Transition-Metal Catalyzed Asymmetric 1,3-Dipolar Cycloaddition Reactions between Alkenes and Nitrones

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A transition-metal-catalyzed enantioselective 1,3-dipolar cycloaddition reaction between alkenes and nitrones has been developed employing 10 mol % of a chiral titanium catalyst generated in situ from $Ti(i\text{-}OPr)_2Cl_2$ and chiral diols. Diastereofacial discrimination in favor of the *exo* isomer was achieved in up to a 95:5 ratio. Isoxazolidines with an optical purity of up to 62% ee are obtained from this reaction. By precipitation of a racemate of one of the isoxazolidines an optical purity of >95% ee is obtained.

Introduction

The 1,3-dipolar cycloaddition reaction between an alkene and a nitrone leading to isoxazolidines is an important reaction in organic chemistry.[1] The isoxazolidines formed by this reaction can easily be converted into a variety of different "building blocks" such as 3-amino alcohols, and the isoxazolidine route has often been used for the preparation of a variety of different products.[1,2] The 1,3-dipolar cycloaddition reaction between an alkene and a nitrone can lead to two different regioisomers depending on the choice of substrates and conditions.[3] Each of the two possible regiomers consists of two diastereomers, the *exo* and *endo* forms of the isoxazolidine, and attempts to catalyze and control the *exo/endo* ratio have been achieved by using Lewis acids and transition metal complexes.[4] The greatest challenge for the 1,3-dipolar cycloaddition reaction between alkenes and nitrones is to control both the *exo/endo* selectivity and the enantioselectivity of the addition, as this reaction allows the formation of three contiguous asymmetric centers (reaction 1).

(1)

To some extent it has been possible to control the enantioselectivity of the reaction by employing chiral alkenes,[5] and few examples of the application of chiral nitrones in the cycloaddition to alkenes proved to be useful for the synthesis of isoxazolidines with high optical purities.[6] For the asymmetric 1,3-dipolar cycloaddition reaction of a related 1,3-dipole, the nitrile oxide, alkenes bearing chiral auxiliaries have been applied with success; however, the alkene part was always limited to acrylamides.[7] An asymmetric cycloaddition of a nitrile oxide to allylic alcohol was achieved by the use of diethylzinc and (*R,R*)-diisopropyl tartrate as chiral auxiliary.[8] Kanemasa *et al.* have recently found that the presence of magnesium ions accelerates the nitrile oxide 1,3-dipolar cycloadditions to allylic alcohols and also improves the regio- and diastereoselectivity of the reaction.[9]

The optimal goal for the 1,3-dipolar cycloaddition reaction between an alkene and a nitrone is to control both the diastereoselectivity and, most importantly, the enantioselectivity in the addition step, using catalysts having chiral auxiliaries. But, according to our knowledge no such procedures are yet known. This paper presents the first attempts to catalyze the asymmetric 1,3-dipolar cycloaddition reaction between an alkene and a nitrone by which the asymmetry is catalytically induced from a chiral ligand on the metal complex.

Results and Discussion

In an attempt to accelerate the 1,3-dipolar cycloaddition reaction between an alkene and a nitrone the interaction between a nitrone and a Lewis acid or a transition metal complex has been investigated. Accord-

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Table 1. Catalytic Effects of Ti(*i*-OPr)$_2$Cl$_2$ and Dichlorotitanium Alkoxides 5a-i on the 1,3-Dipolar Cycloaddition Reaction of 1a with 2a[a]

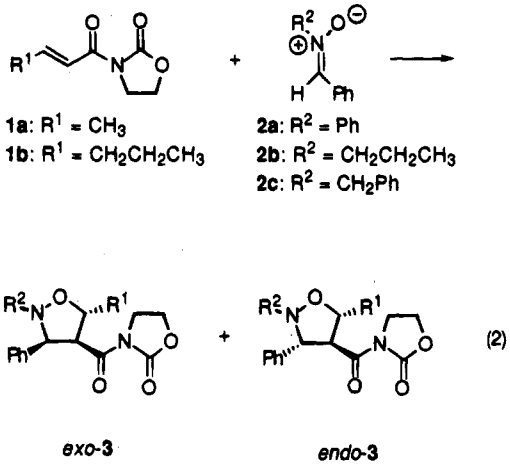
entry	catalyst (mol %)	solvent	*T* (°C)	convn (%)	*exo*/*endo* ratio	ee (%) *exo*-**3a** (*endo*-**3a**)
1		$CHCl_3$	50	39	91:9	
2	Ti(*i*-OPr)$_2$Cl$_2$ (100)	CH_2Cl_2	rt	68	87:13	
3	**5a** (100)	toluene	rt	73	81:19	4
4	**5b** (100)	toluene	rt	83	90:10	8
5	**5c** (100)	toluene	rt	91	94:6	19
6	**5d** (100)	toluene	rt	85	95:5	29
7	**5e** (100)	CH_2Cl_2	rt	90	89:11	47
8	**5e** (100)	CH_2Cl_2	0	85	89:11	56
9	**5e** (100)	CH_2Cl_2	−10	<10		
10	**5e** (10)	CH_2Cl_2	0	83	89:11	51
11	**5e** (10)	toluene	0	94	90:10	58
12	**5f** (100)	CH_2Cl_2	rt	81	77:23	20
13	**5g** (100)	CH_2Cl_2	rt	78	57:43	27 (45)
14	**5h** (100)	CH_2Cl_2	rt	72	87:13	34
15	**5i** (100)	toluene	rt	93	88:12	22
16	**5e** (10)−$ZnCl_2$ (100)	toluene	rt	71	37:63	(43)

[a] Reaction conditions: alkene **1a** (0.1 mmol) and nitrone **2a** (0.11 mmol) were dissolved (1 mL solvent). The dissolved catalyst (0.5 mL solvent) was added, and the reaction was stirred for 20 h.

ing to FMO-energy calculations[10] we have found that the coordination of a Lewis acid, as a proton, BF_3·OEt_2, or $AlCl_3$ to a nitrone lowered the HOMO and LUMO energies of the nitrone−metal complex, compared with the free nitrone. This effect might accelerate the 1,3-dipolar cycloaddition reaction in reactions where the dipole acts as electrophile.[3] However, transition state energy calculations[11] on a model 1,3-dipolar cycloaddition reaction between benzylidenemethylamine *N*-oxide and styrene revealed that the coordination of a Lewis acid like a proton, BF_3·OEt_2, or $AlCl_3$ to the nitrone causes an increase in the transition state energy of the 1,3-dipolar cycloaddition reaction to the alkene, compared with the reaction in the absence of a Lewis acid. These results were in accordance with a series of preparative experiments performed[12] and previous reports.[9e,13]

Thus, the attention was focused on an activation of the dipolarophile. We have found that the dipolarophile, 3-acyl-1,3-oxazolidin-2-one, **1**, which interacts strongly with titanium(IV) complexes, activates the alkene part of **1** for a 1,3-dipolar cycloaddition reaction with a nitrone. A similar activating effect was not found when nitrile oxides were applied in the titanium(IV)-catalyzed 1,3-dipolar cycloaddition reaction to **1**,[9e] probably because nitrile oxides have lower lying HOMO energies than nitrones.[1b] It should also be noted that **1** has been used with success in metal-catalyzed asymmetric Diels−Alder reactions.[14]

The addition of 3-crotonyloxazolidinone, **1a**, to benzylidenephenylamine *N*-oxide, **2a**, using Ti(*i*-OPr)$_2$Cl$_2$ as a catalyst has been investigated as model reaction (reaction 2). The reaction proceeds in a regioselective



3a: R^1 = CH_3, R^2 = Ph
3b: R^1 = CH_3, R^2 = $CH_2CH_2CH_3$
3c: R^1 = CH_3, R^2 = CH_2Ph
3d: R^1 = $CH_2CH_2CH_3$, R^2 = Ph
3e: R^1 = $CH_2CH_2CH_3$, R^2 = $CH_2CH_2CH_3$
3f: R^1 = $CH_2CH_3CH_3$, R^2 = CH_2Ph

manner, both with and without catalyst. The nitrone oxygen atom selectively attacks the β-carbon atom of the α,β-unsaturated imide, **1**.

These preliminary reactions were carried out in a 0.1 mmol scale in dry CH_2Cl_2. Without the presence of a catalyst no addition of **1a** to **2a** took place at room temperature and only 39% conversion was found after 20 h at 50 °C (in $CHCl_3$) (Table 1, entry 1). However, the reaction proceeded smoothly at room temperature in the presence of 1 mol equiv of Ti(*i*-OPr)$_2$Cl$_2$ (entry 2). But, the titanium(IV)-catalyzed reaction showed lower diastereoselectivity compared with the uncatalyzed reaction.[15] On the basis of these results the presence of chiral dichlorotitanium alkoxides as asymmetric catalysts was studied. The chiral titanium complexes were prepared by azeotopical removal of 2-propanol with toluene from a mixture of the chiral diols **4a-i** and Ti(*i*-OPr)$_2$Cl$_2$ (reaction 3).[14a,16] The semisolid residue was dissolved in CH_2Cl_2 or toluene and added to the reactants.

The titanium complex, **5a**, of the chiral diol (*R,R*)-diethyl tartrate, **4a**, was examined first (Table 1, entry 3). The conversion was slightly improved compared with Ti(*i*-OPr)$_2$Cl$_2$ as the catalyst, but the diastereoselectivity was poorer and only a very low ee was induced. The ee of the reaction is determined by ^{1}H NMR using Eu(hfc)$_3$ as chiral shift reagent. Chiral 1,1′-binaphthol complexes of titanium have been applied with success in several chiral transformations,[17] but in the 1,3-dipolar cycloaddition reaction, the presence of catalyst **5b** causes only a slight increase in the diastereoselectivity and only 8% ee of *exo*-**3a** was induced (entry 4). However, application of the chiral titanium complex, **5c**, as a catalyst for the 1,3-dipolar cycloaddition reaction improved both the yield of the reaction and the diastereoselectivity, and 19% ee of *exo*-**3a** was obtained (entry 5). Further improvement of the diastereoselectivity was found when the ethyl

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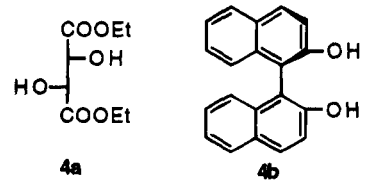
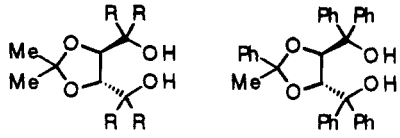
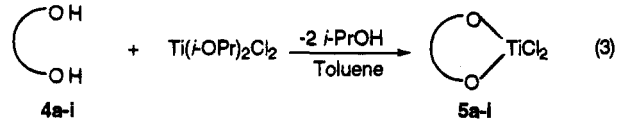


4a 4b



4c: R = Me
4d: R = Et
4e: R = Ph
4f: R = 3,5-$(CH_3)_2$-C_6H_3
4g: R = 2-naphthyl
4h: R = 4-biphenyl

4



4a-i 5a-i (3)

derivative **5d** was used with a diastereoselectivity of 95:5 in favor of *exo*-**3a** (entry 6).[18] However, the ee of 29% which was obtained with **5d** as a catalyst was still not satisfactory. Application of the chiral titanium complex, **5e**, as a catalyst, where the four alkyl substituents in **5c** and **5d** have been replaced for phenyl substituents, causes an improvement of the ee to 47% of *exo*-**3a** (entry 7). With a stoichiometric amount of **5e**, the 1,3-dipolar cycloaddition reaction proceeds at 0 °C with 56% ee of *exo*-**3a** (entry 8), but at lower temperatures unsatisfying conversion was obtained (entry 9). Astonishingly, by application of a catalytic amount of **5e** only a slight decrease in ee of *exo*-**3a** was observed, whereas the reaction yield and diastereoselectivity were unaffected (entry 10), and if the solvent was changed from CH_2Cl_2 to toluene both yield and ee were improved to 94% and 58%, respectively (entry 11). Replacement of the four phenyl substituents in **5e** by 3,5-dimethylphenyl substituents to give **5f** causes a remarkable decrease in both diastereoselectivity and enantioselectivity (entry 12).[19] Changing the catalyst to **5g** also caused a significant lower diastereoselectivity, and only 27% ee of *exo*-**3a**, but here a moderate ee, 45%, of *endo*-**3a** was obtained (entry 13). Application of the titanium complex, **5h**, as catalyst also reduces the ee compared with **5e** (entry 14). These results (entries 3–14) demonstrate that no apparent correlation exists between the steric bulk of the chiral ligand, *exo*/*endo* selectivity, and ee. It should be noted that Narasaka *et al.* have found a remarkable increase of the ee in the titanium-catalyzed Diels–Alder reaction by substitution of one of the two methyl substituents in the 1,3-dioxolane ring in the diol **4e** with a phenyl group to give **4i**.[20] However, in the 1,3-dipolar cycloaddition reaction between the alkene **1a** and the nitrone **2a** the enantioselectivity was dramatically decreased by the use of **5i** as catalyst compared to the application of **5e** (entry 15). When the reaction was catalyzed by 10 mol % of **5e** and additional 100 mol % $ZnCl_2$, the diastereoselectivity inverted to give *endo*-**3a** as the major isomer in 43% ee (entry 16). It should be noted that the reaction is not catalyzed by $ZnCl_2$ alone. When the stronger Lewis acid $BF_3{\cdot}Et_2O$ was applied in stoichiometric amounts, in addition to 10 mol % of **5e**, no reaction occurred.

Table 2. Enantioselective 1,3-Dipolar Cycloaddition Reaction for Alkenes 1a,b with Nitrones 2a-c Catalyzed by 5e[a]

entry	alkene	nitrone	T (°C)	product	yield (*exo*/*endo*)[b] (%)	ee[c] *exo*-3/*endo*-3 (%)
1	**1a**	**2a**	0	**3a**	94 (85:9)	60/62
2	**1a**	**2b**	rt	**3b**	84 (51:33)	15/62
3	**1a**	**2c**	rt	**3c**	71 (38:33)	27/59
4	**1b**	**2a**	rt	**3d**	71 (62:9)	39/48
5	**1b**	**2b**	rt	**3e**	80 (40:40)	10/35[d]
6	**1b**	**2c**	rt	**3f**	85 (44:41)	24/53

[a] Reaction conditions: see Experimental Section. [b] Isolated yields. [c] The ee was determined by ^1H NMR using Eu(hfc)$_3$ as chiral shift reagent. [d] Ee determined with some uncertainty.

In order to optimize the enantioselectivity of the catalytic reaction with **5e** (Table 1, entry 11) we have examined the effect of adding molecular sieves to the reaction mixture as numerous reports have described the successful application of powdered 4 Å molecular sieves in enantioselective titanium(IV)-catalyzed reactions.[21] But, in our case only a slight decrease in enantioselectivity was observed. The exclusion of air from the reaction media did not affect the reaction course significantly. By changing the solvent the diastereo- and enantioselectivity could be slightly improved. When the reaction from Table 1, entry 11, was performed in a 1:1 mixture of toluene and petroleum ether the *exo*/*endo* ratio of **3a** increased slightly to 91:9, and 60% ee of *exo*-**3a** was obtained.

Since reasonable ee has been achieved by employing a catalytic amount of **5e**, the asymmetric 1,3-dipolar cycloaddition reaction for a representative series of alkenes and nitrones was investigated. The results are presented in Table 2.

The reactions were carried out in a 1 mmol scale in the presence of 10 mol % of freshly prepared catalyst (for details see Experimental Section). As the catalyst, dissolved in toluene, was added to the mixture of **1** and **2** a precipitation took place. The precipitate consisted of a 1:1 complex of **1**, and **5e**, as indicated by ^1H NMR. After 48 h the oxazolidinone, **1**, was absent in ^1H NMR spectra of the crude products. The diastereomers could be separated after two eluations on preparative TLC silica gel plates. The *N*-phenylnitrone, **2a**, reacted with a satisfying diastereoselectivity (Table 2, entries 1 and 4), whereas the aliphatic and the benzylic *N*-substituted nitrones, **2b** and **2c**, respectively, reacted with low or no diastereoselectivity, but a relatively high ee of *endo*-**3b** and *endo*-**3c** was obtained in these cases. Without any exception the optical purities of the *endo*-isomers were higher than of the *exo*-isomers. When *exo*-**3a** was dissolved in hot methanol, precipitation of racemic *exo*-**3a** took place on cooling to 5 °C. After two precipitations *exo*-**3a** with an optical purity >95% ee, was isolated from the filtrate in 39% yield.

(18) The chiral diols are not limited to the phenyl and methyl derivatives as claimed in ref 17. The ethyl derivative was easily prepared. However, we failed to prepare the isopropyl derivative.

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Most of the chiral dichlorotitanium alkoxides used as catalyst for the 1,3-dipolar cycloaddition reaction have been applied as catalyst in other reactions, especially the Diels–Alder reaction.[14] Compared with the Diels–Alder reaction the asymmetric 1,3-dipolar cycloaddition reaction developed in the present work differs from the Diels–Alder reactions in several ways. The chiral dichlorotitanium alkoxides **5f** and **5i**, which are the most enantioselective catalysts for the Diels–Alder reaction,[19,20] are not similarly effective in the 1,3-dipolar cycloaddition reaction where **5e** is found to introduce the highest enantioselectivity. The enantioselectivity in the Diels–Alder reactions where only catalytic amounts of the chiral dichlorotitanium alkoxide is applied is very sensitive to traces of water, whereas this is not the case for the enantioselectivity of the 1,3-dipolar cycloaddition reaction. The catalytical effect achieved by the application of Lewis acids in 1,3-dipolar cycloaddition reactions and Diels–Alder reactions has probably the same origin. The coordination of **1** to the Lewis acid lowers the energy of the HOMO and LUMO of the alkene part of the system, leading to an activation for the addition to a diene or a nitrone. One of the major differences between the two reactions is that nitrones are stronger Lewis bases than the dienes and can interact with the Lewis acid catalyst. However, the chelation of **1** to the dichlorotitanium alkoxides **5** seemed to be much more favored compared with the coordination of nitrones **2** to **5**. Generally, the stereoselectivity achieved by the application of a catalytical amount of chiral dichlorotitanium alkoxides **5a-i** was higher in the Diels–Alder reaction compared with the 1,3-dipolar cycloaddition reaction, but in forthcoming work we will try to improve both the diastereo- and enantioselectivity of the reaction.

Experimental Section

General Methods. The ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz, respectively. Chemical shifts for ^{1}H NMR and ^{13}C NMR are reported in ppm downfield from tetramethylsilane (TMS). Mass spectra were recorded at 70 eV with a direct inlet. Preparative thin layer chromatography (TLC) was performed on 200 × 200 × 1.8 mm silica gel ($PF_{254+366}$, Merck) on glass plates. Solvents were dried using standard procedures.

Materials. The starting materials 3-((*E*)-2′-butenoyl)-1,3-oxazolidin-2-one[14a] (**1a**), 3-((*E*)-2′-hexenoyl)-1,3-oxazolidin-2-one[14a] (**1b**), benzylidenephenylamine *N*-oxide[22] (**2a**), benzylidenepropylamine *N*-oxide[23] (**2b**), benzylbenzylideneamine *N*-oxide[22] (**2c**), and the six chiral (2*R*,3*R*)-2,3-*O*-(2-propylidene)-1,1,4,4-tetraaryl-1,2,3,4-butanetetrols[14a] (**4c-h**) and **4i**[14a] were synthesized according to the literature. Dichlorodiisopropoxytitanium(IV)[16] in a 0.1 mol/L toluene solution was synthesized by stirring 5 mmol of Ti(*i*-OPr)$_4$ and 5 mmol of $TiCl_4$ in 100 mL of dry toluene at rt under nitrogen for 1 h. The solution was stored under nitrogen at −18 °C.

Asymmetric 1,3-Dipolar Cycloaddition Reaction. General Procedure for the Reaction Using 10 mol % of the Titanium Reagent. To a 0.1 M dry toluene solution of Ti(*i*-OPr)$_2$Cl$_2$ (1 mL, 0.1 mmol) was added (2*R*,3*R*)-2,3-*O*-(2-propylidene)-1,1,4,4-tetraphenyl-1,2,3,4-butanetetrol (**4e**) (51.3 mg, 0.11 mmol). The solution was stirred for 30 min. 2-Propanol was azeotropically removed with the solvent for 1 h at 10 mmHg and 20–100 °C. The residue was dissolved in dry toluene (1 mL). 3-Acyl-1,3-oxazolidin-2-one (**1**) (1.0 mmol) and the nitrone (**2**) (1.1 mmol) were dissolved in dry toluene (4 mL), and the solution was stirred as petroleum ether (5 mL) was added. The catalyst solution was added, and the reaction flask was filled with nitrogen and sealed. The mixture was stirred at 0 °C (Table 2, entry 1) or 20 °C (Table 2, entry 2–6) for 48 h. The reaction mixture was then stirred with 10 mL of 5% MeOH in $CHCl_3$ 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 $CHCl_3$, the solvent was evaporated *in vacuo*. The residue was subjected to preparative TLC (silica gel, Et_2O: petroleum ether, 2:1). Two bands appeared in the region R_f = 0.2–0.6 from which the lower band could be extracted to give *exo*-**3**. The band with the higher R_f value consisted of a mixture of *endo*-**3** and *exo*-**3**. With this mixture the chromatographic procedure was repeated to give pure *endo*-**3**.

3-(((5′-Methyl-2′-*N*,3′-diphenyl)isoxazolidin-4′-yl)carbonyl)-1,3-oxazolidin-2-one (3a). Yield: 94%.

***exo*-3a.** Yield: 85% (300 mg, 0.85 mmol). Ee: 60%. $[\alpha]_D$: +11.9° (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): 1.46 (d, *J* = 6.2 Hz, 3H), 3.05 (m, 1H), 3.71 (m, 1H), 3.87 (m, 1H), 4.20 (m, 1H), 4.42 (dd, *J* = 10.7, 9.3 Hz, 1H), 4.93 (d, *J* =10.7 Hz, 1H), 5.09 (dq, *J* = 9.3, 6.2 Hz, 1H), 6.95 (m, 3H), 7.17 (m, 2H), 7.37 (m, 3H), 7.48 (m, 2H). ^{13}C NMR ($CDCl_3$): 17.8, 42.7, 60.6, 62.7, 72.3, 75.1, 116.8, 123.0, 128.9, 129.1, 139.0, 150.3, 153.6, 169.8. MS: *m*/*z* 352 (M^+).

***endo*-3a.** Yield: 9% (30 mg, 0.085 mmol) (contains 20% impurity of **1a**). Ee: 62%. $[\alpha]_D$: −11.9° (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): 1.56 (d, *J* = 6.2 Hz, 3H), 3.97–4.10 (m, 2H), 4.31–4.52 (m, 3H), 4.81 (dd, *J* = 7.4, 7.2 Hz, 1H), 5.19 (d, *J* = 7.2 Hz, 1H), 6.91–7.02 (m, 3H), 7.28–7.41 (m, 5H), 7.50 (m, 2H). MS: *m*/*z* 352 (M^+).

3-(((5′-Methyl-3′-phenyl-2′-*N*-propyl)isoxazolidin-4′-yl)carbonyl)-1,3-oxazolidin-2-one (3b). Yield: 84%.

***exo*-3b.** Yield: 51% (161 mg, 0.51 mmol). Ee: 15%. $[\alpha]_D$: +14.8° (*c* = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): 0.76 (t, *J* = 7.4 Hz, 3H), 1.30 (d, *J* = 6.2, 3H), 1.40–1.60 (m, 2H), 2.43–2.68 (m, 2H), 2.96 (m, 1H), 3.50–3.68 (m, 2H), 4.04 (m, 2H), 4.28 (dd, *J* = 10.5, 9.3 Hz, 1H), 4.84 (m, 1H), 7.17–7.31 (m, 5H). ^{13}C NMR ($CDCl_3$): 12.3, 18.4, 21.8, 42.9, 59.2, 60.2, 62.5, 74.8, 128.6, 128.7, 129.5, 137.9, 153.4, 170.8. MS: *m*/*z* 318 (M^+).

***endo*-3b.** Yield: 33% (105 mg, 0.33 mmol). Ee: 60%. $[\alpha]_D$: −2.9° (*c* = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): 0.87 (t, *J* = 7.5 Hz, 3H), 1.50–1.63 (m, 5H), 2.61–2.87 (m, 2 H), 4.02 (m, 2H), 4.26–4.45 (m, 4H), 4.56 (dd, *J* = 7.5, 7.3 Hz, 1H), 7.29–7.43 (m, 5H). ^{13}C NMR ($CDCl_3$): 12.3, 21.2, 21.9, 43.5, 59.0, 62.1, 62.4, 75.4, 78.3, 128.4, 128.5, 129.2, 139.3, 153.5, 172.5. MS: *m*/*z* 318 (M^+).

3-(((2′-*N*-Benzyl-5′-methyl-3′-phenyl)isoxazolidin-4′-yl)carbonyl)-1,3-oxazolidin-2-one (3c). Yield: 71%.

***exo*-3c.** Yield: 38% (140 mg, 0.38 mmol). Ee: 27%. $[\alpha]_D$: +15.0° (*c* = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): 1.34 (d, *J* = 6.1 Hz, 3H), 3.04 (m, 1H), 3.52–3.70 (m, 2H), 3.77 (d, *J* = 14.3 Hz, 1H), 3.92 (d, *J* = 14.3 Hz, 1H), 4.06 (m, 1H), 4.26–4.43 (m, 2H), 4.93 (qd, *J* = 9.1, 6.1 Hz, 1H), 7.19–7.45 (m, 10H). ^{13}C NMR ($CDCl_3$): 18.8, 43.0, 60.1, 60.2, 62.5, 74.0, 75.2, 127.7, 128.7, 128.8, 129.2, 129.6, 137.5, 138.0, 153.5, 170.8. MS: *m*/*z* 366 (M^+).

***endo*-3c.** Yield: 33% (120 mg, 0.33 mmol). Ee: 59%. $[\alpha]_D$: +6.4° (*c* = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): 1.62 (d, *J* = 6.2 Hz, 3H), 3.89–4.02 (m, 3H), 4.10 (d, *J* = 14.5 Hz, 1H), 4.20–4.37 (m, 2H), 4.42 (dq, *J* = 6.2, 6.2, 1H), 4.51 (d, *J* = 7.5 Hz, 1H), 4.62 (dd, *J* = 7.5, 6.2 Hz, 1H), 7.20–7.50 (m, 10H). ^{13}C NMR ($CDCl_3$): 21.5, 43.6, 60.2, 62.0, 62.5, 74.7, 78.9, 127.6, 128.5, 128.7, 128.8, 128.9, 129.4, 138.5, 139.1, 153.6, 172.5. MS: *m*/*z* 366 (M^+).

3-(((2′-*N*,3′-Diphenyl-5′-propyl)isoxazolidin-4′-yl)carbonyl)-1,3-oxazolidin-2-one (3d). Yield: 71%.

***exo*-3d.** Yield: 62% (235 mg, 0.62 mmol). Ee: 39%. $[\alpha]_D$: +10.3° (*c* = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): 1.01 (t, *J* = 6.8, 3H), 1.45–1.83 (m, 4H), 3.00 (m, 1H), 3.64 (m, 1H), 3.81 (m, 1H), 4.11 (m, 1H), 4.52 (dd, *J* = 9.7, 9.0 Hz, 1H), 4.91 (d, *J* = 9.7, 1H), 5.02 (m, 1H), 6.96 (m, 3H), 7.14 (m, 2H), 7.31 (m, 3H), 7.47 (m, 2H). ^{13}C NMR ($CDCl_3$): 14.8, 20.3, 35.3, 42.8, 59.2, 62.7, 72.1, 78.8, 116.9, 123.1, 128.9, 129.1, 138.8, 150.3, 153.6, 170.0. MS: *m*/*z* 380 (M^+).

***endo*-3d.** Yield: 9% (36 mg, 0.09 mmol). Ee: 48%. $[\alpha]_D$: −20.5° (*c* = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): 1.00 (t, *J* = 7.4

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Hz, 3H), 1.38–1.80 (m, 3H), 1.88–2.04 (m, 1H), 3.98 (m, 2H), 4.34 (m, 3H), 4.85 (dd, J = 7.5, 7.5 Hz, 1H), 5.13 (d, J = 7.5 Hz, 1H), 6.96 (m, 3 H), 7.21–7.39 (m, 5H), 7.48 (m, 2H). ^{13}C NMR ($CDCl_3$): 14.6, 20.4, 34.9, 43.6, 61.9, 62.4, 75.2, 84.0, 115.1, 122.3, 127.2, 128.5, 129.4, 129.5, 141.4, 152.1, 153.3, 171.7. MS: m/z 380 (M^+).

3-(((2′-*N*,5′-Dipropyl-3′-phenyl)isoxazolidin-4′-yl)carbonyl)-1,3-oxazolidin-2-one (3e). Yield: 80%.

***exo*-3e.** Yield: 40% (140 mg, 0.40 mmol). Ee: 10%. $[\alpha]_D$: +8.4 (c = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): 0.82 (t, J = 7.3 Hz, 3H), 0.93 (t, J = 6.8 Hz, 3H), 1.29–1.72 (m, 6H), 2.56 (m, 2H), 3.00 (m, 1H), 3.62 (m, 2H), 4.05 (m, 2H), 4.39 (dd, J = 10.5, 7.5 Hz, 1H), 4.77 (m, 1 H), 7.22–7.33 (m, 5H). ^{13}C NMR ($CDCl_3$): 12.4, 14.7, 20.1, 21.8, 35.9, 42.9, 58.7, 59.2, 62.4, 74.8, 78.6, 128.5, 128.6, 129.4, 137.6, 153.4, 171.0. MS: m/z 346 (M^+).

***endo*-3e.** Yield: 40% (137 mg, 0.40 mmol). Ee: 35%. $[\alpha]_D$: −22.1° (c = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): 0.88 (t, J = 7.2 Hz, 3H), 0.95 (t, J = 7.2 Hz, 3H), 1.3–1.8 (m, 5H), 2.01 (m, 1H), 2.68–2.80 (m, 2H), 3.96 (m, 2H), 4.14–4.35 (m, 4H), 4.61 (dd, J = 7.7, 6.3 Hz, 1H), 7.21–7.40 (m, 5H). ^{13}C NMR ($CDCl_3$): 12.3, 14.6, 20.1, 21.9, 37.4, 43.6, 58.7, 60.8, 62.4, 75.9, 82.1, 128.4, 128.6, 129.2, 139.0, 153.4, 172.9. MS: m/z 346 (M^+).

3-(((2′-*N*-Benzyl-3′-phenyl-5′-propyl)isoxazolidin-4′-yl)carbonyl)-1,3-oxazolidin-2-one (3f). Yield: 85%.

***exo*-3f.** Yield: 44% (172 mg, 0.44 mmol). Ee: 23.7%. $[\alpha]_D$: +12.2° (c = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): 0.94 (t, J = 7.5 Hz, 3H), 1.25–1.78 (m, 4H), 3.04 (m, 1H), 3.52–3.71 (m, 2H), 3.86 (d, J = 14.3 Hz, 1H), 3.93 (d, J = 14.3 Hz, 1H), 4.07 (m, 1H), 4.23 (d, J = 10.2 Hz, 1H), 4.50 (dd, J = 10.2, 7.8 Hz, 1H), 4.85 (m, 1H), 7.18–7.42 (m, 10H). ^{13}C NMR ($CDCl_3$): 14.8, 19.9, 35.8, 43.0, 58.4, 60.0, 62.4, 73.8, 78.9, 127.6, 128.6, 128.7, 128.8, 129.4, 129.6, 137.2, 137.9, 153.5, 171.1. MS: m/z 394 (M^+).

***endo*-3f.** Yield: 41% (161 mg, 0.41 mmol). Ee: 53%. $[\alpha]_D$: −18.1° (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): 0.92 (t, J = 7.3, 3H), 1.26–1.65 (m, 2H), 1.71–1.83 (m, 1H), 2.01–2.17 (m, 1H), 3.86–4.01 (m, 4H), 4.19–4.36 (m, 3H), 4.39 (d, J = 7.5 Hz, 1H), 4.72 (dd, J = 7.5, 6.3 Hz, 1H), 7.20–7.45 (m, 10H). ^{13}C NMR ($CDCl_3$): 14.5, 20.0, 37.4, 43.6, 60.0, 60.6, 62.4, 75.2, 82.6, 127.5, 128.5, 128.6, 128.8, 129.0, 129.2, 129.3, 138.4, 138.7, 153.5, 172.9. MS: m/z 394 (M^+).

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Supplementary Material Available: Copies of ^{1}H and ^{13}C NMR spectra (24 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.