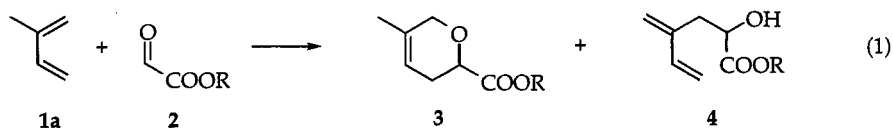# Metal-catalyzed asymmetric hetero-Diels–Alder reactions of unactivated dienes with glyoxylates

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Abstract: The development of a catalytic asymmetric hetero-Diels-Alder methodology for the reaction of unactivated dienes with glyoxylates is presented. Several different asymmetric catalysts can be used, but copper-bisoxazolines and aluminium-BINOL give the highest yield, and the best chemo- and enantioselectivities. The reaction course is dependent on several factors such as the solvent and the anions coordinated to the catalyst. The scope of the reaction is outlined by the total synthesis of a natural occurring actinidiolide.
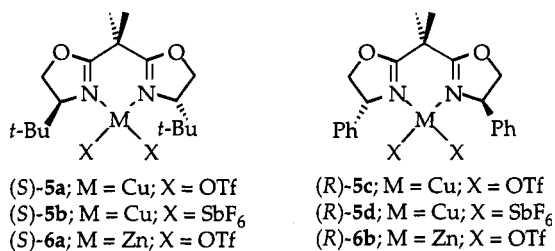
Introduction

The hetero-Diels-Alder (HDA) reaction of unactivated dienes with carbonyl compounds is of fundamental importance in organic chemistry.[1] The reaction of an unactivated diene having an allylic C-H bond, such as isoprene **1a**, with an electron-deficient aldehyde, such as a glyoxylate ester **2**, can take two different reaction paths, leading to either the HDA product **3** or the hetero-éne product **4** [reaction (1)].

The metal-catalyzed asymmetric hetero-éne reaction of dienes with an electron deficient aldehyde has been successfully developed by Nakai *et al.* and Mikami *et al.*[2] The hetero-éne reaction of simple dienes, such as isoprene **1a**, with glyoxylate esters in the presence of chiral titanium-BINOL complexes (BINOL = 1,1'-bi-2-naphthol) gives a HDA:éne ratio of up to 1:9 and a high ee of the hetero-éne product.[2c,d] For the reaction of conjugated dienes, having no allylic C-H bonds, with carbonyl compounds several metal-catalyzed enantioselective HDA reactions have been developed.[3]

The copper- and zinc-bisoxazolines, (*S*)-**5a,b** and (*R*)-**5c,d**, and (*S*)-**6a** and (*R*)-**6b**, respectively, and the aluminium-BINOL **7** are Lewis acid catalysts, which for the reaction of glyoxylate esters with unactivated dienes having an allylic C-H bond can change the reaction course from a hetero-éne- to a HDA reaction.[4]

(*S*)-**5a**; M = Cu; X = OTf
(*S*)-**5b**; M = Cu; X = SbF$_6$
(*S*)-**6a**; M = Zn; X = OTf

(*R*)-**5c**; M = Cu; X = OTf
(*R*)-**5d**; M = Cu; X = SbF$_6$
(*R*)-**6b**; M = Zn; X = OTf

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Results and discussion

The reaction of 2,3-dimethyl-1,3-butadiene **1b** with ethyl glyoxylate **2a** in the presence of the different copper(II)- and zinc(II)-bisoxazolines, (S)-**5a** and (R)-**5c**, and (S)-**6a** and (R)-**6b** respectively, and aluminium-BINOL **7** catalysts have been used as a test reaction to investigate the influence of the catalysts and solvent on the yield, chemo- and enantioselectivity [reaction (2)].

$$\text{(2)}$$

1a: $R^1 = $ Me; $R^2 = $ H   **2a**: $R^3 = $ Et   **3a**: $R^1 = $ Me, $R^2 = $ H, $R^3 = $ Et   **4a**: $R^1 = CH_2$; $R^2 = $ H, $R^3 = $ Et

1b: $R^1 = R^2 = $ Me   **2b**: $R^3 = $ Me   **3b**: $R^1 = R^2 = $ Me, $R^3 = $ Et   **4b**: $R^1 = CH_2$; $R^2 = $ Me, $R^3 = $ Et

1c: $R^1 = R^2 = $ H   **2c**: $R^3 = $ *i*-Pr   **3c**: $R^1 = R^2 = $ H, $R^3 = $ Et   **4d**: $R^1 = CH_2$; $R^2 = $ Me, $R^3 = $ Me

                                         3d: $R^1 = R^2 = $ Me, $R^3 = $ Me   **4e**: $R^1 = CH_2$; $R^2 = $ Me, $R^3 = $ *i*-Pr

                                         3e: $R^1 = R^2 = $ Me, $R^3 = $ *i*-Pr

Table 1. Hetero-Diels-Alder- and hetero-éne reactions of 2,3-dimethyl-1,3-butadiene **1b** with ethyl glyoxylate **2a** in the presence of the different copper(II)- and zinc(II)-bisoxazolines, (S)-**5a** and (R)-**5c**, and (S)-**6a** and (R)-**6b**, respectively, and aluminium-BINOL **7** catalysts.

Entry	Catalyst	Solvent	Hetero-Diels-Alder Product **3b**		Hetero-Éne Product **4b**		**3b:4b** Ratio
			Yield/%	ee /% (config.)	Yield/%	ee /%	
1	(S)-**5a**	CH_2Cl_2	25	85 (S)	36	83	1:1.8
2	(S)-**5a**	CH_3NO_2	38	90 (S)	30	78	1:0.8
3	(R)-**5c**	CH_2Cl_2	31	83 (S)	50	88	1:1.6
4	(S)-**6a**	CH_2Cl_2	41	23 (S)	25	31	1:0.6
5	(S)-**6a**	CH_3NO_2	21	25 (S)	15	11	1:0.7
6	(R)-**6b**	CH_2Cl_2	42	81 (S)	25	68	1:0.6
7	(R)-**6b**	CH_3NO_2	46	≈ 0	26	17	1:0.6
8	**7**	CH_2Cl_2	73	97 (R)	9	88	8:1

It appears from the results in Table 1 that the chemoselectivity in the reaction of 2,3-dimethyl-1,3-butadiene **1b** with ethyl glyoxylate **2a** is dependent on both the catalyst and the solvent. The copper(II)-bisoxazolines (*S*)-**5a** and (*R*)-**5c** gives a nearly 1:1 ratio of the HDA and hetero-éne products **3b:4b** with an increase of the HDA-product in CH_3NO_2 compared with CH_2Cl_2 as the solvent (entries 1-3).[4a,b] The ee of **3b** is high when the copper(II)-bisoxazolines are used as the catalyst and are in the range 83-90%, with the highest ee obtained in CH_3NO_2 (entry 2). It is remarkable that the absolute stereochemistry of the HDA-product **3b** is the same (*S*) when both (*S*)-**5a** and (*R*)-**5c** are used as the catalyst (entries 1-3). The zinc(II)-bisoxazolines (*S*)-**6a** and (*R*)-**6b** give a better HDA:hetero-éne ratio, compared with the copper(II)-bisoxazolines as the catalyst, as the HDA-product now generally is major product (entries 4-7),[4e] but catalyst (*S*)-**6a** gives a low ee of the HDA-product and the ee is independent of the solvent used. The catalyst (*R*)-**6b** gives a high ee of the HDA-product **3b** as 81% is obtained in CH_2Cl_2 (entry 6), whereas changing the solvent to CH_3NO_2 leads to a racemic HDA-product (entry 7). The absolute stereochemistry of the HDA-product **3b** is also (*S*) when both (*S*)-**6a** and (*R*)-**6b** are used as the catalyst (entries 4-6). For both the copper(II)- and zinc(II)-bisoxazoline catalysts the ee of the HDA-product **3b** is generally higher than the ee of the hetero-éne-product **4b**.

The best catalyst, both in terms of yield, chemo- and enantioselectivity, for the HDA reaction is the aluminium-BINOL **7**.[4c] The isolated yield of the HDA-product **3b** is 73% and the HDA:hetero-éne ratio is 8:1 with 97% ee of **3b**.

The copper(II)- and zinc(II)-bisoxazolines, (*S*)-**5a**, (*R*)-**5c** and (*S*)-**6a**, (*R*)-**6b** respectively, and aluminium-BINOL **7** catalysts can also catalyze the reaction of other simple conjugated dienes with glyoxylate esters. The reaction of isoprene **1a**, 2,3-dimethyl-1,3-butadiene **1b**, 1,3-butadiene **1c** and 1,3-cyclohexadiene **1d** with the various glyoxylates **2a-c** in the presence of some of the catalysts are given in Table 2.

Table 2. Hetero-Diels-Alder- and hetero-éne reactions of isoprene **1a**, 2,3-dimethyl-1,3-butadiene **1b**, 1,3-butadiene and 1,3-cyclohexadiene **1d** with the various glyoxylates **2a-c** in the presence of different copper(II)-bisoxazolines, (*S*)-**5a** and (*R*)-**5c**, and aluminium-BINOL **7** catalysts.

| Entry	Catalyst	Diene	Glyox.	Hetero-Diels-Alder Product		Hetero-Éne Product		3:4 Ratio
				Yield/%	ee /% (config.)	Yield/%	ee /%	
1	(*R*)-**5c**	**1a**	**2a**	**3a** - 33	80	**4a** - 34	91	1:1
2	(*R*)-**5c**	**1c**	**2c**	**3c** - 55	87 (*S*)	-	-	-
3	**7**	**1a**	**2a**	**3a** - 29	97 (*R*)	14	88	2:1
4	**7**	**1a**	**2b**	**3d** - 13	70 (*R*)	3	27	4:1
5	(*S*)-**5a**	**1b**	**2a**	**3a** - 20	85 - (*S*)	**4a** - 36	83	1:1.8
6	(*S*)-**5a**	**1b**	**2b**	**3d** - 25	90 - (*S*)	**4d** - 39	85	1:1.6
7	(*S*)-**5a**	**1b**	**2c**	**3e** - 12	77 - (*S*)	**4e** - 12	83	1:1
8	(*S*)-**5a**	**1d**	**2a**	**3f** - 97	95	-	-	-
9	(*R*)-**5c**	**1d**	**2a**	**3f** - 60	72	-	-	-

Isoprene **1a** reacts with ethyl glyoxylate **2a** in the presence of the copper(II)-bisoxazo-line (*R*)-**5c** as the catalyst to give HDA:hetero-éne ratio of 1:1 and with 80% ee of the HDA-product (Table 2, entry 1).[4a] The complex (*R*)-**5c** can catalyses the reaction of 1,3-butadiene with **2c** to give the corresponding HDA-product in 55% isolated yield and with an ee of 87% (entry 2).[4a] The aluminium-BINOL **7** complex catalyzes the reaction of **1a** with **2a** giving the two possible products with a HDA:hetero-éne ratio of 2:1. The ee of the HDA-product in this reaction is also very high - 97% (entry 3).[4c] Using methyl glyoxylate **2b** as the aldehyde re-duces both the yield and ee of the products in the reaction with **1a** catalyzed by (*R*)-**5** (entry 4)

The reaction is also slightly dependent of the glyoxylate ester. For the reaction of 2,3-dimethyl-1,3-butadiene **1b** with the different alkyl glyoxylates **2a-c** in the presence of the copper(II)-bisoxazoline (*S*)-**5a** in CH_2Cl_2, the following HDA:hetero-éne ratios were ob-tained: 1:1.8 (**2a**), 1:1.6 (**2b**) and 1:1 (**2c**).[4a] Changing to CH_3NO_2 as the solvent for the reac-tion leads to a reaction which is independent on the alkyl glyoxylate.[4b] Ethyl glyoxylate is probably the best glyoxylate to use of the glyoxylates tested. To obtain a high yield of the HDA-products in a relatively short time (3-5 h), the quality of the ethyl glyoxylate as well as the use of CH_3NO_2 as the solvent is crucial. The reactions in CH_2Cl_2 as the solvent require longer reaction time compared with CH_3NO_2 as the solvent. We have also found that by us-ing CH_3NO_2 as the solvent and applying not only a freshly destilled ethyl glyoxylate, but one which >95% monomeric, gives a significant improvement in the yield of the HDA-prod-ucts.[4d]

Special attention has been given to the reaction of cyclic dienes, such as 1,3-cyclohexa-diene **1d** and 2,6,6-trimethyl-1,3-cyclohexadiene **1e**, with ethyl glyoxylate **2a** in the presence of the copper-bisoxazolines (*S*)-**5a,b** and (*R*)-**5c,d**.[4a,b,d] The reason for choosing these cyclic dienes is to apply the present HDA-reaction for synthetic purposes .

The reaction of 1,3-cyclohexadiene **1d** with ethyl glyoxylate **2a** giving the HDA-prod-uct **3f** (Scheme 1) has been performed in the presence of the copper-bisoxazolines (*S*)-**5a,b** and (*R*)-**5c,d** as the catalyst and in CH_2Cl_2 or CH_3NO_2 as the solvents.[4a,b,d] Two results for the reaction of **1d** with **2a** catalyzed by (*S*)-**5a** and (*R*)-**5c** are given in Table to illustrate the influence of the chiral ligand on the yield and enantioselecvtivity.
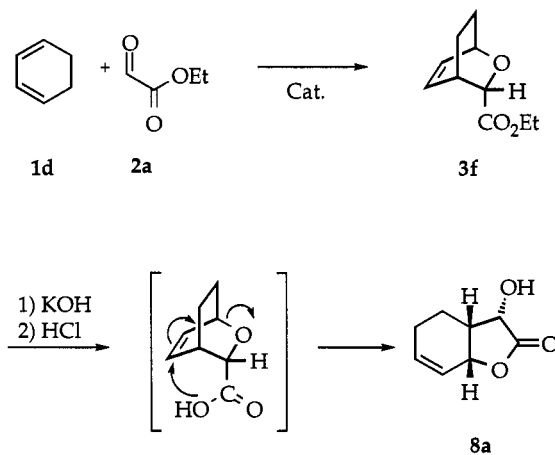
Scheme 1:

The catalyst (*S*)-**5a** has the best properties compared with (*R*)-**5c** for the HDA reaction of 1,3-cyclohexadiene **1d** outlined in Scheme 1 as more than 90% yield of the *endo*-diastere-omer **3f** is obtained. The ee of **3f** is 95% using (*Sl*)-**5a** as the catalyst, whereas 72% is obtained with (*R*)-**5c**. The catalytic properties of (*S*)-**5a,b** in CH_3NO_2 and CH_2Cl_2 as the solvents are: (*S*)-**5b** in CH_3NO_2>(*S*)-**5a** in CH_3NO_2>(*S*)-**5b** in CH_2Cl_2>(*S*)-**5a** in CH_2Cl_2. For the catalyst (*S*)-**5b** in CH_3NO_2 more than 95% conversion is obtained in less than 1 h, while for (*S*)-**5a** in

CH_2Cl_2 only 50% conversion is found after 3h.[4d] The counterion of the catalyst has a small influence on the enantioselectivities for the reaction of 1,3-cyclohexadiene **1c** with ethyl glyoxylate **2a**, as (S)-**5b** in CH_3NO_2 gives 93% ee of **3f**, while the other combinations all give ≥95% ee. The use of (S)-**5a,b** as catalyst for the reaction of **1d** with **2a** is preferable compared with (R)-**5c,d** as the formers give both the highest yield and enantioselectivities.

The HDA-reaction of 1,3-cyclohexadiene **1d** with ethyl glyoxylate **2a** catalyzed by (S)-**5a,b** has been used for the synthesis of the bicyclic lactone **8a** as outlined in Scheme 1.[4a,b] Treatment of the HDA-product **3f** with base followed by acid gives first the carboxylic acid, which undergoes an intramolecular rearrangement giving **8a** as outlined in Scheme 2. The intramolecular reaction proceeds in high yield (>85%) without loss of ee.

The HDA-methodology using the copper bisoxazolines as the catalyst has been used for the total synthesis of the natural occurring bicyclic dihydroactinidiolide **9**[5] which is one of the three components of the pheromone of the queen recognition of the workers of the red fire ant, *Soleneopsis invicta*.[6] The total synthesis of **9** is outlined in Scheme 2:

Scheme 2:
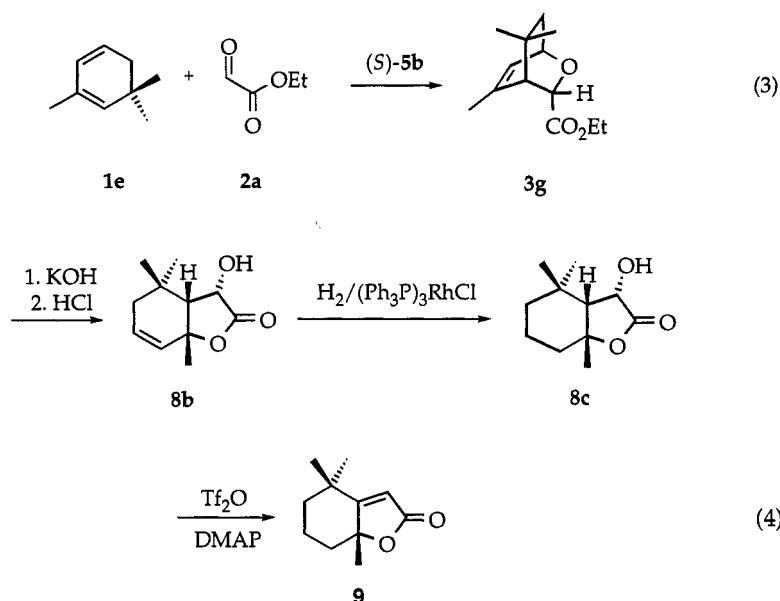
Reaction of 2,6,6-trimethyl-1,3-cyclohexadiene **1e** with ethyl glyoxylate **2a** in the presence of (S)-**5b** as the catalyst affords **3g** in 90% isolated yield with very high diastereo- and enantiomeric excess as only the *endo*-diastereomer is observed having 95% ee (Scheme 2, reaction (3)). Treatment of **3g** with KOH followed by HCl gives **8b** in 88% isolated yield (Scheme 2) and maintaining the ee obtained in the first step. Hydrogenation of alkene in **8b** by $(Ph_3P)_3RhCl/H_2$ gives the saturated compound **8c** from which the bicyclic dihydroactinidiolide **9** is obtained in high overall yield.[5]

For the HDA reactions of 2,3-dimethyl-1,3-butadiene **1b** with ethyl glyoxylate **2b** catalyzed by (S)-**5a** and (R)-**5c** the same absolute stereochemistry of the HDA-product **3b** (S) (Table 1, entries 1-3) was observed. In an attempt to account for the same absolute stereochemistry in the product, when catalysts having different substituents bound to the stereogenic center and different absolute stereochemistry, it has been proposed that the geometry at the copper center is different in the two cases as shown in **10** and **11** below:[4a]

10   **11**
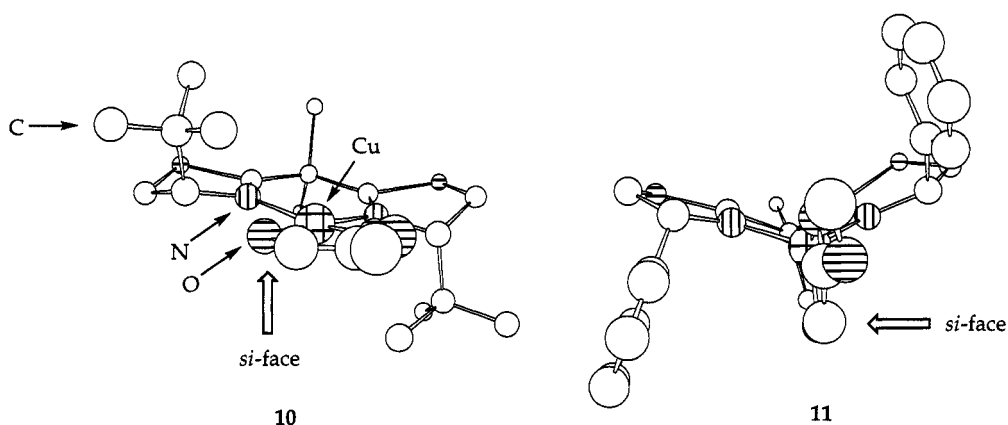
In intermediate **10** it is suggested that the glyoxylate ester is coordinated to the copper bisoxazoline catalyst leading to an intermediate with a planar geometry at the metal center. This intermediate has the *si*-face of the aldehyde of the glyoxylate ester available for attack of the conjugated diene. Moving to the chiral ligand having a phenyl substituent (*R*)-**5c** the tetrahedral intermediate **11** can account for the absolute stereochemistry in the HDA-product. In **11** the *si*-face of the carbonyl functionality is again available for approach of the conjugated diene. The preferred tetrahedral arrangement in the latter case might be due to a π-π interaction of the phenyl substituent and the carbonyl functionality.

The present work shows that activated aldehydes, such glyoxylates, can react with simple unactivated dienes to give the HDA products in good yield with high ee. In cases where a competive reaction course is possible - HDA *vs.* ene reaction - catalysts such as copper(II)- and zinc(II)-bisoxazolines, and especially aluminum-BINOL, can change the reaction course to a HDA reaction and giving the product with very high ee. For cyclic dienes copper(II)-bisoxazolines can catalyze the reaction giving the HDA product with also very high ee.

Acknowledgements

References

1. See *e.g.*: (a) D. L. Boger and S. M. Weinreb in *Hetero Diels-Alder Methodology in Organic Synthesis*, Academic Press: New York 1987. (b) H. B. Kagan and O. Riant *Chem. Rev.*, **92**, 1008 (1992). (c) H. Waldmann *Synthesis*, 535 (1994). (d) K. Narasaka *Synthesis*, **1991**, 1.

2. See *e.g.*: (a) K. Mikami and M. Shimizu *Chem. Rev.*, **92**, 1021 (1992). (b) K. Mikami, Y. Motoyama and M. Terada *J. Am. Chem. Soc.*, **116**, 2812 (1994). (c) M. Terada, K. Mikami and T. Nakai *Tetrahedron Lett.*, **32**, 935 (1991). (d) M. Terada and K. Mikami *J. Chem. Soc., Chem. Commun.*, 2391 (1995).

3. See *e.g.*: (a) G. E. Keck, X.-Y. Li and D. Krishanmurthy *J. Org. Chem.* **60**, 5998 (1995). (b) M. Quimpére and K. Jankowski *J. Chem. Soc., Chem. Commun.*, 676 (1987). (c) A. Togni *Organometallics*, **9**, 3106 (1990). (d) Y. Motoyama and K. Mikami *J. Chem. Soc., Chem. Commun.*, 1563 (1994). (e) Q. Gao, M. Muruyama, M. Mouri and H Yamamoto *J. Org. Chem.* **57**, 1951 (1992). (f) E. J. Corey, C. L. Cywin and T. D. Roper *Tetrahedron Lett.*, **33**, 6907 (1992). (g) K. Maruoka, T. Itoh, T. Shirasaka and H. Yamamoto *J. Am. Chem. Soc.*, **110**, 310 (1988). (f) S. Matsukawa and K. Mikami *Tetrahedron: Asymmetry* **8**, 815 (1997).

4. (a) M. Johannsen and K. A. Jørgensen *J. Org. Chem.*, **60**, 5757 (1995). (b) M. Johannsen and K. A. Jørgensen *Tetrahedron*, **52**, 7321 (1996). (c) A. Graven, M. Johannsen and K. A. Jørgensen *J. Chem. Soc., Chem. Commun.* 2373 (1996). (d) M. Johannsen and K. A. Jørgensen *J. Chem. Soc., Perkin Trans. 2* 1183 (1997). (e) S. Yao, M. Johannsen and K. A. Jørgensen *J. Chem. Soc., Perkin Trans. 1* 2345 (1997).

5. S. Yao, M. Johannsen and K. A. Jørgensen submitted for publication.

6. J. R. Rocca, J. H. Tumlinson, B. M. Glancey and C. S. Lofgren *Tetrahedron Lett.* **1983**, 24, 1889.