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Enantioselective Ruthenium-Catalyzed 1,3-Dipolar Cycloadditions between *C*-Carboalkoxy Ketonitrones and Methacrolein: Solvent Effect on Reaction Selectivity and Its Rational

Khalid B. Selim,[†,‡] Arnaud Martel,[†] Mathieu Y. Laurent,[†] Jérôme Lhoste,[†] Sandrine Py,[§] and Gilles Dujardin*[,†]

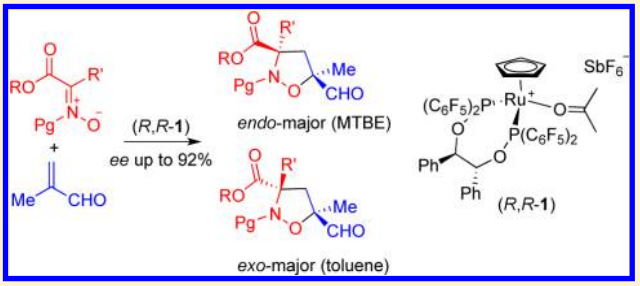
[†]LUNAM Université du Maine, Institut Molécules et Matériaux du Mans, UMR 6283 CNRS, Faculté des Sciences, 72085 Le Mans, Cedex 9, France

[‡]Department of Pharmaceutical Organic Chemistry, Faculty of Pharmacy, Mansoura University, Mansoura 35516, Egypt

[§]Département de Chimie Moléculaire (SERCO) UMR 5250, ICMG FR-2607, CNRS-Université Joseph Fourier, BP 53, 38041 Grenoble Cedex 09, France

Supporting Information

ABSTRACT: A catalytic 1,3-dipolar cycloaddition between carboalkoxy ketonitrones and methacrolein under the effect of chiral ruthenium Lewis acid (*R*,*R*-**1**) was developed with high regio-, diastereo-, and enantiocontrol. The diastereochemical outcome of the cycloaddition reaction is marked by a significant solvent effect, and a divergent *endo* or *exo* control can be tuned by an appropriate choice of both the solvent and the *N*- and *O*-substituents of the ketonitrone. A rationale of the solvent effect, based on the computational study of the interactions between the methacrolein−Ru complex and its counteranion (SbF_6^-), is proposed to explain the selectivities obtained.



INTRODUCTION

1,3-Dipolar cycloaddition (1,3-DC) between nitrones and ethylenic dipolarophiles is one of the most synthetically useful pericyclic reactions, since the resulting isoxazolidines are formed with up to 3 contiguous stereogenic centers and can easily be converted into important chiral building blocks such as complex β-lactams and β-amino acid derivatives (esters, aldehydes, and alcohols).[1] The efficiency of 1,3-DC requires a control of both the regio- and diastereoselectivities in an enantioselective manner. Major breakthroughs in asymmetric 1,3-DC between nitrones and ethylenic dipolarophiles have been achieved upon activation by Lewis acids or organocatalysts.[2] However, if these advances to date have concerned a wide range of dipolarophiles including electron-rich (vinyl, enols ethers and ketene ketals),[3] neutral (allylic alcohols),[4] and electron-poor olefins (enals, ene-esters),[5−15] variations of the nitrone substrates have been more limited. Indeed, the most efficient enantioselective reactions typically involve *C*-aryl-substituted aldonitrones often bearing an aryl group as *N*-substituent and in a lesser extent simple cyclic aldonitrones. Actually, limited progress[3f,4a,8g,15] has been made to develop regio-, diastereo-, and facially controlled 1,3-DC reactions involving other types of nitrones that could be of interest from a synthetic point of view such as aldo- or ketonitrones possessing functional *C*-substituent(s) (e.g., ester, amide) and/or equipped with a deprotectable *N*-substituent. This is the purpose of the approach developed in our group, highlighting the opportunities gained by the use of *C*-ester-substituted ketonitrones that permit the construction of isoxazolidines containing up to two quaternary stereocenters.[16]

It must be pointed out that only rare examples of metal-catalyzed, enantioselective 1,3-DC involving nitrones equipped with an ester function have already been described. In the aldonitrone (glyoxylate) series, reports are restricted to (i) the case of organocatalyzed 1,3-DC reactions involving crotonaldehyde[8g] and (ii) the case of nitrone activation by a chelating Lewis acid (CuBOX) for cycloaddition reactions involving vinyl ethers.[3f] As a result of the inclination of such aldonitrones to undergo quick *Z*/*E* isomerization at room temperature, a mixture of *cis*/*trans* isomeric cycloadducts was obtained in both cases.[3f,8g]

We recently developed aspartate- and alanine-derived *N*-benzyl nitrones, which are configurationally stable *E*-ketonitrones, as new dipoles for controlling asymmetric 1,3-DC under thermal conditions to form highly functionalized isoxazolidine derivatives.[17] In an organocatalyzed version, we demonstrated that the diastereoselectivity could be completely controlled when reacting crotonaldehyde with such a configurationally stable *E*-ketonitrone. Enantioselectivities up to 95% and good yields were achieved.[15] In the present study, we now focus on 1,3-DC of these functional ketonitrones with methacrolein,

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which shows the opposite regioselectivity as crotonaldehyde, and we searched for an appropriate catalytic system. Indeed, as previously shown by MacMillan's group with α-aryl aldonitrones[7] we found that the methodology using a chiral imidazolidinone or another iminium precursor could not be extended to methacrolein.

We thus turned our attention to metallocatalysis. Interestingly, Kündig et al. have introduced a successful asymmetric activation of methacrolein as monodentate dipolarophile, catalyzed by chiral iron and ruthenium Lewis acids.[9] From (*Z*)-diaryl aldonitrones, 1,3-DC reactions proceed with high yields and total *endo* control but suffer from a lack of regiocontrol: the 3,5-adduct is obtained as the major isomer with moderate enantiomeric excesses (ee) in the case of electron-deficient nitrones.[9a−c] This strategy depends on inhibition of the coordination of nitrones to the Lewis acids, which causes deactivation of the catalyst. Subsequently, many developments have been achieved with other monocoordinating chiral Lewis acids based on Co^{III},[10] Ni^{II},[11] Zn^{II},[12] Ti^{IV},[13] and Rh^{III}/Ir^{III}[14,15] with valuable regiochemical outcomes, but as already stated, all of these efforts concentrated on nitrones derived from aromatic aldehydes. Interestingly, a total 3,5-regiocontrol was recently observed, together with high diastereo- and enantioselectivities, by Kundig's group in the reactions of *N*-alkyl *C*-aryl aldonitrones with methacrolein using chiral ruthenium catalyst (*R*,*R*)-**1** (Figure 1).[9d,e]

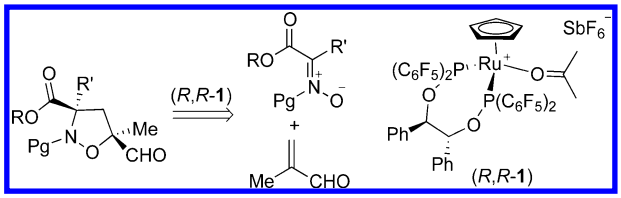

Figure 1. 1,3-DC reaction studied with Ru-catalyst (*R*,*R*)-**1**.

In order to develop an enantioselective version of a 1,3-DC reaction between ketonitrones **2** and methacrolein that would lead to a *N*-deprotectable type of adduct possessing two functionalized quaternary centers (Figure 1), we have achieved in the present work a full experimental and theoretical study with chiral monocationic complex (*R*,*R*)-**1**. This study affords the first examples of enantioselective 1,3-DC reactions between functionalized ketonitrones and methacrolein. The parameters that influence the regio-, diastereo-, and enantiocontrolled formation of the targeted isoxazolidines are discussed on the basis of experiments and calculations, along with the evidence of an unexpected solvent effect on the stereoselectivity of the cycloaddition.

RESULTS AND DISCUSSION

Cycloaddition Study. We started our investigation with the reaction between methacrolein and nitrone **2a** bearing an easily removable *N*-benzyl group (Table 1). Racemic thermal cycloaddition (neat, 90 °C, 2 days) gave 3,5-cycloadduct **3a** with a total conversion as two separated *endo* and *exo* isomers in a 30:70 ratio. In the presence of 5 mol % of *R*,*R*-**1** in dichloromethane, nitrone **2a** was treated with methacrolein at room temperature for 5 days to afford with the same total 3,5-regiocontrol the isoxazolidine **3a** with minored diastereoselectivity and moderate enantioselectivities (entry 1). Lowering the temperature and increasing the amount of the catalyst improved the *endo* selectivity and ee's (entries 2, 3).

To improve the selectivity of the reaction, further investigations were done by variation of the solvent and temperature; we found an unusual effect of the reaction solvent on selectivity and reactivity. First, changing the reaction solvent from dichloromethane to chloroform resulted in a slight increase in diastereocontrol, but conversion over the same reaction time decreased dramatically (entry 4). The use of dichloroethane gave similar results in comparison to dichloromethane (entry 5).

Effects of the coordinating properties of the solvent were evaluated by performing the reaction in toluene and nitromethane. A weakly polar and noncoordinating solvent (e.g., toluene) led to inversion in diastereoselectivity to afford the *exo* product as the major (entry 6), while a polar and weakly coordinating solvent (e.g., nitromethane) switched off the catalytic cycle to afford a sluggish conversion of the starting material with a high *exo* selectivity (entry 7). These strong solvent effects encouraged us to screen other solvents. In THF, the *endo* selectivity was markedly enhanced (dr 93/7), while enantioselectivity and reactivity were comparable to those in dichloromethane (entry 8). *tert*-Butyl methylether (MTBE) was found to be the optimal solvent in terms of selectivities and reactivity, especially when the reaction was performed at −10 °C (*endo*/*exo* 97:3, 87% ee, 95% yield, entries 9, 10). Decreasing the concentration of the reaction medium from 0.4 to 0.2 M of **2a** gave a slight increase in *endo*- and enantioselectivities (entry 11). Reactions performed in 2-methylTHF and diethyl ether also exhibited enhanced selectivities, albeit with a decreased reaction rate (entries 12, 13). Finally, decreasing the temperature to −20 °C did not improve the selectivities (entry 14).

The uncatalyzed (background) reaction at 0 °C in dichloromethane, toluene, THF, or MTBE after 5 days resulted in the same low conversion of **2a** (9%), yielding an *exo* major product (*endo*/*exo* 20:80) and showing no dependence on solvent selection (Table 1, entry 15). Because the solvent does not influence either conversion rate or selectivity in the uncatalyzed reaction, the solvent effect in the Ru-catalyzed reaction might arise from the interaction of the solvent with the methacrolein−Ru complex or with the Ru-complex. In the related reactions involving *N*-benzyl α-arylnitrones and methacrolein recently described by Kündig,[9e] the nature of the solvent was not investigated as a parameter influencing the *exo*/*endo* control. In the present study, we evidence that a solvent effect occurs also in the *N*-benzyl α-aryl-nitrone series (Table 2). Indeed, the cycloaddition of aldonitrone **4** and methacrolein, reported with catalyst (*R*,*R*-**1**) in dichloromethane at rt (Table 2, entry 1),[9e] was tested at −10 °C, and variation of the solvent confirmed our findings: compared to dichloromethane, the use of MTBE as the solvent enhances both the *endo*- and enantioselectivity of the cycloaddition (entries 2 vs 3).

Under these optimized reaction conditions (MTBE, −10 °C), the scope and limitation of the 1,3-DC reactions of methacrolein and *C*-carboxy ketonitrones were investigated by variation of the *C*-alkyl, *N*- and *O*-substituents. *N*-Benzyl methyl ester nitrones **2b** (R^1 = Et) and **2c** (R^1 = *n*-Pr) gave an excellent diastereoselectivity with 84% ee and 86% ee, respectively (Scheme 1), disclosing the successful extension to nitrones bearing a bulkier *C*-substituent.

This procedure was also extended to nitrones bearing different ester groups (Table 3). *tert*-Butyl ester nitrone **2d** afforded the highest enantioselectivity with good *endo* control (92% ee, *endo*/*exo* 92:8, entry 1). Surprisingly, the reaction with

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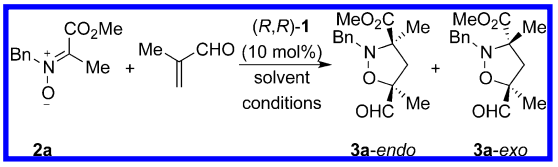
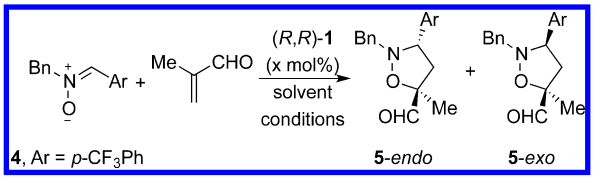
Table 1. Asymmetric 1,3-Dipolar Cycloaddition between Ketonitrone 2a and Methacrolein[a]



entry	solvent	°C, days	yield (%)[b,c]	*endo*/*exo*[d]	ee (%)[e] *endo*	ee (%)[e] *exo*
1[f]	DCM	rt, 5	87 (100)	46/54	66	70
2[f]	DCM	0, 6	58 (72)	47/53	71	75
3	DCM	0, 6	85 (87)	70/30	78	75
4	$CHCl_3$	0, 5	30 (52)	78/22	78	72
5	DCE	0, 5	81 (87)	72/28	76	75
6	toluene	0, 5	74 (84)	39/61	74	68
7	$MeNO_2$	0, 4	- (25)	18/82	-	-
8	THF	0, 5	86 (86)	93/7	76	64
9	MTBE	0, 5	92 (95)	90/10	81	76
10	MTBE	−10, 5	95 (97)	97/3	87	-
11[g]	MTBE	−10, 6	96 (96)[h]	98/2	88	-
12[g]	2-MeTHF	−10, 6	62 (62)	95/5	84	-
13[g]	Et_2O	−10, 6	72 (74)	88/12	90	-
14[g]	MTBE	−20, 6	77 (78)	97/3	91	-
15[i]	MTBE, DCM[j]	0, 5	- (9)	20/80	-	-

[a]Reactions were run with [**2a**] = 0.4 M. [b]Isolated combined yield of *exo* and *endo* products. [c]Conversions are in parentheses. [d]Determined by ^{1}H NMR of the crude product. [e]Determined by HPLC after reduction into the corresponding alcohol. [f]5 mol % of (*R*,*R*)-**1**. [g]Reactions were run with [**2a**] = 0.2 M. [h]90% yield of isolated pure **3a**-*endo*. [i]Reaction performed without catalyst [j]Same result when the reaction is performed in toluene or THF.

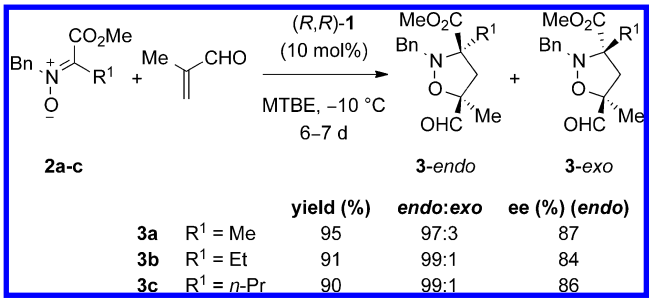
Table 2. Asymmetric 1,3-Dipolar Cycloaddition between *C*-Aryl Aldonitrone 4 and Methacrolein



entry	mol %	solvent	°C, days	yield (%)[a]	*endo*/*exo*[b]	ee (%)[c] *endo*
1[d]	5	DCM	+5, 3	95	95/5	87
2	10	DCM	−10, 5	92	92/8	91
3	10	MTBE	−10, 5	99	99/1	95

[a]Isolated combined yield of *exo* and *endo* products. [b]Determined by ^{1}H NMR of the crude product. [c]Determined by HPLC after reduction to the corresponding alcohol. [d]Reference 9e.

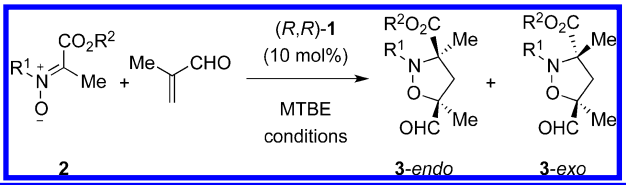
Scheme 1. Extension to Bulkier *C*-Substituents of the Nitrone

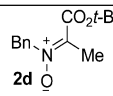
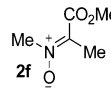
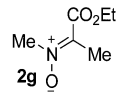


		yield (%)	*endo*:*exo*	ee (%) (*endo*)
3a	R^1 = Me	95	97:3	87
3b	R^1 = Et	91	99:1	84
3c	R^1 = *n*-Pr	90	99:1	86

ethyl ester nitrone **2e** gave the corresponding isoxazolidine with moderate diastereoselectivity and a slow conversion rate of **2e** (entry 2). When the weakly *exo*-selective conditions used in the reaction of methyl ester nitrone **2a** (Table 1, entry 6) were applied to ethyl ester nitrone **2e** (toluene at 0 °C), an increased

Table 3. Asymmetric 1,3-Dipolar Cycloaddition between Ketonitrones 2 and Methacrolein



entry	**2**	**3**	conditions (°C, days)	yield (%)[a]	*endo*/*exo*[b]	ee (%)[c] *endo*/*exo*
1	 **2d**	**3d**	−10, 6	99	92/8	92/-
2	 **2e**	**3e**	−10, 6	42	63/37	84/-
3[d]		**3e**	0, 5.5	85	14/86	-/66
4[e]		**3e**	0, 5.5	84	65/35	79/-
5	 **2f**	**3f**	−10, 6	89	68/32	80/-
6	 **2g**	**3g**	−10, 6	42	15/85	-/77
7[d]		**3g**	−10, 6	65	7/93	-/72
8[e]		**3g**	0, 5.5	86	7/93	-/81

[a]Isolated combined yield of *exo* and *endo* products. [b]Determined by ^{1}H NMR of the crude product. [c]Determined by HPLC after reduction into the corresponding alcohol. [d]Reaction performed in toluene. [e]Reaction performed in dichloromethane.

exo selectivity was observed (*exo*/*endo* dr 86:14), together with moderate enantioselectivity and good yield (entry 3). In contrast, the stereochemical outcome of the reaction performed in dichloromethane (entry 4) was similar to that observed in MTBE.

In order to investigate the possible influence of the *N*-substituent of the nitrone, *N*-diphenylmethyl and *N*-methyl

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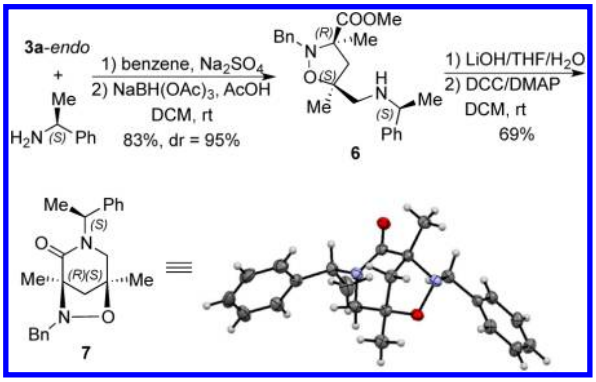
nitrones were tested in a comparative way to *N*-benzyl nitrones. Unfortunately, the *N*-diphenylmethyl-substituted nitrone was found to be unreactive under these catalytic conditions. Increasing the steric bulk at the nitrogen seems to inhibit the Ru-catalyzed reaction. The *N*-Me nitrone **2f** (methyl ester) showed good reactivity, but its cycloaddition with methacrolein exhibited only low *endo* selectivity (Table 3, entry 5). Surprisingly, the *N*-Me nitrone **2g** (ethyl ester) exhibited an interesting inversion of diastereoselectivity in MTBE to afford the *exo* product in a 85:15 *exo*:*endo* ratio, but in low yield and with moderate enantioselectivity (entry 6). Because the use of catalyst *R*,*R*-**1** in toluene was found to favor the formation of an *exo* cycloadduct, the reaction was next performed in toluene and afforded the expected *exo* diastereomer in an improved 93:7 *exo*:*endo* ratio (entry 7). Unexpectedly, with this nitrone dichloromethane also favors the *exo* product, which is produced in high yield with 81% ee (entry 8).

Determination of the Absolute Configuration. The absolute configuration of the major **3a**-*endo* adduct has been established as depicted in Scheme 2. **3a**-*endo* (87% ee, 94% de)

Scheme 2. Determination of the Absolute Configuration of the Major 3a-*endo* Cycloadduct

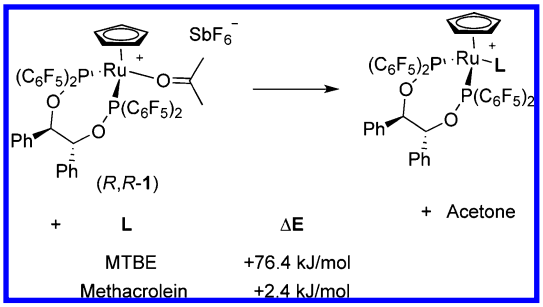


was converted into a diastereomeric mixture of amines through condensation with (*S*)-(−)-α-methylbenzylamine, followed by *in situ* reduction of the resulting imine. The amine **6** was saponified and lactamized to furnish the diastereomerically pure lactam **7** in 69% yield. X-ray analysis of the crystalline **7** unambiguously established the absolute configuration of the stereogenic centers as 1*R*,5*S*, corresponding to the 3*R*,5*S* configuration in the major *endo* **3a** adduct precursor.

DFT Study of Ru-Complex Solvent Interaction. The results obtained experimentally demonstrate that the selectivities of these processes depend on a delicate balance between different factors, such as electronic and/or steric structure of reactants and solvent effects. The modification of selectivity may be reached by three main ways (or by their combinations): coordination of a dipolarophile to a ruthenium Lewis acid, variation of substituents, and use of the appropriate solvent.

The substantial effect of the solvent on selectivity is one of the most intriguing results. Owing to this effect, besides the natural steric hindrance around Ru when methacrolein is chelated, the possibility of a direct interaction of the solvent with Ru was first examined. The geometries of the complexes with acetone, methacrolein, and MTBE were calculated using Truhlar's DFT method M06,[18] described as a well-suited method in the M06 class for modeling transition metal complexes. To facilitate the calculations and to avoid ambiguity on the position of the anion, the complexes were calculated in absence of the anion from the geometry given by the X-ray structure described by Kündig et al.[9f] The calculations were performed using Gaussian 09[19] with LANL2DZ (ECP) basis set for the ruthenium atom and 6-31+G(d) for the other atoms. The geometry was optimized at this level, and then a single-point calculation of the electronic energy[20] (E) using a SMD solvation model was performed with the closest described solvent, based on our experimental data (i.e., diethylether). The electronic energy difference (ΔE) corresponding to the exchange of the molecule of acetone in the initial complex by methacrolein or MTBE was calculated (Scheme 3).

Scheme 3. Energy Difference Associated with the Exchange of Acetone in the Complex



The calculated ΔE for these exchanges unambiguously demonstrates the incapacity for MTBE to compete with methacrolein in the reactive site, probably as a result of the steric hindrance around ruthenium and the bulkiness of MTBE.

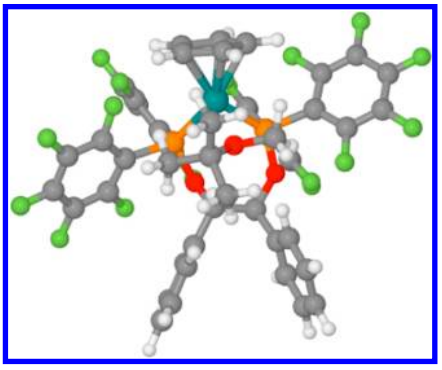


Figure 2. Structure of the complex-(*R*,*R*)-**1** with one molecule of MTBE.

As displayed in both structures (Figures 2 and 3), the ruthenium cation is fully surrounded by the ligands represented, and when the molecule of methacrolein is coordinating the ruthenium by its oxygen atom, no additional ligand can be placed in the coordination sphere of the ruthenium cation. As confirmed by the X-ray structure obtained by Kündig, even the counterion (SbF_6^-) can be pushed away from the ruthenium by the presence of one molecule of methacrolein, and the latter locates very close to one of the pentafluorophenyl rings of the complex.[9f] This possible competition between the anion and methacrolein might be at the origin of the counterion effect on reactivity first observed by Kündig.[9g] Indeed, this group observed an increased reactivity of the complexes with the largest anions that are more easily

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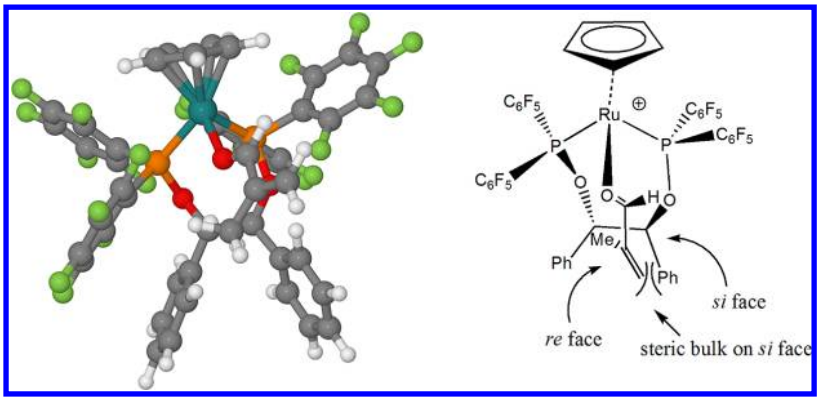

Figure 3. Structure **A** of the complex-(*R*,*R*)-**1** with one molecule of methacrolein and the proposed approach of the nitrone.

displaced by methacrolein, thus enhancing the availability of the active frustrated Lewis pair.

DFT Study of Methacrolein Orientation in the Ru-Complex. In order to investigate the preferred geometry of the methacrolein−Ru complex, we considered the possible rotation around the Ru−O bond (Figure 4), as well as the possible contribution of *s-cis* conformers of methacrolein.

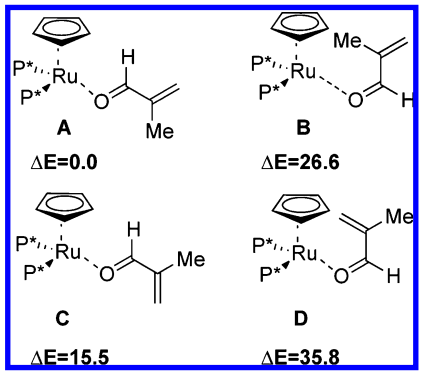

Figure 4. Representation of conformers **A**−**D** and relative electronic energy in kJ/mol.

Conformer **B** was calculated to be less stable than **A** (Figure 4). In addition, the application of the SMD solvation model, using diethylether as the solvent, contributed only slightly to enhance this energy difference by 0.6 kJ/mol, suggesting that the relative stability of the favored conformer should not be significantly altered by a change of solvent. The two corresponding conformers derived from the *s-cis* conformation of methacrolein **C** and **D** (Figure 4) are also less stable than **A** with SMD solvation applied.

Although conformer **C** is more stable than conformer **B**, it is most likely unproductive due to the inaccessibility of the double bond of methacrolein turned into the complex. This double bond stays between one of the phenyl rings and one of the pentafluorophenyl rings of the catalyst, and thus the contribution of conformer **C** to the cycloaddition is expected to be negligible. The X-ray structure described by Kündig et al. corresponds, therefore, to the most stable conformer in solution. If present, the alternative conformers **B** and **C** (Figure 4) would contribute to dramatically decrease the facial selectivity of the reaction, the complex presenting the opposite side of methacrolein.

The quite homogeneous level of enantioselectivity we observed, whatever the orientation of the *exo*/*endo* control, is somewhat intriguing. In addition, the facial selectivity observed in the present case is similar to the one described previously by Kündig and confirms the hypothesis previously formulated on a favored approach on the *re* face.[9f] Structure **A** (Figure 3) gives some clues to explain the high facial selectivity observed. The main facial approach is most probably controlled by the natural orientation of methacrolein when chelated to the ruthenium. Methacrolein is slightly twisted to limit the steric interactions between its methyl group and one of the phenyl groups of the catalyst, thus placing this methyl group in a lipophilic pocket. One of the phenyl rings will then hinder the *si* face, leading the *re* face to be the most accessible as previously described.[9] The facial selectivity is therefore mainly the consequence of the steric repulsion between a phenyl group of the catalyst and the approaching nitrone. However, the methyl group of methacrolein also plays a key role by twisting the methacrolein to offer the *re* face (Figure 3).

Rationale of the Solvent Effect on the Selectivity. The unprecedented influence of the solvent on the *endo*/*exo* selectivity of the cycloaddition remained unexplained at this stage and required further studies. The molecular electrostatic potential of the methacrolein−(*R*,*R*)-**1** complex **A** was then calculated (Figure 5). Represented in blue is the partial

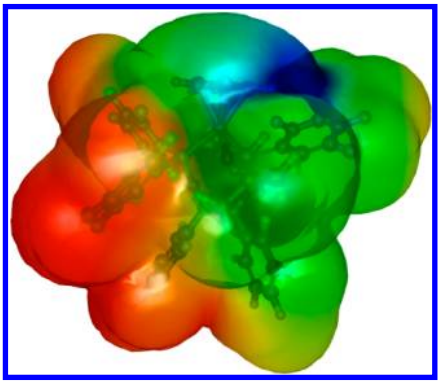

Figure 5. Molecular electrostatic potential of the methacrolein−(*R*,*R*)-**1** complex **A**.

electrostatic positive charge of the catalyst−methacrolein cation complex, the region displaying a natural affinity for a Lewis base, such as the solvent itself. This figure gives evidence that the atoms directly linked to the ruthenium are most affected by the strong withdrawing effect of the ruthenium cation. The aldehydic hydrogen of methacrolein therefore appears as partially positively charged and is one part of the complex

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that will interact with the oxygen of the solvent (MTBE) or the anion (SbF_6^-). This kind of interaction with the anion was postulated by Kündig et al. to explain the influence of the counterion on reactivity and selectivity.[9f] The X-ray structure of complex **1** described by Kündig agrees with the HOESY experiment performed on an acrylonitrile complex to prove the presence of the anion close to a region analogous to the one represented in blue in Figure 5.

In order to evaluate the energy associated with the coordination of the solvent in this region, the methacrolein−(*R*,*R*)-**1** complex **A** was modeled in the presence of one molecule of MTBE (Figure 6). The structure displays a

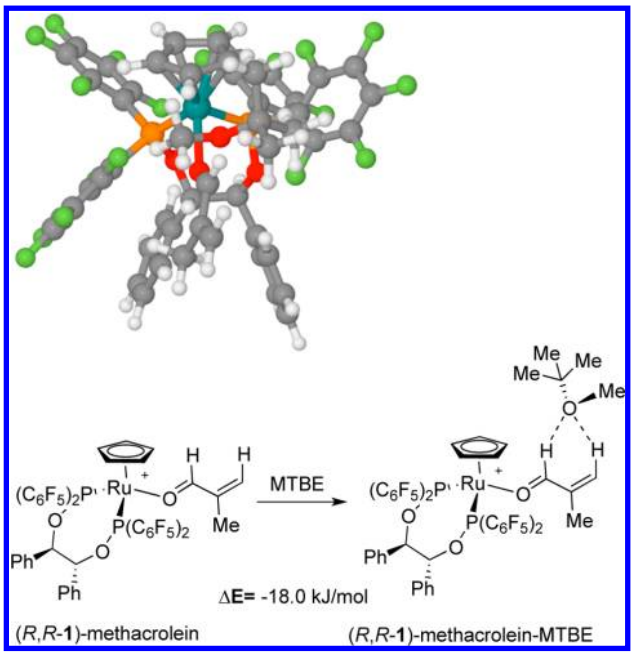

Figure 6. Calculated structure of the full complex methacrolein−MTBE-Ru-catalyst (*R*,*R*)-**1** energy gained through the interaction with MTBE.

proximity between the aldehydic hydrogen and the oxygen of MTBE (2.23 Å), that is adequate to fulfill Desiraju's criteria[21] for existence of a weak hydrogen bond (confirmed by a Wiberg bond index of 0.0148). Various data account for similar weak C−H···O bonds, such as the one between the oxygen of MTBE and a vinylic hydrogen (distance: 2.25 Å; Wiberg bond index: 0.0162).[22] The evidence of analogous C−H···O interactions was well established[23] from small molecules crystals,[24] and the hydrogen bond nature of these interactions is widely accepted.[25]

The significant stabilization gained by the formation of this new complex can be related to the ability of the oxygen in MTBE to act as a better Lewis base due to a stronger inductive effect of the alkyl groups (Figure 6).[26] The mass action of the solvent in the reaction medium will obviously contribute to this interaction with the oxygen of MTBE. At high dilution, MTBE is then fully able to compete with the counterion. The solvent would then displace the anion in this position away from the reactive site.

The full structure with SbF_6^- anion close to its initial position was modeled at the same level of calculation (Figure 7), placing the SbF_6^- anion close to one of the pentafluorophenyl rings and to two of the hydrogen atoms of the cyclopentadienyl ring.

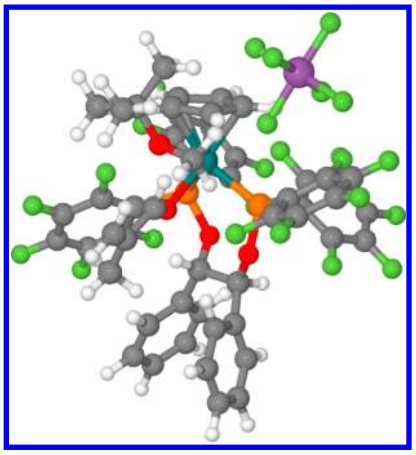

Figure 7. Methacrolein−(*R*,*R*)-**1**-MTBE-SbF_6 complex.

The structure places the pentafluorophenyl ring oriented toward the SbF_6 anion. The key role played by the pentafluorophenyl rings of the ligand is therefore most likely related to their interactions with the polyfluorinated anion, allowing the anion to be pushed away from the reactive site to enhance the reactivity. In addition, a complex methacrolein−(*R*,*R*)-**1**-SbF_6 was calculated at the same level of theory with SMD solvent model to be less stable by 3.3 kJ/mol than the corresponding MTBE complex (Figure 7). This weak energy difference corroborates the assumption of a competition between the solvent and the counterion close to the methacrolein molecule. This change in the position of the anion in the transition state is probably crucial for the *endo*/*exo* selectivity. Hence, in the presence of a weak Lewis base as a solvent such as toluene, the anion might stand very close to the methacrolein. In contrast, good Lewis bases such as MTBE would push the anion away from this position and facilitate the interaction between the aldehyde and the nitrone. Solvents with an intermediate behavior, such as dichloromethane, would then lead to a poor discrimination in the reaction paths and thus to midway selectivities, i.e., changing the environment of the methacrolein from an anion to a lipophilic group (MTBE) would change dramatically the approach of the nitrone.[27]

From this computational study, a better understanding of the solvent effect on the diastereoselectivity of the Ru-catalyzed cycloaddition was made possible. The significant influence of the solvent on the cycloaddition outcome described herein may echo previous reports of Doyle et al.,[14b] who reported an enhancement of reaction rates and selectivities when toluene was used in place of halocarbon solvents with cationic chiral dirhodium carboxamidates catalyzed nitrone cycloadditions.

From the sum of our experimental results, it is clear that the *exo*/*endo* selectivity is also significantly influenced by other parameters such as the nature of the *N*-substituent and of the ester function of the nitrones. At this stage, only a putative computational study of the transition state energies would allow us to take into account the contribution of these different parameters to the global stereochemical outcome of the Ru-catalyzed cycloaddition. However, the present results have already demonstrated that these different parameters and solvent effects can operate in a cooperative way, as it became thus possible to orientate the diastereoselectivity to synthetically useful *endo* or *exo* adducts in highly enantioenriched forms simply by tuning the *N*- and *O*-substituents of the *α*-carboxynitrone with the nature of the solvent.

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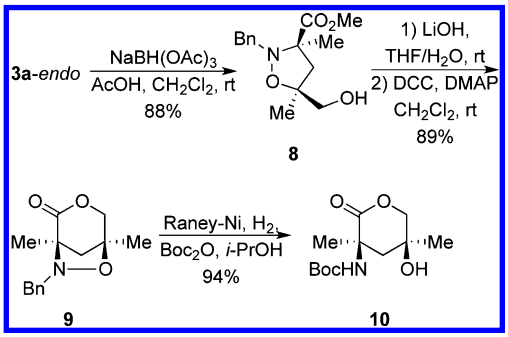
N−O Bond Cleavage. Finally, the synthetic utility of the highly functionalized 5-formyl isoxazolidines **3**, which contain two quaternary centers of controlled configuration, was demonstrated by transformation of the pure *endo* cycloadduct **3a**,[28] obtained with a high enantioselectivity, into the amino alcohol **10** (Scheme 4). To this aim, isoxazolidine **3a**-*endo* was

Scheme 4. Synthesis of 3-Amino-5-hydroxy Lactone 10



reduced to afford alcohol **8**, which was converted into the bicyclic compound **9** after sequential saponification and lactonization. Ring cleavage through N−O bond reduction with Raney-Ni resulted in the protected amino alcohol **10** under conditions allowing concomitant *N*-Boc protection in high yields (74% overall yield from adduct **3a**-*endo* for the 3 steps).

CONCLUSION

In this work, a catalytic 1,3-dipolar cycloaddition between *E*-configured ketonitrones containing an ester function as one of their *C*-substituents and methacrolein was developed with total 3,5-regiocontrol and with high diastereo- and enantioselectivities, using the chiral ruthenium monocationic catalyst (*R*,*R*-**1**). This *mono*-complexing Lewis acid was able to ensure the enantioselective access to isoxazolidines possessing two quaternary centers from functional ketonitrones through a selective activation of the enal and, moreover, in a diastereodivergent manner.

Indeed, the Ru-catalyzed 1,3-dipolar cycloadditions described herein displayed an unreported solvent effect on the diastereoselectivity that allows us to propose a novel vision on the mode of action for the catalyst (*R*,*R*-**1**), which behaves as a frustrated Lewis pair. From the DFT calculations performed, the solvent effect could be rationalized as the consequence of the competition occurring between the counterion of the catalyst and the solvent in the close-shell of complexed methacrolein. Moreover, the invariable facial selectivity ensured by the catalytic system could also be elucidated. By changing the solvent and the *N*- and *O*-substituents on the nitrone, the selectivity of the reaction could be controlled to give either *endo* or *exo* product, with good to excellent enantioselectivities. Finally, a representative [3 + 2] cycloadduct could be easily transformed into a highly enantioenriched lactone (e.g., **10**) and lactam (e.g., **7**) featuring two quaternary centers, as first insights to the synthetic potential displayed by the class of heterocycles that are obtained from this methodology.

EXPERIMENTAL SECTION

General Information. All melting points are uncorrected. Column chromatography was performed using 60 μm silica gel. Thin-layer chromatography was performed with G/UV254 plates, and the products were observed under UV light or with $KMnO_4$ stain. NMR (200 or 400 MHz for ^1H and 100 MHz for ^{13}C) was measured in $CDCl_3$ unless otherwise mentioned, and chemical shifts and coupling constants are presented in parts per million relative to Me_4Si and hertz, respectively. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Proton and carbon assignments were established using COSY, HMQC, HSQC, and DEPT experiments. Relative stereochemistry of cycloadducts was established using NOESY experiments. IR spectroscopy of oil and solid samples were measured as neat liquid films and KBr pellets, respectively. The wave numbers of maximum absorption peaks of IR spectroscopy are presented in cm^{-1}. $MeNO_2$ and MTBE were distilled from CaH_2 before use. All reactions were performed under argon atmosphere unless otherwise mentioned. Reagents were purchased from commercial suppliers and used without purification. Reactions at −10 and −20 °C were performed using a bath cooled by cryogenic flow. High-resolution mass spectra were performed on a GC TOF mass spectrometer. *R*,*R*-**1** catalyst[9f] and nitrones **2a**,[17b] **2b**,[17b] and **2e**[15a] were prepared according to the reported procedures. For HPLC analysis, racemic samples of cycloadducts were prepared under the microwave conditions as reported in our previous paper.[15a]

Typical Procedures for the Preparation of Nitrones. (*E*)-*N*-(1-Methoxy-1-oxopentan-2-ylidene)-1-phenylmethanamine Oxide (2c). A mixture of methyl 2-oxopentanoate (2.48.g, 19 mmol), BnNHOH (2.57 g, 21 mmol), and CH_2Cl_2 (25 mL) was stirred at rt for 36 h and then concentrated *in vacuo*. The residue was purified by column chromatography (cyclohexane/EtOAc = 9:1) to give compound **2c** (2.91 g, 65% yield) as a pale yellow oil. IR: 3034, 2961, 2874, 1709, 1525, 1455, 1321, 1190, 1135, 734, 708. ^1H NMR (400 MHz, $CDCl_3$): 7.47 (2H, dd, *J* = 7.6, 1.7 Hz, 2ArH), 7.36−7.31 (3H, m, 3ArH), 5.64 (2H, s, CH_2), 3.82 (3H, s, CH_3), 2.71−2.67 (2H, m, CH_2), 1.59−1.49 (2H, m, CH_2), 0.94 (3H, t, *J* = 7.4 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 14.1 (CH_3), 18.3 (CH_2), 30.4 (CH_2), 52.6 (CH_3), 67.6 (CH_2), 128.4 (CH), 128.6 (CH × 2), 128.7 (CH × 2), 134.2 (C), 141.5 (C), 163.3 (C═O). HRMS (ESI+): *m*/*z* calcd for $C_{13}H_{17}NO_3$ 236.1281 $[M + H]^+$, found 236.1273; 258.1101 $[M + Na]^+$, found 258.1098; 274.0840 $[M + K]^+$, found 274.0835.

(*E*)-*N*-(1-(*tert*-Butoxy)-1-oxopropan-2-ylidene)-1-phenylmethanamine Oxide (2d). A mixture of *tert*-butyl pyruvate (1.1 mL, 10 mmol) and BnNHOH (1.76 g, 11 mmol) in CH_2Cl_2 (20 mL) was stirred at rt for 16 h and then concentrated *in vacuo*. The residue was dissolved in a mixture of CH_2Cl_2 (50 mL), and the organic phase was washed with H_2O (20 mL × 3), dried over $MgSO_4$, and concentrated *in vacuo* to give crude oil. Column chromatography (cyclohexane/EtOAc = 9:1) gave compound **2d** (0.895 g, 36% yield) as a colorless oil. IR: 2978, 2933, 1705, 1531, 1456, 1369, 1308, 1133, 844. ^1H NMR (400 MHz, $CDCl_3$): 7.48 (2H, dd, *J* = 6.8, 3.2 Hz, Ph), 7.33 (3H, dd, *J* = 5.0, 2.0 Hz, Ph), 5.63 (2H, s, CH_2), 2.21 (3H, s, CH_3), 1.51 (9H, s, *t*-Bu). ^{13}C NMR (100 MHz, $CDCl_3$): 15.8 (CH_3), 28.0 (CH_3 × 3), 66.8 (CH_2), 83.2 (C), 128.4 (CH), 128.5 (CH × 2), 128.9 (CH × 2), 134.3 (C), 139.3 (C), 161.9 (C═O). HRMS (ESI+): *m*/*z* calcd for $C_{14}H_{19}NO_3$ 250.1438 $[M + H]^+$, found 250.1438; 272.1257 $[M + Na]^+$, found 272.1256.

(*E*)-*N*-(1-Methoxy-1-oxopropan-2-ylidene)methanamine Oxide (2f). A mixture of methyl pyruvate (2.3 mL, 20 mmol), MeNHOH·HCl (1.84 g, 22 mmol), $NaOAc·3H_2O$ (3.26 g, 24 mmol), and MeOH (30 mL) was stirred at rt for 14 h and then concentrated *in vacuo*. The residue was dissolved in a mixture of CH_2Cl_2 (50 mL), and the organic phase was washed with H_2O (25 mL), dried over $MgSO_4$, and concentrated *in vacuo* to give crude oil. Column chromatography (cyclohexane/EtOAc = 3:1) gave compound **2f** (2.52 g, 96% yield) as a colorless oil at rt that solidified to a white wax in fridge. IR: 2957, 1713, 1543, 1439, 1309, 1194, 1140, 1034, 806, 751. ^1H NMR (400 MHz, $CDCl_3$): 4.18 (3H, q, *J* = 1.3 Hz, CH_3), 3.84 (3H, s, CH_3), 2.24 (3H, q, *J* = 1.3 Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 14.9 (CH_3), 52.6 (CH_3), 53.4 (CH_3), 138.0 (C), 163.0 (C═O). HRMS (ESI+): *m*/*z* calcd for $C_5H_9NO_3$ 132.0655 $[M + H]^+$, found 132.0661; 154.0475 $[M + Na]^+$, found 154.0477.

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(*E*)-*N*-(1-Ethoxy-1-oxopropan-2-ylidene)methanamine Oxide (2g). A mixture of ethyl pyruvate (2.2 mL, 20 mmol), MeNHOH·HCl (1.84 g, 22 mmol), NaOAc·3H_2O (3.26 g, 24 mmol), and MeOH (30 mL) was stirred at rt for 14 h and then concentrated *in vacuo*. The residue was dissolved in a mixture of CH_2Cl_2 (50 mL), and the organic phase was washed with H_2O (25 mL), dried over $MgSO_4$, and concentrated *in vacuo* to give crude oil. Column chromatography (cyclohexane/EtOAc = 3:1) gave compound **2g** (2.60 g, 90% yield) as a colorless oil. IR: 2983, 2940, 1713, 1542, 1445, 1369, 1304, 1143, 1024, 750. ^{1}H NMR (400 MHz, $CDCl_3$): 4.29 (2H, q, J = 7.1 Hz, CH_2), 4.17 (3H, q, J = 1.1 Hz, CH_3), 2.25 (3H, q, J = 1.1 Hz, CH_3), 1.36 (3H, t, J = 7.1, Hz, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): 14.1 (CH_3), 15.0 (CH_3), 53.1 (CH_3), 61.8 (CH_2), 138.4 (C), 162.6 (C═O). HRMS (ESI+): m/z calcd for $C_6H_{11}NO_3$ 146.0812 $[M + H]^+$, found 146.0808.

Typical Procedures for the Asymmetric 1,3-Dipolar Cycloaddition. (+)-(3*R*,5*S*)-Methyl 2-Benzyl-5-formyl-3,5-dimethylisoxazolidine-3-carboxylate (3a-*endo*) (Table 1, entry11). In a 10 mL tube, (*R*,*R*-**1**) (35.0 mg, 0.025 mmol) and methacrolein (0.04 mL, 0.5 mmol) were charged and suspended in MTBE (0.7 mL). The mixture was cooled to −10 °C and stirred for 5 min before the addition of **2a** (52 mg, 0.25 mmol) in MTBE (0.5 mL) *via* canula. The reaction mixture was stirred at −10 °C and quenched after 6 days by adding acetone (0.5 mL) at −10 °C and stirred at room temperature for 2 min before the addition of pentane (10 mL) to precipitate the catalyst. Filtration over Celite, washing with pentane, and concentration *in vacuo* gave a crude oil. Conversion and diastereoselectivity were determined by ^{1}H NMR of the crude to be 96% and *endo*/*exo* 98:2, respectively. Column chromatography (cyclohexane/EtOAc = 19:1 to 9:1) gave 66.7 mg, 96% total yield and pure **3a**-*endo* adduct was isolated in 62.6 mg, 90% yield as a pale yellow oil. $[\alpha]^{25}_D$ = +84.9 (c 1.01, $CHCl_3$) with 88% ee for pure **3a**-*endo*. R_f = 0.55 (cyclohexane/EtOAc = 3:1). IR: 2982, 2953, 1736, 1497, 145.5, 1265, 1152, 1076. ^{1}H NMR (400 MHz, $CDCl_3$): 9.47 (s, β-CHO, 1H), 7.40 (dd, J = 7.1, 1.4 Hz, Harom, 2H), 7.34−7.30 (tt, J = 7.1, 1.4 Hz, Harom, 2H), 7.26 (tt, J = 6.1, 1.4 Hz, Harom, 1H), 4.04 (d, J = 14.4 Hz, CH_2Ph, 1H), 3.89 (d, J = 14.4 Hz, CH_2Ph, 1H), 3.71 (s, ester Me, 3H), 3.19 (d, J = 13.0 Hz, 4β-CH_2, 1H), 1.94 (d, J = 13.0 Hz, 4α-CH_2, 1H), 1.50 (s, 3α-Me, 3H), 1.27 (s, 5α-Me, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 18.5 (3-CH_3), 19.5 (5-CH_3), 49.8 (4-CH_2), 52.4 (ester CH_3), 55.2 (CH_2Ph), 69.1 (3-C), 83.7 (5-C), 127.2 (CH), 128.19 (CH × 2), 128.23 (CH × 2), 138.0 (C), 172.5 (C═O), 204.7 (CHO). HRMS (FIID): m/z calcd for $C_{15}H_{19}NO_4$ 277.1314 $[M]^+$, found 277.1325. Enantioselectivity was determined by chiral HPLC analysis after reduction of **3a**-*endo* with $NaBH(OAc)_3$ to the corresponding alcohol **8a**-*endo*.

(+)-(3*R*,5*R*)-Methyl 2-Benzyl-5-formyl-3,5-dimethylisoxazolidine-3-carboxylate (3a-*exo*) (Table 1, entry 6). In toluene, 0.5 mmol scale, 0.4 M. Conversion and diastereoselectivity were determined by ^{1}H NMR of the crude to be 84% and *endo*/*exo* 61:39, respectively. Column chromatography (cyclohexane/EtOAc = 19:1 to 9:1) gave 103 mg, 74% total yield as a colorless oil. $[\alpha]^{20}_D$ = +131.3 (c 1.05, $CHCl_3$) with 68% ee for *exo* and 74% ee for *endo* in a major **3a**-*exo* mixture (61:39). R_f = 0.61 (cyclohexane/EtOAc = 3:1). IR: 3032, 2984, 2952, 2808, 1732, 1497, 1455, 1374, 1250, 1165, 1069, 740, 699. ^{1}H NMR (400 MHz, $CDCl_3$): 9.41 (s, α-CHO, 1H), 7.36−7.29 (m, Harom, 4H), 7.26 (tt, J = 6.1, 1.7 Hz, Harom, 1H), 4.02 (d, J = 14.7 Hz, CH_2Ph, 1H), 3.82 (s, ester Me, 3H), 3.71 (d, J = 14.7 Hz, CH_2Ph, 1H), 2.68 (d, J = 12.7 Hz, 4β-CH_2, 1H), 2.50 (d, J = 12.7 Hz, 4α-CH_2, 1H), 1.40 (s, 3α-Me, 3H), 1.30 (s, 5β-Me, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 17.9 (5-CH_3), 21.0 (3-CH_3), 47.4 (4-CH_2), 52.0 (ester CH_3), 55.3 (CH_2Ph), 69.6 (3-C), 83.7 (5-C), 127.2 (CH), 128.1 (CH × 2), 128.3 (CH × 2), 137.9 (C), 172.4 (C═O), 206.1 (CHO). HRMS (FIID): m/z calcd for $C_{15}H_{19}NO_4$ 277.1314 $[M]^+$, found 277.1320. Enantioselectivity was determined by chiral HPLC analysis after reduction of **3a**-*exo* with $NaBH(OAc)_3$ to the corresponding alcohol **8a**-*exo*.

(−)-(3*R*,5*S*)-Methyl 2-Benzyl-3-ethyl-5-formyl-5-methylisoxazolidine-3-carboxylate (3b-*endo*) (Scheme 1). In a 10 mL tube, **2b** (55.4 mg, 0.25 mmol) and (*R*,*R*-**1**) (35.0 mg, 0.025 mmol) were charged and suspended in MTBE (1.2 mL). The mixture was cooled to −10 °C and stirred for 5 min before the addition of methacrolein (0.04 mL, 0.5 mmol). The reaction mixture was quenched after 7 days by adding acetone (0.5 mL) at −10 °C and stirred at room temperature for 20 min before the addition of pentane (10 mL) to precipitate the catalyst. Filtration over Celite, washing with pentane, and concentration *in vacuo* gave a crude oil. Conversion and diastereoselectivity were determined by ^{1}H NMR of the crude to be 94% and *endo*/*exo* 99:1, respectively. Column chromatography (cyclohexane/EtOAc = 19:1 to 15:1) gave 66.4 mg, 91% total yield and pure **3b**-*endo* adduct was isolated in 59.0 mg, 81% yield as a pale yellow oil. $[\alpha]^{20}_D$ = −3.7 (c 1.11, $CHCl_3$) with 84% ee for pure **3b**-*endo*. R_f = 0.46 (cyclohexane/EtOAc = 6:1). IR: 3031, 2973, 2881, 1731, 1497, 1455, 1304, 1241, 1157, 1073, 739, 698. ^{1}H NMR (400 MHz, $CDCl_3$): 9.51 (s, β-CHO, 1H), 7.37 (dd, J = 6.9, 1.4 Hz, Harom, 2H), 7.32 (t, J = 6.9 Hz, Harom, 2H), 7.25 (tt, J = 6.9, 1.4 Hz, Harom, 1H), 4.05 (d, J = 14.4 Hz, CH_2Ph, 1H), 4.02 (d, J = 14.4 Hz, CH_2Ph, 1H), 3.74 (s, ester Me, 3H), 3.18 (d, J = 13.0 Hz, 4β- CH_2, 1H), 2.08 (dq, J = 14.8, 7.4 Hz, 3α-CH_2, 1H), 2.02 (d, J = 13.0 Hz, 4α-CH_2, 1H), 1.74 (dq, J = 14.8, 7.4 Hz, 3α-CH_2, 1H), 1.30 (s, 5α-Me, 3H), 0.96 (t, J = 7.4 Hz, 3α-Me, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 9.4 (3-CH_3), 20.7 (5-CH_3), 25.5 (3-CH_2), 46.1 (4-CH_2), 52.1 (ester CH_3), 55.1 (CH_2Ph), 74.0 (3-C), 83.9 (5-C), 127.1 (CH), 128.0 (CH × 2), 128.3 (CH × 2), 138.3 (C), 171.4 (C═O), 204.1 (CHO). HRMS (DCI +NH_3CH_4): m/z calcd for $C_{16}H_{21}NO_4$ 292.1543 $[M + H]^+$, found 292.1543. Enantioselectivity was determined by chiral HPLC analysis after reduction of **3b**-*endo* with $NaBH(OAc)_3$ to the corresponding alcohol **8b**-*endo*.

(−)-(3*R*,5*S*)-Methyl 2-Benzyl-5-formyl-5-methyl-3-propylisoxazolidine-3-carboxylate (3c-*endo*) (Scheme 1). In a 10 mL tube, **2c** (59.0 mg, 0.25 mmol) and (*R*,*R*-**1**) (35.0 mg, 0.025 mmol) were charged and suspended in MTBE (0.6 mL). The mixture was cooled to −10 °C and stirred for 5 min before the addition of methacrolein (0.04 mL, 0.5 mmol). The reaction mixture was quenched after 6 days by adding acetone (0.5 mL) at −10 °C and stirred at room temperature for 2 min before the addition of pentane (10 mL) to precipitate the catalyst. Filtration over Celite, washing with pentane, and concentration *in vacuo* gave a crude oil. Conversion and diastereoselectivity were determined by ^{1}H NMR of the crude to be 96% and *endo*/*exo* 99:1, respectively. Column chromatography (petroleum ether/EtOAc = 19:1 to 9:1) gave 68.6 mg, 90% total yield with 86% ee as a colorless oil. $[\alpha]^{20}_D$ = −8.8 (c 1.32, $CHCl_3$) for pure **3c**-*endo*. R_f = 0.41 (cyclohexane/EtOAc = 6:1). IR: 3031, 2973, 2881, 1731, 1497, 1455, 1304, 1241, 1157, 1073, 739, 698. ^{1}H NMR (400 MHz, $CDCl_3$): 9.50 (s, β-CHO, 1H), 7.37 (dd, J = 6.9, 1.4 Hz, Harom, 2H), 7.32 (t, J = 6.9 Hz, Harom, 2H), 7.26 (tt, J = 6.9, 1.4 Hz, Harom, 1H), 4.04 (s, CH_2Ph, 2H), 3.74 (s, ester Me, 3H), 3.18 (d, J = 13.0 Hz, 4β- CH_2, 1H), 2.02 (d, J = 13.0 Hz, 4α-CH_2, 1H), 2.00 (dt, J = 12.6, 4.7 Hz, 3α-CH_2, 1H), 1.66 (dt, J = 12.6, 4.7 Hz, 3α-CH_2, 1H), 1.42−1.27 (m, 3α-CH_2, 2H), 1.30 (s, 5α-Me, 3H), 0.98 (t, J = 7.3 Hz, 3α-Me, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.5 (3-CH_3, 3-CH_2), 18.5 (5-CH_3), 34.9 (3-CH_2), 46.6 (4-CH_2), 52.1 (ester CH_3), 55.1 (CH_2Ph), 73.4 (3-C), 84.0 (5-C), 127.1 (CH), 128.0 (CH × 2), 128.3 (CH × 2), 138.3 (C), 171.5 (C═O), 204.2 (CHO). HRMS (DCI+): m/z calcd for $C_{17}H_{23}NO_4$ 306.1700 $[M + H]^+$, found 306.1715. Enantioselectivity was determined by chiral HPLC analysis after reduction of **3c**-*endo* with $NaBH(OAc)_3$ to the corresponding alcohol **8c**-*endo*.

(+)-(3*R*,5*S*)-*tert*-Butyl 2-Benzyl-5-formyl-3,5-dimethylisoxazolidine-3-carboxylate (3d-*endo*) (Table 3, entry 1). In a 10 mL tube, **2d** (62.3 mg, 0.25 mmol) and (*R*,*R*-**1**) (35.0 mg, 0.025 mmol) were charged and suspended in MTBE (1.2 mL). The mixture was cooled to −10 °C and stirred for 5 min before the addition of methacrolein (0.04 mL, 0.5 mmol). The reaction mixture was quenched after 6 days by adding acetone (0.5 mL) at −10 °C and stirred at room temperature for 2 min before the addition of pentane (10 mL) to precipitate the catalyst. Filtration over Celite, washing with pentane, and concentration *in vacuo* gave a crude oil. Conversion and diastereoselectivity were determined by ^{1}H NMR of the crude to be 100% and *endo*/*exo* 92:8, respectively. Column chromatography (cyclohexane/EtOAc = 19:1) gave 79 mg, 99% total yield and pure

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3d-*endo* adduct was isolated in 62.8 mg, 79% yield as a white solid, mp 47−48 °C: $[\alpha]^{20}_D$ = +97.5 (*c* 0.63, CH_2Cl_2) with 92% ee for pure **3d**-*endo*. R_f = 0.62 (cyclohexane/EtOAc = 6:1). IR: 3032, 2978, 2932, 1732, 1497, 1456, 1370, 1309, 1256, 1148, 735. ^{1}H NMR (400 MHz, $CDCl_3$): 9.46 (s, *β*-CHO, 1H), 7.40 (d, *J* = 7.0 Hz, Harom, 2H), 7.33 (t, *J* = 7.0 Hz, Harom, 2H), 7.26 (m, Harom, 1H), 4.05 (d, *J* = 14.5 Hz, CH_2Ph, 1H), 3.85 (d, *J* = 14.5 Hz, CH_2Ph, 1H), 3.18 (d, *J* = 12.8 Hz, 4*β*- CH_2, 1H), 1.88 (d, *J* = 12.8 Hz, 4*α*-CH_2, 1H), 1.46 (s, 3*α*-Me and *t*-Bu, 12H), 1.25 (s, 5*α*-Me, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 18.3 (3-CH_3), 19.3 (5-CH_3), 27.9 (ester *t*-Bu), 50.0 (CH_2), 55.1 (CH_2Ph), 69.6 (3-C), 81.9 (*t*-Bu C), 83.7 (5-C), 127.1 (CH), 128.1 (CH × 2), 128.3 (CH × 2), 138.4 (C), 171.2 (C═O), 205.0 (CHO). HRMS (CI + NH_3CH_4): *m*/*z* calcd for $C_{18}H_{25}NO_4$ 320.1856 [M + H]$^+$, found 320.1868. Enantioselectivity was determined by chiral HPLC analysis after reduction of **3d**-*endo* with $NaBH(OAc)_3$ to the corresponding alcohol **8d**-*endo*.

(+)-(3*R*,5*S*)-Ethyl 2-Benzyl-5-formyl-3,5-dimethylisoxazolidine-3-carboxylate (3e-*endo*) (Table 3, entry 2). In a 10 mL tube, **2e** (55.3 mg, 0.25 mmol) and (*R*,*R*-**1**) (35.0 mg, 0.025 mmol) were charged and suspended in MTBE (1.2 mL). The mixture was cooled to −10 °C and stirred for 5 min before the addition of methacrolein (0.04 mL, 0.5 mmol). The reaction mixture was quenched after 5 days by adding acetone (0.5 mL) at −10 °C and stirred at room temperature for 10 min before the addition of pentane (10 mL) to precipitate the catalyst. Filtration over Celite, washing with pentane, and concentration *in vacuo* gave a crude oil. Conversion and diastereoselectivity was determined by ^{1}H NMR of the crude to be 43% and *endo*/*exo* 63:37, respectively. Column chromatography (cyclohexane/EtOAc = 19:1 to 9:1) gave 30.7 mg, 42% total yield as a pale yellow oil. $[\alpha]^{20}_D$ = +72.6 (*c* 0.49, CH_2Cl_2) with 84% ee for pure **3e**-*endo*. R_f = 0.40 (cyclohexane/EtOAc = 6:1). IR: 2974, 2882, 1731, 1497, 1456, 1373, 1241, 1156, 1007, 738. ^{1}H NMR (400 MHz, $CDCl_3$): 9.47 (s, *β*-CHO, 1H), 7.40 (dd, *J* = 6.9, 2.4 Hz, Harom, 2H), 7.34−7.30 (tt, *J* = 6.9, 1.4 Hz, Harom, 2H), 7.26 (tt, *J* = 6.9, 1.4 Hz, Harom, 1H), 4.17 (q, *J* = 7.1 Hz, ester CH_2, 2H), 4.05 (d, *J* = 14.4 Hz, CH_2Ph, 1H), 3.88 (d, *J* = 14.4 Hz, CH_2Ph, 1H), 3.19 (d, *J* = 13.0 Hz, 4*β*- CH_2, 1H), 1.93 (d, *J* = 13.0 Hz, 4*α*-CH_2, 1H), 1.50 (s, 3*α*-Me, 3H), 1.27 (t, *J* = 7.1 Hz, ester Me, 1H), 1.267 (s, 5*α*-Me, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.1 (5-CH_3), 18.5 (3-CH_3), 19.5 (ester CH_3), 49.8 (4-CH_2), 55.2 (CH_2Ph), 61.4 (ester CH_2), 69.1 (3-C), 83.7 (5-C), 127.2 (CH), 128.19 (CH × 2), 128.25 (CH × 2), 138.1 (C), 172.0 (C═O), 204.8 (CHO). HRMS (CI + NH_3CH_4): *m*/*z* calcd for $C_{16}H_{21}NO_4$ 292.1543 [M + H]$^+$, found 292.1557. Enantioselectivity was determined by chiral HPLC analysis after reduction of **3e**-*endo* with $NaBH(OAc)_3$ to the corresponding alcohol **8e**-*endo*.

(+)-(3*R*,5*R*)-Ethyl 2-Benzyl-5-formyl-3,5-dimethylisoxazolidine-3-carboxylate (3e-*exo*) (Table 3, entry 3). In a 10 mL tube, **2e** (55.3 mg, 0.25 mmol) and (*R*,*R*-**1**) (35.0 mg, 0.025 mmol) were charged and suspended in toluene (1.2 mL). The mixture was cooled to 0 °C and stirred for 5 min before the addition of methacrolein (0.04 mL, 0.5 mmol). The reaction mixture was quenched after 5.5 days by adding acetone (0.5 mL) at −10 °C and stirred at room temperature for 2 min before the addition of pentane (10 mL) to precipitate the catalyst. Filtration over Celite, washing with pentane, and concentration *in vacuo* gave a crude oil. Conversion and diastereoselectivity were determined by ^{1}H NMR of the crude to be 86% and *endo*/*exo* 14:86, respectively. Column chromatography (cyclohexane/EtOAc = 19:1 to 9:1) gave 62 mg, 85% total yield and pure **3e**-*exo* adduct was isolated in 47.0 mg, 65% yield as a colorless oil. $[\alpha]^{20}_D$ = +159.2 (*c* 0. 97, $CHCl_3$) with 66% ee for pure **3e**-*exo*. R_f = 0.44 (cyclohexane/EtOAc = 6:1). IR: 2982, 2936, 2806, 1728, 1497, 1455, 1374, 1288, 1250, 1175, 1068, 739, 699. ^{1}H NMR (400 MHz, $CDCl_3$): 9.42 (s, *α*-CHO, 1H), 7.37−7.30 (m, Harom, 4H), 7.26 (m, Harom, 1H), 4.29 (q, *J* = 7.1 Hz, ester CH_2, 2H), 4.04 (d, *J* = 14.7 Hz, CH_2Ph, 1H), 3.74 (d, *J* = 14.7 Hz, CH_2Ph, 1H), 2.69 (d, *J* = 12.7 Hz, 4*β*- CH_2, 1H), 2.49 (d, *J* = 12.7 Hz, 4*α*-CH_2, 1H), 1.40 (s, 3*α*-Me, 3H), 1.36 (t, *J* = 7.1 Hz, ester Me, 1H), 1.31 (s, 5*β*-Me, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.3 (ester CH_3), 17.9 (5-CH_3), 20.9 (3-CH_3), 47.3 (4-CH_2), 55.1 (CH_2Ph), 61.1 (ester CH_2), 69.4 (3-C), 83.6 (5-C), 127.1 (CH), 128.0 (CH × 2), 128.2 (CH × 2), 138.0 (C), 171.8 (C═O), 206.2 (CHO). HRMS (CI + NH_3CH_4): *m*/*z* calcd for $C_{16}H_{21}NO_4$ 292.1543 [M + H]$^+$, found 292.1543. Enantioselectivity was determined by chiral HPLC analysis after reduction of **3e**-*exo* with $NaBH(OAc)_3$ to the corresponding alcohol **8e**-*exo*.

(+)-(3*R*,5*S*)-Methyl 5-Formyl-2,3,5-trimethylisoxazolidine-3-carboxylate (3f-*endo*) (Table 3, entry 5). In a 10 mL tube, **2f** (33 mg, 0.25 mmol) and (*R*,*R*-**1**) (35.0 mg, 0.025 mmol) were charged and suspended in MTBE (1.2 mL). The mixture was cooled to −10 °C and stirred for 5 min before the addition of methacrolein (0.04 mL, 0.5 mmol). The reaction mixture was quenched after 6 days by adding acetone (0.5 mL) at −10 °C and stirred at room temperature for 2 min before the addition of pentane (10 mL) to precipitate the catalyst. Filtration over Celite, washing with pentane, and concentration *in vacuo* gave a crude oil. Conversion and diastereoselectivity were determined by ^{1}H NMR of the crude to be 95% and *endo*/*exo* 68:32, respectively. Column chromatography (cyclohexane/EtOAc = 19:1 to 6:1) gave 44.6 mg, 89% total yield as a pale yellow oil. $[\alpha]^{20}_D$ = +124.9 (*c* 0.55, $CHCl_3$) for a mixture of *endo* /*exo* (92:8) with 80% ee for **3f**-*endo*. R_f = 0.56 (cyclohexane/EtOAc = 3:1). IR: 2956, 1737, 1640, 1519, 1475, 1375, 1291, 1193, 1156, 1091, 982. ^{1}H NMR (400 MHz, $CDCl_3$): 9.63 (s, *β*-CHO, 1H), 3.71 (s, ester Me, 3H), 3.17 (d, *J* = 13.0 Hz, 4*β*- CH_2, 1H), 2.70 (s, N-Me, 3H), 1.92 (d, *J* = 13.0 Hz, 4*α*-CH_2, 1H), 1.39 (s, 3*α*-Me, 3H), 1.31 (s, 5*α*-Me, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 17.9 (3-CH_3), 19.9 (5-CH_3), 38.2 (N−CH_3), 49.4 (CH_2), 52.4 (ester CH_3), 69.5 (3-C), 83.7 (5-C), 172.4 (C═O), 204.2 (CHO). HRMS (DCI + NH_3CH_4): *m*/*z* calcd for $C_9H_{15}NO_4$ 202.1074 [M + H]$^+$, found 202.1083. Enantioselectivity was determined by chiral HPLC analysis after reduction of **3f**-*endo* with $NaBH(OAc)_3$ to the corresponding alcohol **8f**-*endo*.

(3*R*,5*R*)-Methyl 5-Formyl-2,3,5-trimethylisoxazolidine-3-carboxylate (3f-*exo*). R_f = 0.64 (cyclohexane/EtOAc = 3:1). IR: 2954, 2887, 1732, 1447, 1376, 1289, 1255, 1192, 1169, 1094. ^{1}H NMR (400 MHz, $CDCl_3$): 9.60 (s, *α*-CHO, 1H), 3.76 (s, ester Me, 3H), 2.64 (d, *J* = 12.8 Hz, 4*β*-CH_2, 1H), 2.62 (s, N-Me, 3H), 2.44 (d, *J* = 12.8 Hz, 4*α*-CH_2, 1H), 1.33 (s, 5*β*-Me, 3H), 1.29 (s, 3*αβ*-Me, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 18.1 (3-CH_3), 20.7 (5-CH_3), 38.5 (N−CH_3), 47.0 (CH_2), 51.9 (ester CH_3), 70.3 (3-C), 84.0 (5-C), 172.3 (C═O), 204.6 (CHO). HRMS (CI + NH_3CH_4): *m*/*z* calcd for $C_9H_{15}NO_4$: 202.1074 [M + H]$^+$, found 202.1088.

(+)-(3*R*,5*R*)-Ethyl 5-Formyl-2,3,5-trimethylisoxazolidine-3-carboxylate (3g-*exo*) (Table 3, entry 8). In a 10 mL tube, **2g** (36.3 mg, 0.25 mmol) and (*R*,*R*-**1**) (35.0 mg, 0.025 mmol) were charged and suspended in CH_2Cl_2 (1.2 mL). The mixture was cooled to 0 °C and stirred for 5 min before the addition of methacrolein (0.04 mL, 0.5 mmol). The reaction mixture was quenched after 5.5 days by adding acetone (0.5 mL) at 0 °C and stirred at room temperature for 2 min before the addition of pentane (10 mL) to precipitate the catalyst. Filtration over Celite, washing with pentane, and concentration *in vacuo* gave a crude oil. Conversion and diastereoselectivity were determined by ^{1}H NMR of the crude to be 100% and *endo*/*exo* 7:93, respectively. Column chromatography (cyclohexane/EtOAc = 19:1 to 9:1) gave 46 mg, 86% total yield and pure **3g**-*exo* adduct was isolated in 41.3 mg, 77% yield as a pale yellow oil. $[\alpha]^{20}_D$ = +166.8 (*c* 0.71, CH_2Cl_2) with 81% ee for pure **3g**-*exo*. R_f = 0.38 (cyclohexane/EtOAc = 4:1). IR: 2984, 2939, 1728, 1447, 1376, 1254, 1179, 1094, 1021. ^{1}H NMR (400 MHz, $CDCl_3$): 9.61 (s, *α*-CHO, 1H), 4.23 (q, *J* = 7.1 Hz, ester CH_2, 2H), 2.65 (d, *J* = 12.8 Hz, 4*β*- CH_2, 1H), 2.64 (s, N-Me, 3H), 2.44 (d, *J* = 12.8 Hz, 4*α*-CH_2, 1H), 1.35 (s, 5*β*-Me, 3H), 1.32 (t, *J* = 7.1 Hz, ester Me, 3H), 1.30 (s, 3*α*-Me, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.3 (ester CH_3), 18.0 (5-CH_3), 20.6 (3-CH_3), 38.4 (N−CH_3), 46.9 (CH_2), 61.0 (ester CH_2), 70.0 (3-C), 83.8 (5-C), 171.7 (C═O), 204.7 (CHO). HRMS (DCI + NH_3CH_4): *m*/*z* calcd for $C_{10}H_{17}NO_4$ 216.1230 [M + H]$^+$, found 216.1237. Enantioselectivity was determined by chiral HPLC analysis after reduction of **3g**-*exo* with $NaBH_4$ to the corresponding alcohol **8g**-*exo*.

(−)-(3*R*,5*S*)-Methyl 2-Benzyl-3,5-dimethyl-5-((((*S*)-1-phenylethyl)amino)methyl)isoxazolidine-3-carboxylate (6). To a mixture of **3a** (33.0 mg, 0.120 mmol, *endo*/*exo* = 97:3, 87%

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ee), Na_2SO_4 (20 mg) in CH_2Cl_2 (1.0 mL) was added a solution of (*S*)-α-(−)-methyl benzylamine (14.6 mg, 0.120 mmol) in CH_2Cl_2 (1.0 mL) at room temperature. The reaction mixture was stirred for 20 h, then $NaBH(OAc)_3$ (102 mg, 0.480 mmol) and glacial acetic acid (29 mg, 0.480 mmol) were successively added. After stirring at room temperature for 4 h, the reaction mixture was diluted with CH_2Cl_2 (5 mL) and quenched with H_2O (1 mL) at 0 °C. The mixture was stirred at room temperature for 10 min, then the aqueous layer was extracted with CH_2Cl_2 (10 mL × 3) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude was purified by column chromatography (cyclohexane/EtOAc, 3:1 to 1:1) to afford compound **6** (38 mg, 83%, dr 97.5:2.5) as a colorless oil. $[\alpha]^{25}_D$ = −18.6 (*c* 1.02, $CHCl_3$) along with minor isomer (6 mg, 13%) in 96% global yield. IR: 2953, 2927, 1738, 1495, 1453, 1267, 1128, 1028. ^{1}H NMR (400 MHz, $CDCl_3$): 7.40 (d, *J* = 7.3 Hz, Harom, 2H), 7.32 (t, *J* = 7.3 Hz, Harom, 2H), 7.28−7.24 (m, Harom, 3H), 7.23−7.17 (m, Harom, 3H), 4.00 (d, *J* = 14.4 Hz, CH_2Ph, 1H), 3.83 (d, *J* = 14.4 Hz, CH_2Ph, 1H), 3.69 (s, Me ester, 3H), 3.67 (q, *J* = 6.6 Hz, 5-CHPh, 1H), 3.10 (br s, NH, 1H), 2.86 (d, *J* = 11.5 Hz, 5β-CH_2, 1H), 2.74 (d, *J* = 12.7 Hz, 4β-CH_2, 1H), 2.22 (d, *J* = 11.5 Hz, 5α-CH_2, 1H), 1.87 (d, *J* = 12.7 Hz, 4α-CH_2, 1H), 1.46 (s, 3α-Me, 3H), 1.30 (s, 5α-Me, 3H), 1.19 (d, *J* = 6.6 Hz, Me, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 19.1 (3-CH_3), 24.1 (5-CH_3), 24.9 (CH_3), 51.3 (4-CH_2), 52.0 (ester CH_3), 54.7 (5-CH_2), 55.2 (CH_2Ph), 58.5 (CHPh), 69.3 (3-C), 79.7 (5-C), 126.6 (CH), 126.7 (CH × 2), 126.8 (CH), 128.09 (CH × 2), 128.13 (CH × 2), 128.2 (CH × 2), 139.0 (C), 146.1 (C), 173.5 (C═O). HRMS (ESI+): *m*/*z* calcd for $C_{23}H_{30}N_2O_3$ 383.2329 $[M + H]^+$, found 383.2312.

(−)-(1*R*,5*S*)-7-Benzyl-1,5-dimethyl-3-[(*S*)-1-phenylethyl]-6-oxa-3,7-diazabicyclo[3.2.1]octan-2-one (7). In a 10 mL vial, to a solution of **6** (84 mg, 0.22 mmol, dr 88:12) in a mixture of THF/water (2:1, 3.0 mL) was added LiOH (11 mg, 0.44 mmol) at room temperature. The mixture was stirred for 5 h at room temperature before concentration *in vacuo*, then quenched by adding an aqueous solution of citric acid (160 mg in 5 mL), and stirred at room temperature for 10 min. Extraction of the aqueous layer with CH_2Cl_2 (15 mL × 4), followed by drying the combined organic layers with $MgSO_4$, filtration, and concentration *in vacuo* afforded the crude carboxylic acid. The crude was dissolved in CH_2Cl_2 (3 mL) and treated with DCC (68.0 mg, 0.33 mmol) and DMAP (13.5 mg, 0.11 mmol) at room temperature, and the reaction mixture was stirred for 14 h. The mixture was concentrated *in vacuo* and treated with Et_2O to precipitate the urea derivatives. After filtration, washing with Et_2O, and evaporation *in vacuo*, the resulting crude was purified by column chromatography (petroleum ether/EtOAc = 5:1 to 3:1) to afford compound **7** (53 mg, 69% yield) as a diastereomerically pure white solid, mp 123−124 °C. $[\alpha]^{20}_D$ = −179.5 (*c* 1.0, $CHCl_3$), along with two isomers (16 mg, 21% yield, dr 70:30) in global yield 90%. IR: 3030, 2976, 2935, 1646, 1496, 1454, 1274, 1207, 1170, 1029, 910, 699. ^{1}H NMR (400 MHz, $CDCl_3$): 7.38−7.22 (m, Harom, 10H), 6.11 (q, *J* = 7.1 Hz, CH, 1H), 4.08 (d, *J* = 14.4 Hz, CH_2Ph, 1H), 3.70 (d, *J* = 14.4 Hz, CH_2Ph, 1H), 3.12 (dd, *J* = 12.0, 1.1 Hz, 4β-CH_2, 1H), 2.65 (d, *J* = 12.0 Hz, 4α-CH_2, 1H), 2.39 (dd, *J* = 11.5, 1.3 Hz, 8β-CH_2, 1H), 2.12 (d, *J* = 11.5 Hz, 8α-CH_2, 1H), 1.62 (d, *J* = 7.1 Hz, CHMe, 3H), 1.46 (s, 1α-Me, 3H), 1.28 (s, 5α-Me, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 15.9 (CH_3), 17.7 (1-CH_3), 21.8 (5-CH_3), 46.3 (8-CH_2), 49.7 (CH), 53.9 (4-CH_2), 57.5 (CH_2Ph), 67.0 (1-C), 76.4 (5-C), 127.1 (CH), 127.50 (CH × 2), 127.54 (CH), 128.3 (CH × 2), 128.60 (CH × 2), 128.63 (CH × 2), 138.0 (C), 139.6 (C), 169.1 (CO). HRMS (ESI+): *m*/*z* calcd for $C_{22}H_{26}N_2O_2$ 351.2067 $[M + H]^+$, found 351.2070.

Typical Procedures for the Determination of Enantioselectivity of Adduct 3. (+)-(3*R*,5*S*)-Methyl 2-Benzyl-5-(hydroxymethyl)-3,5-dimethylisoxazolidine-3-carboxylate (8a-*endo*). In a 10 mL vial, to a solution of **3a**-*endo* (40.0 mg, 0.144 mmol, Table 1, entry 14) in THF (2 mL) were added $NaBH(OAc)_3$ (122.0 mg, 0.576 mmol) and AcOH (36 μL, 0.576 mmol) at room temperature. The reaction mixture was quenched after 17 h by adding water (2.0 mL) and stirred at room temperature for 10 min before extraction with CH_2Cl_2 (10 mL × 4) and EtOAc (10 mL × 1). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give a crude oil. Column chromatography (cyclohexane/EtOAc = 6:1 to 2:1) gave 31.2 mg, 78% total yield with 91% ee as a colorless oil. $[\alpha]^{20}_D$ = +45.9 (*c* 0.59, $CHCl_3$) for pure **8a**-*endo*. IR: 3429, 2978, 2952, 1732, 1497, 1455, 1376, 1271, 1195, 1147, 1051, 739. ^{1}H NMR (400 MHz, $CDCl_3$): 7.38 (d, *J* = 7.1 Hz, Harom, 2H), 7.34−7.29 (tt, *J* = 7.1, 1.4 Hz, Harom, 2H), 7.24 (tt, *J* = 7.2, 1.4 Hz, Harom, 1H), 3.98 (d, *J* = 14.4 Hz, CH_2Ph, 1H), 3.82 (d, *J* = 14.4 Hz, CH_2Ph, 1H), 3.74 (s, ester Me, 3H), 3.52 (d, *J* = 3.5 Hz, CH_2, 2H), 3.26 (s, OH, 1H), 2.96 (d, *J* = 12.7 Hz, 4β-CH_2, 1H), 1.95 (d, *J* = 12.7 Hz, 4α-CH_2, 1H), 1.50 (s, 3α-Me, 3H), 1.25 (s, 5α-Me, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 19.0 (3-CH_3), 22.7 (5-CH_3), 49.0 (4-CH_2), 52.2 (ester CH_3), 54.9 (CH_2Ph), 69.1 (5-CH_2), 69.8 (3-C), 80.2 (5-C), 127.1 (CH), 128.0 (CH × 2), 128.3 (CH × 2), 138.1 (C), 173.2 (C═O). HRMS (FI/FD): *m*/*z* calcd for $C_{15}H_{21}NO_4$ 279.1471 $[M]^+$, found 279.1477. Enantioselectivity was determined by chiral HPLC analysis, Chiralpak As-H, isooctane/*i*-PrOH = 99:1, 1 mL/min, 254 nm; t_R (min): 25.3 (minor) and 32.9 (major) with 91% ee for **8a**-*endo*.

(3*R*,5*R*)-Methyl 2-Benzyl-5-(hydroxymethyl)-3,5-dimethylisoxazolidine-3-carboxylate (8a-*exo*). The same procedure as in **8a**-*endo*. Colorless oil, IR: 3431, 2978, 2938, 1731, 1497, 1455, 1375, 1272, 1167, 1055, 738. ^{1}H NMR (400 MHz, $CDCl_3$): 7.36−7.30 (m, Harom, 4H), 7.24 (m, Harom, 1H), 4.02 (d, *J* = 14.6 Hz, CH_2Ph, 1H), 3.81 (s, ester Me, 3H), 3.65 (d, *J* = 14.6 Hz, CH_2Ph, 1H), 3.56 (d, *J* = 11.0 Hz, 5β-CH_2, 1H), 3.47 (d, *J* = 11.0 Hz, 5α-CH_2, 1H), 2.86 (br s, OH, 1H), 2.67 (d, *J* = 12.5 Hz, 4β-CH_2, 1H), 2.23 (d, *J* = 12.5 Hz, 4α-CH_2, 1H), 1.48 (s, 3α-Me, 3H), 1.29 (s, 5β-Me, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 20.7, 20.8 (3-CH_3, 5-CH_3), 47.6 (4-CH_2), 51.9 (ester CH_3), 55.4 (CH_2Ph), 70.3 (3-C and 5-CH_2), 80.2 (5-C), 127.2 (CH), 128.0 (CH × 2), 128.4 (CH × 2), 138.1 (C), 172.7 (C═O). HRMS (ESI+): *m*/*z* calcd for $C_{15}H_{21}NO_4$ 280.1543 $[M + H]^+$, found 280.1542, 302.1363 $[M + Na]^+$, found 302.1367, 318.1102 $[M + K]^+$, found 318.1107. Enantioselectivity for entry was determined by chiral HPLC analysis, Chiralpak As-H, isooctane/*i*-PrOH = 99:1, 1 mL/min, 254 nm; t_R (min): 19.1 (minor) and 23.4 (major) with 68% ee for **8a**-*exo*.

(−)-(3*R*,5*S*)-Methyl 2-Benzyl-3-ethyl-5-(hydroxymethyl)-5-methylisoxazolidine-3-carboxylate (8b-*endo*). The same procedure as in **8a**-*endo* to give 20.0 mg, 96% yield as a colorless oil. $[\alpha]^{20}_D$ = −43.9 (*c* 0.78, $CHCl_3$) with 84% ee for pure **8b**-*endo*. IR: 3465, 2969, 2875, 1728, 1497, 1455, 1307, 1239, 1157, 1053, 735. ^{1}H NMR (200 MHz, $CDCl_3$): 7.39−7.20 (m, Harom, 5H), 4.00 (d, *J* = 14.7, CH_2Ph, 1H), 3.90 (d, *J* = 14.7 Hz, CH_2Ph, 1H), 3.79 (s, ester Me, 3H), 3.56 (s, 5-CH_2, 2H), 2.94 (d, *J* = 12.9 Hz, 4β-CH_2, 1H), 2.01 (d, *J* = 12.9 Hz, 4α-CH_2, 1H), 2.00 (dq, *J* = 14.3, 7.4 Hz, 3-CH_2, 1H), 1.76 (dq, *J* = 14.3, 7.4 Hz, 3-CH_2, 1H), 1.28 (s, 5α-Me, 3H), 1.00 (t, *J* = 7.4 Hz, 3α-Me, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 9.3 (3-Et CH_3), 23.5 (5-CH_3), 26.3 (3-Et CH_2), 44.5 (4-CH_2), 52.0 (ester CH_3), 54.8 (CH_2Ph), 67.6 (5-CH_2), 74.4 (3-C), 80.6 (5-C), 126.9 (CH), 127.8 (CH × 2), 128.2 (CH × 2), 138.6 (C), 172.9 (C═O). HRMS (ESI+): *m*/*z* calcd for $C_{16}H_{23}NO_4$ 294.1700 $[M + H]^+$, found 294.1709.

Enantioselectivity was determined by chiral HPLC analysis after reduction of **3b**-*endo* with $NaBH(OAc)_3$ to the corresponding alcohol, Chiralpak As-H, isooctane/*i*-PrOH = 98:2, 1 mL/min, 254 nm; t_R (min): 18.0 (minor) and 28.3 (major) with 84% ee for **8b**-*endo*.

(−)-(3*R*,5*S*)-Methyl 2-Benzyl-5-(hydroxymethyl)-5-methyl-3-propylisoxazolidine-3-carboxylate (8c-*endo*). The same procedure as in **8a**-*endo* to give 25.0 mg, 92% yield as a colorless oil. $[\alpha]^{20}_D$ = −44.6 (*c* 0.52, $CHCl_3$) with 86% ee for pure **8c**-*endo*. IR: 3447, 2960, 2930, 2873, 1729, 1455, 1224, 1157, 1053, 911. ^{1}H NMR (400 MHz, $CDCl_3$): 7.36 (d, *J* = 6.9 Hz, Harom, 2H), 7.33−7.28 (tt, *J* = 6.9, 1.4 Hz, Harom, 2H), 7.23 (tt, *J* = 7.1, 1.4 Hz, Harom, 1H), 4.00 (d, *J* = 14.7 Hz, CH_2Ph, 1H), 3.91 (d, *J* = 14.7 Hz, CH_2Ph, 1H), 3.78 (s, ester Me, 3H), 3.54 (s, 5-CH_2, 2H), 2.99 (s, OH, 1H), 2.94 (d, *J* = 12.9 Hz, 4β-CH_2, 1H), 2.00 (d, *J* = 12.9 Hz, 4α-CH_2, 1H), 1.96 (dt, *J* = 13.2, 4.7 Hz, 3-CH_2, 1H), 1.69 (dt, *J* = 13.2, 4.7 Hz, 3-CH_2, 1H), 1.45−1.34 (m, 3-CH_2, 2H), 1.27 (s, 5α-Me, 3H), 0.97 (t, *J* = 7.3 Hz, 3α-Me, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.6 (3-CH_3), 18.4 (5-CH_3), 23.5 (3-CH_2), 35.8 (3-CH_2), 45.0 (4-CH_2), 52.0 (ester CH_3), 54.8 (CH_2Ph),

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67.6 (5-CH_2), 73.8 (3-C), 80.6 (5-C), 126.9 (CH), 127.8 (CH × 2), 128.2 (CH × 2), 138.6 (C), 172.9 (C═O). HRMS (ESI+): *m*/*z* calcd for $C_{17}H_{25}NO_4$ 308.1856 $[M + H]^+$, found 308.1853; 330.1676 $[M + Na]^+$, found 330.1697; 346.1415 $[M + K]^+$, found 346.1421. Enantioselectivity was determined by chiral HPLC analysis after reduction of **3c**-*endo* with $NaBH(OAc)_3$ to the corresponding alcohol, Chiralpak As-H, isooctane/*i*-PrOH = 99:1, 1 mL/min, 230 nm; t_R (min): 32.6 (minor) and 41.1 (major) with 86% ee for **8c**-*endo*.

(+)-(3*R*,5*S*)-*tert*-Butyl 2-Benzyl-5-(hydroxymethyl)-3,5-dimethylisoxazolidine-3-carboxylate (8d-*endo*). The same procedure as in **8a**-*endo* to give 11.9 mg, 95% yield as a colorless oil. $[\alpha]^{20}_D$ = +42.8 (*c* 0.1, $CHCl_3$) with 92% ee for pure **8d**-*endo*. IR: 3438, 2977, 2935, 1728, 1497, 1455, 1369, 1256, 1147, 1053, 735. ^{1}H NMR (200 MHz, $CDCl_3$): 7.35−7.13 (m, Harom, 5H), 3.95 (d, *J* = 14.3, CH_2Ph, 1H), 3.70 (d, *J* = 14.3 Hz, CH_2Ph, 1H), 3.49 (d, *J* = 11.5 Hz, 5-CH_2, 1H), 3.42 (d, *J* = 11.5 Hz, 5-CH_2, 1H), 3.31 (br s, OH, 1H), 2.87 (d, *J* = 12.6 Hz, 4*β*-CH_2, 1H), 1.84 (d, *J* = 12.6 Hz, 4*α*-CH_2, 1H), 1.42 (s, ester *t*-Bu, 9H), 1.40 (s, 3*α*-Me, 3H), 1.16 (s, 5*α*-Me, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 18.9 (3-CH_3), 22.6 (5-CH_3), 28.1 (*t*-Bu CH_3 × 3), 49.1 (4-CH_2), 55.0 (CH_2Ph), 69.4 (5-CH_2), 70.2 (3-C), 80.1 (5-C), 82.0 (*t*-Bu C), 127.1 (CH), 128.0 (CH × 2), 128.4 (CH × 2), 138.5 (C), 172.0 (C═O). HRMS (ESI+): *m*/*z* calcd for $C_{18}H_{27}NO_4$ 322.2013 $[M + H]^+$, found 322.2005; 344.1832 $[M + Na]^+$, found 344.1837. Enantioselectivity was determined by chiral HPLC analysis after reduction of **3d**-*endo* with $NaBH_4$ to the corresponding alcohol, Chiralpak As-H, isooctane/*i*-PrOH = 99:1, 1 mL/min, 218 nm; t_R (min): 8.9 (minor) and 11.3 (major) with 92% ee for **8d**-*endo*.

(+)-(3*R*,5*S*)-Ethyl 2-Benzyl-5-(hydroxymethyl)-3,5-dimethylisoxazolidine-3-carboxylate (8e-*endo*). The same procedure as in **8a**-*endo* to give 10.2 mg, 60% yield as a colorless oil. $[\alpha]^{20}_D$ = +33.8 (*c* 0.32, $CHCl_3$) with 84% ee for pure **8e**-*endo*. IR: 3445, 2980, 2936, 2875, 1733, 1497, 1455, 1375, 1268, 1167, 1051, 735. ^{1}H NMR (200 MHz, $CDCl_3$): 7.34−7.17 (m, Harom, 5H), 4.14 (q, *J* = 7.1 Hz, ester CH_2, 2H), 3.93 (d, *J* = 14.5 Hz, CH_2Ph, 1H), 3.73 (d, *J* = 14.5 Hz, CH_2Ph, 1H), 3.46 (s, CH_2, 2H), 2.90 (d, *J* = 12.7 Hz, 4*β*-CH_2, 1H), 1.89 (d, *J* = 12.7 Hz, 4*α*-CH_2, 1H), 1.44 (s, 3*α*-Me, 3H), 1.23 (t, *J* = 7.1 Hz, ester Me, 3H), 1.18 (s, 5*α*-Me, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.2 (Et CH_3), 18.9 (3-CH_3), 22.7 (5-CH_3), 49.0 (4-CH_2), 55.0 (CH_2Ph), 61.3 (Et CH_2), 69.4 (5-CH_2), 69.7 (3-C), 80.2 (5-C), 127.1 (CH), 128.0 (CH × 2), 128.3 (CH × 2), 138.3 (C), 172.8 (C═O). HRMS (ESI+): *m*/*z* calcd for $C_{16}H_{23}NO_4$ 294.1700 $[M + H]^+$, found 294.1703; 316.1519 $[M + Na]^+$, found 316.1529. Enantioselectivity was determined by chiral HPLC analysis after reduction of **3e**-*endo* with $NaBH_4$ to the corresponding alcohol, Chiralpak As-H, isooctane/*i*-PrOH = 99:1, 1 mL/min, 210 nm; t_R (min): 20.1 (minor) and 26.5 (major) with 84% ee for **8e**-*endo*.

(+)-(3*R*,5*R*)-Ethyl 2-Benzyl-5-(hydroxymethyl)-3,5-dimethylisoxazolidine-3-carboxylate (8e-*exo*). The same procedure as in **8a**-*endo* to give 23.0 mg, 99% yield as a colorless oil. $[\alpha]^{20}_D$ = +85.3 (*c* 0.93, $CHCl_3$) with 66% ee for pure **8e**-*exo*. IR: 3435, 2980, 2935, 2873, 1725, 1497, 1455, 1375, 1260, 1167, 1060, 737. ^{1}H NMR (200 MHz, $CDCl_3$): 7.29−7.14 (m, Harom, 5H), 4.21 (q, *J* = 7.1 Hz, ester CH_2, 2H), 3.97 (d, *J* = 14.6 Hz, CH_2Ph, 1H), 3.61 (d, *J* = 14.6 Hz, CH_2Ph, 1H), 3.49 (d, *J* = 11.0 Hz, 5-CH_2, 1H), 3.40 (d, *J* = 11.0 Hz, 5-CH_2, 1H), 2.78 (br s, OH, 1H), 2.61 (d, *J* = 12.5 Hz, 4*β*-CH_2, 1H), 2.16 (d, *J* = 12.5 Hz, 4*α*-CH_2, 1H), 1.41 (s, 3*α*-Me, 3H), 1.29 (t, *J* = 7.1 Hz, ester Me, 3H), 1.22 (s, 5*α*-Me, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.4 (Et CH_3), 20.7, 20.8 (3-CH_3, 5-CH_3), 47.6 (4-CH_2), 55.3 (CH_2Ph), 61.1 (Et CH_2), 70.2, 70.4 (5-CH_2, 3-C), 80.2 (5-C), 127.2 (CH), 128.0 (CH × 2), 128.4 (CH × 2), 138.2 (C), 172.2 (C═O). HRMS (ESI+): *m*/*z* calcd for $C_{16}H_{23}NO_4$ 294.1700 $[M + H]^+$, found 294.1701; 316.1519 $[M + Na]^+$, found 316.1517. Enantioselectivity was determined by chiral HPLC analysis after reduction of **3e**-*exo* with $NaBH(OAc)_3$ to the corresponding alcohol, Chiralpak As-H, isooctane/*i*-PrOH = 99:1, 1 mL/min, 254 nm; t_R (min): 16.3 (minor) and 19.9 (major) with 66% ee for **8e**-*exo*.

(+)-(3*R*,5*S*)-Methyl 5-(Hydroxymethyl)-2,3,5-trimethylisoxazolidine-3-carboxylate (8f-*endo*). The same procedure as in **8a**-*endo* to give 14.4 mg, 75% yield as a colorless oil. $[\alpha]^{20}_D$ = +12.2 (*c* 0.05, $CHCl_3$) with 80% ee for pure **8f**-*endo*. IR: 3385, 2925, 2854, 1740, 1458, 1377, 1273, 1202, 1165. ^{1}H NMR (400 MHz, $CDCl_3$): 3.75 (s, ester Me, 3H), 3.63 (d, *J* = 11.3 Hz, 5-CH_2, 1H), 3.52 (d, *J* = 11.3 Hz, 5-CH_2, 1H), 2.96 (d, *J* = 12.8 Hz, 4*β*-CH_2, 1H), 2.63 (s, NCH_3, 3H), 1.95 (d, *J* = 12.8 Hz, 4*α*-CH_2, 1H), 1.63 (br s, OH, 1H), 1.40 (s, 3*α*-Me, 3H), 1.28 (s, 5*α*-Me, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 23.0 (3-CH_3), 29.7 (5-CH_3), 37.9 (N−CH_3), 49.0 (4-CH_2), 52.3 (ester CH_3), 70.1 (3-C and 5-CH_2), 80.3 (5-C), 173.2 (C═O). HRMS (ESI+): *m*/*z* calcd for $C_9H_{17}NO_4$ 204.1230 $[M + H]^+$, found 204.1221. Enantioselectivity was determined by chiral HPLC analysis after reduction of **3f**-*endo* with $NaBH(OAc)_3$ to the corresponding alcohol, Chiralpak As-H, isooctane/*i*-PrOH = 99:1, 1 mL/min, 254 nm; t_R (min): 23.2 (minor) and 29.2 (major) with 80% ee for **8f**-*endo*.

(+)-(3*R*,5*R*)-Ethyl 5-(Hydroxymethyl)-2,3,5-trimethylisoxazolidine-3-carboxylate (8g-*exo*). The same procedure as in **8a**-*endo* to give 10.1 mg, 65% yield as a colorless oil. $[\alpha]^{20}_D$ = +100.2 (*c* 0.19, $CHCl_3$) with 81% ee for pure **8g**-*exo*. IR: 3414, 2976, 2937, 2874, 1725, 1447, 1376, 1274, 1179, 1066. ^{1}H NMR (200 MHz, $CDCl_3$): 4.23 (q, *J* = 7.1 Hz, ester CH_2, 2H), 3.66 (d, *J* = 11.0 Hz, 5-CH_2, 1H), 3.54 (br s, OH, 1H), 3.53 (d, *J* = 11.0 Hz, 5-CH_2, 1H), 2.65 (d, *J* = 12.5 Hz, 4*β*-CH_2, 1H), 2.60 (s, NCH_3, 3H), 2.29 (d, *J* = 12.5 Hz, 4*α*-CH_2, 1H), 1.39 (s, 3*α*-Me, 3H), 1.32 (t, *J* = 7.1 Hz, ester Me, 3H), 1.31 (s, 5*α*-Me, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.3 (Me CH_2), 20.3 (3-CH_3), 20.8 (5-CH_3), 38.2 (N−CH_3), 47.6 (4-CH_2), 60.9 (Et CH_2), 70.7 (3-C), 71.3 (5-CH_2), 80.3 (5-C), 171.9 (C═O). HRMS (ESI+): *m*/*z* calcd for $C_{10}H_{19}NO_4$ 218.1387 $[M + H]^+$, found 218.1380. Enantioselectivity was determined by chiral HPLC analysis after reduction of **3g**-*exo* with $NaBH_4$ to the corresponding alcohol, Chiralpak As-H, isooctane/*i*-PrOH = 99:1, 1 mL/min, 254 nm; t_R (min): 14.0 (minor) and 20.7 (major) 81% ee for **8g**-*exo*.

(−)-(1*R*,5*S*)-7-Benzyl-1,5-dimethyl-3,6-dioxa-7-azabicyclo-[3.2.1]octan-2-one (9). In a 25 mL flask, to a solution of **8a**-*endo* (80 mg, 0.286 mmol) in a mixture of THF/water (2:1, 4.5 mL) was added LiOH (13.7 mg, 0.572 mmol) at room temperature. The mixture was stirred for 1 h at room temperature, and then the reaction mixture was diluted with CH_2Cl_2 (4 mL), quenched by adding 1 N HCl (2 mL) at 0 °C, and stirred at room temperature for 10 min. Extraction of the aqueous layer with CH_2Cl_2 (10 mL × 4), followed by drying the combined organic layers with $MgSO_4$, filtration, and concentration *in vacuo* afforded the crude carboxylic acid. The crude was dissolved in CH_2Cl_2 (4 mL) and treated with DCC (89.0 mg, 0.427 mmol) and DMAP (17.5 mg, 0.143 mmol) at room temperature, and the reaction mixture was stirred for 2 h. The mixture was concentrated *in vacuo* and treated with Et_2O to precipitate the urea derivatives. After filtration, washing with Et_2O, and evaporation *in vacuo*, the resulting crude solid was purified by column chromatography (petroleum ether/EtOAc = 4:1) leading to compound **9** (63.0 mg, 89% yield) as a white solid, mp 90−91 °C. $[\alpha]^{20}_D$ = −175.0 (*c* 0.53, $CHCl_3$) with 88% ee. IR: 2982, 2935, 1739, 1455, 1378, 1272, 1139, 1035. ^{1}H NMR (400 MHz, $CDCl_3$): 7.37 (dd, *J* = 7.1, 1.7 Hz, Harom, 2H), 7.35−7.30 (tt, *J* = 7.1, 1.7 Hz, Harom, 2H), 7.27 (tt, *J* = 6.1, 1.6 Hz, Harom, 1H), 4.25 (dd, *J* = 11.2, 2.0 Hz, 4*β*-CH_2, 1H), 4.16 (d, *J* = 11.2 Hz, 4*α*-CH_2, 1H), 4.03 (dd, *J* = 14.1 Hz, CH_2Ph, 1H), 3.77 (d, *J* = 14.1 Hz, CH_2Ph, 1H), 2.51 (dd, *J* = 11.9, 2.0 Hz, 8*β*-CH_2, 1H), 2.37 (d, *J* = 11.9 Hz, 8*α*-CH_2, 1H), 1.45 (s, 1*α*-Me, 3H), 1.35 (s, 5*α*-Me, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 17.8 (1-CH_3), 18.9 (5-CH_3), 45.4 (8-CH_2), 57.8 (CH_2Ph), 67.3 (1-C), 76.7 (5-C), 78.9 (4-CH_2), 127.4 (CH), 128.4 (CH × 2), 128.6 (CH × 2), 137.1 (C), 170.1 (C═O). HRMS (ESI+): *m*/*z* calcd for $C_{14}H_{17}NO_3$ 248.1281 $[M + H]^+$, found 248.1272; 270.1101 $[M + Na]^+$, found 270.1094. Enantioselectivity was determined by chiral HPLC analysis, Chiralpak As-H, isooctane/*i*-PrOH = 97:3, 1 mL/min, 230 nm; t_R (min): 33.5 (minor) and 36.8 (major) ; 88% ee.

(+)-*tert*-Butyl ((3*R*,5*S*)-5-Hydroxy-3,5-dimethyl-2-oxotetrahydro-2*H*-pyran-3-yl)carbamate (10). In a 25 mL flask, to a solution of **9** (57 mg, 0.23 mmol, 88% ee) in 2-propanol (3 mL) were added Boc_2O (0.251 g, 1.15 mmol) and Raney-Ni (0.419 g) in 2-propanol (2 mL) at room temperature. Hydrogen gas (balloon) was then charged to the reaction flask. After stirring for 1 h at 80 °C, Raney-Ni was filtered over Celite and then washed with methanol, and the solvent was evaporated in vacuo to afford the crude residue. Column chromatography (CH_2Cl_2/MeOH = 30:1) gave compound

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10 (56 mg, 94% yield) as white amorphous solid, mp 107−108 °C. $[\alpha]^{20}_{D}$ = +5.5 (*c* 1.07, $CHCl_3$). IR: 3354, 2979, 2933, 1760, 1705, 1519, 1455, 1368, 1249, 1166, 1090, 961, 758. ^{1}H NMR (400 MHz, $CDCl_3$): 4.98 (s, NH, 1H), 3.70 (d, *J* = 12.1 Hz, 6*β*-CH_2, 1H), 3.49 (d, *J* = 12.1 Hz, 6*α*-CH_2, 1H), 3.33 (br s, OH, 1H), 2.43 (d, *J* = 13.3 Hz, 4*β*-CH_2, 1H), 2.39 (d, *J* = 13.3 Hz, 4*α*-CH_2, 1H), 1.55 (s, 3*α*-Me, 3H), 1.52 (s, 5*α*-Me, 3H), 1.44 (s, *t*-Bu, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): 23.9 (5-CH_3), 25.2 (3-CH_3), 28.3 (*t*-Bu), 42.7 (4-CH_2), 58.2 (3-C), 68.6 (6-CH_2), 80.5 (C, *t*-Bu), 83.7 (5-C), 154.3 (CO, Boc), 178.1 (CO, lactone). HRMS (FI/FD): *m*/*z* calcd for $C_{12}H_{21}NO_5$ 282.1312 $[M + Na]^+$, found 282.1315; 298.1051 $[M + K]^+$, found 298.1055.

■ ASSOCIATED CONTENT

Supporting Information

Additional experimental procedures and spectroscopic data. Cartesian coordinates (in xyz format) and energies of optimized structures. Results of the Quantum Theory of Atoms In Molecules (QTAIM) study. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: gilles.dujardin@univ-lemans.fr

Notes

The authors declare no competing financial interest.

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