Copper(II)-*(S)*-bisoxazoline and zinc(II)-*(S)*-bisoxazoline catalysed asymmetric 1,3-dipolar cycloaddition reactions of nitrones with electron-deficient alkenes

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A transition-metal-catalysed regio-, diastereo- and enantioselective 1,3-dipolar cycloaddition reaction between nitrones and electron-deficient alkenes has been developed employing 25 mol% of chiral copper(II)- or zinc(II)-(S)-bisoxazolines as catalysts. In the presence of powdered 4 Å molecular sieves and copper(II)-(S)-bisoxazoline as catalyst, the nitrones smoothly react with alkenes at –60°C to give isoxazolidines in good yields and diastereoselectivity and with high enantioselectivities of up to 62% ee. By crystallisation of the isoxazolidines from MeOH an optical purity of >97% ee is obtained. The influence of the metal salts, temperature, molecular sieves, catalyst amount and solvents on the reaction course was discussed.

Keywords: bisoxazoline, 1,3-dipolar cycloaddition reaction, metal complexes, diastereoselectivity, chiral catalyst

The 1,3-dipolar cycloaddition reaction is a very important reaction for the construction of five-membered heterocycles and has been used in numerous syntheses using 1,3-dipoles such as nitrones, nitrile oxides, azomethine ylides and nitronates.[1] These cycloadducts have found wide applications in synthesis and as synthons in total synthesis by their conversion into, for example, 3-amino alcohols and alkaloids.[1-3] The typical 1,3-dipolar cycloaddition reaction of nitrones with alkenes involves a dominant interaction of the $HOMO_{nitrone}$ and the $LUMO_{alkene}$ resulting in eight possible stereoisomers, including two regioisomers, each as two diastereomers, and each of these two diastereomers as two enantiomers. To prepare enantiopure isoxazolidines, the chirality in the cycloadduct has mostly been achieved through incorporation of chiral centre(s) in both the nitrone and/or the alkene in the 1,3-dipolar cycloaddition reaction.[4] However, this has several disadvantages, such as waste of optically active material and elevated temperatures. This can be circumvented using chiral Lewis acids for the activation of the alkene or nitrone, resulting in a lowering of the energy of the $LUMO_{alkene\ or\ nitrone}$ and enhancement of the diastereo- and enantioselective of the reaction.[3a]

Contrary to the chiral Lewis acid catalysed asymmetric carbo- and hetero-Diels–Alder reactions,[5] the use of chiral Lewis acids as catalyst in asymmetric 1,3-dipolar cycloaddition reactions is relatively unexplored. In recent years, focus has been put on this field[6-10] and great advances on the regio-, diastereo- and enantioselectivity of the reaction have been achieved.[11-17] The focus in the chiral Lewis acid catalysed 1,3-dipolar cycloaddition reaction has mainly been devoted to the activation of electron-deficient alkenes by the catalyst,[13-15,18-26] and chiral titanium(IV), magnesium(II), and ytterbium(III) complexes have been introduced in the reactions between different nitrones and various alkenes.[13-15,24-25]

Contrary to the 1,3-dipolar cycloaddition of *β*-substituted 3-alkenoyloxazolidin-2-ones with nitrones, the reaction of acryloyl derivatives **1** often proceeds with lack of regioselectivity because of both electronic and steric factors.[27] This paper presents the attempts to control both regio-, diastereo- and enantioselectivity of the 1,3-dipolar cycloaddition reaction between acryloyl derivatives **1** and nitrone by appling $Cu(OTf)_2$ or $Zn(OTf)_2$-bisoxazolines as catalysts and investigates the influence of metal salts on the reaction rate and stereoselectivity.

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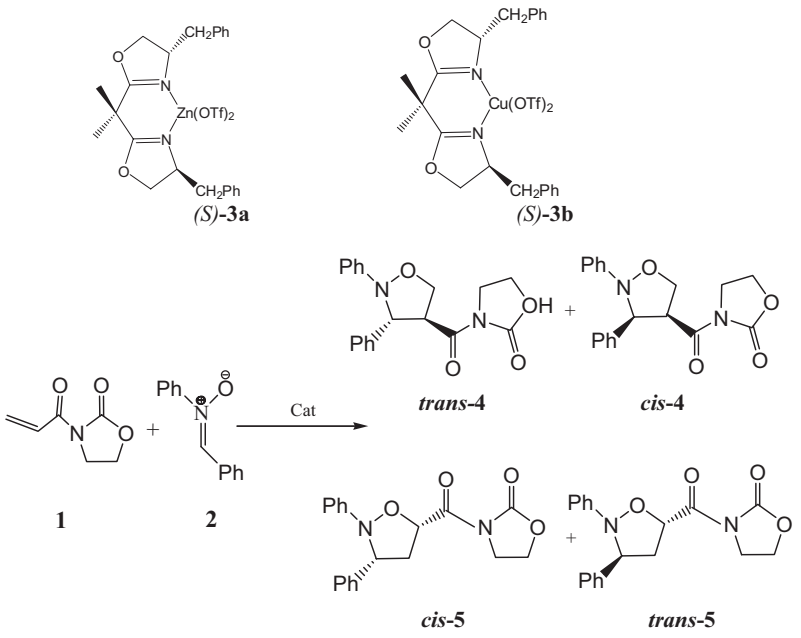
Results and discussion

The reactions of alkene **1** with nitrone **2** catalysed by different catalysts *(S)*-**3a**, *(S)*-**3b** in the presence or absence of 4 Å molecular sieves, different temperatures and different solvents have been studied (Scheme 1) (see Experimental). A series of results are presented in Table 1.

The addition of acryloyloxazolidnone 1, to C,N-diphenylnitrone 2 without the presence of *(S)*-**3a**, *(S)*)-**3b** as catalysts, has been investigated as model reaction in different solvents. The reactions proceed in a less regioselective manner and give a mixture of all regio- and diastereomers.

The effect of the solvent is investigated first. The 1,3-dipolar cycloaddition reactions between **1** and **2** proceed at room temperature without a catalyst to give 90% yield after 72 h and a approximately 50:50 ratio of the 4-substituted isoxazolidine **4** and the 5-substituted isoxazolidine **5** in CH_2Cl_2, respectively (Table 1, entry 1). In toluene, the reactions show similar trends in both regioselectivity with a 4:5 ratio of 40:60 and diastereoselectivity with an *cis*-**4**: *trans*-**4** ratio of 80:20 after 90 h (Table 1, entry 5). However, in the presence of 0.25 mol equiv of catalysts *(S)*-**3b**, the reactions between **1** and **2** are faster and, more importantly, only one regioisomer, **4** is obtained.

The *(S)*-**3a**-catalysed reaction shows lower yield and enantioselectivity, but higher diastereoselectivity compared with the *(S)*-**3b**-catalysed reaction in both CH_2Cl_2 and toluene. In the reaction of **1** with **2** catalysed by 25 mol% *(S)*-**3b** in CH_2Cl_2, a *trans*-**4**: *cis*-**4** ratio of 40 : 60 with an ee of 47% *cis*-**4** is obtained, while *trans*-**4** is formed in 40% ee (Table 1, entry 3). Performing the analogous reaction catalysed by 25 mol% *(S)*-**3a** in CH_2Cl_2 leads dramatically to *trans*-isoxazolidine *trans*-**4** as the major diastereomer with a *trans*-**4**/*cis*-**4** ratio of 68:32 and 11% ee of *trans*-**4**, while *cis*-**4** is formed in 10% ee (Table 1, entry 2). However, if the solvent is changed from CH_2Cl_2 to toluene, a remarkable decrease in both diastereoselectivity and especially, enantioselectivity is observed respectively. With the presence of *(S)*-**3b** as catalyst in toluene, the diastereoselectivity is lowered with a *trans*-**4**/*cis*-**4** ratio of 57:43, compared to reaction in CH_2Cl_2, and the enantioselectivity decreases to 31% ee of *trans*-**4** and 30% ee of *cis*-**4** respectively (Table 1, entry 7). Similarly, use of *(S)*-**3a** as catalyst also leads to a remarkable decrease in the stereoselectivities in toluene (Table 1, entry 6). It should also be noted that the reactions of **1** with **2** in the presence of *(S)*-**3b** as the catalyst proceed with complete regioselectivity, which is not the case in the absence of a catalyst and the presence of *(S)*-**3a** as a catalyst.



Scheme 1

Table 1 Reaction of acryloyloxazolidnone **1**, with *C,N*-Diphenylnitrone **2** in the presence of the chiral copper(II)- and zinc(II)-*(S)*-bisoxazolines catalysts under various reaction conditions[a]

Entry	Solvents	Catalyst	Time/h	Yield[f] /%	*Trans*-**4**/*cis*-**4**[d]	ee [e] (%)	
						Trans-**4**	*cis*-**4**
1	CH_2Cl_2	–	72	90[g]	20:80		
2[i]	CH_2Cl_2	*(S)*-**3a**	48	42	68:32	11	10
3	CH_2Cl_2	*(S)*-**3b**	24	80	40:60	40	47
4	CH_2Cl_2	*(S)*-**3b**[c]	24	>95	15: 85	50	44
5	toluene	–	90	86[h]	20:80		
6[i]	toluene	*(S)*-**3a**	48	44	65:35	8	5
7	toluene	*(S)*-**3b**	42	71	57:43	31	30
8	CH_2Cl_2	*(S)*-**3b**	44[b]	<20	39: 61	47	51
9	CH_2Cl_2	*(S)*-**3b**[c]	44[b]	77	29:71	62	53
10	CH_2Cl_2	*(S)*-**3a**[c]	44[b]	35	47:53	7	0

[a]The reactions were carried out on a 0.5 mmol scale in 15 ml of CH_2Cl_2 or toluene at room temperature with 25 mol% catalyst. [b]The reactions were carried out at –60°C for 24 h then at 15°C over 20 h. For details, see Experimental. [c]the presence of MS 4 **Å**. [d]*Trans*-**4**: *cis*-**4** ratios were determined by ^{1}H NMR spectroscopy of the crude product. [e]The enantiomeric excess of *trans*-**4** and *cis*-**4** was determined by HPLC (Daicel Chiralcel OD using hexane/*i*-PrOH, 70:30). [f]Isolated yields of **4**. [g]Isolated yields of **4** and **5,** ratio 4/5: 50:50. [h]Isolated yields of **4** and **5**, ratio **4**/**5**: 40:60. [i]Ratio **4**/**5**: >90:<10.

In order to get good stereoselectivities, it appeared that catalyst *(S)*-**3b** is most suitable for the reaction and CH_2Cl_2 is a better solvent on the basis of these results listed in table 1, entry 1–7.

To study the influence of the temperature on the stereoselectivities, the reaction of **1** with **2** catalysed by 25 mol% *(S)*-**3b** in CH_2Cl_2 has been carried out at –60°C (Table 1, entry 8). Compared to the analogous reaction at room temperature (Table 1, entry 3), the *trans*-4/*cis*-4 ratio is not been changed, but the ee of product is improved to 47% ee of *trans*-**4** and 51% ee of *cis*-**4** respectively. However, it should also be noted that low temperature leads to a low conversion.

As numerous reports have described the successful application of powdered 4 Å molecular sieves in enantioselective titanium(IV)-catalysed reactions,[28] we also examined the effect of adding molecular sieves to the reaction mixture. By application of powdered 4 Å molecular sieves, only a slight decrease in ee of *cis*-**4** is observed, whereas reaction yield (>95%), *cis*-diastereoselectivity (*trans*-**4**: *cis*-**4** = 15:85) and the ee of *trans*-**4** are improved remarkablely compared to the similar reaction in the absence of 4 Å molecular sieves (Table 1, entry 4).

The present results encouraged us to test the catalysed reaction in the presence of powdered 4 Å molecular sieves at –60°C (in CH_2Cl_2). The reaction catalysed by 25 mol% *(S)*-**3b** proceeds in a *cis*-selective manner with a *trans*-**4**/*cis*-**4** ratio of 29:71 and gives satisfactory yield. What is most notable, the optical purity of the *trans*-isoxazolidine obtained in this reaction is 62% ee the best result obtained so far in our present work, and furthermore, the ee of *cis*-**4** is up to 53% also the best result in *cis*-isoxazolidine in our present work so far (Table 1, entry 9). Unfortunatelly, performing the reaction catalysed by 25 mol% *(S)*-**3a** leads to a remarkable decrease of reactivity and stereoselectivity (Table 1, entry 10).

Enhancing the catalyst (*(S)*-**3b**) amount to 50 mol% gives a satisfactory conversion after 48 h (Table 2, entry 1). Compared to the analogous reaction with 0.25 mol equiv of catalyst (Table 1, entry 3), the diastereoselectivity is also *cis*-selectivity in the reaction, as *cis*-**4** and *trans*-**4** are improved to a ratio of 72:28 with 47% and 40% ee, respectively. When we changed metal salt from $Cu(OTf)_2$ to $Co(CH_3COO)_2$, the results for the reaction is not changed compared to the model reaction in CH_2Cl_2 (Table 2, entry 2).

Table 2 1,3-Dipolar cycloaddition reaction of acryloyl-oxazolidnone 1, with *C,N*-diphenylnitrone 2 in the presence of the chiral metal(II)-*(S)*-bisoxazolines catalysts under other reaction conditions

Entry[a]	Solvent	Conv.[b]/%	*Trans*-**4** /*cis*-**4**[b]	ee [b] (%) *Trans*-**4**	ee [b] (%) *Cis*-**4**
1	CH_2Cl_2[c]	>95	28:72	40	47
2	CH_2Cl_2[d]	>95	14:86	0	0

[a]The reactions were carried out on a 0.5 mmol scale with 0.5 mol equiv of catalysts at room temperature for 48 h. [b]The conversion, *trans*-**4**: *cis*-**4** ratios and the enantiomeric excess were determined by HPLC. [c]*(S)*-**3b** as catalyst. [d]the metal salt is $Co(CH_3COO)_2$.

Conclusion

A new copper(II)-*(S)*-bisoxazoline catalysed regio-, diastereo- and enantioselective 1,3-dipolar cycloaddition reaction between nitrone and electron-deficient alkene has been developed. The effect of solvents, molecular sieves, temperature, catalyst amount and the metal salts has been investigated. It appeared that CH_2Cl_2 is a better solvent for the reaction. The adding of 4 Å molecular sieves leads to remarkable increase in the yield and stereoselectivities; low temperature improves the ee of the isoxazolidines remarkablely but also leads to a low conversion; enhancing the *(S)*-**3b** amount to 50 mol% from 25 mol% improves *cis*-selectivity, but enantioselectivity is not changed compared to the latter; metal salts are crucial for both reaction rate and stereoselectivity of the catalysed reaction of electron-deficient alkene **1** with nitrone **2** and $Cu(OTf)_2$-bisoxazoline (*(S)*-**3b**) has the best catalytic activity in this reaction. In the presence of powdered 4 Å molecular sieves, the *(S)*-**3b** catalysing reaction of **1** and **2** smoothly proceedes at –60°C (in CH_2Cl_2), giving isoxazolidines in good yield, diastereoselectivity with high enantioselectivities of up to 62% ee of *trans*-**4**. The ee can be improved to >97% by crystallisation of the *cis*-isoxazolidine from MeOH.

Experimental

General methods

The ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively. Chemical shifts for ^1H and ^{13}C NMR are reported in $CDCl_3$ and in ppm downfield from tetramethylsilane (TMS). Mass spectra were recorded using 1100 Series LC/MSD Trap from Agilent. HPLC was performed using a 4.6 mm × 25 cm Daicel Chiracel OD column. Preparative thinlayer chromatography (PTLC) was performed on 200 × 200 × 0.4 mm silica gel on glass plates. Solvents were dried using standard procedures. The 4 Å powdered molecular sieves were activated by heating to 250°C for 5 h. All glass equipment was dried in an oven before use.

Materials

3-(prop-2-enoyl)-1,3-oxazolidin-2-one **1**, and benzylidenephenylamine N-oxide **2** were synthesised according to the literatures.[13,14] The chiral bis(oxazolines) 2,2-bis[(4*S*)-4-benzyl-4,5-dihydro-1,3-oxazol-2-yl] propane was synthesised according to the literature.[29] $Cu(OTf)_2$, $Zn(OTf)_2$, were purchased from Alfa Aesar.

Asymmetric 1,3-dipolar cycloaddition reactions; general procedure for the reaction using 25 mol% of catalyst (S)-**3b**

A flame-dried Schlenk tube was charged with $Cu(OTf)_2$ (45.2 mg, 0.125 mmol) and the *(S)*-bisoxazoline (50 mg, 0.138 mmol) under a stream of N_2. Dry CH_2Cl_2 or dry toluene (15 ml) was added, and the mixture was then stirred at room temperature for 1–2 h. To the green solution nitrone **2** (119 mg, 0.60 mmol) and alkene **1** (70.5 mg, 0.50 mmol) were added with a glass pipette (250 mg powdered 4 Å molecular sieves was also added according to Table 1). The solution was then stirred at room temperature for the time given in the tables (For the reactions at –60°C, the mixture is cooled to –60°C for 24 h then allowed to warm to room temperature over 20 h). The reaction mixture was stirred with 10 ml of 5% MeOH in CH_2Cl_2 and filtered through a 20 mm layer of silica gel. After the silica gel layer was washed with another 10 ml of 5% MeOH in CH_2Cl_2, the solvent was evaporated. The residue was subjected to preparative TLC (silica gel, ethyl acetate:petroleum ether, 4:5). Two bands appeared in the region R_f = 0.4–0.7 from which the lower band could be extracted to give *cis*-**4**. The band with the higher R_f value consisted of a mixture of *trans*-**4** and *cis*-**4**. With this mixture the chromatographic procedure was repeated to give pure *trans*-**4**.

The physical data for compounds **4** and **5** have been reported previously.[27]

(trans-**4***)* was synthesised according to the general procedure under the conditions in Table 1: yellow oil, HPLC (Diacel Chiralcel OD, hexane/i-PrOH) = 7/3, flow rate = 1.0 ml/min); t_R = 19 min (minor), t_R = 28 min (major). ^1H NMR ($CDCl_3$): δ 4.02 (t, *J* = 8.3 Hz, 2H), 4.14 (dd, *J* = 5.5, 8.2 Hz, 1H), 4.42 (m, 2H), 4.56 (dt, *J* = 5.5,8.2 Hz, 1H),4.75 (t, *J* = 8.2, 1H), 5.27 (d, *J* = 5.5 Hz, 1H), 7.00 (m, 3H), 7.23 (m, 2H),7.35 (m, 3H),7.53 (d, *J* = 7.1 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 43.3, 59.6, 62.9, 70.2, 71.3, 116.3, 122.9, 127.6, 128.4, 129.2, 129.5, 141.4, 150.7, 153.7, 170.8. MS: *m/z* 338 (M^+)

(cis-**4***)* was also synthesised according to the general procedure under the conditions in Table 1: yellow oil, HPLC (Diacel Chiralcel OD, hexane/i-PrOH) = 7/3, flow rate = 1.0 ml/min); t_R = 20 min (minor), t_R = 29 min (major). ^1H NMR (CDCl3): δ 3.02–3.09(m, 1H), 3.68–3.75(m, 1H), 3.81–3.91(m, 1H), 4.13–4.26(m, 2H), 4.85(dd, *J* = 6.0,5.9 Hz, 1H), 4.96(dd, *J* = 6.0,5.9 Hz, 1H), 5.17(d, *J* = 8.3 Hz, 1H), 6.93–7.01(m, 3H), 7.21–7.33(m, 5H), 7.45–7.47(d, *J* = 6.5 Hz, 2H). MS: *m/z* 338 (M^+)

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