# 140. Control of Regio-, Diastereo-, and Enantioselectivity in the [Ti(OTs)$_2$(TADDOLato)]-Catalyzed 1,3-Dipolar Cycloaddition Reaction between 3-Acryloyloxazolidin-2-one and Nitrones

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Dedicated to Professor *Dieter Seebach* on the occasion of his 60th birthday

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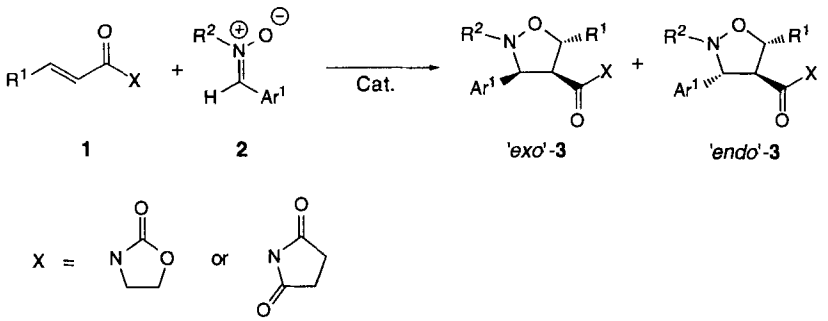
Catalytic control of regio-, diastereo-, and enantioselectivity in the 1,3-dipolar cycloaddition of 3-acryloyloxazolidin-2-one (**4**) with different nitrones **2** by the application of a [TiX$_2$(TADDOLato)] complex as the catalyst was developed (TADDOL = α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanol). In the absence of a catalyst, the 1,3-dipolar cycloaddition of **4** with **2** proceeded to give a mixture of regioisomers, whereas, in the presence of a catalyst, the regioselectivity of the reaction could be controlled. Three asymmetric [TiX$_2$(TADDOLato)] catalysts were tested, and it was found that use of the [Ti(OTs)$_2$(TADDOLato)] complex gave complete regioselectivity, high *'endo'*-selectivities (> 90% d.e.), and enantioselectivities corresponding to 48–70% e.e.

**Introduction.** – One of the great challenges in organic chemistry today is to introduce heteroatoms into alkenes in a simple and stereoselective manner from easily available starting materials. Several excellent methods for the stereospecific introduction of two vicinal heteroatoms in an alkene have been developed, such as the asymmetric epoxidation [1], asymmetric dihydroxylation [2], and recently the asymmetric aminohydroxylation [3]. No such direct catalytic asymmetric methods are available for the introduction of a 1,3-diheteroatom functionality. However, the 1,3-dipolar cycloaddition of a nitrone with an alkene offers an effective indirect route to 3-amino alcohols, as the isoxazolidines obtained in the reactions are easily converted into 3-amino alcohols [4]. Several attempts to control the stereochemistry of the reaction using chiral starting material have been performed, and the isoxazolidines obtained in these 1,3-dipolar cycloaddition reactions have often been key adducts in total syntheses [5].

In recent years, the first attempts to develop a metal-catalyzed asymmetric 1,3-dipolar cycloaddition reaction between alkenes and nitrones have been published [6–9]. We have found that the 1,3-dipolar cycloaddition reaction of 3-(alk-2-enoyl)oxazolidin-2-ones and various nitrones can be catalyzed by *Lewis* acids such as $Ti^{IV}$, $Mg^{II}$, and $Yb^{III}$ complexes [6]. The reaction of **1** with **2** proceeded with complete regioselectivity when $R^1$ was different from H, both in the presence, and at elevated temperatures in the absence of catalyst (*Scheme 1*). Only the products **3** arising from attack of the nitrone O-atom at the β-position of the alkenoyl moiety were obtained. In the presence of the catalyst [TiCl$_2$(TADDOLato)] **7**, generated from the now widely applied TADDOL (= α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanol) ligands [10] and [TiCl$_2$(i-PrO)$_2$], the *'exo'*-isomer was formed as the primary product with an e.e. of up to 60% [6a]. Recently, we

applied succinimide instead of the oxazolidinone as the auxiliary for the alkenoyl moiety in the reaction of **1** with **2**, which promoted in most cases a highly *'exo'*-selective reaction accompanied by e.e.s of up to 73% [11]. Application of [Ti(OTs)$_2$(TADDOLato)] [6b], [MgI$_2$(bisoxazoline)] [6c], or [Yb(OTf)$_3$(PyBOX)] (PyBOX = 2,6-bis[(4*S*)-4-isopropyl-2-oxazolin-2-yl]pyridine) [6f] complexes as catalysts led to highly *'endo'*-selective 1,3-dipolar reactions producing e.e.s of up to 93%. The catalytic asymmetric 1,3-dipolar cycloaddition of alkenes with nitrones were also studied by others. *Seerden et al.* used a chiral oxazaborolidine catalyst for the activation of nitrones for the cycloaddition with electron-rich alkenes [7]. *Seebach* and coworkers developed a number of polymer- and dendrimer-bound [TiCl$_2$(TADDOLato)] catalysts and investigated their application in the 1,3-dipolar cycloaddition of alkenes with nitrones [8]. In a recent work by *Furukawa* and coworkers, the application of chiral[Pd(BINAP)] catalysts (BINAP = 2,2'-bis-(diphenylphosphino)-1,1'-binaphthyl) for the 1,3-dipolar cycloaddition was described [9].

*Scheme 1*



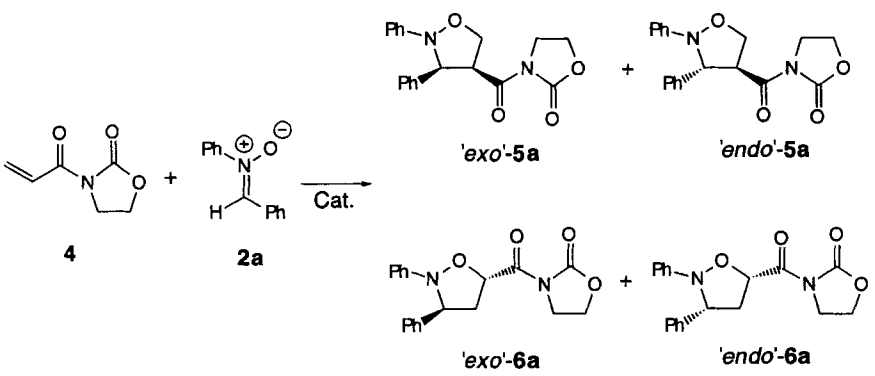

Contrary to the 1,3-dipolar cycloaddition of $\beta$-substituted 3-alkenoyloxazolidin-2-ones **2** ($R^1 \neq H$) with nitrones, the reaction of acryloyl derivatives **1** ($R^1 = H$) often proceeds with lack of regioselectivity [4] [12]. In the present work, we describe the control of both regio-, diastereo-, and enantioselectivity of the 1,3-dipolar cycloaddition of acryloyl derivatives **1** ($R^1 = H$) with nitrones **2** by the application of chiral [TiX$_2$-(TADDOLato)] catalysts.

**Results and Discussion.** – The regioselectivity of the 1,3-dipolar cycloaddition of alkenes with nitrones is controlled by both electronic and steric factors [4]. In the present case involving reactions of acryloyl derivatives **1** ($R^1 = H$), these two factors oppose each other. The interaction between the frontier molecular orbitals (FMO) of the alkene and the nitrone is, in this case, dominated by the HOMO$_{nitrone}$-LUMO$_{alkene}$ interaction. The LUMO$_{alkene}$ has the largest amplitude at C($\beta$), while the HOMO$_{nitrone}$ has the largest amplitude at the nitrone O-atom; thus the attack of the nitrone O-atom at the $\beta$-position of the acryloyl moiety is favored for electronic reasons [4] [6c]. On the other hand, attack of the nitrone O-atom at the $\alpha$-position of the acryloyl moiety is favored for steric reasons [4]. Hence, the lack of regioselectivity in 1,3-dipolar cycloadditions of acryloyl derivatives with nitrones often constitutes a major problem. Chiral auxiliaries for the acryloyl moiety have successfully been applied in the 1,3-dipolar cycloaddition with nitrile oxides [13]; however, probably due to the lack of regioselectivity, only few reports describe the

application of chiral acryloyl derivatives in nitrone cycloadditions [12]. In some cases, the regioselectivity problem was overcome by the use of cyclic (*E*)-nitrones where the steric factor is decreased, leading to attack of the nitrone O-atom at the β-position of the acryloyl moiety [12c,d].

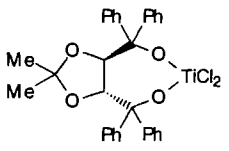
We considered the possibility of controlling the regioselectivity of the reaction between 3-acryloyloxazolidin-2-one (**4**) and acyclic nitrones **2** by the application of a metal catalyst (*Scheme 2*). The coordination of **4** to a *Lewis* acid such as [$TiCl_2$(TADDOLato)] might increase the amplitude of the $LUMO_{alkene}$ in the β-position of the alkene leading to a dominance of the electronic over the steric factors [6c].

*Scheme 2*

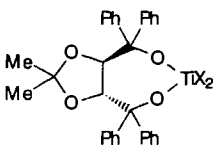



The 1,3-dipolar cycloaddition between **4** and **2a** proceeded at room temperature in the absence of a catalyst to give 91% conversion after 68 h and a 39:61 ratio of the 4-substituted isoxazolidine **5a** and the 5-substituted isoxazolidine **6a**, respectively (*Table 1, Entry 1*). The *'endo'/'exo'*-selectivities of **5a** and **6a** were also poor. In the presence of 10 mol-% of the catalyst [$TiCl_2$(*i*-PrO)$_2$], the reaction between **4** and **2a** was faster and, more importantly, only one regioisomer, **5a** was obtained (*Entry 2*). However, the reaction showed no *'endo'/'exo'*-selectivity. Now being able to control the regioselectivity of the reaction, we were looking for the possibility of controlling the *'endo'/'exo'*-selectivity (diastereoselectivity) and the enantioselectivity. Application of [$TiCl_2$-(TADDOLato)], **7** as a chiral catalyst for the reaction also led to a completely regioselective reaction, but both the *'endo'/'exo'*-selectivity and the enantioselectivities were low (*Entry 3*). The results were not improved when the reaction was performed at lower temperatures. As mentioned above, the use of catalyst **8a** for the 1,3-dipolar cycloadditions of alkenes such as **1** with various nitrones led to e.e.s of up to 93% [6b]; the reaction was slow, and 50 mol-% of the catalyst was required to obtain satisfactory conversions. For the reaction of **4** with **2a** (*Scheme 2*), 5 mol-% of catalyst **8a** was sufficient to control the regioselectivity (*Entry 4*). Furthermore, a high *'endo'/'exo'*-ratio of 92:8 was obtained, accompanied by 66% of e.e. for *'endo'*-**5a**. The *'endo'*-selectivity was improved by the application of 10 mol-% of **8a**, which also enhanced the e.e. to 70%. Further increase of the amount of **8a** did not improve the results. To optimize the catalyst, the pentafluorobenzene sulfonate analogue **8b** (5 mol-%) was used instead of **8a** (*Entry 6*); this resulted in a faster conversion and a satisfactory *'endo'*-selectivity, while the e.e. de-

creased to some extent. It should also be mentioned that application of 5 mol-% of catalyst **8b** in the reaction of the 3-crotonoyloxazolidin-2-one with nitrone **2a** gave the *'endo'*-product selectively with an e.e. of 81%.



**7**



**8a** X = 4-$MeC_6H_4SO_3$
**b** X = $C_6F_5SO_3$

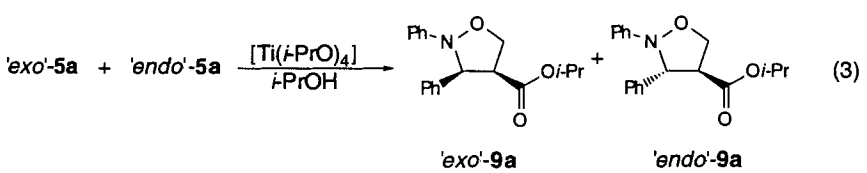
Table 1. *1,3-Dipolar Cycloadditions of Alkene* **4** *with Nitrone* **2a** *in the Absence and Presence of the Catalysts* **7** *and* **8a,b** *at Room Temperature*

| *Entry* [a]) | Catalyst [mol-%] | Reaction time [h] | Conversion [%] [b]) | Ratio **5a**/**6a** | *'endo'*/*'exo'* | | e.e. of *'endo'*-(*'exo'*)-**5a** [c]) |
|---|---|---|---|---|---|---|---|
| | | | | | **5a** [b]) | **6a** [b]) | |
| *1* | = | 68 | 91 | 39:61 | 17:83 | 56:44 | – |
| *2* | $[TiCl_2(i\text{-}PrO)_2]$ (10) | 20 | 95 | >95:<5 | 46:54 | – | – |
| *3* | **7** (10) | 20 | >95 | >95:<5 | 43:57 | – | 39% (29%) |
| *4* | **8a** (5) | 33 | >95 | >95:<5 | 92:8 | – | 66% (22%) |
| *5* | **8a** (10) | 20 | >95 | >95:<5 | 98:2 | – | 70% (43%) |
| *6* | **8b** (5) | 20 | >95 | >95:<5 | 92:8 | | 56% (8%) |

[a]) The reactions were performed on a 0.25-mmol scale in dry toluene. [b]) Conversion of *'exo'*/*'endo'*-ratios were determined by $^1$H-NMR spectroscopy. [c]) The e.e. of **5a** was determined by HPLC (*Daicel Chiralcel OD*, hexane i-PrOH) after conversion to the ester **9a** (see *Scheme 3*).

The e.e.s of *'exo'*- and *'endo'*-**5a** given in *Table 1* could not be determined directly from these products, since they partly decomposed during attempted separations of the enantiomers by chiral HPLC, and application of $^1$H-NMR spectroscopy in the presence of a chiral shift reagent also failed. However, *'exo'*- and *'endo'*-**5a** were converted into corresponding isopropyl esters *'exo'*- and *'endo'*-**9a** [6b,c] which allowed the separation of all four stereoisomers by HPLC using a *Daicel Chiralcel* column (*Scheme 3*).

*Scheme 3*

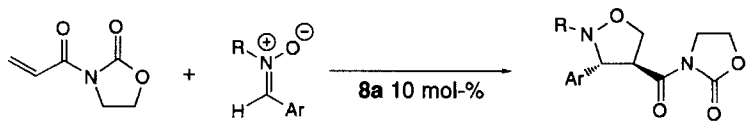



*'exo'*-**9a** *'endo'*-**9a**

The next step in the development of this new approach to a regioselective asymmetric 1,3-dipolar cycloaddition of acryloyl derivatives with nitrones was to apply catalyst **8a** in the reaction of **4** with different nitrones **2a–e** (*Scheme 4*). All the reactions given in *Table 2* proceeded smoothly at room temperature, and the products were obtained in good yields. Without exception, complete regioselectivity was observed, the 4-substituted isoxazolidines **5a–e** being the only products. The reactions were also highly *'endo'*-selec-

tive, giving in all cases the *'endo'*-isomer with 90–100% d.e. For the reactions of **4** with nitrones **2a,e**, satisfactory enantioselectivities (70% e.e.) were obtained (*Entries 1* and *5*), whereas for the reactions of nitrones **2b–d**, the enantioselectivities were lower (48–56% e.e.). As described for **5a** (see above), the products **5b–e** were converted into the corresponding isopropyl esters **9b–e** for the determination of the e.e. by HPLC.

*Scheme 4*




**4**

**2a** R = Ar = Ph
**b** R = $PhCH_2$, Ar = Ph
**c** R = Ph, Ar = 4-$MeC_6H_4$
**d** R = Ph, Ar = 4-$MeOC_6H_4$
**e** R = Ph, Ar = 4-$ClC_6H_4$

*'endo'*-**5a** R = Ar = Ph
**b** R = $PhCH_2$, Ar = Ph
**c** R = Ph, Ar = 4-$MeC_6H_4$
**d** R = Ph, Ar = 4-$MeOC_6H_4$
**e** R = Ph, Ar = 4-$ClC_6H_4$

Table 2. *Asymmetric 1,3-Dipolar Cycloadditions of Alkene* **4** *with* **2a–e** *Catalyzed by 10 mol-% of [Ti(OTs)$_2$(TADDOLato)]* **8a**

| *Entry*[a]) | Nitrone | Reaction time [h] | Yield [%][b]) | *'endo'/'exo'*[c]) | e.e. of *'endo'('exo')*-**5**[d]) |
|---|---|---|---|---|---|
| *1* | **2a** | 22 | 77 | 98:2 | 70% (43%) |
| *2* | **2b** | 28 | 80 | 100:0 | 57% |
| *3* | **2c** | 20 | 73 | 96:4 | 48% (44%) |
| *4* | **2d** | 20 | 65 | 95:5 | 52% (49%) |
| *5* | **2e** | 24 | 82 | 98:2 | 70% |

[a]) The reactions were performed on a 0.25-mmol scale in dry toluene. [b]) Isolated yields. [c]) The *'endo'/'exo'*-ratios were determined by $^1$H-NMR spectroscopy. [d]) The e.e. of **5a–e** were determined by HPLC (*Daicel Chiralcel OD* or *AD*, hexane i-PrOH) after conversion to the esters **9a–e** (*cf. Scheme 4*).

The diastero- and enantioselectivities of the above described [$TiX_2$(TADDOLato)]-catalyzed 1,3-dipolar cycloadditions involving 3-acryloyloxazolidine-2-one (**4**) are comparable to those obtained in similar reactions involving other 3-(alk-2-enoyl)oxazolidin-2-ones as dipolarophile [6a–c]. The involved reaction mechanisms are probably comparable. The mechanism of the latter has been studied extensively, both for the 1,3-dipolar cycloaddition and the *Diels-Alder* reaction [6b–e] [8] [14–16]. We thus propose that the alkenoyl moiety of **4** possesses a s-*cis* conformation in the transition state when coordinated to the [$TiX_2$(TADDOLato)] catalyst. However, in spite of this assumption, there are still several possible arrangements of the (alkenoyl)oxazolidinone, the TADDOLato, and the two X ligands (X = Cl or OTs) around the Ti-center. We have argued for an intermediate in which the four O-atoms of the TADDOLato and the (alkenoyl)oxazolidinone ligands are arranged in the same plane and the two X ligands are arranged orthogonal to this plane, *trans* to each other [6b,e] [14]. A complex with this arrangement has been characterized by X-ray crystallography [14a]. *DiMare* and coworkers [15], and *Seebach* and coworkers [16] argued for another key intermediate in

which the X ligands (X = Cl) are arranged *cis* to each other. Recently, *Seebach* and coworkers made the very interesting observation that for the $[TiX_2(TADDOLato)]$ catalyzed *Diels-Alder* reaction, a positive nonlinear effect is found, whereas a linear relationship between the optical purity of the ligand and the e.e. of the product exists for the analogous 1,3-dipolar cycloaddition [8], indicating that the two reactions might proceed *via* different intermediates. Based on these observations, *Seebach* and coworkers suggested the $[TiCl_2(TADDOLato)]$-catalyzed *Diels-Alder* reaction to involve a cationic intermediate in which one of the Cl ligands is dissociated.

In summary, the results presented in this work demonstrate that by the use of the catalyst $[Ti(OTs)_2(TADDOLato)]$ for the 1,3-dipolar cycloaddition between acryloyloxazolidinone **4** and the five nitrones **2a–e**, complete regioselectivity, high *'endo'*-selectivities, and enantioselectivities corresponding to 48–70% e.e. can be achieved in a reaction which in the absence of a catalyst, proceeds to give a complex mixture of all 8 isomers.

## Experimental Part

*General.* Solvents were dried using standard procedures. All glass equipment was dried with a flame under vacuum before use. Prep. TLC: 200 × 200 × 1.8 mm silica gel *60 $HP_{254+366}$* (*Merck*) on glass plates. HPLC: 4.6 mm × 25 cm *Daicel Chiracel OD* or *AD* column; $t_R$ in min. Optical rotations $[\alpha]_D$: at 24°, *Perkin-Elmer-241* polarimeter. $^1H$- and $^{13}C$-NMR Spectra: at 300 and 75 MHz, resp.; chemical shift $\delta$ in ppm downfield from $SiMe_4$, and $J$ in Hz. MS: at 70 eV with a direct inlet *m/z* (rel. %).

*Materials.* The starting materials 3-acryloyloxazolidin-2-one (**4**) [17], *N*-benzylidenebenzenamine *N*-oxide (**2a**) [18], *N*-benzylidenebenzenemethanamine *N*-oxide (**2b**) [19], *N*-(4-methylbenzylidene)benzenamine *N*-oxide (**2c**) [19], *N*-(4-methoxybenzylidene)benzenamine *N*-oxide (**2d**) [19], *N*-(4-chlorobenzylidene)benzenamine *N*-oxide (**2e**) [19], a 0.1M toluene soln. of $[TiCl_2(i\text{-}PrO)_2]$ [6a], 0.2 M/0.4 M mixture of $[Ti(i\text{-}PrO)_4]$/i-PrOH in toluene [6b], the chiral ligand (*R,R*)-2,2-dimethyl-α,α,α′,α′-tetraphenyl-1,3-dioxolane-4,5-dimethanol (TADDOL) [10], and silver pentafluorobenzene sulfonate [20] were synthesized according to the literature. Silver *p*-toluenesulfonate was from *Fluka* and *Millex* filter units (0.45 μm pore size) were from *Millipore*.

*[(*R,R*)-2,2-Dimethyl-α,α,α′,α′-tetraphenyl-1,3-dioxolane-4,5-dimethanolato-κO,κO′]bis(4-methylbenzenesulfonato-κO)titanium(4+)* (**8a**) *and [(*R,R*)-2,2-Dimethyl-α,α,α′,α′-tetraphenyl-1,3-dioxolane-4,5-dimethanolato-κO,κO′]bis(pentafluorobenzenesulfonato-κO)titanium(4+)* (**8b**). To the silver arenesulfonate (0.3 mmol) under $N_2$, a soln. of $[TiCl_2(i\text{-}PrO)_2]$ (1 ml, 0.1 mmol) in toluene was added. The suspension was stirred for 20–24 h at r.t., then transferred to a syringe, and filtered through a *Millex* filter unit into a 5-ml flask containing the TADDOL ligand (51.3 mg 0.11 mmol) under $N_2$. The 0.1M soln. of catalyst **8a** or **8b** was stirred for 30 min prior to use.

*Asymmetric 1,3-Dipolar Cycloaddition Reactions: General Procedure for the Reaction Using 10 mol-% of the [Ti(OTs)$_2$(TADDOLato)] Catalyst* **8a**. A soln. of 3-acryloxazolidin-2-one **4** (35.3 mg, 0.25 mmol) in dry toluene (2 ml) in a *Schlenk* flask was stirred for 5 min at r.t. under $N_2$. Then the catalyst soln. (0.25 ml, 0.025 mmol) was added. After a few minutes, 1.15 equiv. of nitrone **2** (0.29 mmol) was added. Toluene (1 ml) was used to wash the inner glass side from the nitrone deposited. After stirring for 20–28 h, the mixture was filtered by suction through a 30-mm layer of silica gel. The silica gel was washed with 10 ml of 5% $MeOH/CH_2Cl_2$ and the solvent evaporated. The crude product was purified by prep. TLC (silica gel, $Et_2O$/petroleum ether 8:2, or AcOEt/petroleum ether 1:1 or $MeOH/CH_2Cl_2$ 1:99). For *'endo'*-**5c,e**, the prep. TLC purification was performed twice. The band was extracted with 5% $MeOH/CH_2Cl_2$: pure *'endo'*-**5a–e** containing only minor amounts of the *'exo'*-isomers.

*Esters* **9a–e**: *General Procedure.* The purified oxazolidinone adduct was stirred for 6–16 h in a refluxing mixture of 10 equiv. of $[Ti(i\text{-}PrO)_4]$ and 20 equiv. of i-PrOH in toluene. The solvent was evaporated and the product filtered through a 30-mm layer of silica gel. The silica gel was washed with 20 ml of $CH_2Cl_2$, the org. phase concentrated, washed with $H_2O$ (2 ×), dried ($Na_2SO_4$), and evaporated: ester **9a–e**.

*(+)-(3′S,4′R)/(3′R,4′S)-3-[(2′,3′Diphenylisoxazolidin-4′-yl)carbonyl]oxazolidin-2-one* (*endo*-**5a**). Yield 77%: $[\alpha]_D$ = + 14.0 ($c$ = 1.0, $CHCl_3$). $R_f$ ($Et_2O$/petroleum ether 8:2) 0.20. $^1H$-NMR ($CDCl_3$): 4.02 (*t*, $J$ = 8.3, 2 H); 4.14 (*dd*, $J$ = 5.5, 8.2, 1 H); 4.42 (*m*, 2 H); 4.56 (*dt*, $J$ = 5.5, 8.2, 1 H); 4.75 (*t*, $J$ = 8.2, 1 H); 5.27 (*d*, $J$ = 5.5,

1 H); 7.00 (*m*, 3 H); 7.23 (*m*, 2 H); 7.35 (*m*, 3 H); 7.53 (*d*, *J* = 7.1, 2 H). $^{13}$C-NMR ($CDCl_3$): 43.3, 59.6, 62.9, 70.2, 71.2, 116.3, 122.9, 127.6, 128.4, 129.2, 129.5, 141.4, 150.7, 153.7, 170.8. MS: 338 ($M^+$).

*(−)-Isopropyl (3S,4R)/(3R,4S)-2,3-Diphenylisoxazolidine-4-carboxylate* (*endo*-**9a**). $[\alpha]_D = -50.6$ (*c* = 1.0, $CHCl_3$). HPLC (*Daicel Chiralcel OD*, hexane/i-PrOH 99:1, 0.5 ml/min): $t_R$ (major) 19.4 $t_R$ (minor) 22.3; e.e. 70%. $^1$H-NMR ($CDCl_3$): 1.18 (*m*, *J* = 6.6, 6 H); 3.54 (*ddd*, *J* = 5.5, 6.2, 6.6, 1 H); 4.37 (*m* 2 H); 4.99 (*sept.*, *J* = 6.6, 1 H); 5.02 (*d*, *J* = 6.1, 1 H); 6.98 (*m*, 3 H); 7.23 (*m*, 2 H); 7.39 (*m*, 3 H); 7.57 (*d*, *J* = 6.6, 2 H). $^{13}$C-NMR ($CDCl_3$): 21.7, 58.8, 68.9, 69.1, 72.3, 115.1, 122.1, 126.6, 127.7, 128.7, 128.8, 128.9, 141.4, 150.6, 170.4. MS: 311 ($M^+$).

*(+)-(3'S,4'R)/(3'R,4'S)-3-[(2'-Benzyl-3'-phenylisoxazolidin-4'-yl)carbonyl]oxazolidin-2-one* (*endo*-**5b**). Yield 80%. $[\alpha]_D = +21.2$ (*c* = 1.0, $CHCl_3$). $R_f$ (AcOEt/petroleum ether 1:1) 0.36. $^1$H-NMR ($CDCl_3$): 3.81 (*d*, *J* = 14.3, 1 H); 4.00 (*m*, 4 H); 4.36 (*m*, 3 H); 4.55 (*m*, 2 H); 7.32 (*m*, 8 H); 7.53 (*d*, *J* = 6.6, 2 H). $^{13}$C-NMR ($CDCl_3$): 42.6, 56.9, 59.5, 62.2, 69.6, 71.6, 127.3, 128.2, 128.2, 128.7, 128.8, 137.1, 137.9, 153.1, 171.1. MS: 352 ($M^+$).

*(−)-Isopropyl (3S,4R)/(3R,4S)-2-Benzyl-3-phenylisoxazolidine-4-carboxylate* (*endo*-**9b**). $[\alpha]_D = -14.5$ (*c* = 1.0, $CHCl_3$). HPLC (*Daicel Chiralcel OD*, hexane/i-PrOH 99:1, 0.5 ml/min): $t_R$ (major) 17.6, $t_R$ (minor) 15.0; e.e. 57%. $^1$H-NMR ($CDCl_3$): 1.21 (*d*, *J* = 6.0, 3 H); 1.22 (*d*, *J* = 6.0, 3 H); 3.44 (*m*, 1 H); 3.82 (*d*, *J* = 13.8, 1 H); 4.01 (*d*, *J* = 13.8, 1 H); 4.11 (*d*, *J* = 7.7, 1 H); 4.29 (*m*, 2 H); 5.04 (*sept.*, *J* = 6.0, 1 H); 7.33 (*m*, 8 H); 7.52 (*d*, *J* = 7.1, 2 H). $^{13}$C-NMR ($CDCl_3$): 21.7, 21.8, 57.0, 59.6, 68.8, 73.4, 127.4, 127.9, 128.1, 128.3, 128.8, 128.8, 137.1, 138.4, 171.6. MS: 325 ($M^+$).

*(+)-(3'S,4'R)/(3'R,4'S)-3-{[3'-(4''-Methylphenyl)-2'-phenylisoxazolidin-4'-yl]carbonyl}oxazolidin-2-one* (*endo*-**5c**). Yield 73%. $[\alpha]_D = +3.7$ (*c* = 1.0, $CHCl_3$). $R_f$ ($MeOH/CH_2Cl_2$ 1:99) 0.25; $R_f$ ($Et_2O$/petroleum ether 8:2) 0.32. $^1$H-NMR ($CDCl_3$): 2.35 (*s*, 3 H); 3.99 (*t*, *J* = 7.5, 2 H); 4.12 (*dd*, *J* = 5.5, 8.8, 1 H); 4.39 (*m*, 2 H); 4.51 (*dt*, *J* = 5.5, 8.3, 1 H); 4.68 (*t*, *J* = 8.3, 1 H); 5.19 (*d*, *J* = 6.0, 1 H); 6.97 (*m*, 3 H); 7.21 (*m*, 4 H); 7.40 (*d*, *J* = 8.2). $^{13}$C-NMR ($CDCl_3$): 21.1, 42.7, 58.9, 62.3, 69.6, 70.5, 115.8, 122.3, 126.9, 128.6, 129.5, 137.6, 137.7, 150.2, 153.1, 170.2. MS: 352 ($M^+$).

*(−)-Isopropyl (3S,4R)/(3R,4S)-3-(4'-Methylphenyl)-2-phenylisoxazolidine-4-carboxylate* (*endo*-**9c**). $[\alpha]_D = -23.4$ (*c* = 1.0, $CHCl_3$). HPLC (*Daicel Chiralcel OD*, hexane/i-PrOH 99.5:0.5, 0.5 ml/min): $t_R$ (major) 30.7, $t_R$ (minor) 34.8; e.e. 48%. $^1$H-NMR ($CDCl_3$): 1.17 (*d*, *J* = 6.6, 3 H); 1.18 (*d*, *J* = 6.0, 3 H); 2.37 (*s*, 3 H); 3.51 (*m*, 1 H); 4.34 (*m*, 2 H); 4.96 (*d*, *J* = 6.1, 1 H); 4.98 (*sept.*, *J* = 6.6, 1 H); 6.98 (*m*, 3 H); 7.23 (*m*, 4 H); 7.44 (*d*, *J* = 8.3, 2 H). $^{13}$C-NMR ($CDCl_3$): 21.1, 21.6, 58.8, 68.9, 69.0, 72.2, 115.2, 122.1, 126.5, 128.8, 129.5, 137.4, 138.3, 150.7, 170.5, MS: 325 ($M^+$).

*(+)-(3'S,4'R)/(3'R,4'S)-3-{[3'-(4''-Methoxyphenyl)-2'-phenylisoxazolidin-4'-yl]carbonyl}oxazolidin-2-one* (*endo*-**5d**). Yield 65%. $[\alpha]_D = +3.2$ (*c* = 1.0, $CHCl_3$). $R_f$ ($Et_2O$/petroleum ether 8:2) 0.20. $^1$H-NMR ($CDCl_3$): 3.80 (*s*, 3 H); 3.98 (*t*, *J* = 8.0, 2 H); 4.11 (*dd*, *J* = 5.5, 8.3, 1 H); 4.39 (*m*, 2 H); 4.50 (*dt*, *J* = 5.5, 8.3, 1 H); 4.68 (*t*, *J* = 8.3, 1 H); 5.15 (*d*, *J* = 5.5, 1 H); 6.90 (*d*, *J* = 8.8, 2 H); 6.97 (*m*, 3 H); 7.22 (*m*, 2 H); 7.43 (*d*, *J* = 8.8, 2 H). $^{13}$C-NMR ($CDCl_3$): 42.8, 55.3, 58.8, 62.3, 69.6, 70.5, 114.3, 116.0, 122.5, 128.4, 128.6, 132.6, 150.2, 153.2, 159.3, 170.4. MS: 368 ($M^+$).

*(−)-Isopropyl (3S,4R)/(3R,4S)-3-(4'-Methoxyphenyl)-2-phenylisoxazolidine-4-carboxylate* (*endo*-**9d**). $[\alpha]_D = -33.0$ (*c* = 1.0, $CHCl_3$). HPLC (*Daicel Chiralcel AD*, hexane/i-PrOH = 99:1, 1.0 ml/min): $t_R$ (minor) 19.4, $t_r$ (major) 24.8; e.e. 52%. $^1$H-NMR ($CDCl_3$): 1.15 (*d*, *J* = 6.6, 3 H); 1.16 (*d*, *J* = 6.6, 3 H); 3.47 (*m*, 1 H); 3.81 (*s*, 3 H); 4.33 (*m*, 2 H); 4.90 (*d*, *J* = 5.5, 1 H); 4.97 (*sept.*, *J* = 6.0, 1 H); 6.94 (*m*, 5 H); 7.21 (*m*, 2 H); 7.44 (*d*, *J* = 8.8, 2 H). $^{13}$C-NMR ($CDCl_3$): 21.7, 55.3, 58.8, 68.9, 69.0, 72.0, 114.2, 115.3, 122.2, 127.9, 128.8, 133.2, 150.6, 159.2, 170.5. MS: 341 ($M^+$).

*(+)-(3'S,4R)/(3'R,4'S)-3-{[3'-(4''-Chlorophenyl)-2'-phenylisoxazolidin-4'yl]carbonyl}oxazolidin-2-one* (*endo*-**5e**). Yield 82%. $[\alpha]_D = +5.6$ (*c* = 1.0, $CHCl_3$). $R_f$ ($MeOH/CH_2Cl_2$ 1:99) 0.35; $R_f$ ($Et_2O$/petroleum ether 8:2) 0.25. $^1$H-NMR ($CDCl_3$): 3.96 (*t*, *J* = 8.2, 2 H); 4.12 (*dd*, *J* = 5.5, 8.2, 1 H); 4.37 (*m*, 2 H); 4.47 (*dt*, *J* = 5.5, 8.2, 1 H); 4.66 (*t*, *J* = 8.2, 1 H); 5.23 (*d*, *J* = 6.0, 1 H); 6.96 (*m*, 3 H); 7.22 (*d*, *J* = 8.3, 2 H); 7.33 (*d*, *J* = 6.6, 2 H); 7.45 (*d*, *J* = 8.8, 2 H). $^{13}$C-NMR ($CDCl_3$): 42.7, 58.9, 62.3, 69.5, 69.9, 115.7, 122.6, 128.4, 128.7, 129.0, 133.6, 139.3, 149.9, 153.1, 169.9. MS: 372 ($M^+$).

*(−)-Isopropyl (3S,4R)/(3R,4S)-3-(4'-Chlorophenyl)-2-phenylisoxazolidine-4-carboxylate* (*endo*-**9e**). $[\alpha]_D = -57.5$ (*c* = 1.0, $CHCl_3$). HPLC (*Daicel Chiralcel AD*, hexane/i-PrOH = 99:1, 0.5 ml/min): $t_R$ (minor) 21.0, $t_R$ (major) 25.5; e.e. 70%. $^1$H-NMR ($CDCl_3$): 1.17 (*d*, *J* = 6.6, 6 H); 3.47 (*m*, 1 H); 4.33 (*m*, 2 H); 4.98 (*d*, *J* = 5.5, 1 H); 4.99 (*sept.*, *J* = 6.6, 1 H); 6.96 (*m*, 3 H); 7.23 (*t*, *J* = 7.1, 2 H); 7.35 (*d*, *J* = 8.7, 2 H); 7.49 (*d*, *J* = 8.3, 2 H). $^{13}$C-NMR ($CDCl_3$): 21.6, 58.7, 68.8, 69.2, 71.6, 115.1, 122.3, 128.0, 128.9, 129.0, 133.5, 139.9, 150.3, 170.1. MS: 345 ($M^+$).

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