Solvent *vs.* counterion acceleration of enantioselective carbo and hetero Diels–Alder reactions

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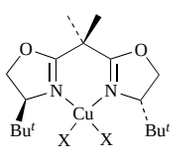
The influence of solvents (CH_2Cl_2 and CH_3NO_2) *vs.* non-coordinating counterions (OTf and SbF_6; Tf = CF_3SO_2) on the catalytic properties of CuX_2–bisdihydrooxazoles in carbo and hetero Diels–Alder reactions has been studied. It has been observed that the use of CH_3NO_2 as the solvent enhances the reactivity of the $Cu(OTf)_2$–bisdihydrooxazole catalyst compared with the reactivity of CuX_2–bisdihydrooxazole in CH_2Cl_2 in these reactions. The use of CH_3NO_2 as the solvent in the carbo Diels–Alder reaction gives an 87% yield of the Diels–Alder adduct with 96% enantiomeric excess (ee), while in the hetero Diels–Alder reaction 98% yield and 97% ee is found under similar reaction conditions.

Introduction

The metal-catalysed carbo Diels–Alder (CDA) and hetero Diels–Alder (HDA) reactions are of fundamental importance in organic chemistry and the development of mild, efficient and easy to carry out procedures for these reactions is highly desirable. The use of C_2-symmetric cationic CuX_2–bisdihydrooxazole complexes[1] such as (*S*)-**1a**,**b** as chiral Lewis acids for CDA[2] and HDA[3] reactions has shown promising results.



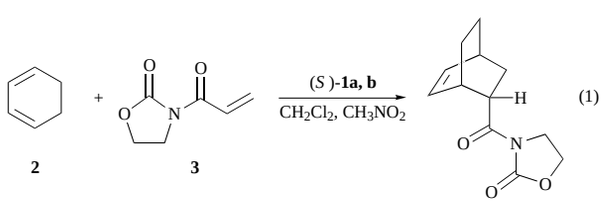
(*S*)-**1a:** X = OTf
(*S*)-**1b:** X = SbF_6

In an attempt to increase the catalytic activity of the CuX_2–bisdihydrooxazole complexes, a 'tuning' of the properties of the catalyst and the reaction conditions is becoming necessary. Evans *et al.* have found a large counterion effect in the CDA reactions, when changing X from X = BF_4 to SbF_6 in the CuX_2–bisdihydrooxazole and CuX_2–pybox bis(oxazolinyl)pyridine complexes.[2b] In the HDA reactions we have observed that the solvent plays an important role both in terms of yield, enantiomeric excess (ee) and absolute stereochemistry of the HDA adducts.[3b]

This paper presents the results of the first comparative study of the CDA and HDA reactions using the CuX_2–bisdihydrooxazole complexes (*S*)-**1a**,**b** as catalysts in different solvents in an attempt to investigate the influence of the counterion and the solvent on the properties of the catalyst. Furthermore, it will be shown that the yield of the HDA adduct can be significantly improved by changing the composition of the glyoxylate ester used.

Results and discussion

The CDA reaction has been studied for the reaction of cyclohexa-1,3-diene **2** with 3-acryloyloxazolidine-2-one **3** in the presence of (*S*)-**1a**,**b** as the catalyst and CH_2Cl_2 or CH_3NO_2 as the solvents [reaction (1)] (see Experimental section for details).



2 **3** **4** (1)

Table 1 The carbo Diels–Alder (CDA) reaction between cyclohexa-1,3-diene **2** and 3-acryloyloxazolidine-2-one **3** catalysed by (*S*)-**1a**,**b** in CH_2Cl_2 and CH_3NO_2 as the solvents (Tf = CF_3SO_2)

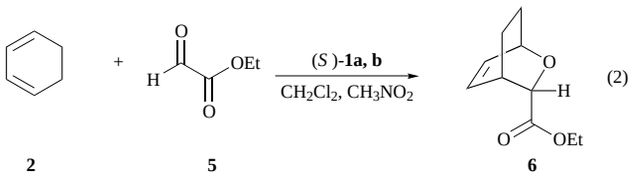
Entry	Catalyst X	Reaction time/h	Solvent	CDA product yield (%)[a] (ee)[b]
1	(*S*)-**1a** (X = OTf)	48	CH_2Cl_2	90 (82)[2b]
2	(*S*)-**1b** (X = SbF_6)	5	CH_2Cl_2	90 (93)[2b]
3	(*S*)-**1a** (X = OTf)	4	CH_3NO_2	90 (92)
4	(*S*)-**1b** (X = SbF_6)	3	CH_3NO_2	98 (88)
5	(*S*)-**1b** (X = SbF_6)	4[c]	CH_3NO_2	87 (96)

[a] Isolated yield. [b] Determined by HPLC using a CHIRALCEL OD column. [c] The initial reaction temperature is −15 °C and increasing to 0 °C during the reaction.

In the CDA reaction catalysed by (*S*)-**1a** in CH_2Cl_2, a 90% yield of the CDA-adduct **4** having an ee of 82% is formed after 48 h (Table 1, entry 1).[2b] Changing the counterion in the catalyst from OTf [(*S*)-**1a**] to SbF_6 [(*S*)-**1b**] leads to an increase of the reaction rate as the reaction time now is reduced from 48 to 5 h to obtain 90% yield of **4** (entry 2).[2b] Furthermore, an increase in the ee to 93% of **4** is found (entry 2).[2b] The results in entries 3–5 show the improvement of the catalytic properties of (*S*)-**1a**,**b** by changing the solvent from CH_2Cl_2 to CH_3NO_2. The reaction performed in CH_3NO_2 and using (*S*)-**1a** as the catalyst leads to an increase in reactivity of the catalyst, compared with the reaction using (*S*)-**1b** as the catalyst in CH_2Cl_2, as 4 h is now necessary for obtaining 90% yield of **4** in the first case. To our surprise, the ee at the same time rises by 10% compared with the reaction in CH_2Cl_2 (entry 3). The combination of the catalyst (*S*)-**1b** and CH_3NO_2 as the solvent for the CDA reaction (entry 4) shows that the use of SbF_6 as the counterion in CH_3NO_2 leads to a further reduction in reaction time for the CDA reaction, but that the ee at the same time is slightly lower (88%) compared with the reaction catalysed by (*S*)-**1b** in CH_2Cl_2 and (*S*)-**1a** in CH_3NO_2. The ee in the first reaction can be improved to 96% with only a small reduction in the yield by lowering the reaction temperature to −15 °C and increasing it to 0 °C over 4 h (entry 5). It should be noted that the stereochemistry of **4** (*R*) is the same in all entries in Table 1 and that the *endo*:*exo* selectivity according to ^{1}H NMR spectroscopy is >95:<5 in all the reactions.

To investigate whether the use of CH_3NO_2 as the solvent or

the approach by Evans *et al.* using non-coordinating counterions[2b] is the catalytic system of choice for the HDA reaction, the reactions of cyclohexa-1,3-diene **2** with ethyl glyoxylate **5** in the presence of (*S*)-**1a**,**b** as the catalyst in CH_2Cl_2 or CH_3NO_2 have also been performed [reaction (2)] (see Experimental section for details).



2 **5** **6** (2)

The results obtained for the HDA reaction of cyclohexa-1,3-diene **2** with ethyl glyoxylate **5** catalysed by (*S*)-**1a**,**b** (10 mol%) in CH_2Cl_2 or CH_3NO_2 [reaction (2)] are presented in Fig. 1. It should be noted that the use of CH_3CN or dimethylformamide (DMF) as the solvent for the reaction leads to a less active catalyst.

It appears from Fig. 1 that the use of catalyst (*S*)-**1b** in CH_2Cl_2 and CH_3NO_2 and catalyst (*S*)-**1a** in CH_3NO_2 increases the catalytic activity of the CuX_2–bisdihydrooxazole complexes, compared to the reaction catalysed by (*S*)-**1a** in CH_2Cl_2. The upper curve represents the combination of SbF_6 as the counterion and CH_3NO_2 as the solvent and the reaction rate with this combination is the highest obtained, but on the other hand the ee is the lowest found (93%), whereas for all the other combinations the ee is ⩾97%. It is notable that the use of CH_3NO_2 as the solvent in the presence of (*S*)-**1a** as the catalyst gives a faster reaction compared with the use of catalyst (*S*)-**1b** in CH_2Cl_2. Here the stereochemistry of **6** is also independent of the counterion and the solvent.

To obtain a high yield of the HDA-adduct **6** in a relatively short time (3–4 h), the quality of the ethyl glyoxylate as well as the use of CH_3NO_2 as solvent is important. We have previously mentioned that the HDA addition can proceed in CH_2Cl_2 as the solvent, but with a rather long reaction time.[3b] Using CH_3NO_2 as the solvent under these reaction conditions increases the reaction rate, but still only 66% of **6** can be isolated after a reaction time of 12 h.[3b] However, using not only a freshly distilled sample of ethyl glyoxylate, but one which is >95% monomeric, gives an almost quantitative yield of **6** within 1–2 h of reaction time [reaction (2)]. Is has long been known that the polymerisation of alkyl glyoxylates is reversible, and that one sometimes can use the semipolymerised form in reactions,[4] but the yield does not exceed 60–80% in these cases. One way to ensure a high yield of the HDA-adduct is to use freshly distilled alkyl glyoxylates, which, depending on the batch, often consist of monomeric glyoxylates. The procedure, however, for synthesising these glyoxylates can be quite crucial for obtaining the pure monomer. We have tested several methods, and found two procedures which normally lead to glyoxylates of a very high quality.[5] We recommend the use of these methods, although the last one especially can fail, and give some by-products, which are very difficult to remove by distillation.

The present results show that both the anion and the solvent have influence on the catalytic activity of the CuX_2–bisdihydrooxazole complexes. In order to achieve the optimum conditions for the catalyst in the CDA- and HDA-reactions both the anion and solvent have to be considered, as it is shown here that both the reaction rate and the enantioselectivity is dependent on these two factors. The results for the reactions using (*S*)-**1b** as the catalyst in CH_2Cl_2 and (*S*)-**1a** in CH_3NO_2 show a comparable increase in activity of the catalyst. However, combining (*S*)-**1b** as the catalyst and CH_3NO_2 as the solvent leads to a further increase in the reaction rate. The latter improvement in reaction rate might be related to the presence of a more cationic complex under these combined conditions, whereas the anions, OTf and

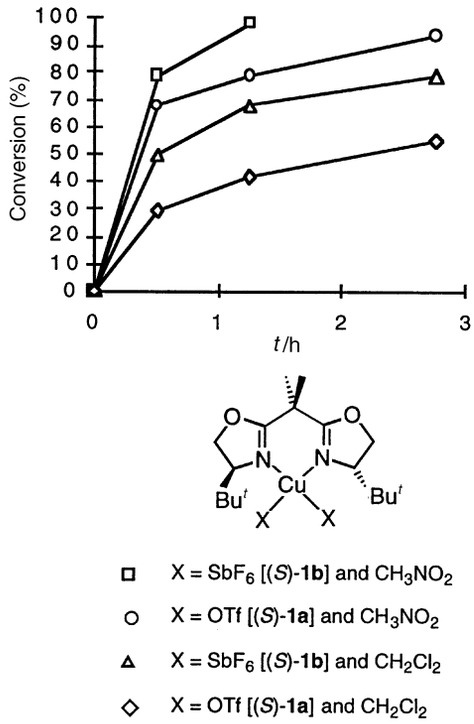


Fig. 1 Plot of the conversion (%) as a function of the reaction time (h) for the hetero Diels–Alder (HDA) reaction of cyclohexa-1,3-diene **2** with ethyl glyoxylate **5** in the presence of (*S*)-**1a**,**b** as the catalyst in CH_2Cl_2 and CH_3NO_2 as the solvents

SbF_6, are weakly coordinating to the copper centre in the two former cases. But we cannot exclude a minor interaction of the anions and the copper metal taking place in the present combination of the anion and the solvent. These results indicate that the catalytic properties of the CuX_2–bisdihydrooxazole complexes can be improved further by a careful tuning of the anion and the solvent.

Experimental

General

The ^1H NMR and ^{13}C NMR spectra were obtained on a Varian Gemini at 300 and 75 MHz, respectively. Chemical shifts for ^1H NMR and ^{13}C NMR are recorded in $CDCl_3$ and reported in ppm downfield from $SiMe_4$. *J* Values are given in Hz.

$Cu(OTf)_2$ and cyclohexa-1,3-diene, 2,2′-isopropylidenebis-[(4*S*)-4-*tert*-butyl-4,5-dihydrooxazole] [2,2-bis(4-*tert*-butyl-4,5-dihydrooxazol-2-yl)propane], $Cu(OTf)_2$, $CuBr_2$ and $AgSbF_6$ were purchased from Aldrich and used without further purification. $Cu(OTf)_2$, $CuBr_2$ and $AgSbF_6$ were stored under N_2. Ethyl glyoxylate was prepared as described in the literature,[5] stored at −18 °C and distilled under water vacuum prior to use. Solvents were dried according to standard procedures.

Standard procedure for the CDA reaction: reaction of 3-acryloyloxazolidine-2-one 3 with cyclohexa-1,3-diene 2 catalysed by (*S*)-1b in CH_3NO_2

To a dry flask was added $CuBr_2$ (22 mg, 0.10 mmol), $AgSbF_6$ (69 mg, 0.20 mmol) and 2,2′-isopropylidenebis[(4*S*)-4-*tert*-butyl-4,5-dihydrooxazole] (31 mg, 0.11 mmol) under an N_2 stream. Dry CH_3NO_2 (1–2 ml) was added and the heterogeneous solution was stirred vigorously for 20 h, and then filtered through a pasteur pipette with a plug of cotton and Hyflo. To the deep-green solution **3** (141 mg, 1.0 mmol) and **2** (191 μl, 2.0 mmol) were added. The solution was allowed to stir for 3 h at room temp. The solvent was evaporated *in vacuo* and to the resulting green syrup was added 2 ml of CH_2Cl_2. This was then directly applied to a preparative TLC plate, and the product

was separated using diethyl ether–light petroleum (1:2, R_f = 0.24) as eluent. Yield 216 mg (0.98 mmol, 98%) of a white solid with 88% ee [chiral HPLC, CHIRALCEL OD column; eluent 2% Pr^iOH–98% hexane, flow 1 ml min^{-1}; t_r (major enantiomer) = 72.8, t_r (minor enantiomer) = 81.1]; δ_H(300 MHz, $CDCl_3$) 6.33 (dd, 1H, *J* 7.7, 7.1, CH=C*H*), 6.14 (dd, 1H, *J* 7.1, 6.6, CH=C*H*), 4.37 (m, 2H, OCH_2), 3.96 (m, 2H, NCH_2), 3.74 (m, 1H, C*H*), 2.81 (m, 1H, bridgehead *H*), 2.61 (m, 1H, bridgehead *H*), 1.84 (m, 1H, HC*H*), 1.74–1.49 (m, 3H, HC*H* and CH_2), 1.33–1.20 (m, 2H, CH_2).[2]

Standard procedure for the HDA reaction: reaction of ethyl glyoxylate 5 with cyclohexa-1,3-diene 2 catalysed by (*S*)-1a in CH_3NO_2

To a dry flask was added Cu(OTf)$_2$ (18 mg, 0.05 mmol) and 2,2′-isopropylidenebis[(4*S*)-4-*tert*-butyl-4,5-dihydrooxazole] (18 mg, 0.06 mmol) under an N_2 stream. Dry CH_3NO_2 (1–2 ml) was added and the solution was stirred for 3 h. The deep-green solution was cooled to 0 °C, and a mixture of freshly distilled **5**[5] (102 mg, 1.0 mmol) in CH_3NO_2 (0.5 ml) was added by canula followed by **2** (191 μl, 2.0 mmol). After stirring for 3 h at 0 °C the solvent was evaporated and CH_2Cl_2 (2 ml) was added. This was then applied to a preparative TLC plate, and the product was purified with a mixture of diethyl ether–light petroleum (1:2, R_f = 0.39) as eluent. Yield 180 mg (0.98 mmol, 98%) of a colourless oil with 97% ee [chiral GC, Chrompack Chirasil-DEX CB column 25 m × 0.25 mm, oven temperature = 130 °C, t_r (minor enantiomer) = 15.6, t_r (major enantiomer) = 16.6]. Spectral data were consistent with those previously published.[3a]

The reaction to be monitored was performed as above with two exceptions. (*i*) The reactions were run with 10% of catalyst and (*ii*) naphthalene (30 mg) was added as internal standard for monitoring GC. Samples of 50 μl were removed and filtered through a small plug of silica gel with 1 ml of EtOAc. The mixture was then analysed on GC and the reaction progress was calculated on the basis of naphthalene. A 1:1 test run on naphthalene and HDA was made to ensure the relative intensities of the GC results.

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