily available from (1S)-(-)-camphor[11] furnished the (2S)-adduct III in equally high chemical and optical yields. It thus follows that the alcohols 2m and 3n constitute the first reported chiral auxiliaries which on acrylate/cyclopentadiene-cycloaddition afford efficiently and predictably either (2R)- or (2S)-adducts, respectively, with virtually quantitative chiral induction. Examination of models (Scheme 3) assuming a staggered conformation of the

Scheme 3



neopentyloxy-chain indicates indeed a strong steric blocking of the 2m-acrylate C_α-*re*-face by the *t*-butyl group. The superiority of 2m over 1h and in general of 2 over 1 may be attributed to a buttressing by the (C,10)-methyl group which pushes the ether chain closer to the acrylate. Presently we employ these findings for the syntheses of natural products and continue to develop even more practical chiral alcohols, generally applicable to a range of enantioselective reactions[12].

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3) *S. Hashimoto, N. Komeshima, K. Koga*, J. Chem. Soc. Chem. Commun. 437 (1979).

4) All new compounds were characterised by IR, ^{1}H-NMR and MS. The following compounds showed the indicated optical rotations $[\alpha]_D^{25}$(EtOH): 1c, +23.92° (c 1.25); 1e, +8.36° (c 0.742); 1g, +21.43 (c 0.975); 1h, -18.79° (c 1.075); 2i, -107.64° (c 1.70); 2k, -61.49° (c 0.571); 2l, -76.22° (c 0.90); 2m, -42.55° (c 1.14); 3n, +42.60 (c 1.31).

5) *S.J. Angyal, R.J. Young*, J. Am. Chem. Soc. *81*, 5467 (1959).

6) The following procedures are representative: Preparation of 1h and 2m (Method A): i) (1R)-(-)-*cis*-3-hydroxyisoborneol[5], NaH (1.1 eq), DMF, r.t. 3h; ii) 1-bromo-2,2-dimethylpropane (1.5 eq), 100°, 6h; iii) chromatography (SiO_2, hexane/EtOAc), crystallisation (pentane)→ 1h (35%) + 2m (40%). Preparation of 2k (Method B): i) (+)-3-exo-hydroxycamphor[7], NaH (1 eq), DMF, r.t., 2h; ii) 2-naphthylmethyl bromide (1.1 eq), -60°, 6h then r.t., 8h (48%); iii) L-Selectride (1.14 eq), THF, -78°, 4h→ r.t. 1h (92%). Preparation of 2m (Method C): i) (1R)-3,3-ethylenedioxy-camphor[10], L-Selectride (1.26 eq), THF, -78°, 4h→ r.t., 1h (92%); ii) NaH (1.5 eq), 1-bromo-2,2-dimethylpropane (3 eq), NMP, 130°, 18h (92%); iii) 50% aq. H_2SO_4, 60°, 19h (92%); iv) L-Selectride (1.05 eq), THF, -78°, 2h → r.t., 1h (86%). Esterification: 2m, NEt_3 (2 eq), DMAP (0.15 eq), acryloyl chloride (2 eq), CH_2Cl_2, r.t. 24 h (91%). Cycloaddition: i) add 1N mixture of $TiCl_4$/$Ti(OiPr)_4$ (1:1, 1.5 eq) in CH_2Cl_2 to 0.1 N 2m-acrylate in CH_2Cl_2, -20°; ii) cyclopentadiene (3 eq), -20°, 4h (96%).

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8) 1:1-mixture of $TiCl_4$/$Ti(OiPr)_4$: *T. Mukaiyama*, Angew. Chem. *89*, 858 (1977); Angew. Chem. Int. Ed. Engl. *16*, 817 (1977); *M.T. Reetz*, Angew. Chem. *94*, 97 (1982); Angew. Chem. Int. Ed. Engl. *21*, 96 (1982).

9) 1:1-mixture of $TiCl_4$/$Ti(OEt)_4$.

10) *I. Fleming, R.B. Woodward*, J. Chem. Soc. (C), 1289 (1968).

11) i) IV, R=H, (R)-(-)-1-(1-naphthyl)-ethyl isocyanate (1 eq), N,N-dimethylethanolamine (cat), C_6H_6, 80°, 36h (*W.H. Pirkle, J.R. Hauske*, J. Org. Chem. *42*, 1839 (1977)); ii) HPLC: column (Knauer) 0.8x50 cm, Li Chrosorb Si 60, 7µ (Merck), hexane/EtOAc 24:1, 2.5 ml/min, ± 0.1%.

12) For highly enantioselective Lewis-acid promoted additions to chiral enoates see: a) intramolecular ene-type reactions, *W. Oppolzer, C. Robbiani, K. Bättig*, Helv. Chim. Acta *63*, 2015 (1980); b) conjugated additions of RCu, *W. Oppolzer, H.J. Löher*, Ibid. *64*, 2808 (1981).

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