Improvement of TADDOLate−$TiCl_2$-Catalyzed 1,3-Dipolar Nitrone Cycloaddition Reactions by Substitution of the Oxazolidinone Auxiliary of the Alkene with Succinimide

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A significant improvement of metal-catalyzed asymmetric 1,3-dipolar cycloaddition reactions of acyclic nitrones with α,β-unsaturated carbonyl compounds is described using succinimide as a new auxiliary for the α,β-unsaturated carbonyl moiety. In the absence of a catalyst, *N*-crotonoylsuccinimide reacts with *C,N*-diphenylnitrone to give the *endo*-isoxazolidine, whereas in the presence of 10 mol % $TiCl_2(i\text{-}PrO)_2$ the *exo*-product is obtained. Four different $TiCl_2$−TADDOLate complexes have been tested as catalysts for the 1,3-dipolar cycloaddition reactions, and the most successful catalyst was applied (5 mol %) in a series of reactions between two different alkenoylsuccinimides and three different nitrones. The crude products containing an *N*-acylsuccinimide moiety were converted directly into the corresponding carboxamides upon treatment with hydrazine. The 1,3-dipolar cycloaddition reactions proceed with a high degree of *exo*-selectivity, often >90% de, which is an improvement compared with previous experiments performed using the oxazolidinone auxiliary for the alkenoyl moiety. Furthermore, the enantioselectivities are also improved compared with previous work, and ee up to 73% is obtained, which is the highest ee found for these metal-catalyzed *exo*-selective 1,3-dipolar cycloaddition reactions. The ee can be improved to >90% by recrystallization. The absolute structure of the 1,3-dipolar cycloaddition adduct is determined on the basis of the X-ray crystal structure of a compound with a known configuration. On the basis of this knowledge of the absolute structure of the product the mechanism of the reaction is briefly discussed.

Introduction

One of the most important reactions for the construction of 5-membered hetereocyclic rings is the 1,3-dipolar cycloaddition reaction between an alkene and a nitrone.[1] In this reaction, up to three new chiral centers can be formed in the isoxazolidine adduct, and several papers describe the use of chiral nitrones[2] or chiral alkenes[3] for the purpose of controlling the stereoselectivity of this 1,3-dipolar cycloaddition reaction. The application of achiral metal complexes as catalysts for the reaction has also been studied.[4] Recently, the use of chiral metal complexes as catalysts for the 1,3-dipolar cycloaddition reaction has been studied by others.[5]

In previous papers we have described the development of a metal-catalyzed asymmetric 1,3-dipolar cycloaddition reaction between nitrones and alkenes.[6,7] By the application of various metal catalysts, especially titanium(IV) and magnesium(II) complexes, *N*-alk-2′-enoyl-1,3-oxazolidin-2-ones were activated for a 1,3-dipolar cycloaddition reaction by coordination of the two carbonyl oxygen atoms of the alkenoyloxazolidinone to the metal catalyst. By this coordination the LUMO-energy of the alkene is significantly lowered compared with the free alkene, and this change of the LUMO-energy increases the rate of the reaction with the nitrone.[7a,c] The reaction between *N*-crotonoyloxazolidinone and *C,N*-diphenylnitrone does not proceed at room temperature (rt) in the

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absence of a catalyst, and only a slow conversion is observed at 50 °C. However, by the use of titanium(IV) or magnesium(II) catalysts (5−50 mol %) the reaction proceeds at rt.

In the previously reported reactions the diastereoselectivity could be controlled, especially in favor of the *endo*-diastereomer.[7] By using semiempirical calculations it was found that the *exo*-transition state of the reaction between **1** and **2** is preferred if no steric hindrance is present (eq 1).[7a] However, in the metal-catalyzed reactions, the presence of steric interference between the *C*-aryl group of the nitrone and a bulky ligand on the metal, located orthogonal to the plane consisting of the metal and the two carbonyl oxygen atoms of **1**, favors the formation of the *endo*-diastereomer.[7a,b] Use of 10 mol % of $TiCl_2$−TADDOLate, **4a**, as a catalyst for the reaction gave an excess of the *exo*-diastereomer, and in one case an *exo:endo* ratio of 90:10 could be achieved with this catalyst, whereas for other substrates the *exo*-selectivity was lower.[6] The highest enantioselectivity obtained for the *exo*-isomer so far is 60% ee. Both titanium catalyst **5** and magnesium catalyst **6** induce a high degree of *endo*-selectivity for all substrate combinations tested, and application of the $Ti(OTos)_2$−TADDOLate catalyst led to induction of enantioselectivities >90% in several cases.[7b] When the MgI_2−bisoxazoline catalyst **6** was used the maximum ee obtained was 82%.[7a] The mechanism of the titanium-catalyzed reactions and the structure of the intermediate between **1** and **4a** have been discussed by us[7,8] and others.[5c,9]

In order to obtain a strong bidentate coordination of the alkene moiety to the metal catalyst we have applied 1,3-oxazolidin-2-one as an auxiliary for the alkenoyl moiety. This auxiliary and 4,5-substituted chiral analogs **7** that were introduced by Evans *et al.* are now very commonly used in Lewis acid-catalyzed reactions.[10] Auxiliaries in which the ring oxygen is substituted with nitrogen **8**,[10,11] or the oxygen atoms with sulfur atoms **9**,[12] have also been described. But to the best of our knowledge the application of succinimide **10** as an auxiliary for alkenoyl compounds has not been reported.

In the present work we will describe the improvement of both the *exo*-selectivity and the enantioselectivity of the $TiCl_2$−TADDOLate-catalyzed 1,3-dipolar cycloaddition reaction by the introduction of succinimide as auxiliary on the alkenoyl moiety instead of the oxazolidinone.

Results and Discussion

1. Synthetic Development. The synthesis of *N*-alk-2′-enoylsuccinimide has not been described previously; however, there are a few reports on the synthesis of *N*-acylsuccinimides or *N*-acylphthalimides.[13] These compounds are most commonly synthesized from succinimide or phthalimide, which is deprotonated with a base and reacted with an activated carbonyl compound such as an acid chloride. In the present case we found that the best method was by deprotonation of succinimide with *n*-BuLi and subsequent treatment with the alk-2-enoyl chloride (eq 2).[10] The products are relatively unstable, and a partial decomposition takes place during work up. The *N*-crotonoyl- and *N*-hex-2′-enoylsuccinimides, **11a** and **11b**, are obtained in 50% and 61% isolated yield, respectively. We have also synthesized the analogous phthalimide derivatives by a similar procedure; however, these products were too unstable to be used for the 1,3-dipolar cycloaddition reaction.

The reaction between the *C,N*-diphenylnitrone (**2a**) and *N*-crotonoylsuccinimide (**11a**) has been compared with the reaction of *N*-crotonoyloxazolidinone (**1a**) (eq 3).[6] The reaction between **1a** and **2a** needs elevated temperatures to proceed, whereas **11a** reacts with **2a** at rt to give 94% conversion after 71 h (Table 1, entries 1−4). The succinimide derivative **11a** thus seems to be more reactive toward a 1,3-dipolar cycloaddition reaction with **2a** than the corresponding oxazolidinone derivative **1a**. To our great surprise the uncatalyzed reactions of **11a** and **1a** with **2a** proceeded with opposite diastereoselectivity.[14] In the reaction of **1a** with **2a** the expected *exo*-

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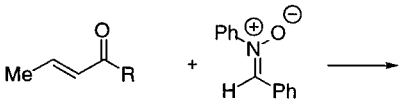
(14) In an attempt to account for the *endo*-selectivity in the 1,3-dipolar cycloaddition reaction of nitrone **2a** with *N*-crotonoylsuccinimide (**11a**) a series of *ab initio* calculations have been performed using a 3-21G* basis set. The geometry of both **11a**-*s-cis* (total energy = −583.970 au) and **11a**-*s-trans* have been optimized, and it has been found that the former is 5 kcal/mol more stable than the latter. The

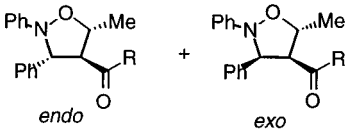
Table 1. Comparison of the 1,3-Dipolar Cycloaddition Reaction of Alkenes 11a and 1a with Nitrone 2a in the Absence and Presence of $TiCl_2(i\text{-PrO})_2$ as the Catalyst

entry	alkene[a]	solvent	catalyst (amount)	reaction time (h)	*T* (°C)	product	convn[b] (%)	endo:exo[b]
1	**1a**	$CHCl_3$	−	−20	50	**3a**	39	9:91
2	**1a**	Toluene	−	−20	50	**3a**	36	29:71
3	**11a**	CH_2Cl_2	−	−20	rt	**12a**	68	86:14
4	**11a**	Toluene	−	−71	rt	**12a**	94	95:5
5	**1a**	Toluene	$TiCl_2(i\text{-PrO})_2$ (10%)	20	rt	**3a**	61	14:86
6	**11a**	Toluene	$TiCl_2(i\text{-PrO})_2$ (5%)	20	0 to rt	**12a**	100	6:94

[a] The reactions were performed on a 0.1 mmol scale. [b] Conversions and *endo:exo* ratios were determined by ^{1}H NMR spectroscopy.



1a R = oxazolidinone
11a R = succinimide **2a**



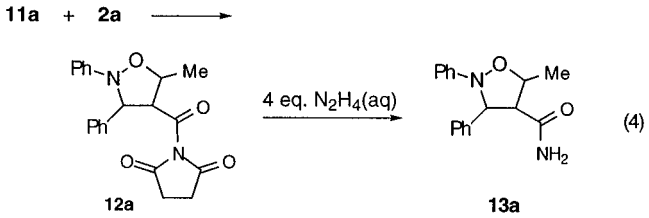
endo *exo*

3a R = oxazolidinone
12a R = succinimide

(3)

3a was primarily obtained, especially when the reaction is performed in $CHCl_3$ (Table 1, entries 1 and 2). Surprisingly, the reaction of **11a** with **2a** gave *endo*-**12a**, and when the reaction was performed in toluene a high preference for *endo*-**12a** was obtained (Table 1, entries 3,4). In the presence of 10 mol % of $TiCl_2(i\text{-OPr})_2$ as the catalyst the reaction of **1a** proceeds at rt to give primarily *exo*-**12a** with 61% conversion (Table 1, entry 5), whereas the reaction of **11a** takes place at 0 °C to rt in the presence of 5 mol % of the catalyst to give complete conversion after 20 h (Table 1, entry 6). The reaction of **11a** in the presence of $TiCl_2(i\text{-OPr})_2$ as the catalyst gives the *exo*-isomer with a high degree of selectivity.[15]

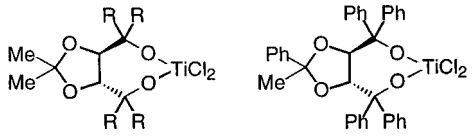
In the reactions presented in Table 1 the conversions and diastereoselectivities have been determined from the ^{1}H NMR spectra of the crude products. However, in attempts to isolate the product it was observed that **12a**, as well as derivatives of **12a**, decompose during various chromatography procedures. This problem was avoided by converting **12a** directly into the stable amide derivative **13a**, by addition of a 4-fold excess of aqueous hydrazine to the crude reaction product **12a** (eq 4).[16]



12a **13a**

(4)

The reaction of *N*-crotonoylsuccinimide (**11a**) with *C,N*-diphenylnitrone (**2a**) has been performed in the presence of 2 or 5 mol % of various $TiCl_2$−TADDOLates **4a**−**d**.[17] The products **12** were converted directly into the crude amide derivatives **13**, similar to the reaction outlined in eq 4. The results are presented in Table 2.



4a: R = Ph
4b: R = Et
4c: R = 3,5-$(Me)_2$-C_6H_3 **4d**

In the presence of 5 mol % of catalyst **4a** in CH_2Cl_2 as the solvent a quantitative conversion is obtained after 20 h (Table 2, entry 1). The *exo*-selectivity is high; however, the enantioselectivity of the reaction is lower than the analogous reaction of the oxazolidinone derivative.[6] The reaction was also performed in a mixture of toluene/petroleum ether, a solvent mixture that has been used successfully in similiar reactions,[6,18] and in the present reaction the enantioselectivity was improved (Table 2, entry 2). If the reaction is performed in toluene with 5 mol % of **4a** as the catalyst, an enantioselectivity of 73% is obtained, the highest observed for the *exo*-selective reaction so far (Table 2, entry 3). Application of catalysts **4b**,**c** leads to high *exo*-selectivities, but the enantioselectivities are poorer (Table 2, entries 4 and 5). Surprisingly, the reaction catalyzed by **4b** leads to an excess of the opposite enantiomer. The catalytic properties of **4d** are comparable to those of catalyst **4a** (Table 2, entry 6). It appears from the results listed in Table 2 that catalyst **4a** is most suitable for the reaction and that toluene should be used as the solvent. The *exo*-selectivity is much better than for the analogous reactions with the oxazolidinone derivative **1a**.[6]

The more general application of this new *exo*-selective catalytic approach to the 1,3-dipolar cycloaddition reaction is demonstrated by performing the reaction with other derivatives of the starting materials. We have chosen the *N*-alk-2′-enoylsuccinimides **11a** and **11b** and the three different nitrones **2a**−**c**. The most successful $TiCl_2$−TADDOLate catalyst **4a** was applied (5 mol %) in these reactions (eq 5). The intermediate products **12** are directly transformed to the amides **13**. The reactions are allowed to continue until ^{1}H NMR spectra of the reaction mixtures reveal that >95% conversion has taken place. The reactions are performed at a temperature starting at −20 to −13 °C, and the temperature is then allowed to raise slowly to rt. The results are presented in Table 3.

dihedral angle of the alkene plane relative to the succinimide plane of **11a**-*s-trans* is 24°. A comparison of the approach of **2a** to **11a**-*s-cis* leading to *endo*-**12a** and *exo*-**12a** reveals that for the latter a steric repulsion between the *C*-phenyl substituent of the nitrone and one of the carbonyls of the succinimide group may account for the former reaction path.

(15) We have also tried to use *N*-crotonoylsuccinimide (**11a**) as the substrate in Ti−TADDOLate catalyzed Diels−Alder reactions with cyclopentadiene as the reagent, but the Diels−Alder product was formed with low diastereoselectivity.

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Table 2. Effects of Catalysts 4a−d in the 1,3-Dipolar Cycloaddition Reaction between 11a and 2a

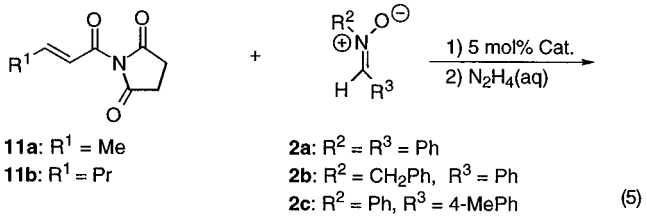
entry	catalyst (mol %)	solvent	reaction time (h)	*T* (°C)	convn[a] (%)	*endo*-**13a**:*exo*-**13a**	ee[b] *exo*-**13a**
1	**4a** (5)	CH_2Cl_2	20	−18 to rt	>95	<5:>95	52
2	**4a** (5)	tolene/petroleum ether	5 d	−15 to rt	>95	<5:>95	68
3	**4a** (5)	toluene	19	−18 to −10	>95	<5:>95	73
4	**4b** (5)	toluene	48	−13 to rt	>95	<5:>95	44[c]
5	**4c** (5)	toluene	7 d	−12 to rt	>95	<5:>95	42
6	**4d** (2)	toluene	40	−20 to −10	>95	<5:>95	71

[a] Determined by ^{1}H NMR spectroscopy of the crude product. [b] The ee was determined by HPLC (Daicel Chiralcel OD using hexane:*i*-PrOH) after conversion of the crude product into **13a** and purification. [c] Opposite enantiomer.

Table 3. Asymmetric 1,3-Dipolar Cycloaddition Reactions between 11a,b and 2a−c Catalyzed by 5 Mol % of $TiCl_2$−TADDOLate Catalyst 4a

entry	alkene	nitrone	ratio[a] **11**/**2**	product	reaction time	yield[b] (%)	*endo*-**13**:*exo*-**13**[c]	ee *exo*
1	**11a**	**2a**	1/1.1	**13a**	24 d	76	<5:>95	72[d]
2	**11a**	**2b**	1/1.1	**13b**	48	38	36:64	55[d]
3	**11a**	**2c**	1/1.1	**13c**	44	64	<5:>95	65[d]
4	**11b**	**2a**	1.4/1	**13d**	24	70	7:93	59[e]
5	**11b**	**2b**	1.4/1	**13e**	44	38	<5:>95	14[e]
6	**11b**	**2c**	1.4/1	**13f**	24	63	11:89	52[e]

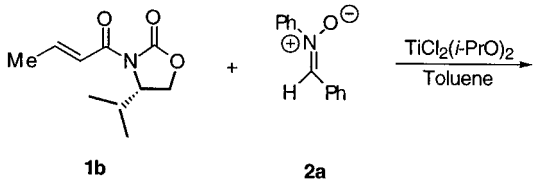
[a] The reactions were performed on a 1.0 mmol scale. For details see the Experimental Section. [b] Isolated yields. [c] The *endo*:*exo* ratio was determined by ^{1}H NMR spectroscopy. [d] The ee was determined by HPLC (Daicel Chiralcel OD using hexane:*i*-PrOH). [e] The ee was determined by ^{1}H NMR spectroscopy using $Eu(hfc)_3$ as a chiral shift reagent.



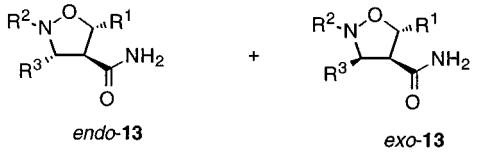
11a: R^1 = Me
11b: R^1 = Pr

2a: R^2 = R^3 = Ph
2b: R^2 = CH_2Ph, R^3 = Ph
2c: R^2 = Ph, R^3 = 4-MePh

(5)

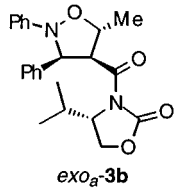


1b **2a**



endo-**13** *exo*-**13**

13a: R^1 = Me, R^2 = R^3 = Ph
13b: R^1 = Me, R^2 = CH_2Ph, R^3 = Ph
13c: R^1 = Me, R^2 = Ph, R^3 = 4-MePh
13d: R^1 = Pr, R^2 = R^3 = Ph
13e: R^1 = Pr, R^2 = CH_2Ph, R^3 = Ph
13f: R^1 = Pr, R^2 = Ph, R^3 = 4-MePh



exo$_a$-**3b** (6)

The *exo*-selectivity of the reactions involving these new succinimide auxiliaries is very high for almost all entries and indeed better than those obtained for the corresponding oxazolidinone derivatives (Table 3).[6] The isolated yields of the *exo*-diastereomers are satisfying for most entries; however, for the reactions involving the *N*-benzyl nitrone, yields tend to be lower (Table 3, entries 2 and 5). With one exception, the ee's obtained in these *exo*-selective reactions are also higher than those obtained in the similar reactions involving the oxazolidinone auxiliary.[6] The product *exo*-**13a** is crystalline, and by recrystallization from a mixture of EtOAc and petroleum ether the optical purity could be increased to 94% ee.

2. X-ray Structure Determination and Absolute Assignment of the Stereochemistry. The reaction between **2a** and the chiral valine-derived oxazolidinone **1b** was performed in order to obtain an *exo*-product with a known configuration of one of the stereocenters (eq 6).[7a] The reaction between **1b** and **2a** is catalyzed by $TiCl_2$-$(i\text{-PrO})_2$ and gives one of the four possible diastereoisomers, *exo*$_a$-**3b**, with a high degree of selectivity since only minor amounts (<5%) of other isomers could be detected by ^{1}H NMR spectroscopy.

For the aim of determining the absolute configuration of the product *exo*-**13a**, obtained from the asymmetric 1,3-dipolar cycloaddition reaction catalyzed by **4a**, it was necessary to determine the absolute configuration of *exo*$_a$-**3b**, which contains a stereocenter with a known configuration. After purification by PTLC, *exo*$_a$-**3b** was recrystallized from MeOH to give crystals suitable for an X-ray crystallographic investigation. The structure of *exo*$_a$-**3b** is presented in Figure 1.

The X-ray structure of *exo*$_a$-**3b** shows that it has two molecules in the unit cell of space group $P2_1$. Inspection of the X-ray structure in Figure 1 reveals that the substituents at C3 and C4 are *cis* to each other in the isoxazolidine ring, in agreement with the NMR experiments. The isoxazolidine ring adopts an envelope conformation, with a dihedral angle C3−C4−C5−O1 of 30.4(2)°. The structural data for the isoxazolidine ring turn out to be very similar to other isoxazolidines characterized[19] and will not be considered further.

From the structure of *exo*$_a$-**3b**, the configuration of the three stereocenters in the isoxazolidine ring can be assigned to be *3S,4S,5R*. For the determination of the absolute structure of *exo*-**13a**, this compound and *exo*$_a$-**3b** should be transformed into the same derivative. Several methods have been tested for the conversion of

(19) (a) Reference 7a and references therein. (b) The authors have deposited atomic coordinates for the structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

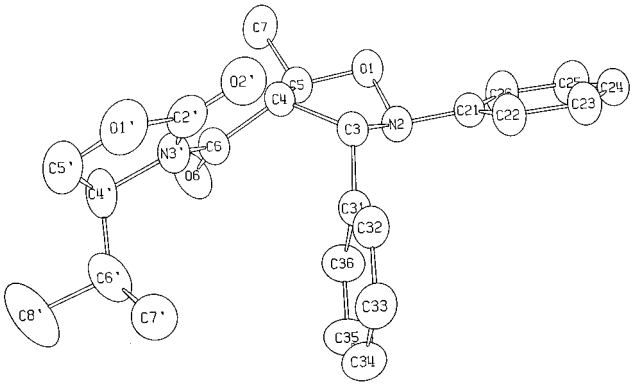
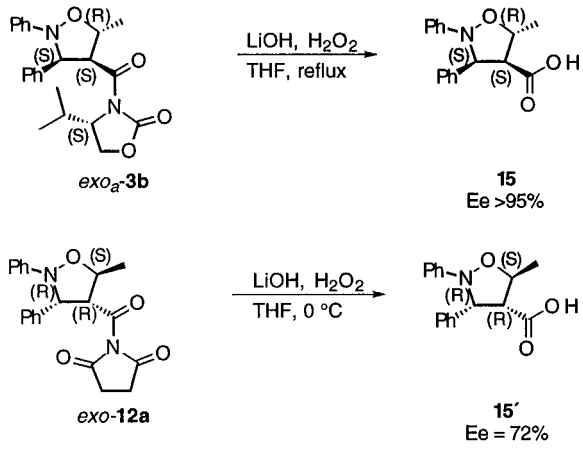


Figure 1. X-ray structure of *exo*$_a$-**3b** showing the absolute stereochemistry of the isoxazolidine ring.

Scheme 1



the oxazolidinone derivative into the corresponding isopropyl ester without success, such as treatment with Ti(*i*-PrO)$_4$ and *i*-PrOH in toluene, as described in previous work.[7a] However, upon treatment with LiOH and H_2O_2 in refluxing THF, *exo*$_a$-**3b** could be transformed into the carboxylic acid derivative **15** (Scheme 1).[20] This procedure failed for the final product of the asymmetric 1,3-dipolar cycloaddition reaction, *exo*-**13a**; however, using the same procedure as described for *exo*$_a$-**3b**, performed at 0 °C, the crude product of the reaction, *exo*-**12a**, was converted to the acid derivative **15′** (Scheme 1). By HPLC analysis using a Chiralcel OD column the two enantiomers in **15′** (72% ee) were separated. The minor enantiomer in **15′** and the only enantiomer in **15** have identical retention times, whereas the major enantiomer in **15′** and the only enantiomer in **15** have different retention times. On the basis of this information the absolute configuration of the major enantiomer in **15′**, and therefore also in *exo*-**12a** and *exo*-**13a**, can be assigned to be *3R,4R,5S*.

3. Mechanistic Acpects of the 1,3-Dipolar Cycloaddition Reaction. On the basis of the assignment of the absolute configuration of *exo*-**12a** (*3R,4R,5S*) the nitrone has to approach the α-*Re* face of the alkene **11a** in the 1,3-dipolar cycloaddition reaction with **2a** catalyzed by **4a**.

The intermediate in the Ti−TADDOLate-catalyzed reactions involving alkenes such as *N*-crotonoyloxazolidinone (**1a**) has received considerable interest,[5c,8,9] and we will apply these observations for the present investigations. Several intermediates consisting of the Ti−TADDOLate catalyst **4a** and the *N*-crotonoylsuccinimide (**11a**) can be considered, depending on the arrangement of the chloride ligands and **11a** at the titanium atom. If the chloride ligands are located *trans* relative to the plane of the titanium atom and the four oxygen atoms of the TADDOLate and the *N*-crotonoylsuccinimide ligands coordinated to the titanium atom, the intermediate is very similar to a complex that has been isolated and characterized.[8a] The approach of the nitrone **2a** in an *exo*-fashion to the α-*Re* face of the alkene in this intermediate is outlined in Figure 2.

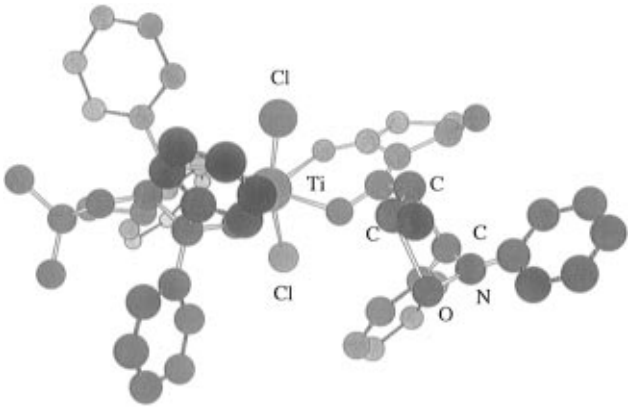


Figure 2. Approach of the nitrone **2a** in an *exo*-fashion to the *N*-crotonoylsuccinimide (**11a**) coordinated to the Ti−TADDOLate **4a**, in which the two chloride ligands are facing *trans* to the plane consisting of titanium and the four oxygen atoms.

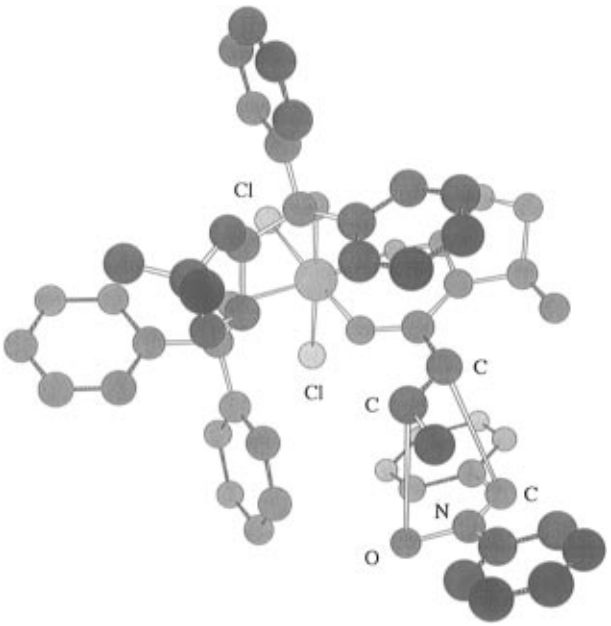


Figure 3. Approach of the nitrone **2a** in an *exo*-fashion to the *N*-crotonoylsuccinimide (**11a**) coordinated to the Ti−TADDOLate **4a**, in which the two chloride ligands are facing *cis* to each other.

The absolute configuration of the isoxazolidine ring obtained by the approach of the nitrone to the intermediate as outlined in Figure 2 is in accordance with the experimental results. Due to the chloride ligands at the titanium atom, the nitrone reacts with the alkene to give the *exo*-diastereomer, since no steric repulsion between the chloride ligand and the *C*-phenyl substituent at the nitrone is present.[7b] The mechanism of the 1,3-dipolar cycloaddition presented in Figure 2 is similar to the

(20) (a) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141. (b) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996**, *96*, 835.

mechanism of the 1,3-dipolar cycloaddition and Diels–Alder reactions catalyzed by the Ti–TADDOLate complexes using *N*-crotonoyloxazolidinone (**1a**), as the alkene suggested earlier by us.[6–8]

Another intermediate in the Ti–TADDOLate-catalyzed addition reactions that is based on a *cis* arrangement of the chloride ligands at the titanium intermediate has been suggested to be the most active intermediate.[9] A similar intermediate containing the *N*-crotonoylsuccinimide (**11a**) is outlined in Figure 3.

In Figure 3 the nitrone also approaches the α-*Re* face of the alkene leading to the same absolute configuration of the isoxazolidine ring as the approach presented in Figure 2.

On the basis on the present results we cannot distinguish if the reaction proceeds via the intermediates presented in Figures 2 or 3, but only conclude that both reaction paths can account for the observed diastereo- and enantioselectivity.

It should also be noted that very recently Seebach *et al.* have suggested that the reaction proceeds via a cationic intermediate.[5c]

Conclusion

The diastereo- and enantioselectivity of the 1,3-dipolar cycloaddition reaction of nitrones with alkenes using Ti–TADDOLates as the catalyst has been significantly improved by exchanging the oxazolidinone auxiliary with succinimide. The reaction gives *exo*-isoxazolidines with generally >90% diastereoselectivity and in some cases ee's >70%, the highest obtained for the *exo*-diastereomer in metal-catalyzed 1,3-dipolar cycloaddition reactions. The ee can be improved to >90% by recrystallization. The absolute configuration of the *exo*-diastereomer is determined to be *3R,4R,5S* on the basis of the X-ray structure of an *exo*-isoxazolidine with known absolute configuration. Two intermediates can account for the absolute configuration of the *exo*-isoxazolidine, one in which the two chloride ligands at the titanium atom are located trans to the plane of the titanium atom and the four oxygens of the TADDOLate- and the *N*-alk-2′-enoylsuccinimide ligands, while the other has the two chloride ligands located *cis*. With these intermediates the nitrone can approach the α-*Re* face of the alkene leading to the *exo*-isoxazolidine with the same absolute configuration as observed experimentally.

Experimental Section

General Methods. The ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively. Chemical shifts for ^{1}H NMR and ^{13}C NMR are reported in ppm downfield from tetramethylsilane (TMS). HPLC was performed using a 4.6 mm × 25 cm Daicel Chiracel OD column. Mass spectra were recorded at 70 eV with a direct inlet. Preparative thin-layer chromatography (PTLC) was performed on 200 × 200 × 1.8 mm silica gel (60 $HP_{254+366}$, Merck) on glass plates. Solvents were dried using standard procedures. The 4 Å molecular sieves were activated by heating to 250 °C overnight in high vacuum. All glass equipment were dried in an oven at 160 °C before use.

Materials. The starting materials 3-((*E*)-2′-butenoyl)-1,3-oxazolidin-2-one (**1a**),[10,20] benzylidenephenylamine *N*-oxide (**2a**),[21] benzylbenzylideneamine *N*-oxide (**2b**),[21] (4-methylbenzylidene)phenylamine *N*-oxide (**2c**),[21] and the four chiral (2*R*,3*R*)-2,3-O-(2-propylidene)-1,1,4,4-tetraphenyl-1,2,3,4-butanetetraols[17] were synthesized according to the literature. $TiCl_2(i\text{-}PrO)_2$ as a 0.1 M toluene solution was synthesized by stirring $Ti(i\text{-}OPr)_4$ (2 mmol) and $TiCl_4$ (2 mmol) in dry toluene (39.19 mL) at rt under N_2 for 1 h. The solution was stored under N_2 at rt. (+)-(*S*)-3-Crotonoyl-4-isopropyl-2-oxazolidinone (**1b**), $Eu(hfc)_3$, (*E*)-crotonyl chloride, (*E*)-2-hexenoyl chloride, and 4 Å molecular sieves were received from Aldrich.

1-*N*-((*E*)-2′-Butenoyl)succinimide (11a). Succinimide (2.99 g, 30.0 mmol) was dissolved in dry THF (105 mL). The mixture was stirred at −78 °C, and BuLi (1.6 M in hexane, 20.6 mL, 33.0 mmol) was added. After 1 h, (*E*)-crotonyl chloride (3.45 g, 33 mmol) was added, and the mixture was stirred overnight while the temperature increased to rt. The mixture was quenched with excess aqueous NH_4Cl and extracted two times with Et_2O. Then the organic layer was washed with brine. The organic phases were collected and dried, and the solvent was evaporated. The crude product was refluxed in $(i\text{-}Pr)_2O$ and filtered while the solution was still hot. The precipitate was crystallized by dissolving with the smallest quantity of $CHCl_3$ and then adding $(i\text{-}Pr)_2O$ while refluxing until the solution started to precipitate, and $CHCl_3$ was added until the solution was clear again. The solution stood overnight and the product precipitated. Yield: 50%. Mp: 103–5 °C. Yellow powder. ^{1}H NMR ($CDCl_3$): δ 1.99 (dd, J = 7.2, 1.7 Hz, 3H), 2.82 (s, 4H), 6.42 (dq, J = 15.4, 1.7 Hz, 1H), 7.26 (dq, J = 14.9, 7.1 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 19.3, 29.2, 125.2, 150.7, 164.6, 175.2. MS: m/z 167 (M^+).

1-*N*-((*E*)-2′-Hexenoyl)succinimide (11b) was synthesized according to the above procedure on a 17.0 mmol scale. Before addition of (*E*)-2-hexenoyl chloride (2.43 g, 18.31 mmol), the temperature was raised to −10 °C and then decreased to −78 °C again to assure that BuLi had reacted completely. After extraction and washing, the crude material was purified by flash chromatography on silica gel (Et_2O). Yield: 61%. Orange oil. R_f = 0.27 (Et_2O). ^{1}H NMR ($CDCl_3$): δ 0.94 (t, J = 7.5 Hz, 3H), 1.52 (sextet, J = 7.5 Hz, 2H), 2.26 (dq, J = 6.2, 1.6 Hz, 2H), 2.80 (s, 4H), 6.37 (dt, J = 15.4, 1.1 Hz, 1H), 7.21 (dt, J = 15.9, 7.1 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 14.2, 21.6, 29.2, 35.3, 123.8, 155.4, 164.7, 175.2. MS: m/z = 196 (M^+ + 1).

Asymmetric 1,3-Dipolar Cycloaddition Reactions. General Procedure for the Reaction Using 5 Mol % of the $TiCl_2$–TADDOLate Catalyst. To a 0.1 M dry toluene solution of $Ti(i\text{-}OPr)_2Cl_2$ (1 mL, 0.1 mmol) was added the appropriate TADDOL ligand (0.11 mmol). The solution was stirred for 30 min. In another flask 1-*N*-alk-2′-enoylsuccinimide **11** (1.0–1.4 mmol, see Table 3) was dissolved in dry toluene (8 mL), and 4 Å molecular sieves were added (200–300 mg). This mixture was stirred for 10–15 h at rt under N_2, and then the catalyst solution (0.5 mL, 0.05 mmol) was added. The temperature of the mixture was then decreased to −18 °C, and the nitrone **2** (1.0–1.1 mmol, see Table 3) was added. Toluene (2 mL) was used to wash the inner glass side from the nitrone deposited. After the mixture was stirred for 48 h, 4 equiv of N_2H_4(aq) (194 μL, 4 mmol) was added, and the mixture was stirred for 1–2 h. The mixture was acidified with 4 M HCl and stirred for another 30 min. The mixture was filtered and washed with toluene. Aqueous $NaHCO_3$ 1 M (60 mL) was added to the filtrate, and the solution was extracted three times with Et_2O (80–100 mL). The organic layer was dried and the solvent evaporated. The crude product was purified by PTLC (silica gel, EtOAc: petroleum ether, 50:50, and a few drops of Et_3N). The band from *exo*-**13** appeared in the region R_f = 0.26–0.51. The band was extracted with 5% MeOH in CH_2Cl_2.

(+)-(*3R,4R,5S*)-5-Methyl-2-*N*,3-diphenylisoxazolidine-4-carboxamide (*exo*-13a). Yield: 76%. $[\alpha]_D$ = +132° (c = 1.0, $CHCl_3$). R_f = 0.26 (EtOAc:petroleum ether 60:40). HPLC (Daicel Chiralcel OD, hexane:*i*-PrOH = 89:11, flow rate = 1.0 mL/min): t_R = 11.4 min (major), t_R = 16.7 min (minor). Ee = 72%. ^{1}H NMR ($CDCl_3$): δ 1.37 (d, J = 7.1 Hz, 3H), 3.35 (dd, J = 7.9, 5.2 Hz, 1H), 4.79 (dq, J = 6.0, 5.5 Hz, 1H), 4.93 (d, J = 8.8 Hz, 1H), 5.08 (s, br, 1H), 5.85 (s, br, 1H), 6.95 (m, 3H),

(21) (a) Kamm, O. *Organic Synthesis*; Wiley: New York, 1932; Collect. Vol. I, p 435. (b) Wheeler, O. H.; Gore, P. H. *J. Am. Chem. Soc.* **1956**, *78*, 3363.

(22) (a) Murahashi, S.-I.; Shiota, T.; Imada, Y. *Org. Synth.* **1992**, *70*, 265. (b) Beckett, A. H.; Coutts, R. T.; Ogunbona, F. A. *Tetrahedron* **1973**, *29*, 4189.

7.21 (m, 2H), 7.34 (m, 3H), 7.48 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 19.4, 62.2, 71.8, 77.5, 115.8, 122.6, 128.0, 128.7, 129.2, 129.3, 137.8, 151.8, 171.9. MS: m/z = 282 (M^+).

(+)-(*3R,4R,5S*)-2-*N*-Benzyl-5-methyl-3-phenylisoxazolidine-4-carboxamide (*exo*-13b). Yield: 38%. $[\alpha]_D$ = +68° (c = 1.0, $CHCl_3$). R_f = 0.28 (EtOAc:petroleum ether 60:40). HPLC (Daicel Chiralcel OD, hexane:*i*-PrOH = 90:10, flow rate = 1.0 mL/min): t_R = 12.7 min (major) and 16.5 min (minor). Ee = 55%. ^{1}H NMR ($CDCl_3$): δ 1.36 (d, J = 6.1 Hz, 3H), 3.04 (dd, J = 8.8, 5.5 Hz, 1H), 3.74 (d, J = 14.3 Hz, 1H), 4.14 (d, J = 14.8 Hz, 1H), 4.15 (d, J = 8.2 Hz, 1H), 4.58 (dq, J = 6.1, 5.5 Hz, 1H), 5.35 (s, br, 1H), 5.83 (s, br, 1H), 7.27−7.43 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 20.9, 60.7, 63.0, 72.5, 76.9, 127.9, 128.7, 128.7, 128.8, 129.1, 129.4, 136.0, 137.7, 173.4. MS: m/z = 296 (M^+).

(+)-(*3R,4R,5S*)-5-Methyl-3-(4′-methylphenyl)-2-*N*-phenylisoxazolidine-4-carboxamide (*exo*-13c). Yield: 62%. $[\alpha]_D$ = +183° (c = 1.0, $CHCl_3$). R_f = 0.38, (EtOAc:petroleum ether 60:40). HPLC (Daicel Chiralcel OD, hexane:*i*-PrOH = 90:10, flow rate = 1.0 mL/min): t_R = 12.6 min (major), t_R = 17.3 min (minor). Ee = 66%. ^{1}H NMR ($CDCl_3$): δ 1.36 (d, J = 6.0 Hz, 3H), 2.34 (s, 3H), 3.27 (dd, J = 8.8, 5.5 Hz, 1H), 4.75 (dq, J = 6.05, 6.05 Hz, 1H), 4.86 (d, J = 8.8 Hz, 1H), 5.31 (s, br, 1H), 5.91 (s, br, 1H), 6.95 (m, 3H), 7.19 (m, 4H), 7.35 (d, J = 8.2 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 19.5, 21.8, 62.4, 71.6, 77.5, 115.8, 122.5, 127.9, 129.2, 129.9, 134.7, 138.3, 151.9, 172.0. MS: m/z = 296 (M^+).

(+)-(*3R,4R,5S*)-2-*N*,3-Diphenyl-5-propylisoxazolidine-4-carboxamide (*exo*-13d). Yield: 70%. $[\alpha]_D$ = +87° (c = 1.0, $CHCl_3$). R_f = 0.42 (EtOAc:petroleum ether 50:50). Ee determined by ^{1}H NMR spectroscopy using Eu(hfc)$_3$: ee = 59%. ^{1}H NMR ($CDCl_3$): δ 0.95 (t, J = 7.2 Hz, 3H), 1.45−1.66 (m, 4H), 3.33 (dd, J = 8.5, 5.2 Hz, 1H), 4.60 (dt, J = 7.7, 5.0 Hz, 1H), 4.86 (d, J = 8.8 Hz, 1H), 5.46 (s, br, 1H), 5.97 (s, br, 1H), 6.94 (m, 3H), 7.18−7.36 (m, 5H), 7.45 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 14.6, 20.1, 36.1, 61.2, 71.6, 81.4, 115.9, 122.6, 128.0, 128.6, 129.1, 129.2, 137.7, 151.6, 172.2. MS: m/z = 310 (M^+).

(+)-(*3R,4R,5S*)-2-*N*-Benzyl-3-phenyl-5-propylisoxazolidine-4-carboxamide (*exo*-13e). Yield: 38%. $[\alpha]_D$ = +50° (c = 1.0, $CHCl_3$). R_f = 0.37, (EtOAc:petroleum ether 50:50). Ee determined by ^{1}H NMR spectroscopy using Eu(hfc)$_3$: ee = 14%. ^{1}H NMR ($CDCl_3$): δ 0.94 (t, J = 7.2 Hz, 3H), 1.37−1.70 (m, 4H), 3.10 (dd, J = 8.2, 5.0 Hz, 1H), 3.73 (d, J = 14.3 Hz, 1H), 4.11 (d, J = 7.7 Hz, 1H), 4.15 (d, J = 14.3 Hz), 4.43 (dt, J = 6.6, 4.3 Hz, 1H), 5.30 (s, br, 1H), 5.98 (s, br, 1H), 7.28−7.42 (m, 10H). ^{13}C NMR ($CDCl_3$): δ 14.0, 19.0, 37.4, 60.0, 61.4, 71.5, 80.2, 127.3, 128.0, 128.1, 128.2, 128.6, 129.0, 135.1, 137.0, 173.1. MS: m/z = 324 (M^+).

(+)-(*3R,4R,5S*)-3-(4′-Methylphenyl)-2-*N*-phenyl-5-propylisoxazolidine-4-carboxamide (*exo*-13f). Yield: 63%. $[\alpha]_D$ = +77° (c = 1.0, $CHCl_3$). R_f = 0.51 (EtOAc:petroleum ether 50:50). Ee determined by ^{1}H NMR spectroscopy using Eu(hfc)$_3$: ee = 52%. ^{1}H NMR ($CDCl_3$): δ 0.93 (t, J = 6.9 Hz, 3H), 1.42−1.65 (m, 4H), 2.33 (s, 3H), 3.37 (dd, J = 8.3, 4.4 Hz, 1H), 4.60 (dt, J = 7.7, 4.3 Hz, 1H), 4.85 (d, J = 8.8 Hz), 5.11 (s, br, 1H), 5.93 (s, br, 1H), 6.94 (m, 3H), 7.14−7.23 (m, 4H), 7.35 (d, J = 8.2 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 14.5, 20.0, 21.8, 36.2, 61.7, 71.2, 81.6, 115.8, 122.5, 127.8, 129.2, 130.0, 134.5, 138.3, 151.7, 172.2. MS: m/z = 324 (M^+).

(−)-(*3S′,4S,4′S,5′R*)-4-Isopropyl-3-[(5′-methyl-2′-*N*,3′-diphenylisoxazolidin-4′-yl)carbonyl]-1,3-oxazolidin-2-one (*exo*$_a$-3b). Synthesized according to the general procedure on a 0.253 mmol scale using the catalyst $TiCl_2$(*i*-PrO)$_2$ (10 mol %) in CH_2Cl_2 at rt for 5 days. The mixture was filtered through a 20−30 mm layer of silica gel, and the silica gel layer was washed with 2% MeOH in CH_2Cl_2 (3 mL). After evaporation of the solvent, the crude material was purified by PTLC (silica gel, MeOH:CH_2Cl_2, 1:99). The crude product was recrystallized in MeOH. Yield: 53%. De was determined by ^{1}H NMR spectroscopy: de >95%. R_f = 0.4−0.54 (MeOH:CH_2Cl_2, 1:99). ^{1}H NMR ($CDCl_3$): δ 0.22 (d, J = 6.6 Hz, 3H), 0.66 (d, J = 7.2 Hz, 3H), 1.44 (d, J = 6.1 Hz, 3H), 1.55 (d-sep J = 7.2, 2.1 Hz, 1H), 4.04−4.20 (m, 4H), 5.10 (dq J = 10.9 Hz, 1H), 6.92 (m, 3H), 7.16 (m, 2H), 7.23- 7.34 (m, 3H), 7.52 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 15.0, 17.7, 18.7, 29.0, 59.2, 60.7, 64.2, 73.1, 75.9, 116.6, 122.9, 128.9, 129.1, 129.3, 129.7, 138.8, 150.5, 154.2, 169.1.

Procedure for the Conversion of Isoxazolidine *exo*-12a into (+)-(*3R,4R,5S*)-5-Methyl-2-*N*,3-diphenylisoxazolidine-4-carboxylic Acid (15′). To the crude product **12a** (about 0.125 mmol) from the asymmetric 1,3-dipolar cycloaddition reaction between **2a** and **11a**, dissolved in THF/H_2O (3:1, 1.5 mL) at 0 °C, was added 6 equiv of H_2O_2 (35%, 0.1 mL, 0.75 mmol) followed by addition of 2.0 equiv of LiOH (7.4 mg, 0.25 mmol). The mixture was stirred at 0−25 °C for 7 h. The excess of H_2O_2 was quenched with sodium hydrogensulfite at 0 °C. THF was removed by evaporation, and the water layer was extracted two times with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, filtered by suction, and evaporated *in vacuo*. The crude material was purified twice by PTLC (silica gel, MeOH:CH_2Cl_2, 5:95 and a few drops of Et_3N). Two bands appeared in the region R_f = 0.20−0.50. The lower band was the acid **15′**. R_f = 0.26−0.34 (MeOH:CH_2Cl_2, 5:95). HPLC (Daicel Chiralcel OD, hexane:*i*-PrOH:formic acid = 97:3:0.2, flow rate = 1.0 mL/min):[23] t_R = 5.6 min (minor), t_R = 6.8 min (major). Ee = 72%. ^{1}H NMR ($CDCl_3$): δ 1.47 (d, J = 6.1 Hz, 3H), 3.37 (dd, J = 9.7, 9.7 Hz, 1H), 4.76 (dq, J = 6.0, 9.8 Hz, 1H), 4.89 (d, J = 9.4 Hz, 1H), 6.97 (m, 3H), 7.21 (m, 2H), 7.31 (m, 3H), 7.49 (m, 2H). MS: m/z = 283 (M^+).

Procedure for the Conversion of Isoxazolidine *exo*$_a$-3b into (−)-(3S,4S,5R)-5-Methyl-2-*N*,3-diphenylisoxazolidin-4-carboxylic Acid (15). *exo*$_a$-**3b** (10.5 mg, 26.6 μmol) was treated similar to the above procedure, but the mixture was refluxed for 3 days. The excess of H_2O_2 was quenched at rt with sodium hydrogensulfite. The mixture was acidified with 4 M HCl and extracted with Et_2O. The organic layer was dried over $MgSO_4$. Work up procedures followed the above procedure, but the chromatographic purification was only performed once. R_f = 0.26−0.34, (MeOH:CH_2Cl_2, 5:95). HPLC (Daicel Chiralcel OD, hexane:*i*-PrOH:formic acid = 97:3:0.2, flow rate = 1.0 mL/min):[23] t_R = 5.6 min (major). Ee = >99%. ^{1}H NMR ($CDCl_3$): δ 1.46 (d, J = 6.0 Hz, 3H), 3.35 (dd, J = 9.9, 9.9 Hz, 1H), 4.74 (dq, J = 6.1, 9.9 Hz, 1H), 4.88 (d, J = 9.9 Hz, 1H), 6.97 (m, 3H), 7.21 (m, 2H), 7.32 (m, 3H), 7.49 (m, 2H). MS: m/z = 283 (M^+).

X-ray Analysis of *exo*$_a$-3b. X-ray diffraction analysis of *exo*$_a$-**3b** was carried out on a HUBER 4-circle diffractometer at 298 K. The structure of *exo*$_a$-**3b** $C_{23}H_{26}N_2O_4$ (M_w 394.48 amu) was determined from a monoclinic crystal of dimensions 0.8 × 0.5 × 0.5 mm^3 (space group $P2_1$) with unit cell a = 9.572(1) Å, b = 8.541(1) Å, c = 13.778(2) Å, β = 109.119(9)°, V = 1064.2(2) Å^3. It has two molecules per cell, D_x = 1.2 g·cm^{-3}, μ = 0.079 mm^{-1}. The cell dimensions were determined from the setting angles of 29 reflections with 20 < 2θ < 28° using Mo Kα radiation (λ = 0.710 73 Å). A total of 4655 reflections were measured (2θ < 60°) using the ω−2θ step scan technique. Data reduction included corrections for background, deadtime, and Lorentz polarization, and absorption effects were considered insignificant. Crystal deterioration was found to be negligible. The structure was solved using SIR92[24] and refined by full-matrix least-squares methods including positional and anisotropic displacement parameters for non-hydrogen atoms. Hydrogen atoms were refined isotropically. The final R values were 0.043 for 3195 reflections ($I > 2\sigma(I)$) and 366 variables.

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Supporting Information Available: Copies of NMR spectra and HPLC data (22 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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