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Asymmetric cycloaddition reactions between 2-benzopyrylium-4-olates and 3-(2-alkenoyl)-2-oxazolidinones in the presence of 2,6-bis(oxazolinyl)pyridine-lanthanoid complexes

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Abstract—Highly enantioselective (96% ee) and *endo*-selective (>99:1) cycloaddition reactions were observed between carbonyl ylides, generated from *o*-(*p*-bromobenzyloxy)carbonyl-α-diazoacetophenone, and 3-crotonoyl-2-oxazolidinone using (4*S*,5*S*)-Pybox-4,5-Ph_2-Yb$(OTf)_3$ (20 mol %) as the chiral Lewis acid catalyst. In contrast, high *exo*-selectivity (*exo*/*endo*=82:18; 96% ee, *exo*) was observed for the reaction of *o*-methoxycarbonyl-α-diazoacetophenone with 3-acryloyl-2-oxazolidinone under similar conditions as reported previously. In the case of cycloaddition reactions between 2-benzopyrylium-4-olate, generated from *o*-methoxycarbonyl-α-diazoacetophenone, and 3-cinnamoyl- or 3-[(*E*)-3-(ethoxycarbonyl)propenoyl]-2-oxazolidinones, using the same chiral Lewis acid, the reaction favored the *endo*-adduct with relatively good enantioselectivity (72 and 78% ee, respectively).

1. Introduction

The 1,3-dipolar cycloaddition reactions between 1,3-dipoles and dipolarophiles have proven to be an efficient and popular procedure in the synthesis of biologically important five-membered heterocyclic compounds, with construction of up to four stereocenters in one concerted process.[1] Accordingly, several examples of highly enantioselective chiral Lewis acid-catalyzed asymmetric cycloaddition reactions of 1,3-dipoles such as nitrones,[2] nitrile oxides,[3] nitrile imines,[4] and diazo alkanes[5] have been developed over the last decade. We have previously reported on the efficient asymmetric induction observed for cycloaddition reactions between a carbonyl ylide, generated from *o*-methoxycarbonyl-α-diazoacetophenone (**1**) via an intramolecular carbenoid–carbonyl reaction, and benzyloxyacetaldehyde derivatives, α-ketobenzyl ester derivatives, and 3-acryloyl-2-oxazolidinone, in the presence of chiral 2,6-bis(oxazolinyl)pyridine (Pybox)-rare earth metal complexes as the Lewis acid catalysts (Scheme 1).[6] From a synthetic point of view, it is valuable to investigate the scope of substrates for the asymmetric cycloadditions of carbonyl ylides[8] toward the preparation of naturally occurring optically active oxabicyclic compounds and their derivatives via tandem intramolecular carbenoid–carbonyl cyclization–cycloaddition sequence.[1a,7] Although various carbonyl dipolarophiles, which can be coordinated in bidentate fashion, have exhibited high enantioselectivities, only 3-acryloyl-2-oxazlidinone (**4a**) has been investigated as an olefinic dipolarophile. To elucidate the scope and limitations of cycloadditions that involve olefinic dipolarophiles, we undertook studies to investigate the reactions of *o*-alkoxycarbonyl-α-diazoacetophenones with 3-crotonoyl-, 3-(2-pentenoyl)-, 3-cinnamoyl-, and 3-[(*E*)-3-(ethoxycarbonyl)propenoyl]-2-oxazolidinones. In this paper, we present our findings on the highly *endo*-selective,[9] with modest to relatively good enantioselectivities, reactions between 1-methoxy-2-benzopyrylium-4-olate and the above 3-(2-alkenoyl)-2-oxazolidinones, in the presence of chiral Pybox-lanthanoid triflate complexes. In contrast, a cycloaddition that involves 3-acryloyl-2-oxazolidinone (**4a**) exhibited high *exo*-selectivity[9] with high enantioselectivity of *exo*-adduct as reported previously.[6] Moreover, high enantioselectivity along with extremely high *endo*-selectivity has been found to obtain for a reaction between *o*-(*p*-bromobenzyloxy)carbonyl-α-diazoacetophenone (**3**) and 3-crotonoyl-2-oxazolidinone using (4*S*,5*S*)-Pybox-4,5-Ph_2-Yb$(OTf)_3$ as a chiral Lewis acid catalyst.

2. Results and discussion

Previous studies have shown that, in addition to the presence of achiral Lewis acids, the ionic radius of the rare earth metal triflates can influence the diastereoselectivity of the

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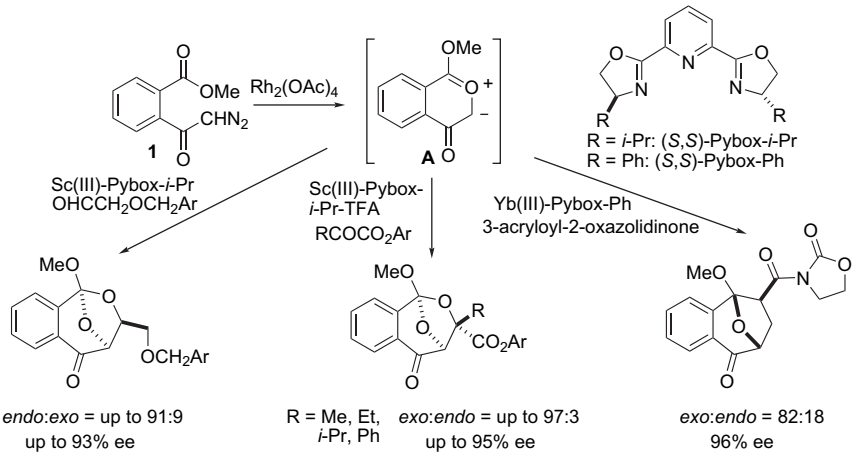


Scheme 1. Asymmetric cycloaddition reactions of 2-benzopyrylium-4-olate catalyzed by chiral Pybox-rare earth metal complexes.

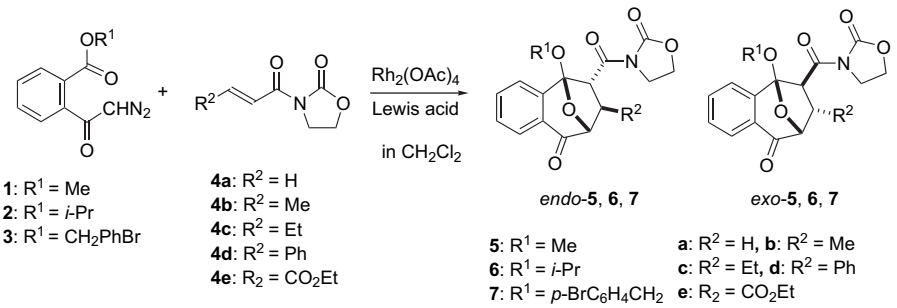
cycloaddition reaction between 1-methoxy-2-benzopyrylium-4-olate (**A**) and 3-acryloyl-2-oxazolidinone (**4a**).[10] To determine whether a similar relationship exist for 3-crotonoyl-2-oxazolidinone (**4b**),[10] the cycloaddition reaction was carried out using several rare earth metal triflates (10 mol %), which involved the slow addition (over a period of 1 h) of a solution of *o*-methoxycarbonyl-α-diazoacetophenone (**1**) to oxazolidinone **4b** (2 equiv) under $Rh_2(OAc)_4$-catalyzed conditions in CH_2Cl_2 at room temperature (Table 1, entries 4 and 5). In the case of $Yb(OTf)_3$ (10 mol %), the presence of the Lewis acid catalyst resulted in only a slight increase of the *exo*-adduct (entry 5 vs 3); significant differences in the diastereoselectivities were not observed. In contrast, the cycloaddition reaction of 3-acryloyl-2-oxazolidinone (**4a**) in the presence of $Yb(OTf)_3$ exhibited a drastic difference in the diastereoselectivities (entry 2 vs 1).[10] Extending the addition time (from 1 to 6 h) of diazocarbonyl substrate **1** slightly increased the *exo*-adduct and resulted in a practically nonstereoselective reaction (entry 6). Cycloaddition reactions using various lanthanoid triflates (entries 6–11) revealed that the diastereoselectivity of the reactions is influenced by the ionic radius of the rare earth metal, of which, under the similar conditions, $Tm(OTf)_3$ exhibited the highest *exo*-selectivity (*exo*/*endo*=63:37). The use of lanthanoid triflates with metal having larger ionic radius than that of Tm increased the amount of the *endo*-adducts (entries 8–11). In the case of $La(OTf)_3$, which has the largest ionic radius, the catalyst was moderately *endo*-selective (entry 11).

Table 1. Reactions of α-diazoacetophenone **1** with oxazolidinone **4a** or **4b** in the absence and in the presence of rare earth metal triflates[a]

Entry	R	Olefin	Lewis acid	Ionic radius (Å)[b]	Addition time (h)	Yield (%)	*endo*:*exo*[c]
1[d]	H	**4a**	None	—	1	82	80:20
2[d]	H	**4a**	$Yb(OTf)_3$	0.87	1	88	19:81
3	Me	**4b**	None	—	1	71	83:17
4	Me	**4b**	$Sc(OTf)_3$	0.75	1	33	85:15
5	Me	**4b**	$Yb(OTf)_3$	0.87	1	55	60:40
6	Me	**4b**	$Yb(OTf)_3$	0.87	6	58	48:52
7	Me	**4b**	$Tm(OTf)_3$	0.88	6	70	37:63
8	Me	**4b**	$Er(OTf)_3$	0.89	6	84	39:61
9	Me	**4b**	$Ho(OTf)_3$	0.90	6	75	46:54
10	Me	**4b**	$Eu(OTf)_3$	0.95	6	78	62:38
11	Me	**4b**	$La(OTf)_3$	1.03	6	41	70:30

[a] The reaction was carried out by adding a solution of diazo compound **1** in CH_2Cl_2 over a period of 1 or 6 h to a suspension of the Lewis acid (10 mol %), MS 4 Å, $Rh_2(OAc)_4$ (2 mol %), and oxazolidinone **4a** or **4b** (2 equiv) in CH_2Cl_2.
[b] See Ref. 11.
[c] Determined by ^1H NMR (400 MHz).
[d] Previously reported, see Ref. 10.

Next, the reaction between diazoacetophenone **1** and oxazolidinone **4b** (Scheme 2) was employed to determine the asymmetric induction using chiral Lewis acid catalysts that were prepared from various chiral Pybox ligands (Fig. 1) and rare earth metal triflates. First, the chiral $Yb(OTf)_3$ catalysts involving (*S*,*S*)-Pybox-Ph or (4*S*,5*S*)-Pybox-4,5-Ph_2 were examined under several reaction temperatures (Table 2, entries 2–5 and 11–13). The catalysts were prepared by stirring the corresponding Pybox ligands and $Yb(OTf)_3$ in THF for 2 h at room temperature, then by drying in vacuo for 1 h. The cycloaddition reactions were conducted by adding a solution of **1** in CH_2Cl_2 to a suspension of the catalyst (10 mol %) in CH_2Cl_2 over a period of 6 h. In terms of the reaction temperatures, reflux or room temperature resulted in relatively good yields (entries 2 and 3), whereas lower temperature resulted in decreased yields (entries 4 and 5). Interestingly, high *endo*-selectivity was observed in all cases, which is in contrast to the reaction without Pybox ligand (Table 1, entry 6), and also to the reaction with 3-acryloyl-2-oxazolidinone (**4a**) under similar conditions (Table 2, entry 1).[6] The difference in the diastereoselectivities of the oxazolidinones **4b** and **4a** reactions using the chiral Yb(III) catalyst can be attributed to dissimilar stabilities of the *endo*- and *exo*-products, which would also govern the character of the corresponding transition states. Although the energy differences may seem minor, simple calculations of the heats of formation by a semi-empirical PM3 method reveal that *endo*-**5b** is more stable than *exo*-**5b** by 1.38 kcal/mol, whereas *exo*-**5a** is more stable than *endo*-**5a** by 3.12 kcal/mol. The higher *endo*-selectivity of the Pybox-$Yb(OTf)_3$ catalyst is attributable to the larger chiral Yb(III) complex, relative to those of achiral lanthanoid triflates, and the increased steric repulsion between the methoxy and the coordinated oxazolidinone moieties during the transition state leads to *exo*-**5b**. The enantioselectivities of *endo*-**5b**, however, were unsatisfactory.



Scheme 2. Reactions of diazoacetophenones **1**, **2**, and **3** with 2-oxazolidinone **4a**–**e**.

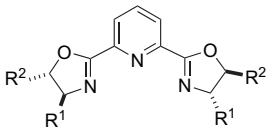


Figure 1. Structures of chiral Pybox ligands.

Effects of the ionic radius on the enantio- and diastereoselectivities of chiral catalysts were examined using several lanthanoid triflates (entries 6–10 and 14–18). Although high enantioselectivity was observed for the minor *exo*-adduct in several cases, especially those utilizing (4*S*,5*S*)-Pybox-4,5-Ph_2 as the chiral ligand (entries 11, 14, and 16), the enantioselectivity of the *endo*-adduct did not improved significantly. Our studies show that the enantioselectivities are somewhat affected by the ionic radius of the metal triflate, and sense of asymmetric induction was switched between Ho and Er when Pybox-Ph was used as a chiral ligand (entries 8 and 9). Improved enantioselectivity of the *endo*-adduct was obtained using the (*S*,*S*)-Pybox-Ph-$Tm(OTf)_3$ catalyst, unfortunately, the enantioselectivity was not reproducible with several runs (entry 6). In contrast to the behavior of the bare lanthanoid triflates (without the Pybox ligands), it is interesting that the ionic radius of the metal complexes did not influence the diastereoselectivity when Pybox-lanthanoid triflates were used as catalysts.

The influence of the alkoxy substituent (OR^1) of the diazo substrate (Scheme 2) on the enantio- and diastereoselectivities was investigated. Reactions using diazo substrates **2** and **3**, which contain isopropyl ester and *p*-bromobenzyl ester, respectively, were carried out in the presence of chiral catalysts that involve (*S*,*S*)-Pybox-Ph or (4*S*,5*S*)-Pybox-4,5-Ph_2 with $Yb(OTf)_3$ or $Tm(OTf)_3$ (Table 3). In the case of (4*S*,5*S*)-Pybox-4,5-Ph_2-$Yb(OTf)_3$-catalyzed reaction of diazo substrate **2** (isopropyl ester), both the yield of the adducts and the enantioselectivity of major *endo*-cycloadduct were considerably less than that of substrate **1** (methyl ester) (entry 1). The reaction of substrate **3** (*p*-bromobenzyl ester), however, was promising in terms of enantioselectivity and extremely high *endo*-selectivity. Thus, in the cases of $Yb(OTf)_3$ with chiral ligand (*S*,*S*)-Pybox-Ph or (4*S*,5*S*)-Pybox-4,5-Ph_2, the catalyzed (10 mol %) reaction afforded only *endo*-cycloadduct as the sole product with over 80% ee (entries 2 and 4). Moreover, increasing the catalyst to

Table 2. Reactions of diazoacetophenone **1** with oxazolidinone **4b** in the presence of chiral Pybox-lanthanoid complexes[a]

Entry	4	Pybox	$M(OTf)_3$	IR (Å)[b]	Temp	Yield (%)	*endo*:*exo*[c]	% ee[d] (*endo*)	% ee[d] (*exo*)
1[e]	**4a**	Ph	$Yb(OTf)_3$	0.87	−10	94	18:82	8	96
2	**4b**	Ph	$Yb(OTf)_3$	0.87	Reflux	65	97:3	30	52
3	**4b**	Ph	$Yb(OTf)_3$	0.87	rt	71	99:1	28	20
4	**4b**	Ph	$Yb(OTf)_3$	0.87	−10	18	97:3	38	52
5	**4b**	Ph	$Yb(OTf)_3$	0.87	−25	5	97:3	30	52
6	**4b**	Ph	$Tm(OTf)_3$	0.88	rt	81–68	95:5 to 93:7	74–26	10–4
7	**4b**	Ph	$Er(OTf)_3$	0.89	rt	53	96:4	18	20
8	**4b**	Ph	$Ho(OTf)_3$	0.90	rt	50	95:5	22	20
9	**4b**	Ph	$Eu(OTf)_3$	0.95	rt	88	97:3	−8	38
10	**4b**	Ph	$La(OTf)_3$	1.03	rt	34	90:10	−24	36
11	**4b**	4,5-Ph_2	$Yb(OTf)_3$	0.87	Reflux	79	97:3	50	>99
12	**4b**	4,5-Ph_2	$Yb(OTf)_3$	0.87	rt	67	92:8	40	16
13	**4b**	4,5-Ph_2	$Yb(OTf)_3$	0.87	−10	8	94:6	44	42
14	**4b**	4,5-Ph_2	$Tm(OTf)_3$	0.88	rt	50	96:4	40	>99
15	**4b**	4,5-Ph_2	$Er(OTf)_3$	0.89	rt	59	97:3	42	76
16	**4b**	4,5-Ph_2	$Ho(OTf)_3$	0.90	rt	57	96:4	52	90
17	**4b**	4,5-Ph_2	$Eu(OTf)_3$	0.95	rt	96	98:2	24	50
18	**4b**	4,5-Ph_2	$La(OTf)_3$	1.03	rt	83	90:10	8	16

[a] The reaction was carried out by adding a solution of diazo compound **1** in CH_2Cl_2 over a period of 6 h to a suspension of the chiral catalyst (10 mol %), MS 4 Å, $Rh_2(OAc)_4$ (2 mol %), and **4a** or **4b** (2 equiv) in CH_2Cl_2.
[b] See Ref. 11.
[c] Determined by ^1H NMR analysis (400 MHz).
[d] Determined by HPLC analysis (Daicel Chiralpak AD-H).
[e] Previously reported, see Ref. 6.

Table 3. Reactions of diazoacetophenones **2** or **3** with oxazolidinone **4b** in the presence of chiral Pybox-lanthanoid complexes[a]

Entry	Diazo substrate	R^1	Pybox	$M(OTf)_3$	mol %	Yield (%)	*endo*:*exo*[b]	% ee[c] (*endo*)
1	**2**	*i*-Pr	4,5-Ph_2	$Yb(OTf)_3$	10	39	89:11[d]	8
2	**3**	*p*-$BrC_6H_4CH_2$	Ph	$Yb(OTf)_3$	10	40	>99:1	84
3	**3**	*p*-$BrC_6H_4CH_2$	Ph	$Tm(OTf)_3$	10	51	>99:1	72
4	**3**	*p*-$BrC_6H_4CH_2$	4,5-Ph_2	$Yb(OTf)_3$	10	57	>99:1	81
5	**3**	*p*-$BrC_6H_4CH_2$	4,5-Ph_2	$Yb(OTf)_3$	20	60	>99:1	96
6	**3**	*p*-$BrC_6H_4CH_2$	4,5-Ph_2	$Yb(OTf)_3$	30	25	>99:1	92

[a] The reaction was carried out at room temperature by adding a solution of diazo substrate **2** or **3** in CH_2Cl_2 over a period of 6 h to a suspension of the chiral catalyst (10 mol %), MS 4 Å, $Rh_2(OAc)_4$ (2 mol %), and **4b** (2 equiv) in CH_2Cl_2.
[b] Determined by ^1H NMR analysis (400 MHz).
[c] Determined by HPLC analysis (Daicel Chiralpak IA).
[d] Calculated from yields.

20 mol % in (4*S*,5*S*)-Pybox-4,5-Ph_2-$Yb(OTf)_3$-catalyzed reaction increased the enantioselectivity to 96% ee (entry 5). Although the absolute configuration of the *endo*-adduct has yet to be determined, the enantio-facial selection is probably similar to that reported by Desimoni in the Mukaiyama–Michael reaction between 2-trimethylsilyloxyfuran and 3-crotonoyl-2-oxazolidinone, which is catalyzed by a chiral Pybox-4,5-Ph_2–$La(OTf)_3$ complex (shown as tetrahydrate by X-ray analysis).[12] According to the proposed structure of the (4*S*,5*S*)-Pybox-4,5-Ph_2-$La(OTf)_3$-3-crotonoyl-2-oxazolidinone complex, the carbonyl ylide presumably approaches from the *re*-face of 3-crotonoyl-2-oxazolidinone with *endo*-orientation.

As shown in Scheme 2, cycloadditions between 3-(2-pentenoyl)- (**4c**), 3-cinnamoyl- (**4d**), or 3-[(*E*)-3-(ethoxycarbonyl)-propenoyl]-2-oxazolidinones (**4e**) and diazoacetophenone **1** or **3**, as the diazo substrates, were carried out using (*S*,*S*)-Pybox-Ph- or (4*S*,5*S*)-Pybox-4,5-Ph_2-$Yb(OTf)_3$ as the catalyst. With the exception of the reaction between **4e** and **3**, the reactions favored the *endo*-cycloadduct, which was similar to that of **4b**. In the case of **1** and oxazolidinone **4c**, the reaction exhibited high *endo*-selectivity but moderate enantioselectivity, which did not substantially improve by increasing the catalyst load (Table 4, entries 1–3). Unfortunately, the reaction between **3** and **4c** at room temperature in the presence of (4*S*,5*S*)-Pybox-4,5-Ph_2-$Yb(OTf)_3$ (10 mol %) did not occur, presumably due to the low reactivity of **4c** as a dipolarophile. Despite the sluggish reaction of oxazolidine **4d**, which required reflux conditions (CH_2Cl_2) to drive the cycloaddition, even with **1** as a carbonyl ylide precursor, relatively good enantioselectivity with high *endo*-selectivity was obtained (entry 4). The reaction between **1** and olefinic dipolarophile **4e** afforded relatively good enantioselectivity of the *endo*-cycloadduct (entries 5–7). It is interesting to note that the diastereoselectivity improved as the catalyst was increased from 10 to 30%. Surprisingly, in contrast to the cycloaddition reactions, which have been described to this point, the reaction between diazoacetophenone **3** and oxazolidinone **4e** in the presence of (4*S*,5*S*)-Pybox-4,5-Ph_2-$Yb(OTf)_3$ (10 and 20 mol %) afforded only the opposite regioisomer with an *exo*-configuration (*exo*-**7e′**).[9] The regiochemistry of *exo*-**7e′** was determined by comparing the chemical shifts of the methine protons (H-6, H-7, and H-8) of the epoxy-bridged bicyclic ring with those of cycloadducts *endo*-**5b**, *endo*-**7b**, and *endo*-**5e** (Fig. 2). In contrast to the comparable chemical shifts of *endo*-**5b** and *endo*-**7b**, the chemical shifts of *endo*-**5e** and *exo*-**7e′** were drastically dissimilar. Coupling constants between the methine protons (H-6, H-7, and H-8) of the four cycloadducts were comparable. These ^1H NMR data suggest that *endo*-**5b** and *endo*-**7b** share the same regio- and stereochemistries, whereas *endo*-**5e** and *exo*-**7e′** have similar stereo-, but different regiochemistries. In comparison to the other cycloadducts, the upfield shift of H-6 for cycloadduct *exo*-**7e′** indicates substitution of the ethoxycarbonyl group at C-6. Furthermore, NOEs were observed between H-6 and the benzyl methylene, and between H-6 and H-8. Based on these NMR studies, *exo*-**7e′** was determined to have the opposite regiochemistry of *endo*-**5b**, *endo*-**7b**, and *endo*-**5e**. Although the switch in the regioselectivity remains unclear, it is important to note such reactions that exhibit high regio- and diastereoselectivities with moderate enantioselectivity.

Table 4. Reactions of diazoacetophenone **1** or **3** with oxazolidinone **4c**–**4e** in the presence of chiral Pybox-$Yb(OTf)_3$ complexes[a]

Entry	Diazo substrate	Oxazolidinone	Pybox	mol %	Temp (°C)	Yield (%)	*endo*:*exo*[b]	% ee[c] (*endo*)
1	1	**4c**	4,5-Ph_2	10	rt	32	>99:1	30
2	1	**4c**	4,5-Ph_2	20	rt	47	99:1	28
3	1	**4c**	4,5-Ph_2	30	rt	49	98:2	38
4	1	**4d**	Ph	10	Reflux	13	>99:1	72
5	1	**4e**	4,5-Ph_2	10	rt	54	76:24	78
6	1	**4e**	4,5-Ph_2	20	rt	51	83:17	78
7	1	**4e**	4,5-Ph_2	30	rt	55	93:7	68
8	3	**4e**	4,5-Ph_2	10	rt	15[d]	>1:99[e]	56 (*exo*)
9	3	**4e**	4,5-Ph_2	20	Reflux	15[d]	>1:99[e]	66 (*exo*)

[a] The reaction was carried out by adding a solution of diazo compound **1** or **3** in CH_2Cl_2 over a period of 6 h to a suspension of the chiral Yb catalyst (10 mol %), MS 4 Å, $Rh_2(OAc)_4$ (2 mol %), and **4c**–**4e** (2 equiv) in CH_2Cl_2.
[b] Determined by ^1H NMR analysis (400 MHz).
[c] Determined by HPLC analysis (Daicel Chiralpak IA).
[d] Regioisomer *exo*-**7e′** was obtained.
[e] Only *exo*-isomer was obtained.

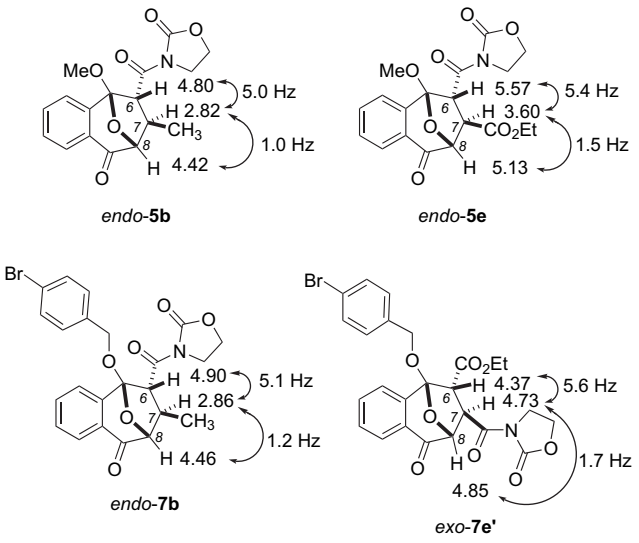


Figure 2. Regiochemistry of cycloadducts.

3. Conclusion

We have found that the cycloaddition reaction between a carbonyl ylide, which was generated from **3**, and 3-crotonoyl-2-oxazolidinone, in the presence of (4*S*,5*S*)-Pybox-4,5-Ph_2-Yb$(OTf)_3$ (20 mol %) as the chiral Lewis acid catalyst, afforded the *endo*-cycloadduct as a sole product (*endo*/*exo*=>99:1) with extremely high enantioselectivity (96% ee). In contrast, the reaction between **1**, as a carbonyl ylide precursor, and 3-acryloyl-2-oxazolidinone, under the similar conditions, exhibited *exo*-selectivity (*exo*/*endo*= 82:18). Although the cycloaddition reactions of **3** with other 3-(2-alkenoyl)-2-oxazolidinones were slow or problematic, the reaction between **1** and 3-cinnamoyl- (**4d**) or 3-[(*E*)-3-(ethoxycarbonyl)propenoyl]-2-oxazolidinones (**4e**), using the same catalyst, exhibited *endo*-selectively with relatively high enantioselectivity (72 and 78% ee, respectively). Studies to expand this methodology of enantioselective cycloaddition to other diazo substrates are currently underway.

4. Experimental

4.1. General

Melting points are uncorrected. IR spectra were obtained using an FT–IR spectrophotometer. ^{1}H NMR spectra were obtained using a 400 MHz instrument; chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (internal standard). ^{13}C NMR spectra were recorded using a 100 MHz instrument with broadband proton decoupling; chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane, with the middle resonance of $CDCl_3$ (77.0 ppm) as the internal standard. Preparative and medium-pressure column chromatography were performed using columns packed with Wakogel C-300HG. All reactions were carried out using dried glass and under an argon atmosphere.

o-Methoxycarbonyl-α-diazoacetophenone (**1**), *o*-isopropoxycarbonyl-α-diazoacetophenone (**2**) and *o*-(*p*-bromobenzyloxy)carbonyl-α-diazoacetophenone (**3**) were prepared by following procedures as described in a previous paper.[13] With the exception of rare earth metal triflates, the commercially available Lewis acids including $Rh_2(OAc)_4$ were used without further purifications. The rare earth metal triflates were individually dried in vacuo in an Schlenk tube at 200 °C for 12 h before use. Commercially available powdered 4 Å molecular sieves (MS 4 Å) were dried in vacuo at 250 °C for 12 h before use. CH_2Cl_2 was purified by distillation, first over $CaCl_2$ and then over CaH_2, under argon.

4.2. General procedures for the reactions of *o*-(alkoxycarbonyl)-α-diazoacetophenones with 3-(2-alkenoyl)-2-oxazolidinones

Typical procedures are exemplified by the asymmetric cycloaddition reaction between **3** and **4b**. To a solution of Yb$(OTf)_3$ (62.2 mg, 0.10 mmol) in THF (2 mL) was added a solution of 2,6-bis[(4*S*,5*S*)-(−)-4,5-diphenyl-2-oxazolin-2-yl]pyridine [(4*S*,5*S*)-Pybox-4,5Ph_2, 52.16 mg, 0.10 mmol] in THF (3.0 mL). After stirring the mixture for 2 h, the solvent was removed in vacuo and the resulting solid was dried in vacuo (<3 mmHg) at room temperature for 1 h. The residue was used as a catalyst without further purification. To a suspension of 3-crotonoyl-2-oxazolidinone (155.2 mg, 1.0 mmol) and 4 Å MS (0.5 g) in CH_2Cl_2 (1 mL) were added a solution of the catalyst prepared above in CH_2Cl_2 (4 mL), followed by $Rh_2(OAc)_4$ (4.4 mg, 0.01 mmol) and CH_2Cl_2 (1 mL), and finally a solution of diazoacetophenone **3** (180.1 mg, 0.5 mmol) in CH_2Cl_2 (5 mL) over a period of 6 h. After removal of 4 Å MS through filtration (Celite), the reaction mixture was further filtered through a plug of silica gel using AcOEt/hexane (1:1, 100 mL) as the eluant. After concentrating the filtrate in vacuo, the resulting residue was purified by column chromatography (AcOEt/hexane 1:4) to provide *endo*-**7b** (116.5 mg, 60%) (*endo*/*exo* >99:1 using ^{1}H NMR, 400 MHz).

4.2.1. 5-*p*-Bromobenzyloxy-7-*exo*-methyl-6-*endo*-(2-oxazolidinoyl)carbonyl-8-oxabenzo[*c*]bicyclo[3.2.1]octan-2-one (*endo*-7b). Pale yellow prisms; mp 205–206 °C; $[\alpha]_D^{25}$ −19.83 (*c* 1.00, $CHCl_3$); 96% ee estimated using chiral HPLC; IR (KBr) 637, 708, 752, 802, 839, 896, 936, 972, 1011, 1069, 1121, 1272, 1340, 1461, 1489, 1546, 1599, 1894, 2371, 2875, 2920, 2977, 2997, 3031, 3057, 3094 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.48 (3H, d, *J*=7.1 Hz), 2.86 (1H, m), 3.44–3.51, 3.80–3.89, 4.29–4.43 (4H, m), 4.46 (1H, d, *J*=1.2 Hz), 4.85 (1H, d, *J*=11.9 Hz), 4.90 (1H, d, *J*=5.1 Hz), 4.95 (1H, d, *J*=11.9 Hz), 7.28–7.36 (2H, m), 7.46–7.50 (2H, m), 7.28–7.34, 7.45–7.57, 8.03–8.08 (4H, m); ^{13}C NMR ($CDCl_3$) δ 20.7 (CH_3), 38.6 (CH), 43.3 (CH_2), 55.9 (CH), 61.9 (CH_2), 65.2 (CH_2), 87.1 (CH), 108.9 (C), 121.4 (C), 122.8 (CH), 126.7 (CH), 129.1 (CH), 129.3 (CH), 130.1 (C), 131.3 (CH), 133.3 (CH), 136.5 (C), 142.1 (C), 152.9 (C), 169.9 (C), 193.5 (C); Mass spectrometry (EI) *m*/*z* 487 (M^++2), 485 (M^+), 400, 382, 356, 332, 316, 298, 270, 254, 229, 214, 201, 187, 171, 155, 133, 117, 104, 90, 76, 63, 37, 13; HRMS (EI) calcd for $C_{23}H_{20}BrNO_6$: 485.0473 (M^+), found: 485.0498. Anal. Calcd for $C_{23}H_{20}BrNO_6$: C, 56.80; H, 4.15; N, 2.88%. Found: C, 57.15; H, 4.17; N, 2.52%.

The enantiomeric excess was determined using chiral HPLC analysis (Daicel Chiralpak IA; hexane/2-PrOH, 4:1 v/v;

UV detection, 254 nm; flow rate, 0.5 mL/min; 35 °C; t_{minor}=42.64 min, t_{major}=35.69 min).

4.2.2. 5-Methoxy-7-*exo*-methyl-6-*endo*-(2-oxazolidinoyl)-carbonyl-8-oxabenzo[*c*]bicyclo[3.2.1]octan-2-one (*endo*-5b). Colorless prisms; mp 181–183 °C; $[\alpha]_D^{25}$ +56.11 (*c* 1.00, $CHCl_3$); *endo*/*exo*=95:5; 74% ee (*endo*) estimated using chiral HPLC; IR (KBr) 708, 758, 1044, 1202, 1252, 1304, 1387, 1458, 1508, 1541, 1653, 1699, 1773, 2361, 2976 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (3H, d, *J*=7.3 Hz), 2.82 (1H, m), 3.40–3.59, 3.75–3.85, 4.30–4.42 (4H, m), 3.60 (3H, s), 4.42 (1H, d, *J*=1.0 Hz), 4.80 (1H, d, *J*=5.0 Hz), 7.2–8.0 (4H, m); ^{13}C NMR ($CDCl_3$) δ 20.6 (CH_3), 38.5 (CH), 43.3 (CH_2), 51.5 (CH_3), 55.0 (CH), 61.8 (CH_2), 86.9 (CH), 109.0 (C), 122.8 (CH), 126.6 (CH), 129.1 (CH), 129.9 (C), 133.2 (CH), 142.2 (C), 152.8 (C), 170.1 (C), 193.6 (C); Mass spectrometry (EI) *m*/*z* 331 (M^+), 299, 271, 244, 216, 187, 163, 133, 105, 69, 41, 14; HRMS (EI) calcd for $C_{17}H_{17}NO_6$: 331.1054 (M^+), found: 331.1028. Anal. Calcd for $C_{17}H_{17}NO_6$: C, 61.63; H, 5.17; N, 4.23%. Found: C, 61.70; H, 5.08; N, 4.24%.

4.2.3. 5-Methoxy-7-*endo*-methyl-6-*exo*-(2-oxazolidinoyl)-carbonyl-8-oxabenzo[*c*]bicyclo[3.2.1]octan-2-one (*exo*-5b). ^1H NMR ($CDCl_3$) δ 0.86 (3H, d, *J*=7.6 Hz), 3.39 (3H, s), 3.60–3.68 (1H, m), 4.00–4.50 (4H, m), 4.15 (1H, d, *J*=5.1 Hz), 4.87 (1H, d, *J*=8.9 Hz), 7.20–8.0 (4H, m). The minor *exo*-adduct was characterized using ^1H NMR; unfortunately, isolation of the *exo*-adduct using column chromatography was unsuccessful.

The enantiomeric excess was determined using chiral HPLC analysis (Daicel Chiralpak AD-H; hexane/2-PrOH, 4:1 v/v; UV detection, 254 nm; flow rate, 0.5 mL/min; 35 °C; t_{minor} (*endo*)=43.83 min, t_{major} (*endo*)=32.51 min, t_{minor} (*exo*)=62.68 min, t_{major} (*exo*)=18.64 min).

4.2.4. 7-*exo*-Ethyl-5-methoxy-6-*endo*-(2-oxazolidinoyl)-carbonyl-8-oxabenzo[*c*]bicyclo[3.2.1]octan-2-one (*endo*-5c). Colorless prisms; mp 122–123 °C; $[\alpha]_D^{25}$ +25.39 (*c* 1.00, $CHCl_3$); 30% ee estimated using chiral HPLC; IR (KBr) 632, 665, 782, 816, 835, 893, 918, 934, 972, 1126, 1166, 1460, 1481, 1512, 1600, 1965, 1989, 2857, 2874, 2931, 2992, 3069, 3376 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00 (3H, t, *J*=7.3 Hz), 1.72–1.91 (2H, m), 2.59 (1H, m), 3.50–3.60, 3.80–3.90, 4.35–4.42 (4H, m), 3.60 (3H, s), 4.50 (1H, d, *J*=1.5 Hz), 4.86 (1H, d, *J*=5.6 Hz), 7.20–8.10 (4H, m); ^{13}C NMR ($CDCl_3$) δ 12.3 (CH_3), 27.7 (CH_2), 43.3 (CH_2), 45.7 (CH), 51.6 (CH_3), 53.2 (CH), 61.8 (CH_2), 84.9 (CH), 108.6 (C), 122.9 (CH), 126.6 (CH), 129.0 (CH), 130.0 (C), 133.2 (CH), 142.1 (C), 152.9 (C), 170.1 (C), 193.7 (C); Mass spectrometry (EI) *m*/*z* 345 (M^+), 313, 284, 269, 258, 243, 226, 201, 199, 187, 176, 163, 148, 133, 105, 91, 77, 55, 38, 24, 12; HRMS (EI) calcd for $C_{18}H_{19}NO_6$: 345.1211 (M^+), found: 345.1187. Anal. Calcd for $C_{18}H_{19}NO_6$: C, 62.60; H, 5.55; N, 4.06%. Found: C, 62.87; H, 5.50; N, 4.05%.

The enantiomeric excess was determined using chiral HPLC analysis (Daicel Chiralpak IA; hexane/2-PrOH, 4:1 v/v; UV detection, 254 nm; flow rate, 0.5 mL/min; 35 °C; t_{minor}=31.44 min, t_{major}=23.88 min).

4.2.5. 7-*endo*-Ethyl-5-methoxy-6-*exo*-(2-oxazolidinoyl)-carbonyl-8-oxabenzo[*c*]bicyclo[3.2.1]octan-2-one (*exo*-5c). ^1H NMR ($CDCl_3$) δ 0.84 (3H, t, *J*=7.3 Hz), 1.23–1.40 (2H, m), 3.39 (3H, s), 3.64 (1H, m), 4.05–4.24 (4H, m), 4.26 (1H, d, *J*=5.1 Hz), 4.92 (1H, d, *J*=8.8 Hz), 7.20–8.10 (4H, m). The minor *exo*-adduct was characterized using ^1H NMR; unfortunately, isolation of the *exo*-adduct using column chromatography was unsuccessful.

4.2.6. 5-Methoxy-6-*endo*-(2-oxazolidinoyl)carbonyl-7-*exo*-phenyl-8-oxabenzo[*c*]bicyclo[3.2.1]octan-2-one (*endo*-5d). Colorless prisms; mp 210–212 °C; $[\alpha]_D^{25}$ +30.35 (*c* 1.00, $CHCl_3$); 72% ee estimated using chiral HPLC; IR (KBr) 638, 674, 706, 785, 837, 986, 1051, 1077, 1113, 1150, 1161, 1223, 1257, 1299, 1317, 1359, 1388, 1459, 1475, 1520, 1602, 1700, 1780, 2995, 3029, 3060 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.69 (3H, s), 3.90 (1H, dd, *J*=1.7, 6.1 Hz), 4.80 (1H, d, *J*=1.7 Hz), 3.52–3.60, 3.78–3.88, 4.32–4.38 (4H, m), 5.34 (1H, d, *J*=6.1 Hz), 7.32–7.43 (5H, m), 7.26–7.30, 7.50–7.62, 8.08–8.11 (4H, m); ^{13}C NMR ($CDCl_3$) δ 43.6 (CH_2), 48.2 (CH), 53.7 (CH_3), 55.8 (CH), 62.0 (CH_2), 85.6 (CH), 108.6 (C), 124.8 (CH), 126.5 (CH), 127.5 (CH), 128.0 (CH), 128.5 (CH), 129.2 (CH), 131.1 (C), 134.1 (CH), 134.7 (C), 142.7 (C), 153.4 (C), 169.8 (C), 192.7 (C); Mass (EI) *m*/*z* 393 (M^+), 361, 335, 317, 306, 278, 247, 235, 218, 187, 176, 163, 148, 133, 115, 103, 91, 77, 55, 38, 24, 13; HRMS (EI) calcd for $C_{22}H_{19}NO_6$: 393.1211 (M^+), found: 393.1187. Anal. Calcd for $C_{22}H_{19}NO_6$: C, 67.17; H, 4.87; N, 3.56%. Found: C, 67.40; H, 4.80; N, 3.40%.

The enantiomeric excess was determined using chiral HPLC analysis (Daicel Chiralpak IA; hexane/2-PrOH, 4:1 v/v; UV detector, 254 nm; flow rate, 0.5 mL/min; 35 °C; t_{minor}=46.98 min, t_{major}=25.86 min).

4.2.7. 7-*exo*-Ethoxycarbonyl-5-methoxy-6-*endo*-(2-oxazolidinoyl)carbonyl-8-oxabenzo[*c*]bicyclo[3.2.1]octan-2-one (*endo*-5e). Colorless prisms; mp 179 °C; $[\alpha]_D^{25}$ +20.67 (*c* 0.80, $CHCl_3$); 78% ee estimated on the basis of chiral HPLC; IR (KBr) 654, 707, 769, 825, 867, 943, 1019, 1051, 1107, 1158, 1244, 1369, 1474, 1600, 1787, 2920, 2958 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32 (3H, t, *J*=7.1 Hz), 3.60 (1H, dd, *J*=1.5, 5.4 Hz), 3.65 (3H, s), 3.34–3.48, 3.79–3.90, 4.34–4.44 (4H, m), 4.22–4.33 (2H, m), 5.13 (1H, dd, *J*=1.5, 0.49 Hz), 5.57 (1H, d, *J*=5.4 Hz), 7.35–7.38, 7.46–7.61, 8.01–8.05 (4H, m); ^{13}C NMR ($CDCl_3$) δ 14.2 (CH_3), 43.0 (CH_2), 48.1 (CH), 50.2 (CH), 51.6 (CH_3), 61.9 (CH_2), 62.1 (CH_2), 82.2 (CH), 108.6 (C), 122.7 (CH), 126.8 (CH), 129.3 (CH), 129.5 (C), 133.5 (CH), 141.9 (C), 152.5 (C), 169.0 (C), 170.5 (C), 192.1 (C); Mass spectrometry (EI) *m*/*z* 389 (M^+), 357, 343, 329, 316, 302, 284, 271, 257, 243, 229, 215, 201, 199, 187, 176, 163, 148, 133, 115, 104, 92, 77, 63, 50, 38, 24, 13; HRMS (EI) calcd for $C_{19}H_{19}NO_8$: 389.1109 (M^+), found: 389.1078. Anal. Calcd for $C_{19}H_{19}NO_8$: C, 58.61; H, 4.92; N, 3.60%. Found: C, 58.63; H, 4.85; N, 3.65%.

The enantiomeric excess was determined using chiral HPLC analysis (Daicel Chiralpak IA; hexane/2-PrOH, 4:1 v/v; UV detection, 254 nm; flow rate, 0.5 mL/min; 35 °C; t_{minor}=42.16 min, t_{major}=35.76 min).

4.2.8. 7-*endo*-Ethoxycarbonyl-5-methoxy-6-*exo*-(2-oxazolidinoyl)carbonyl-8-oxabenzo[*c*]bicyclo[3.2.1]octan-2-one (*exo*-5e). ^{1}H NMR ($CDCl_3$) δ 1.15 (3H, t, J=7.2 Hz), 3.40 (3H, s), 3.99–4.53 (6H, m), 4.54 (1H, dd, J=5.2, 9.2 Hz), 4.99 (1H, d, J=5.2 Hz), 5.14 (1H, d, J=9.2 Hz), 7.47–7.70 (3H, m), 7.96–7.98 (1H, m). The minor *exo*-adduct was characterized using ^{1}H NMR; unfortunately, isolation of the *exo*-adduct using column chromatography was unsuccessful.

4.2.9. 5-Isopropoxy-7-*exo*-methyl-6-*endo*-(2-oxazolidinoyl)carbonyl-8-oxabenzo[*c*]bicyclo[3.2.1]octan-2-one (*endo*-6b). Colorless prisms; mp 178 °C; $[\alpha]_D^{25}$ +7.24 (*c* 1.00, $CHCl_3$); 8% ee estimated on the basis of chiral HPLC; IR (KBr) 634, 708, 751, 807, 846, 899, 921, 953, 970, 1004, 1031, 1048, 1114, 1165, 1219, 1246, 1269, 1296, 1337, 1385, 1463, 1511, 1540, 1563, 1600, 1683, 2371, 2876, 2931, 2973, 2996 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.29 (3H, d, J=6.1 Hz), 1.32 (3H, d, J=6.4 Hz), 1.44 (3H, d, J=7.1 Hz), 2.66 (1H, m), 3.56–3.65, 3.81–3.91, 4.16–4.27, 4.32–4.38 (4H, m), 4.41 (1H, m), 4.39 (1H, d, J=1.7 Hz), 4.82 (1H, d, J=5.9 Hz), 7.28–7.33, 7.44–7.50, 7.50–7.58, 7.98–8.07 (4H, m); ^{13}C NMR ($CDCl_3$) δ 20.4 (CH_3), 24.2 (CH_3), 24.5 (CH_3), 39.0 (CH), 43.3 (CH_2), 57.0 (CH), 61.8 (CH_2), 68.9 (CH), 87.0 (CH), 109.8 (C), 123.5 (CH), 126.5 (CH), 128.9 (CH), 130.0 (C), 133.0 (CH), 143.2 (C), 152.8 (C), 170.4 (C), 193.8 (C); Mass spectrometry (EI) *m/z* 359 (M^+), 299, 272, 260, 245, 229, 213, 201, 185, 173, 156, 145, 129, 114, 104, 88, 69, 50, 39, 24, 13; HRMS (EI) calcd for $C_{19}H_{21}NO_6$: 359.1368 (M^+), found: 359.1362. Anal. Calcd for $C_{19}H_{21}NO_6$: C, 63.50; H, 5.89; N, 3.74%. Found: C, 63.68; H, 5.87; N, 3.74%.

The enantiomeric excess was determined using chiral HPLC analysis (Daicel Chiralpak IA; hexane/2-PrOH, 4:1 v/v; UV detection, 254 nm; flow rate, 0.5 mL/min; 35 °C; t_{minor}=27.32min, t_{major}=20.12 min).

4.2.10. 5-Isopropoxy-7-*endo*-methyl-6-*exo*-(2-oxazolidinoyl)carbonyl-8-oxabenzo[*c*]bicyclo[3.2.1]octan-2-one (*exo*-6b). Colorless prisms; mp 174–175 °C; $[\alpha]_D^{25}$ +6.10 (*c* 0.25, $CHCl_3$); 1% ee estimated on the basis of chiral HPLC; IR (KBr) 633, 709, 749, 803, 890, 920, 949, 974, 1002, 1032, 1048, 1114, 1170, 1223, 1246, 1274, 1295, 1333, 1391, 1440, 1523, 1545, 1571, 1611, 1673, 2351, 2865, 2902, 2973, 2996 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.84 (3H, d, J=7.3 Hz), 1.18 (3H, d, J=2.7 Hz), 1.19 (3H, d, J=2.9 Hz), 3.65 (1H, m), 3.99 (1H, m), 4.06–4.17 (2H, m), 4.21 (1H, d, J=4.9 Hz), 4.39–4.51 (2H, m), 4.85 (1H, d, J=9.0 Hz), 7.44–7.51, 7.60–7.68, 7.98–8.02 (4H, m); ^{13}C NMR ($CDCl_3$) δ 15.3 (CH_3), 24.0 (CH_3), 24.6 (CH_3), 35.1 (CH), 43.3 (CH_2), 58.0 (CH), 62.0 (CH_2), 69.5 (CH), 84.7 (CH), 108.4 (C), 124.7 (CH), 126.2 (CH), 128.8 (CH), 130.2 (C), 133.9 (CH), 145.2 (C), 153.5 (C), 170.2 (C), 194.1 (C); Mass spectrometry (EI) *m/z* 359 (M^+), 316, 300, 272, 260, 245, 229, 212, 201, 185, 173, 156, 145, 127, 115, 105, 88, 68, 57, 47, 35, 24, 13; HRMS (EI) calcd for $C_{19}H_{21}NO_6$: 359.1368 (M^+), found: 359.1352.

The enantiomeric excess was determined using chiral HPLC analysis (Daicel Chiralpak IA; hexane/2-PrOH, 4:1 v/v; UV detection, 254 nm; flow rate, 0.5 mL/min; 35 °C; t_{minor}=17.89 min, t_{major}=12.79 min).

4.2.11. 5-*p*-Bromobenzyloxy-6-*endo*-ethoxycarbonyl-7-*exo*-(2-oxazolidinoyl)carbonyl-8-oxabenzo[*c*]bicyclo[3.2.1]octan-2-one (*exo*-7e′). Colorless solid; mp 43–45 °C; $[\alpha]_D^{25}$ −34.77 (*c* 1.00, $CHCl_3$); 56% ee estimated using chiral HPLC; IR (KBr) 624, 986, 1015, 1042, 1071, 1109, 1215, 1298, 1368, 1387, 1460, 1480, 1489, 1601, 1709, 1732, 1788, 2340, 2361, 2402, 2926, 3021, 3393 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.05 (3H, t, J=7.1 Hz), 3.75–3.93 (2H, m), 4.04–4.18 (2H, m), 4.37 (1H, d, J=5.6 Hz), 4.41–4.53 (2H, m), 4.73 (1H, dd, J=5.6, 1.7 Hz), 4.85 (1H, d, J=1.7 Hz), 4.86 (1H, d, J=12.2 Hz), 4.96 (1H, d, J=12.2 Hz), 7.43–7.53 (4H, m), 7.32–7.38, 7.54–7.60, 7.99–8.11 (4H, m); ^{13}C NMR ($CDCl_3$) δ 14.0 (CH_3), 43.1 (CH_2), 46.6 (CH), 52.5 (CH), 61.5 (CH_2), 62.3 (CH_2), 65.7 (CH_2), 82.6 (CH), 107.9 (C), 121.5 (C), 124.3 (CH), 127.2 (CH), 129.0 (CH), 129.2 (C), 129.5 (CH), 131.4 (CH), 133.6 (CH), 136.3 (C), 141.4 (C), 152.6 (C), 168.0 (C), 170.5 (C), 190.1 (C); Mass spectrometry (EI) *m/z* 545 (M^++2), 543 (M^+), 501, 340, 315, 287, 272, 242, 215, 186, 171, 149, 133, 104, 90, 63, 40, 24; HRMS (EI) calcd for $C_{25}H_{22}BrNO_8$: 543.0528 (M^+), found: 543.0495. Satisfactory elemental analysis was not obtained because only a small amount of product was obtained.

The enantiomeric excess was determined using chiral HPLC analysis (Daicel Chiralpak IA; hexane/2-PrOH, 4:1 v/v; UV detection, 254 nm; flow rate, 0.5 mL/min; 35 °C; t_{minor}=115.87 min, t_{major}=154.54 min).

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