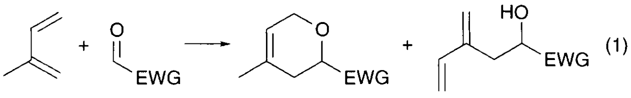
A highly chemo- and enantio-selective hetero-Diels–Alder reaction catalysed by chiral aluminium complexes

Anette Graven, Mogens Johannsen and Karl Anker Jørgensen*

Department of Chemistry, Aarhus University, DK-8000 Aarhus C, Denmark

A new, highly chemo- and enantio-selective catalytic hetero-Diels–Alder reaction of conjugated dienes containing allylic C–H bonds with carbonyl compounds has been developed; with the use of (*S*)-(−)-BINOL-AlMe (BINOL = 1,1′-bi-2-naphthol) as a catalyst, simple conjugated dienes react with glyoxylate esters, giving the (*R*)-enantiomer of the hetero-Diels–Alder adduct as the major product with up to 97% ee.

The hetero-Diels–Alder (HDA) reaction of conjugated dienes with carbonyl compounds is a fundamental reaction in organic chemistry.[1] The reaction of a conjugated diene having an allylic C–H bond with an electron deficient aldehyde can take two different reaction courses, leading to the formation of both the HDA product and the hetero-ene product [eqn. (1)].[1–3] Great progress has been made in metal-catalysed enantio- and diastereo-selective C–C bond forming reactions.[4] However, in the field of catalytic HDA reactions one of the fundamental problems, controlling the chemoselectivity (the HDA–ene ratio) while maintaining high enantioselectivity, still remains to be solved.



EWG = electron-withdrawing group

The metal-catalysed enantioselective HDA reaction of conjugated dienes having no allylic C–H bonds with carbonyl compounds has been successfully developed.[5] Moreover, a high hetero-ene selectivity has been obtained in the chiral BINOL-titanium (BINOL = 1,1′-bi-2-naphthol) complex-catalysed reaction of a simple diene such as isoprene with glyoxylate esters, where an HDA–ene ratio of up to 1 : 9 was obtained.[2c,d] Thus, for these chiral BINOL-titanium-catalysed reactions, attention has been focused on the hetero-ene reaction.[2b–d,6] We, on the other hand, have focused on the development of a HDA selective reaction and were recently able to improve the HDA–ene ratio to 1 : 1 in the reaction between 2,3-dimethylbuta-1,3-diene and glyoxylate esters using chiral copper bis(oxazoline) complexes as the catalyst, and in some cases an ee of 90% was obtained.[3] This communication presents the first Lewis acid-catalysed chemoselective reaction of conjugated dienes having allylic C–H bonds with glyoxylate esters, which mainly leads to formation of the HDA product with very high enantioselectivity. The choice of catalyst is crucial for the HDA selectivity and we have found that a combination of $AlMe_3$ and BINOL gives a very high chemo- and enantio-selective complex [(*S*)-(−)-BINOL-AlMe].[5g,7]

The metal-catalysed HDA reaction with alkyl glyoxylates has been studied with 2,3-dimethylbuta-1,3-diene **1a** and isoprene **1b** as the dienes, as they are capable of participating in both the HDA and hetero-ene reactions. The HDA-selective catalyst for the reaction of these dienes with methyl and ethyl glyoxylates **2a** and **b** is (*S*)-(−)-BINOL-AlMe [eqn. (2)].

A representative experimental procedure is given by the (*S*)-(−)-BINOL-AlMe catalysed reaction of 2,3-dimethylbuta-1,3-diene **1a** with methyl glyoxylate **2a**: (*S*)-(−)-BINOL (31.5 mg, 0.11 mmol) was dissolved in dry CH_2Cl_2 (2 ml) under an inert atmosphere. A 2 M solution of $AlMe_3$ in toluene was added (50 µl, 0.1 mmol). The resulting solution was stirred for 1 h at room temp. Compound **2a**[†] (88 mg, 1 mmol) dissolved in CH_2Cl_2 (0.2 ml) was added to the catalyst, the reaction mixture was cooled to −78 °C and **1a** (170 µl, 2.8 mmol) was added. The mixture was stirred at −78 °C for 2 h, then it was allowed to warm slowly to ambient temperature. Stirring was continued for another 18 h. The mixture was poured into 1 M HCl and extracted with CH_2Cl_2. The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give the crude adducts which were purified by flash chromatography on silica gel with 10 : 90 ethyl acetate–light petroleum as the eluent to yield **3a** (63 mg, 37%) and **4a** (20 mg, 12%) as colourless oils. The enantioselectivities were determined by high-performance liquid chromatography (HPLC) to be 94% ee for **3a** and 56% ee for **4a** (Table 1, entry 1).

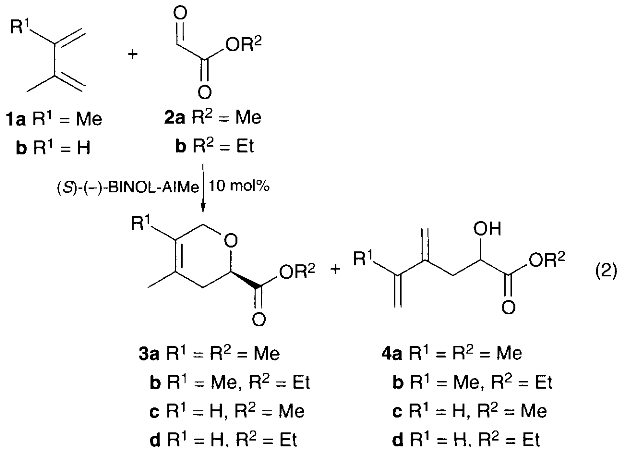


Table 1 summarizes the results obtained for the (*S*)-(−)-BINOL-AlMe catalysed reactions of 2,3-dimethylbuta-1,3-diene **1a** and isoprene **1b** with methyl and ethyl glyoxylate **2a** and **b**, respectively. The characteristic features are that in all instances the reactions resulted in formation of the HDA product in excess of the ene product, in ratios ranging from 7 : 1 (entry 3) to 2 : 1 (entry 4). The ees of the HDA products are in all cases excellent, whereas the ees of the ene products are poor (entry 2) to good (entry 3, 4). In the (*S*)-(−)-BINOL-AlMe catalysed reaction of **1a** with **2b**, the HDA product **3c** is isolated in 73% yield (entry 3). No attempts have been made to optimize the reaction conditions. The absolute configuration of the HDA product was assigned as (*R*).[8] It is remarkable that the asymmetric configuration of the HDA product is opposite to that observed by Terada *et al.*, using their BINOL-derived titanium catalyst in the reaction of isoprene with methyl glyoxylate.[2c]

Since both enantiomers of BINOL are readily available, this new procedure allows for the selective formation of both enantiomers of the HDA product, simply by choosing the appropriate chiral catalyst.

Table 1 Hetero-Diels–Alder reactions and hetero-ene reactions of 2,3-dimethylbuta-1,3-diene **1a** and isoprene **1b** with methyl and ethyl glyoxylates **2a** and **2b**, respectively, in the presence of 10 mol% of (*S*)-(−)-BINOL-AlMe

			Diels–Alder product			Ene product			
Entry	Diene	Glyoxylate	Product	Yield (%)[a]	Ee (%)[b]	Product	Yield (%)[a]	Ee (%)[b,c]	Ratio **3**:**4**
1	**1a**	**2a**	**3a**	37	94 (*R*)	**4a**	12	56	3 : 1
2	**1b**	**2a**	**3b**	13	70 (*R*)	**4b**	3	27	4 : 1
3	**1a**	**2b**	**3c**	73	97 (*R*)	**4c**	9	88	7 : 1
4	**1b**	**2b**	**3d**	29	97 (*R*)	**4d**	14	88	2 : 1

[a] Isolated yield. [b] Ee determined by HPLC on a CHIRALCEL OD column; eluent: 99% hexane–1% $\mathrm{Pr^iOH}$. Configuration shown in parentheses. [c] Stereochemistry not assigned.

The catalytic properties of other chiral BINOL-aluminium complexes have also been tested in the reaction of **1a** with **2a**: the use of (*R*)-(+)-BINOL-AlOTf results in an HDA–ene ratio of 1 : 1 (total yield 28%) with a very low ee of the HDA product **3a**. Catalysts derived from substituted BINOL ligands were also tested in the reaction. The use of (*R*)-(+)-3,3′-biphenyl-BINOL-AlMe results in an HDA–ene ratio of 1 : 1 and a total yield of 40%, with ees of 21% for **3a** of (*R*) configuration and 12% for **4a**. Use of the Yamamoto catalyst (*S*)-(−)-3,3′-bis(triarylsilyl)-BINOL-AlMe[5g] also results in a product ratio of 1 : 1 and a poor total yield of 20%. The ees of the products were determined to be 18% [(*S*)-configuration] for **3a** and 7% for **4a**. It is worth noting that the observed asymmetric induction with the substituted ligands is opposite to that observed for the naked BINOL-Al-catalysts. We also used the weak Lewis acid [(*S*)-(−)-BINOL]$_2$-AlLi[7i,j] as catalyst for the reaction of **1a** with **2a**, but here also no successful results were obtained.

Further work is now in progress on the BINOL-AlMe-catalysed HDA and hetero-ene reactions and on the reaction mechanism.

Footnote

† It is of the utmost importance for the success of these reactions that the glyoxylate esters are monomeric.

References

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Received, 1st August 1996; Com. 6/05393I