Periselective and Enantioselective Carbonyl–Ene Reaction of Isoprene with Fluoroalkyl Glyoxylate Catalysed by Modified Binaphthol–Titanium Complex: Asymmetric Catalytic Synthesis of Enantiomerically Pure Ipsdienol

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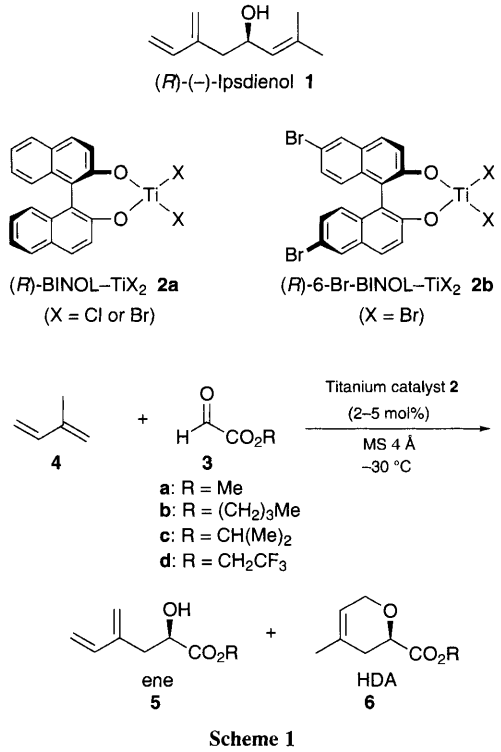
The asymmetric reaction of trifluoroethyl glyoxylate **3d** with isoprene **4** catalysed by the modified binaphthol–titanium complex **2b** provides the ene product **5d** in high periselectivity (92%) and complete enantioselectivity, which can be converted to ipsdienol **1**, a component of the aggregation pheromone of the bark beetle, genus *Ips*, in enantiomerically pure form.

Insect pheromones are of great interest and importance from both a scientific and a practical point of view. The monoterpenoid allylic alcohol, ipsdienol **1**,[1,2] is one of the components of the aggregation pheromone of several species of the bark beetle, genus *Ips*. This insect pheromone exhibits the interesting relationships between biological activity and not only absolute configuration but also enantiomeric purity of ipsdienol **1**.[2] Therefore, much attention has been focused on the enantiomerically pure synthesis of ipsdienol **1**.[3] Herein we report the enantiopure synthesis of ipsdienol **1** *via* the periselective and enantioselective catalysis of the carbonyl–ene reaction[4] of glyoxylate **3** with isoprene **4** by the chiral titanium complex **2**,[5] predominating over the hetero-Diels–Alder (HDA) reaction (Scheme 1). The key to the success is modification not only of the binaphthol (BINOL) ligand of the chiral titanium complex **2** but also of the ester alkyl group (R) in glyoxylate **3**.

The asymmetric reaction of glyoxylate **3** with isoprene **4** catalysed by the chiral titanium complex **2a** derived from the parent BINOL and $(Pr^iO)_2TiX_2$ (X = Cl or Br) provides preferentially the ene products **5**, along with some HDA products **6**.[6] Although both products exhibit high levels of enantioselectivity, the ene product **5**, which can be used as the synthetic intermediate of ipsdienol **1**,[3a] is obtained in only moderate periselectivity. In order to develop an efficient access to the enantiopure synthesis of ipsdienol **1**, the peri- and enantio-selectivity have to be enhanced leading predominantly to the desired ene products **5** in enantiomerically pure form.



Scheme 1

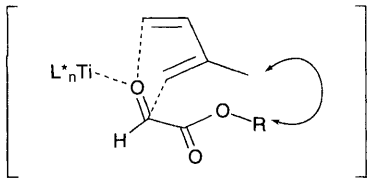
Table 1 summarizes the results obtained in the chiral titanium complex catalysed reaction along with that by an achiral titanium complex, $(Pr^iO)_2TiCl_2$. Inspection of the data reveals the characteristic features of the peri- and enantio-selectivity in the titanium complex-catalysed reaction of glyoxylate **3** with isoprene **4**. The most striking feature is that the ene-selectivity is dependent not only on the solvent employed but also on the alkoxy ligand of the chiral titanium catalyst **2** and further on the steric bulkiness of the alkyl group (R) in glyoxylate **3**. The more polar solvent, CH_2Cl_2, is favourable for ene-selectivity (entry 2 *vs.* 3). A small enhancement is observed in periselectivity by changing the counter anion (X) of the chiral titanium complex **2a** from Cl to Br (entry 2 *vs.* 4); here the chemical yield increases by virtue of the higher Lewis acidity of the titanium dibromide complex (**2a**, X = Br). It is noteworthy that the modification of the BINOL ligand, 6,6′-dibromo-1,1′-bi-2-naphthol (6-Br-BINOL),[7] is quite effective for enhancement of both the ene-selectivity and enantioselectivity as compared with those by the parent BINOL–TiX_2 catalyst **2a** (entry 5 *vs.* 4). Interestingly enough, the increase in the bulkiness of the alkyl group (R)[8] in glyoxylate **3** leads to a substantial increase in the periselectivity for the ene product **5** (entries 5–8): With the more bulky alkyl group (R), the *endo* orientation of the ester moiety becomes less favourable due to the repulsive interaction between the alkyl group (R) and the methyl substituent of isoprene **4** in the transition state **A** for the HDA reaction (Fig. 1), resulting, in turn, in the predominant formation of the ene products **5**. Thus, the periselectivity for the ene reaction is increased to 92% for the trifluoroethyl glyoxylate **3d** (entry 8), accompanied by high chemical yield (84%) and complete enantioselectivity.† The enhanced ene-selectivity is presumably due not only to the steric but also to the electronic effect of the electron-withdrawing CF_3 group.[8,9]

This successful enhancement of the peri- and enantioselectivity by virtue of the modification of the BINOL-ligand

Table 1 The titanium complex-catalysed reaction of glyocylate **3** with isoprene **4**[a]

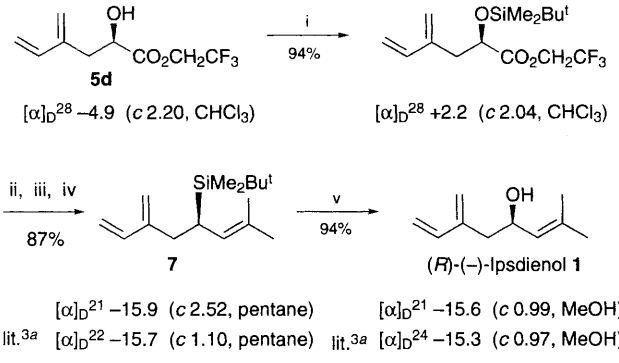
Entry	3	Catalyst	(mol%)	Yield (%)	Product ratio Ene[b] (% ee)[c] : HDA[b] (% ee)
1	a	$(Pr^iO)_2TiCl_2$	(10)	62	70 (—) : 30 (—)
2	a	**2a** (X = Cl)	(2)	89	78 (97) : 22 (97)[d]
3[e]	a	**2a** (X = Cl)	(2)	85	74 (98) : 26 (—)
4	a	**2a** (X = Br)	(2)	94	79 (97) : 21 (—)
5	a	**2b** (X = Br)	(2)	95	83 (99) : 17 (—)
6	b	**2b** (X = Br)	(2)	86	85 (>99) : 15 (—)
7[f]	c	**2b** (X = Br)	(5)	61	90 (92) : 10 (—)
8	d	**2b** (X = Br)	(2)	84	92 (>99) : 8 (—)

[a] All reactions were carried out in the presence of 4 Å molecular sieves (MS 4 Å) at −30 °C for 1 h in CH_2Cl_2 solution, unless otherwise noted. [b] The product ratio was determined by capillary GC analysis (PEG 20M). [c] The ee was determined by ^1H NMR analysis after conversion to the corresponding MTPA esters. [d] The ee was determined by lanthanide induced shift (LIS)-NMR analysis. [e] The reaction was carried out in toluene. [f] The reaction was carried out at −30 °C for 3 h.



A

Fig. 1 *Endo* transition state of the hetero-Diels–Alder reaction



Scheme 2 *Reagents*: i, Bu^tMe_2SiCl, imidazole; ii, DIBAL-H; iii, $(COCl)_2$, DMSO, NEt_3; iv, $[Ph_3PCH(CH_3)_2]^+I^-$; Bu^nLi; v, TBAF

and alkyl group (R) prompted us to undertake the conversion of the ene product **5d** to ipsdienol **1** *via* the standard operations (Scheme 2). After desilylation of **7**, (*R*)-(−)-ipsdienol **1** was obtained in 59% overall yield without any loss of enantiomeric purity, *via* a total of 6 steps from the starting glyoxylate **3d** and isoprene **4**.

The present asymmetric catalytic process is promising in terms of not only direct introduction of the 1,3-dienyl moiety but also complete control at the newly created stereogenic centre by the use of only a catalytic amount of chiral sources. Since both enantiomers of the chiral ligand, 6-Br-BINOL, are now commercially available, the present procedure provides efficient entries to either (*R*)- or (*S*)- ipsdienol **1** in enantiomerically pure form.

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Footnote

† A significant decrease in the enantioselectivity was observed for the carbonyl–ene reaction of isopropyl glyoxylate **3c** catalysed by the parent BINOL–TiX_2 complex (**2a**). See ref. 5*a*.

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