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Catalytic Asymmetric Synthesis of Substituted Benzocycloalkenes via the Glyoxylate Ene Reaction

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Abstract: α -Hydroxypropionic ester-substituted-benzocyclo-1,3-hepta-diene, -indene and -3,4-dihydronaphthalenes are produced in 63->99% enantiomeric excess via the (R)-BINOL-TiX₂ glyoxylate ene reaction.

Catalytic enantioselective carbon-carbon bond formation via carbonyl-ene reactions¹ is particularly attractive in synthesis as it allows simultaneous introduction of functional groups in a stereocontrolled manner. Both intra²- and inter³-molecular carbonyl-ene reactions with high enantiomeric excess (e.e.) using various chiral Lewis acids have recently been reported. Nakai and Mikami have made impressive progress in the enantioselective carbonyl-ene reaction⁴ with methylglyoxylate catalyzed by the chiral titanium complex **4**.

As part of a program aimed at catalytic routes to chiral functionalized carbocyclic building blocks⁵ for natural product synthesis we report herein the catalytic glyoxylate ene addition to exocyclic olefins **1** to proceed with excellent enantioselectivities. The chiral Lewis acid is prepared in situ from diisopropoxytitanium dihalide and optically pure (R)-binaphthol ((R)-BINOL) in the presence of molecular sieves.⁶

Using a slightly modified procedure as compared to acyclic substrates the olefins **1** and methylglyoxylate **2**⁷ dissolved in CH₂Cl₂ were reacted in the presence of **4a** or **4b** and powdered molecular sieves (4A) at -30°C. After normal workup and column chromatography over silica gel (n-hexane, ethylacetate) α -hydroxyesters were obtained in modest yields⁸ and high enantiomeric excesses.⁹ The results of the catalytic asymmetric ene reaction with different exocyclic olefins are summarized in table 1.

Table 1. Catalytic asymmetric glyoxylate ene reactions with exocyclic olefins 1^a

Entry	Hydroxy ester <u>3</u>	n	R ₁	R ₂	Catalyst <u>4</u> X ^b	Yield [%] ^c	E.e. [%] ^d
1	<u>3a</u>	1	H	H	Cl	66	94
2	<u>3a</u>	1	H	H	Br	69	94
3	<u>3b</u>	1	OCH ₃	H	Cl	57	94
4	<u>3b</u>	1	OCH ₃	H	Br	49	>99
5	<u>3c</u>	1	H	OCH ₃	Br	52	>99
6	<u>3d</u>	2	H	H	Br	59	99
7	<u>3e</u>	0	H	H	Cl	62	18
8	<u>3e</u>	0	H	H	Br	60	63

^aAll reactions were carried out using 2.0 mmol of 2, 4.0 mmol of 1 and 0.2 mmol of 4.

^bReaction time was 15 h when X=Cl and 3 h when X=Br. ^cYield after purification.

^dDetermined by GLC analysis.

Similar levels of enantioselectivity are found for the dichloro- and dibromo-catalyst except for the indene-system for which the dibromo-catalyst is far superior. It is remarkable that increasing the conformational flexibility in the benzannulated exocyclic olefins in the series 3e-3a-3d results in enhancement of the e.e. to > 99%. Furthermore remote methoxy-substituents both in and out of conjugation with the exocyclic olefin lead to an unexpected improvement of the enantioselectivity (entries 4 and 5). No trace of the enantiomeric products could be detected in these last cases. The significance of these findings for the mechanism of the asymmetric ene reaction, catalyzed by 4, are currently investigated.

References and Notes

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- Nakai et.al.^{4b} have investigated the role of molecular sieves in this ene reaction. The results show that the MS 4A were essential for the formation of the chiral catalyst and not for the ene reaction.
- All reactions were performed under N₂ atmosphere; methylglyoxylate of high purity was prepared according to J.M. Hook (*Synth. Commun.* **1984**, 14, 83) and stored at -70°C under N₂.
- All new compounds showed ¹H-, ¹³C-NMR, MS and HRMS data in accordance with the structures shown.
- Enantiomeric excess determination: GLC on cyclodextrine capillary column, Conditions; injection temperature, 225°C; column temperature, 190°C; flow rate 80 ml/min. For racemic 3a (R₁=R₂=H, n=1) two base line separated signals were observed (t_R=42.8 and 43.5 min).

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