C_1-Symmetrical $Ti(OTos)_2$- and $TiCl_2$-TADDOLate-catalysed 1,3-dipolar cycloaddition reactions of nitrones to electron-deficient alkenes

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A regio-, diastereo- and enantioselective 1,3-dipolar cycloaddition reaction between nitrones and electron-deficient alkenes has been developed employing C_1-symmetrical $Ti(OTos)_2$- and $TiCl_2$-TADDOLate as catalysts. In the presence of powdered 4 Å molecular sieves and 100 mol% of $Ti(OTos)_2$-TADDOLate as the catalyst, the nitrones smoothly react with alkenes at room temperature to give isoxazolidines in high conversion, giving the *trans*-diastereomer of the isoxazolidines with de's up to >90% and ee up to 58%. Furthermore, C_1-symmetrical $TiCl_2$-TADDOLate has a better chiral induction, giving the *trans*-diastereomer of the isoxazolidines with high enantioselectivity up to 70% ee. The influence of catalyst amount, temperature and solvents on the reaction course has been investigated

Keywords: TADDOLate, 1,3-dipolar cycloaddition reaction, chiral catalyst, diastereoselectivity, enantioselectivity

The 1,3-dipolar cycloaddition reaction is an important reaction for the construction of five-membered heterocycles and can form up to four new chiral centres.[1] These cycloadducts have found wide applications in synthesis.[1-3] Due to the concerted nature and the often high degree of regioselectivity of the 1,3-dipolar cycloaddition reaction, only a limited number of product isomers are formed,[1] and attempts to control the stereoselectivity, especially enantioselectivity with respect to the four possible stereoisomers formed by this reaction have attracted further attention during the last decade.[4] 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 reaction. However, this has several disadvantages, such as waste of optically active material and time. This can be circumvented using chiral Lewis acids as catalysts, resulting in a lowering of the energy of the $LUMO_{alkene\ or\ nitrone}$ and enhancement of the regio-, diastereo- and enantioselective of the reaction.[3]

Gothelf and Jørgensen have introduced the first example of a transition metal-catalysed asymmetrical 1,3-dipolar cycloaddition reaction between 3-crotonoyl-1,3-oxazolidin-2-one and C,N-diphenylnitrone.[5] Use of 10 mol% of $TiCl_2$-TADDOLate as catalyst, generated *in situ* from $Ti(i\text{-}PrO)_2Cl_2$ and chiral diols, gave an excess of the *cis*-diastereomer with an ee up to 62% from this reaction, whereas for other substrates the *cis*-selectivity was lower.[5] Subsequently $Ti(OTos)_2$-TADDOLate induced a high degree of *trans*-selectivity for all substrate combinations tested and led to the induction of enantioselectivities >90% in several cases.[6] The mechanism of the titanium-catalysed reactions and the structure of the intermediate between electron-deficient alkene and $TiCl_2$-TADDOLate have been discussed.[6-14] $TiCl_2$-TADDOLates have also been introduced in the 1,3-dipolar cycloaddition reaction of N-crotonoylsuccinimide and C,N- diphenylnitrone. The reactions proceed with a high degree of *cis*-selectivity, often >90% de and up to 73% ee.[15]

In the 1,3-dipolar cycloaddition reaction, the focus of attention on the chiral TADDOLate has mainly been devoted to C_2-symmetrical ones, but C_1-symmetrical TADDOLate are relatively unexplored in the present. Because of lack of regioselectivity between acryloyl derivatives **1** and nitrones **2**,[16,17] few papers have been found concerning this reaction. In this paper, we turn our interest to C_1-symmetrical TADDOLate and attempt to control both regio-, diastereo- and enantioselectivity of this reaction by appling C_1-symmetrical $Ti(OTos)_2$- and $TiCl_2$-TADDOLate as catalysts.

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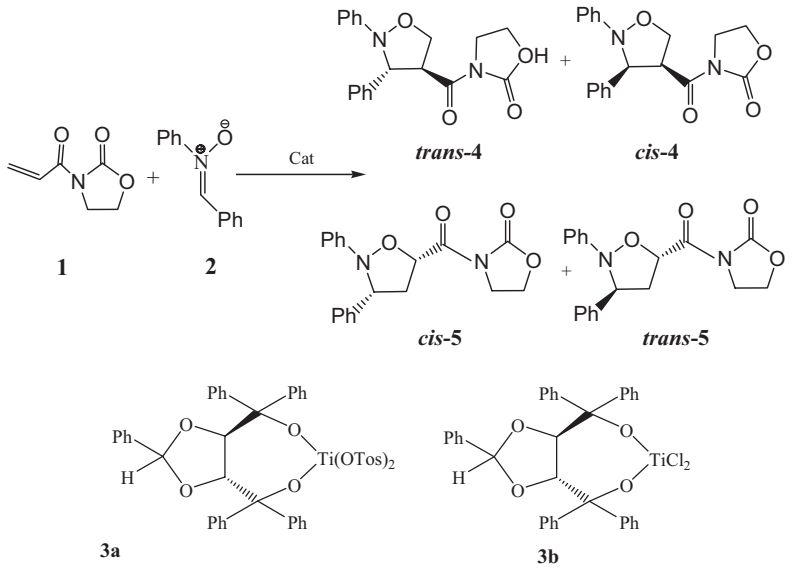
Results and discussion

The reactions of acryloyloxazolidnone **1** with C,N-diphenylnitrone **2** catalysed by chiral $Ti(OTos)_2$-TADDOLate catalyst **3a** in different solvents, catalyst amount and different temperatures have been studied. (Scheme 1) (see Experimental for details). A series of results are presented in Table 1.

The addition of **1** to **2**, in the absence of **3a**, has been investigated as a central reaction in different solvents. The reactions proceeded in a less regioselective manner and gave a mixture of all regio- and diastereomers. This reactions proceeded at room temperature without a catalyst to give high conversion after 90 h and an approximately 40:60 ratio of the 4-substituted isoxazolidine **4** and the 5-substituted isoxazolidine **5** in toluene, respectively (Table 1, entry 1). In CH_2Cl_2, the reactions show similar trends in both regioselectivity with a **4**:**5** ratio of 50:50 and diastereoselectivity with a *cis*-4:*trans*-4 ratio of 80:20 after 72 h (Table 1, entry 6).

Increasing the amount of the catalyst **3a** gave a satisfactory regioselectivity. Using **3a**(>50%mol), only the 4-substituted isoxazolidine **4** was obtained in the reaction. As in previous papers,[15,18] the amount of $Ti(OTos)_2$-TADDOLate catalyst also played an important role in the diastereoselectivity and enantioselectivity. By using 10 mol% and 25 mol% catalyst, the diastereoselectivity showed little change compared to blank reaction with a *trans*-4:*cis*-4 ratio of 19:81, whereas the enantioselectivity of the isoxazolidine **4** is low (Table 1, entries 2,3). However, increasing the catalyst amount to 50 mol% gave a completely conversion after 48 h (Table 1, entry 4) and a reverse diastereoselectivity giving a remarkable excess of the *trans*-isomer with a *trans*-4:*cis*-4 ratio of 85:15, and what is most notable, the enantioselectivity was improved to 44% ee of *trans*-4, while *cis*-4 was formed in 9% ee. By using 100 mol% catalyst, the reaction between **1** and **2** proceeded with greater *trans*-selectivity as the *trans*-4:*cis*-4 ratio is 96:4. The ee for *trans*-4 is improved to 58% in the reaction (Table 1, entry 5).

The diastereo- and enantioselectivity in the reaction of alkene **1** with nitrone **2** in presence of **3a** was very solvent dependent. On changing from toluene to CH_2Cl_2, a remarkable decrease in both diastereoselectivity and especially, enantioselectivity was observed. Using 50 mol% **3a** as catalyst for the reaction of **1** with **2** leads to *trans*-4 as the major diastereomer with a *trans*-4/*cis*-4 ratio of 65 : 35, while *trans*-4 is formed in 25% ee in CH_2Cl_2 (Table 1, entry 7). By increasing the catalyst amount to 100 mol%, a similar results on the stereoselectivity of the reaction were observed (Table 1, entry 8), giving an excellent *trans*-selectivity with the *trans*-4:*cis*-4 ratio of 93:7, and the optical purity of the *trans*-4 obtained in this reaction was also improved to 40% ee.



Scheme 1

Table 1 Reaction of acryloyloxazolidnone **1**, with *C,N*-Diphenylnitrone **2** in the presence of the chiral $Ti(OTos)_2$- TADDOLate **3a** catalyst under various reaction conditions[a]

Entry	Solvents	Amount /mol%	Conv[b] /%	*trans*-4/*cis*-4[b]	ee[b]/% *trans*-4	ee[b]/% *cis*-4
1	Toluene	–	>90[d]	20:80		
2	Toluene	10	>95	19:81	8	<5
3	Toluene	25	>95	21:79	12	<5
4	Toluene	50	>95	85:15	44	9
5	Toluene	100	>95	96:4	58	<5
6	CH_2Cl_2	–	>95[e]	20:80		
7	CH_2Cl_2	50	>95	65:35	25	<5
8	CH_2Cl_2	100	95	93:7	40	<5
9[c]	Toluene	100	>80	82:18	16	13
10[c]	CH_2Cl_2	100	>80	87:13	6	7

[a]The reactions were carried out on a 0.5 mmol scale in the presence of 4 Å MS at room temperature for 48 h. See Experimental.
[b]Conversion, *cis*-4:*trans*-4 ratio and the enantiomeric excess were determined by HPLC.
[c]Reaction temperature –30°C for 4 days.
[d]Reaction time: 90 h, isolated conversion of **4** and **5** with ratio 4/5 = 40:60.
[e]Reaction time: 72 h, isolated conversion of **4** and **5** with ratio 4/5 = 50:50.

When the reactions of **1** with **2** catalysed by **3a** were carried out at low temperature (–78°C) in toluene or CH_2Cl_2, no reactions occurred in 5 days. However, at –30°C the reactions were completed within 4 days giving satisfactory conversion, but there was a remarkable decrease in both diastereoselectivity and enantioselectivity (Table 1, entries 9 and 10). In toluene, the reaction of **1** with **2** catalysed by **3a** also proceeded in a highly *trans*-selective manner with a *trans*-4:*cis*-4 ratio of 82:18 and with a slight increase in ee of *cis*-4 (13%), whereas the ee of *trans*-4 decreases to 16% remarkablely (Table 1, entry 9). A similar result was observed in the reaction of **1** and **2** at –30°C in CH_2Cl_2 (Table 1, entry 10).

Changing the tosylate ligands of the $Ti(OTos)_2$-TADDOL catalyst with chlorine also leads to 4-substituted isoxazolidine **4** as the major product. The influence of solvents and catalyst amount on the stereoselectivity has been investigated and a series of results are presented in Table 2.

By increasing the catalyst amount, a remarkable increase in both diastereoselectivity and especially, enantioselectivity was observed. When the reaction of alkene **1** with nitrone **2** catalysed by **3b** was carried out in toluene, an almost complete conversion is achieved. Compared to the reaction catalysed by 10 mol% **3a** in toluene, the diastereoselectivity is also *cis*-selective manner, giving a slight excess of the *cis*-4, and the enantioselectivity is improved to 36% ee for *trans*-4 (Table 2, entry 1). By the application of 25 mol% **3b**, the diastereoselectivity still maintained a *cis*-selectivity in the reaction, as the *cis*-4/*trans*-4 is improved to a ratio of 67:33. Remarkably, the optical purity of the *trans*-isoxazolidine obtained in this reaction was 67% ee, and furthermore, the ee of *cis*-4 is up to 19% (Table 2, entry 2). Increasing the catalyst amount to 50 mol% also gave *cis*-selective manner with a *trans*-4/*cis*-4 ratio of 39:61 and a slight increase in ee of *trans*-4 (70%), whereas the ee of *cis*-4 increased to 43% (Table 2,

Table 2 Diastero- and enantioselectivity of the 1,3-dipolar cycloaddition reaction of **1** with **2** catalysed by **3b** at room temperature[a]

	Solvent	Amount /mol%	*trans*-4 /*cis*-4[b]	ee[b]/% *trans*-4	ee[b]/% *cis*-4
1	Toluene	10	43:57	36	6
2	Toluene	25	33:67	67	19
3	Toluene	50	39:61	70	43
4	CH_2Cl_2	10	61:39	44	12
5	CH_2Cl_2	50	62:32	67	35

[a]The reactions were carried out on a 0.5 mmol scale with the presence of 4 Å MS at room temperature for 48 h. For details, see Experimental.
[b]Conversion, *cis*-4:*trans*-4 ratio and the enantiomeric excess were determined by HPLC, and the conversion is >95%.

entry 3). However, the catalysed reaction in CH_2Cl_2 proceeded in a *trans*-selective manner. Using 10 mol% catalyst for this reaction gave moderate *trans*-selectivity with an *cis*/*trans* ratio of 39:61 and an ee of 12% *cis*-4, while *trans*-4 is formed in 44% ee (Table 2, entry 4). It appears that no appreciable change in diastereoselectivity is observed when going from 10 mol% catalyst to 50 mol% (Table 2, entry 5). But a remarkable improvement was obtained in the enantioselectivity with the ee of *trans*-4 and *cis*-4 up to 67% and 35% respectively.

Conclusion

A new C_1-symmetrical $Ti(OTos)_2$- and $TiCl_2$-TADDOLate catalysing regio-, diastereo- and enantioselective 1,3-dipolar cycloaddition reaction between C,N-diphenylnitrone and electron-deficient alkene has been developed. The influence of catalyst amount, temperature and solvents on the reaction course has been investigated. The catalyst amount is crucial for regio-, diastereo- and enantioselectivity of the catalysed reaction of electron-deficient alkene **1** with nitrone **2**. Increasing the amount of $Ti(OTos)_2$-TADDOLate gives a satisfactory regioselectivity and leads dramatically to a change in diastereoselectivity, from *cis*-selectivity to *trans*-selectivity, and enantioselectivity also has a remarkable increase. In the presence of 100 mol% of $Ti(OTos)_2$-TADDOLate, the nitrones reacted smoothly with alkenes at room temperature to give isoxazolidines in complete conversion, giving the *trans*-diastereomer with de up to >90% and ee up to 58%; Furthermore, C_1-symmetrical $TiCl_2$-TADDOLate has better chiral induction, giving the *trans*-diastereomer with high enantioselectivity up to 70% ee; Low temperature leads to a remarkable decrease in both diastereoselectivity and especially, enantioselectivity; The solvents also played an important role on the stereoselectivity, especially enantioselectivity in the reaction of **1** and **2**, and both CH_2Cl_2 and toluene are suited for this reaction.

Experimental

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 thin-layer 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 before use.

Materials

The starting materials 3-(prop-2-enoyl)-1,3-oxazolidin-2-one **1**, and *C,N*-diphenylnitrone **2**,[9,10] (2*R*,3*R*)-2,3-O-(1-Phenylethylidene)-1,1,4,4-tetraphenyl-1,2,3,4-butanetetrol,[19] $Ti(OTos)_2$-(*R,R*)-TADDOLate,[19] $TiCl_2$-(*R,R*)-TADDOLate, dichlorodiisopropoxytitanium(IV)[20] were synthesised according to the literature. Titanium(IV)isopropoxide was purchased from Alfa Aesar.

Asymmetrical 1,3-dipolar cycloaddition reactions; general procedure for the reaction using 10 mol% of catalyst

To a dry toluene solution of $Ti(i\text{-}OPr)_2Cl_2$ (1 ml, 0.05 mmol in toluene), (2*R*,3*R*)-2,3-O- (1-Phenylethylidene)-1,1,4,4- tetraphenyl-1,2,3,4-butanetetrol (0.055 mmol) was added. The solution was stirred 5 hours. In another flask, 3-(prop-2-enoyl) 1,3-oxazolidin-2-one **1** (0.5 mmol) was dissolved in dry toluene (8 ml) and 4Å molecular sieves were added (250 mg), then the catalyst solution was added. The mixture was stirred for 10–15 hours at room temperature under a stream of N_2. Finally, the nitrone (0.6 mmol) was added. The solution was then stirred at room temperature for the time given in the tables. 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.[10,11]

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). 13C NMR (CDCl3): 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 ($CDCl_3$): 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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