JOC The Journal of Organic Chemistry

ARTICLE

pubs.acs.org/joc

Asymmetric Cycloaddition Reactions of Diazoesters with 2-Alkenoic Acid Derivatives Catalyzed by Binaphthyldiimine−Ni(II) complexes

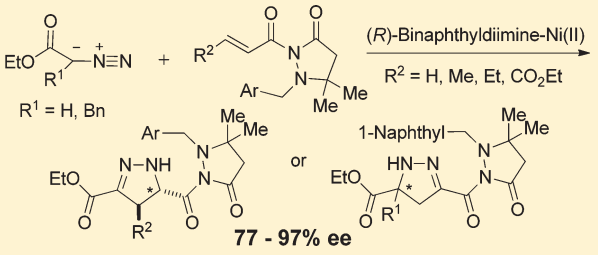
Hiroyuki Suga,*[,†] Yasuhisa Furihata,[†] Atsushi Sakamoto,[†] Kennosuke Itoh,[†] Yukihisa Okumura,[†] Teruko Tsuchida,[†] Akikazu Kakehi,[†] and Toshihide Baba[‡]

[†]Department of Chemistry and Material Engineering, Faculty of Engineering, Shinshu University, Wakasato, Nagano 380-8553, Japan

[‡]Department of Environmental Chemistry & Engineering, Interdisciplinary Graduate School of Science & Engineering, Tokyo Institute of Technology, G1-14, 4259 Nagatsuta, Midori-ku, Yokohama 226-8503, Japan

Supporting Information

ABSTRACT: The catalytic activity of chiral binaphthyldiimine (BINIM)−Ni(II) complexes for asymmetric enantioselective diazoalkane cycloadditions of ethyl diazoacetate with 3-acryloyl-2-oxazolidinone and 2-(2-alkenoyl)-3-pyrazolidinone derivatives was evaluated. The cycloadditions of 3-acryloyl-2-oxazolidinone and its 5,5-dimethyl derivative, in the presence of the BINIM−Ni(II) complex (10 mol %; prepared from (*R*)-BINIM-4Ph-2QN (ligand **C**) and $Ni(ClO_4)_2 \cdot 6H_2O$) afforded 2-pyrazolines having a methine carbon substituted with an oxazolidinonyl group in moderate ratios (70:30 to 72:28), along with high enantioselectivities (90−92% ee) via 1,3-proton migration. On the basis of the investigations on the counteranions of the Ni(II) complex, the N-substituent of pyrazolidinone, and reaction temperatures, the optimal enantioselectivity (97% ee) and ratio (85:15) of 2-pyrazoline were obtained for the reaction of 2-acryloyl-1-benzyl-5,5-dimethyl-3-pyrazolidinone in the presence of (*R*)-BINIM-4Ph-2QN−Ni(II) ((*R*)-**C**/Ni(II)) complex prepared using $Ni(BF_4)_2 \cdot 6H_2O$. In the cases of 1-benzyl-2-crotonoyl-5,5-dimethyl-3-pyrazolidinone, 1-benzyl-2-(2-butenoyl)-5,5-dimethyl-3-pyrazolidinone, and 1-benzyl-5,5-dimethyl-2-(3-ethoxycarbonyl)propenoyl-3-pyrazolidinone, the use of the (*R*)-BINIM-2QN−Ni(II) ((*R*)-**A**/Ni(II)) complex gave good to high enantioselectivities (85−93% ee) with the sole formation of the 2-pyrazoline having a methine carbon substituted with a pyrazolidinonyl group. Relatively good enantioselectivity (77% ee) was observed for the reaction between 2-acryloyl-5,5-dimethyl-1-naphthylmethyl-3-pyrazolidinone and an α-substituted diazo ester, ethyl 2-diazo-3-phenylpropanoate, which has yet to be employed as a diazo substrate in asymmetric cycloaddition reactions catalyzed by a chiral Lewis acid.



INTRODUCTION

Catalytic asymmetric 1,3-dipolar cycloadditions have been recognized as one of the most efficient reactions for the construction of five-membered heterocyclic compounds containing several stereogenic centers.[1] Accordingly, during the past two decades, numerous enantioselective 1,3-dipolar cycloadditions catalyzed by chiral Lewis acids have been developed, which include successful examples of isolable 1,3-dipoles such as nitrones,[1c−e,2−4] trimethylsilyldiazomethane,[5] diazoacetates,[6] and azomethine imines,[7,8] and also unstable 1,3-dipoles such as nitrile oxides,[9] nitrile imines,[10] and carbonyl ylides.[11] Organocatalytic asymmetric cycloadditions have also been reported for isolable 1,3-dipoles such as nitrones[12] and azomethine imines.[13] Although numerous chiral Lewis acids have been developed as efficient catalysts in the enantioselective 1,3-dipolar cycloadditions, a chiral Lewis acid for the cycloaddition of 1,3-dipoles possessing strong basic or unstable properties has remained elusive. Recently, we have reported on the use of chiral Ni(II) complexes of binaphthyldiimine (BINIM) as highly effective catalysts in providing high levels of asymmetric induction for the cycloadditions of nitrones,[3i] azomethine imines,[7a] nitrile oxides,[9e] and carbonyl ylides.[11d,e]

The 1,3-dipolar cycloaddition reactions between diazoalkanes and alkenes form relatively unstable 1-pyrazolines as the initial cycloadducts that either spontaneously release nitrogen to give the corresponding cyclopropanes, or undergo a 1,3-proton migration to give the thermodynamically more stable 2-pyrazoline derivatives. Diazo substrates such as trimethylsilyldiazomethane and diazoacetates undergo enantioselective diazoalkane cycloadditions in the presence of a chiral Lewis acid to give the 2-pyrazolines with high levels of asymmetric induction. In the case of trimethylsilyldiazomethane, Kanemasa reported the first successful examples of the enantioselective cycloaddition reactions using 3-(2-alkenoyl)-2-oxazolidinones and *R,R*-DBFOX/Ph−transition metal aqua complexes as the chiral Lewis acids.[5] For the diazoacetates, Maruoka reported on the highly enantioselective 1,3-dipolar cycloadditions using monodentate α-substituted acroleins and a chiral titanium BINOLate.[6a] Furthermore, Sibi described the highly enantioselective synthesis of 2-pyrazolines via Mg(II)-catalyzed cycloadditions of diazoesters in the formation of *β*-substituted, α-substituted, and α,*β*-disubstituted α,*β*-unsaturated pyrazolidinone imides.[6b]

Received: May 26, 2011
Published: July 28, 2011

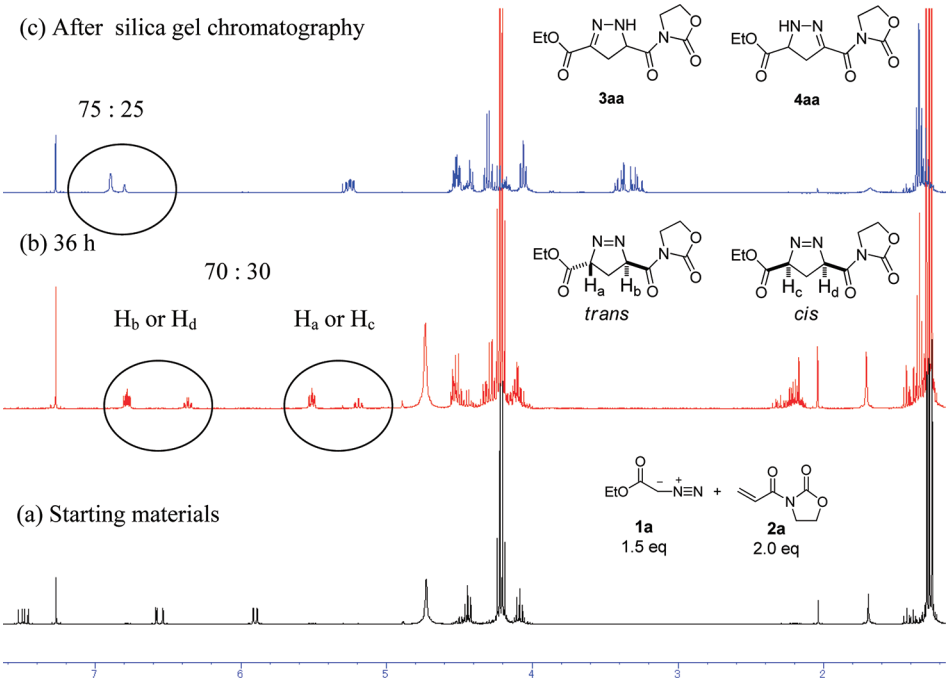
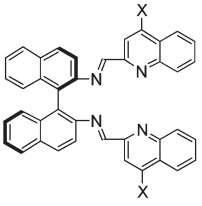


Figure 1. Reaction of ethyl diazoacetate (**1a**) with 3-acryloyl-2-oxazolidinone (**2a**) in $CDCl_3$.



Ligand
A: (*R*)-BINIM-2QN: X = H
B: (*R*)-BINIM-4Me-2QN: X = Me
C: (*R*)-BINIM-4Ph-2QN: X = Ph
D: (*R*)-BINIM-4(3,5-Xylyl)-2QN: X = 3,5-Xylyl
E: (*R*)-BINIM-4(3,5-TFXylyl)-2QN: X = 3,5-$(CF_3)_2C_6H_3$

Figure 2. (*R*)-BINIM-4X-2QN ligands.

In this paper, we describe our investigations to evaluate the effectiveness and scope of BINIM−Ni(II) as chiral Lewis acid catalysts for the enantioselective diazoalkane cycloaddition reactions of diazoacetates and α-substituted diazo ester with 3-(2-alkenoyl)-2-oxazolidinones and/or 2-(2-alkenoyl)-3-pyrazolidinone derivatives. Several Ni(II)-complexes of chiral *N*,*N*′-bis(2-quinolylmethylene)-1,1′-binaphthyl-2,2′-diamine (BINIM-2QN) derivatives (Figure 2, ligands **A**−**E**) were employed for the asymmetric cycloadditions of ethyl diazoacetate with 3-alkenoyl-2-oxazolidinone and several 2-(2-alkenoyl)-3-pyrazolidinone derivatives to give the products with good to high enantioselectivities (up to 97% ee). Our investigations revealed that, depending on the diopolarophile, the enantioselectivities are affected by the counteranion of the Ni(II)-complex and by the 4-substituent of the quinoline ring on BINIM-2QN. Relatively good enantioselectivities (up to 77% ee) were obtained for the chiral BINIM−Ni(II) catalyzed reactions between 2-acryloyl-3-pyrazolidinone derivatives and an α-substituted diazo ester, ethyl 2-diazo-3-phenylpropanoate, which has yet to be employed as a diazo substrate for asymmetric cycloaddition reactions catalyzed by a chiral Lewis acid.

RESULTS AND DISCUSSION

Cycloaddition Reactions of Ethyl Diazoacetate with Acrylic Acid Derivatives. Initially, the cycloaddition was carried out between ethyl diazoacetate (**1a**) and 3-acryloyl-2-oxazolidinone (**2a**) in the absence of any Lewis acids. The reaction was carried out in $CDCl_3$ at rt for 36 h in a NMR tube. As shown in Figure 1b, the ^{1}H NMR spectrum of the mixture exhibited two sets of methine protons (5.52 (ddd), 6.79 (ddd), and 5.19 (dt), 6.37 (dt) ppm) in a ratio of 70:30, which presumably correspond to those of *trans*- and *cis*-1-pyrazolines. Treatment of the mixture by silica gel chromatography facilitated the smooth 1,3-proton migration to give 2-pyrazolines that exhibit NH protons (6.87 and 6.09 ppm) by ^{1}H NMR in a ratio of 75:25, as shown in Figure 1c. The reaction in CH_2Cl_2 under similar conditions also gave the 2-pyrazolines in a ratio of 76:24 with a purified yield of 98%. The major product was determined to be 2-pyrazoline **3aa**, possessing a methine carbon substituted with an oxazolidinonyl group that causes the chemical shift of the methine protons (5.25 vs 4.39−4.56 ppm).

The chiral (*R*)-BINIM-2QN−Ni(II) ((*R*)-**A**/Ni(II)) complex was prepared by mixing (*R*)-BINIM-2QN (Figure 2, ligand **A**) and $Ni(ClO_4)_2 \cdot 6H_2O$ in CH_2Cl_2 at rt for 6 h. A mixture of **1a** with **2a**, in the presence of the (*R*)-**A**/Ni(II) complex (10 mol %), was stirred in CH_2Cl_2 at rt for 24 h to give the cycloaddition products after purification by silica gel chromatography (Scheme 1). Similar to that of the uncatalyzed reaction, 2-pyrazoline **3aa** was obtained as the major product along with 2-pyrazoline **4aa** (**3aa**/**4aa** = 63:37) in 80% total yield (Table 1, entry 1); the enantiomeric excesses were determined to be 70% ee for **3aa** and 37% ee for **4aa** using HPLC analysis (Daicel Chiralpak AD-H). To improve the **3aa**/**4aa** ratio of the 2-pyrazolines and the enantioselectivities, the reactions were carried out using different solvents (Table 1, entries 3−8), and a different substituent at the 4-position at a quinoline ring of the BINIM-4X-2QN ligands (ligands **B**−**E**, Table 1, entries 2, 3, 9, and 10). The **3aa**/**4aa** ratio was improved using solvents such as chlorobenzene and acetonitrile, whereas the best enantioselectivity was obtained using CH_2Cl_2 as the solvent (entry 3). Substitution at the 4-position resulted in slightly higher **3aa**/**4aa** ratios, in which

dx.doi.org/10.1021/jo201061f |*J. Org. Chem.* 2011, 76, 7377–7387

Scheme 1. Reaction of Ethyl Diazoacetate (1a) with 3-Acryloyl-2-oxazolidinone (2a) Catalyzed by BINIM−Ni(II) Complexes

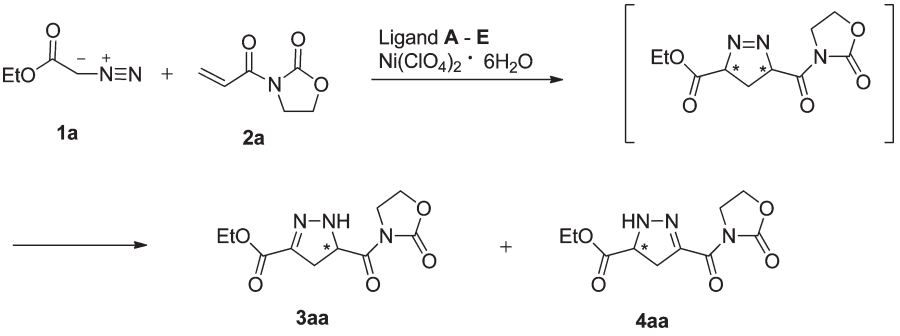


Table 1. Reaction of Ethyl Diazoacetate (1a) with 3-Acryloyl-2-oxazolidinone (2a) Catalyzed by BINIM−Ni(II) Complexes[a]

		X	time	yield		% ee[c]	
entry	solvent	(ligand)	(h)	(%)	3aa:4aa[b]	3aa	4aa
1	CH_2Cl_2	H (**A**)	24	80	63:37	70	37
2	CH_2Cl_2	Me (**B**)	24	86	80:20	69	25
3	CH_2Cl_2	Ph (**C**)	24	93	72:28	90	47
4	$CHCl_3$	Ph (**C**)	25	68	65:35	44	23
5	benzene	Ph (**C**)	51	73	84:16	12	10
6	C_6H_5Cl	Ph (**C**)	44	41	92:8	18	11
7	THF	Ph (**C**)	46	55	70:30	30	4
8	MeCN	Ph (**C**)	51	66	90:10	11	1
9	CH_2Cl_2	3,5-xylyl (**D**)	24	77	71:29	70	45
10	CH_2Cl_2	3,5-$(CF_3)_2$-C_6H_3 (**E**)	24	80	78:22	58	28

[a] Reactions were carried out on a 0.5-mmol scale (**1a**/**2a** = 1.5:1) at rt in the presence of the Ni(II) complex (10 mol %), which was prepared by mixing the corresponding BINIM ligand, $Ni(ClO_4)_2 \cdot 6H_2O$, and MS 4 Å for 6 h at rt. [b] Determined by ^1H NMR analysis. [c] Determined by HPLC analysis (Daicel Chiralpak AD-H).

a phenyl substituent (X = Ph, ligand **C**) exhibited the highest enantioselectivity (90% ee) of **3aa** (entry 3).

Next, dimethyl-substituted oxazolidinone and pyrazolidinone derivatives as dipolarophiles were employed to investigate their effects on the 2-pyrazoline ratio and enantioselectivity (Scheme 2 and Table 2). In the case of 4,4-dimethyloxazolidione **2b**, the cycloaddition under similar conditions resulted in a high 2-pyrazoline **3ab**/**4ab** ratio of 85:15 but with a significantly lower enantioselectivity of **3ab** (entry 2). In contrast, the reaction of 5,5-dimethyl-substituted **2c** showed slightly higher enantioselectivity of **3ac** with a comparable ratio of the 2-pyrazolines to that of **2a** (entry 3). The cycloaddition of pyrazolidinone **5a** resulted in both higher enantioselectivity and higher ratio of the 2-pyrazolines (entry 4). It is interesting to note that a shorter reaction time was required when pyrazolidinone **5a** was used as a dipolarophile. Among the several counteranions for the Ni(II) complex (entries 4, 6, and 7), the use of BF_4^- exhibited the highest 2-pyrazoline ratio (85:15), and with a high enantioselectivity (93% ee) of **6aa**.

Next, the influence on enantioselectivity was investigated using pyrazolidinone with various substitutents (CH_2R) on the 1-position (Scheme 3 and Table 3) as the dipolarophiles. In accordance to the chiral relay concept,[3h,9a,14] replacement of the phenyl substituent with a methyl group resulted in a significantly lower enantioselectivity of the major 2-pyrazoline (entry 3). In the case of 1-naphthylmethyl **5b** (R = 1-naphthyl, entry 2), the enantioselectivity (95% ee) of the major 2-pyrazoline was slightly higher, whereas the 2-pyrazoline ratio was similar to that of phenyl-substituted **5a**. Furthermore, the effect of temperature was investigated using pyrazolidinone **5a** and pyrazolidinone **5b** as the dipolarophiles (entries 1, 2, and 4−7). For pyrazolidinone **5a**, higher enantioselectivities of the major 2-pyrazoline were obtained at low reaction temperatures (entries 1 and 4−6); 97% ee was achieved using a reaction temperature of −45 °C (entry 6). In contrast, for pyrazolidinone **5b**, lower enantioselectivity was obtained at −45 °C (entry 7), albeit at a slightly higher ratio of 2-pyrazoline.

Cycloaddition Reactions between Ethyl Diazoacetate and Other 2-(2-Alkenoyl)-3-pyrazolidinone Derivatives. To further investigate the applicability of our methodology, the cycloaddition reactions were carried out using other 2-(2-alkenoyl)-3-pyrazolidinone derivatives under various conditions (Scheme 4, Table 4). First, to investigate the effect of substitution at the 4-position, different BIMIN−Ni(II) complexes (10 mol %) were prepared with a series of (*R*)-BINIM-4X-2QN ligands (ligands **A**−**C**) with $Ni(BF_4)_2 \cdot 6H_2O$. Using these catalysts, cycloaddition reactions between ethyl diazoacetate (**1a**) and 1-benzyl-2-crotonoyl-5,5-dimethyl-3-pyrazolidinone (**8a**) were carried out in CH_2Cl_2 at rt to yield only 2-pyrazoline **9aa** bearing an ethoxycarbonyl group at the 3-position in high yield and enantioselectivity (entries 1−3). Among the three ligands (ligands **A**−**C**), the one without any substituents at the 4-position on the quinoline ring (ligand **A**, entry 3) exhibited enantioselectivity (93% ee) slightly higher than those of the 4-Me or 4-Ph derivatives.

The reaction of 1-benzyl-5,5-dimethyl-2-(2-pentenoyl)-3-pyrazolidinone (**10a**) under similar conditions gave 2-pyrazoline **11aa** in a high yield with good enantioselectivity (entry 4). For the reactions of 1-benzyl-5,5-dimethyl-2-(3-ethoxycarbonyl)-propenoyl-3-pyrazolidinone (**12a**), slightly higher enantioselectivity was obtained using the Ni complex of (*R*)-BINIM-4Ph-2QN (X = Ph, ligand **C**) prepared from $Ni(ClO_4)_2 \cdot 6H_2O$ (entry 6) compared to that from $Ni(BF_4)_2 \cdot 6H_2O$ (entry 5). For the reactions of **12a** catalyzed by Ni complexes prepared from $Ni(ClO_4)_2 \cdot 6H_2O$, the ligand without any substituents on the 4-position (X = H, ligand **A**) showed an enantioselectivity (85% ee, entry 8) higher than those with the 4-Ph and 4-Me substituents (entries 6 and 7, respectively). These studies show that our asymmetric BINIM−Ni(II)-catalyzed cycloaddition reactions of ethyl diazoacetate can be successfully applied to other 2-(2-alkenoyl)-3-pyrazolidinone derivatives with good to excellent enantioselectivities (85−93% ee).

dx.doi.org/10.1021/jo201061f |*J. Org. Chem.* 2011, 76, 7377–7387

Scheme 2. Reactions of Ethyl Diazoacetate (1a) with Acryloyloxazolidinones 2a−c and Pyrazolidinone 5a Catalyzed by (*R*)-BINIM-4Ph-2QN−Ni(II) ((*R*)-C/Ni(II)) Complex

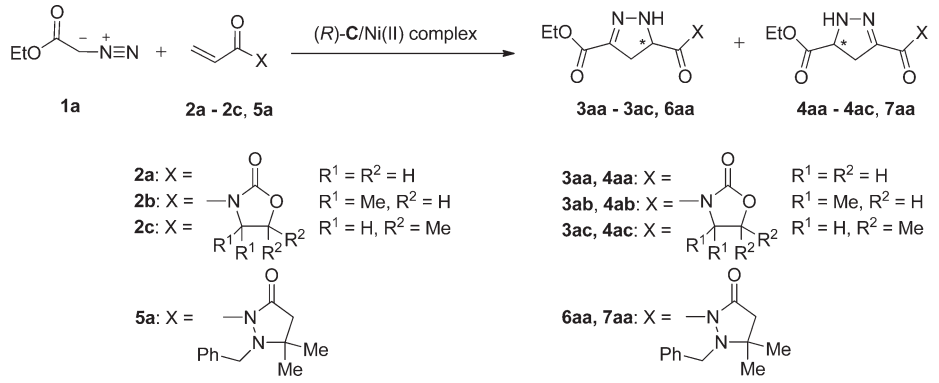
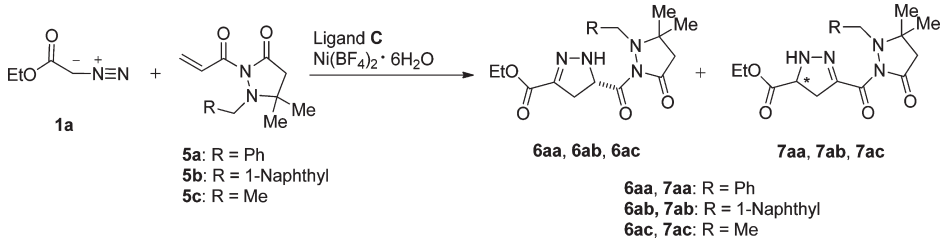


Table 2. Reactions of Ethyl Diazoacetate (1a) with Acryloyloxazolidinones 2a−c and Pyrazolidinone 5a Catalyzed by (*R*)-C/Ni(II) Complex[a]

							% ee[c]	
entry	dipolarophile	Ni salt	time (h)	products	yield (%)	**3**:**4** (**6**:**7**)[b]	**3** (**6**)	**4** (**7**)
1	**2a**	$Ni(ClO_4)_2$	24	**3aa, 4aa**	93	72:28	90	47
2	**2b**	$Ni(ClO_4)_2$	54	**3ab, 4ab**	91	85:15	25	28
3	**2c**	$Ni(ClO_4)_2$	24	**3ac, 4ac**	77	70:30	92	70
4	**5a**	$Ni(ClO_4)_2$	5	**6aa, 7aa**	84	83:17	93	ND[d]
5[e]	**5a**	$Ni(ClO_4)_2$	5	**6aa, 7aa**	80	73:27	90	ND[d]
6	**5a**	$Ni(OTf)_2$	7	**6aa, 7aa**	80	82:18	63	ND[d]
7	**5a**	$Ni(BF_4)_2$	5	**6aa, 7aa**	83	85:15	93	ND[d]

[a] Reactions were carried out on a 0.5-mmol scale (**1a**/**2a**−**c**, or **5a** = 1.5:1) at rt in CH_2Cl_2 in the presence of the Ni(II) complex (10 mol %), which was prepared by mixing the corresponding (*R*)-BINIM-4Ph-2QN (ligand **C**), Ni salt·$6H_2O$, and MS 4 Å in CH_2Cl_2 for 6 h at rt. [b] Determined by ^1H NMR analysis. [c] Determined by HPLC analysis (Daicel Chiralpak AD-H). Although the absolute configuration of 2-pyrazoline **6aa** could only be assigned to be 5*S* based on the optical rotation previously reported,[6b] the other major products probably have the same configurations. [d] Not determined. [e] Chloroform was used as the solvent.

Scheme 3. Reactions of Ethyl Diazoacetate (1a) with 2-Acryloyl-3-pyrazolidinones 5a, 5b, and 5c Catalyzed by (*R*)-C/Ni(II) Complex



Cycloaddition Reactions of α-Substituted Diazo Esters with 2-Acryloyl-3-pyrazolidinone. To examine the applicability of our methodology toward other diazo esters, we carried out the (*R*)-BINIM−Ni(II)-catalyzed cycloaddition reactions of 2-acryloyl-3-pyrazolidinone **5a** using various α-substituted diazo esters, which have yet to be reported as diazo substrates for asymmetric cycloaddition reactions catalyzed by chiral Lewis acids. Initially, reactions were carried out in CH_2Cl_2 using ethyl diazophenylacetate (**1b**) as the diazo substrate, and catalyzed by (*R*)-**C**/Ni(II) complexes that were prepared using either $Ni(ClO_4)_2·6H_2O$ or $Ni(BF_4)_2·6H_2O$ as the Ni(II) salts (Scheme 5). Using the complex derived from $Ni(ClO_4)_2·6H_2O$, the cycloaddition at 0 °C afforded **7ba** (15% yield, 70% ee), along with cyclopropane **14** (33% yield) and olefin **15** (38% yield). In contrast, the $Ni(BF_4)_2·6H_2O$-derived complex afforded 2-pyrazoline **7ba** in a higher yield (40% yield) but with much lower enantioselectivity (13% ee), along with cyclopropane **14** (40% yield) and olefin **15** (11% yield). Attempts to improve the yield of 2-pyrazoline **7ba**, which included different reaction temperatures (rt, −20 °C, or −40 °C) and quenching the reaction with silica gel, were unsuccessful. It is important to note that, for these reactions, the ratio among products **7ba**/**14**/**15** was somewhat irreproducible.

The formation of cyclopropane **14** and alkene **15** can be attributed to the biradical generated via elimination of nitrogen from the 1-pyrazoline. In the case of diazo substrate **1b**

Table 3. Reactions of Ethyl Diazoacetate (1a) with 2-Acryloyl-3-pyrazolidinones 5a, 5b, and 5c Catalyzed by (*R*)-C/Ni(II) Complex[a]

entry	pyrazolidinone (R)	temp (°C)	time (h)	product	yield (%)	6a:7a[b]	%ee[c] (6a)
1	**5a** (Ph)	rt	5	**6aa**, **7aa**	83	85:15	93
2	**5b** (1-naphthyl)	rt	1	**6ab**, **7ab**	85	84:16	95
3	**5c** (Me)	rt	48	**6ac**, **7ac**	68	79:21	8
4	**5a** (Ph)	0	5	**6aa**, **7aa**	89	88:12	95
5	**5a** (Ph)	−20	12	**6aa**, **7aa**	89	87:13	94
6	**5a** (Ph)	−45	24	**6aa**, **7aa**	87	85:15	97
7	**5b** (1-naphthyl)	−45	18	**6ab**, **7ab**	78	89:11	81

[a] Reactions were carried out on a 0.5-mmol scale (**1a**/**2a**−**2c**, or **5a** = 1.5:1) in CH_2Cl_2 in the presence of the Ni(II) complex (10 mol %), which was prepared by mixing the corresponding (*R*)-BINIM-4Ph-2QN (ligand **C**), $Ni(BF_4)_2 \cdot 6H_2O$, and MS 4 Å in CH_2Cl_2 for 6 h at rt. [b] Determined by ^1H NMR analysis. [c] Determined by HPLC analysis (Daicel Chiralpak AD-H). Although the absolute configuration of 2-pyrazoline **6aa** could only be assigned to be 5*S* based on the optical rotation previously reported,[6b] the other major products were also assigned similar to **6aa**.

Scheme 4. Reactions of Ethyl Diazoacetate (1a) with 2-(2-Alkenoyl)-3-pyrazolidinones 8a, 10a, and 12a Catalyzed by (*R*)-BINIM−Ni(II) Complexes

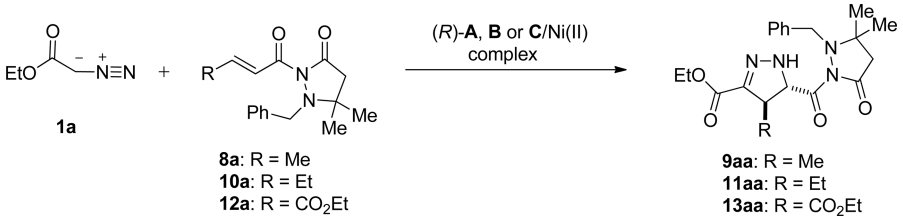


Table 4. Reactions of Ethyl Diazoacetate (1a) with 2-(2-Alkenoyl)-3-pyrazolidinones 8a, 10a, and 12a Catalyzed by (*R*)-BINIM−Ni(II) Complexes[a]

entry	R	counter anion	X (ligand)	time (h)	yield (%)	%ee[b]
1	Me	BF_4^-	Ph (**C**)	86	87	91
2	Me	BF_4^-	Me (**B**)	96	97	92
3	Me	BF_4^-	H (**A**)	96	94	93
4	Et	BF_4^-	H (**A**)	96	88	86
5	CO_2Et	BF_4^-	Ph (**C**)	36	91	77
6	CO_2Et	ClO_4^-	Ph (**C**)	36	92	79
7	CO_2Et	ClO_4^-	Me (**B**)	48	94	82
8	CO_2Et	ClO_4^-	H (**A**)	36	92	85

[a] Reactions were carried out on a 0.5-mmol scale (**1a**/**2a** = 1.5:1) at rt in CH_2Cl_2 in the presence of the Ni(II) complex (10 mol %), which was prepared by mixing the corresponding BINIM ligand (ligands **A**−**C**), $Ni(ClO_4)_2 \cdot 6H_2O$ or $Ni(BF_4)_2 \cdot 6H_2O$, and MS 4 Å for 6 h at rt. [b] Determined by HPLC analysis (Daicel Chiralpak AD-H). Although the absolute configuration of 2-pyrazolines **9aa** and **11aa** could only be assigned based on the optical rotation previously reported,[6b] 2-pyrazoline **13aa** was also assigned similar to **9aa** and **11aa**.

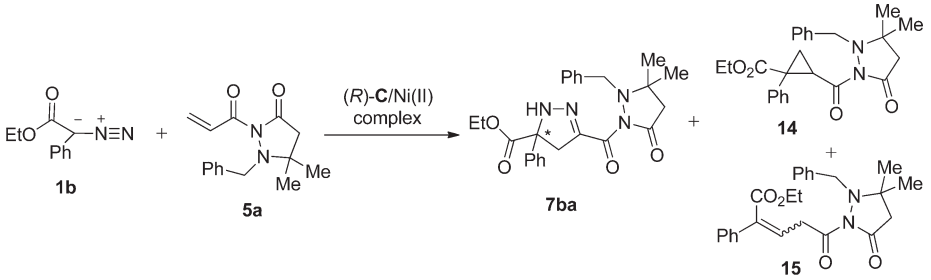
(Scheme 5), the α-phenyl substituent presumably facilitates such transformation. In contrast, the α-benzyl substituent of ethyl 2-diazo-3-phenylpropanoate (**1c**) discourages such transformation. As shown in Scheme 6, the reaction between 2-acryloyl-3-pyrazolidinone **5a** and **1c** in the presence of (*R*)-**C**/Ni(II) complex proceeded smoothly at 0 °C for 1 h to give only 2-pyrazoline **7ca** in high yield (83%, 63% ee) without any formation of the corresponding cyclopropane and alkene (Table 5, entry 1). The moderate enantioselectivity (63% ee) was improved by lowering the reaction temperature to −40 °C (entry 2, 75% ee). Varying the X-substituents of the (*R*)-BINIM-4X-2QN ligands (ligands **B**−**D**) or the counteranion of the Ni(II) catalyst did not improve the enantioselectivity (entries 3−5). Although a bulky ester substituent on the diazo substrate (R = *t*-Bu, **17c**) decreased both yield and enantioselectivity (entry 8), a bulky 1-naphthylmethyl substituent on the pyrazolidinone dipolarophiles slightly improved the enantioselectivity to 77% ee (entries 6 and 7).

Selective Conversion of 2-Pyrazoline 9aa to the Corresponding Alcohol. For some demonstration of how the final products can be processed, selective conversion of the pyrazolidinone moiety of 2-pyrazoline **9aa** to the corresponding alcohol was investigated. 2-Pyrazoline **9aa** was treated with $NaBH_4$ (4 equiv) in THF at −40 °C for 24 h to give the desired alcohol **20** in 69% yield without reduction of an ethyl ester moiety. The enantiomeric excess (96% ee) of **9aa** could be also maintained to be 96% ee by this reduction process (Scheme 7).

Proposed Mechanism for Asymmetric Induction. The high enantioselectvity of the cycloaddition reactions can be explained as the *Si*-face approach of the diazo esters toward the hexa-coordinated Ni(II) complex, which has been suggested for BINIM−Ni(II)-catalyzed azomethine imine[7a] and nitrile oxide[9e] cycloaddition reactions, by means of molecular modeling program using PM3 calculations (Figure 3).[15] In the proposed mechanism, during the transition state, the 4-phenylquinoline moiety of the Ni(II) complex and *N*-benzyl group of the pyrazolidinone dipolarophile efficiently shield the *Re*-face of the dipolarophile. In contrast, the *Si*-face is located in a relatively open space. This *Si*-face approach can reasonably explain the selective formation of (5*S*)-2-pyrazoline **6aa** and (4*S*,5*S*)-2-pyrazoline **9aa**, their absolute configurations being reported by Sibi.[6b]

dx.doi.org/10.1021/jo201061f |*J. Org. Chem.* 2011, 76, 7377–7387

Scheme 5. Reactions of Ethyl Diazophenylacetate (1b) with 3-Pyrazolidinone 5a Catalyzed by (*R*)-C/Ni(II) Complex



Scheme 6. Reactions of 2-Diazo-3-phenylpropanoic Acid Esters 1c, 16c, and 17c with 3-Pyrazolidinones 5a and 5b Catalyzed by (*R*)-BINIM−Ni(II) Complexes

1c: R = Et
16c: R = Me
17c: R = *t*-Bu

5a: Ar = Ph
5b: Ar = 1-Naphthyl

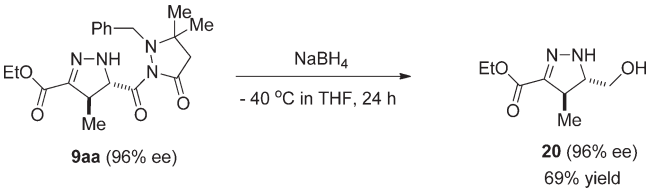
7ca: R = Et, Ar = Ph
7cb: R = Et, Ar = 1-Naphthyl
18cb: R = Me, Ar = 1-Naphthyl
19ca: R = *t*-Bu, Ar = Ph

Table 5. Reactions of 2-Diazo-3-phenylpropanoic Acid Esters 1c, 16c, and 17c with 3-Pyrazolidinones 5a and 5b Catalyzed by (*R*)-BINIM−Ni(II) Complexes[a]

entry	R	Ar	counter anion	X (ligand)	temp (°C)	time (h)	product	yield (%)	%ee[b]
1	Et	Ph	ClO_4^-	Ph (**C**)	0	1	**7ca**	82	63
2	Et	Ph	ClO_4^-	Ph (**C**)	−40	15	**7ca**	73	75
3	Et	Ph	ClO_4^-	Me (**B**)	−40	20	**7ca**	53	27
4	Et	Ph	ClO_4^-	3,5-Xylyl (**D**)	−40	15	**7ca**	61	71
5	Et	Ph	BF_4^-	Ph (**C**)	−40	56	**7ca**	79	59
6	Et	1-naph[c]	ClO_4^-	Ph (**C**)	−40	15	**7cb**	86	77
7	Me	1-naph[c]	ClO_4^-	Ph (**C**)	−40	10	**18cb**	83	77
8	*t*-Bu	Ph	ClO_4^-	Ph (**C**)	−40	4	**19ca**	41	44

[a] Reactions were carried out on a 0.5-mmol scale (diazo compound/dipolarophile = 1.5:1) at rt in CH_2Cl_2 in the presence of the Ni(II) complex (10 mol %), which was prepared by mixing the corresponding BINIM ligand (ligands **B**−**D**), $Ni(ClO_4)_2 \cdot 6H_2O$, or $Ni(BF_4)_2 \cdot 6H_2O$, and MS 4 Å for 6 h at rt. [b] Determined by HPLC analysis (Daicel Chiralpak OZ-3). The absolute configuration was not determined. [c] 1-Naphthyl.

Scheme 7. Reduction of 2-Pyrazoline 9aa to the Corresponding Alcohol 20



9aa (96% ee)

20 (96% ee)
69% yield

CONCLUSION

Our studies have shown that the BINIM−Ni(II) catalysts are extremely effective in affording high levels of asymmetric induction (up to 97% ee) for 1,3-dipolar cycloaddition reactions between ethyl diazoacetate and 3-acryloyl-2-oxazolidinones or 2-(2-alkenoyl)-3-pyrazolidinone derivatives in the selective formation of 2-pyrazolines having a methine carbon substituted to the coordination auxiliary groups. The enantioselectivity was found to be affected by both the counteranion of the Ni(II)-complex and the 4-substituent of the quinoline ring on the BINIM-2QN ligand. Relatively good enantioselectivity (up to 77% ee) was also observed in the reactions of an α-substituted diazo ester **1c** with 2-acryloyl-3-pyrazolidinone derivatives in the presence of the BINIM−Ni(II) catalysts.

EXPERIMENTAL SECTION

General. Melting points were determined on a melting point apparatus and are uncorrected. IR spectra were taken with a FT/IR spectrophotometer. ^{1}H NMR spectra were recorded on a 400 MHz spectrometer. Chemical shifts are expressed in parts per million downfield from tetramethylsilane as an internal standard. ^{13}C NMR spectra were recorded on a 100 MHz spectrometer using broadband proton decoupling. Chemical shifts are expressed in parts per million using the middle resonance of

dx.doi.org/10.1021/jo201061f |*J. Org. Chem.* 2011, 76, 7377–7387

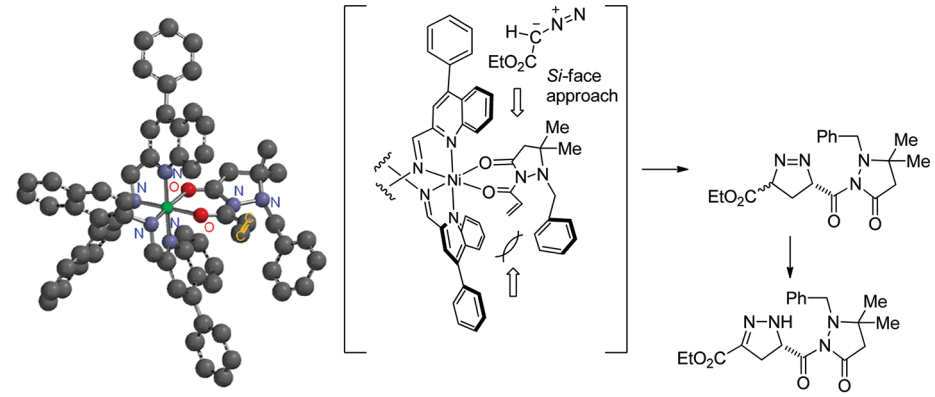


Figure 3. Proposed mechanism for (*R*)-**C**/Ni(II)-catalayzed reaction.

$CDCl_3$ (77.0 ppm) as an internal standard. Hydrogen multiplicity (C, CH, CH_2, CH_3) information was obtained from the carbon DEPT spectrum. For preparative column chromatography, Wakogel C-300HG was employed. All reactions were carried out under an argon atmosphere in dried glassware.

Materials. Known chiral binaphthyldiimine (BINIM) ligands were prepared by the procedure reported previously.[9e,16] 3-Acryloyl-2-oxazolidinone (**2a**),[17,18] 3-acryloyl-4,4-dimethyl-2-oxazozolidinone (**2b**),[22] 2-acryloyl-1-benzyl-5,5-dimethyl-3-pyrazolidinone (**5a**),[6b] 2-acryloyl-5,5-dimethyl-1-(1-naphthylmethyl)-3-pyrazolidinone (**5b**),[14a] 2-acryloyl-5,5-dimethyl-1-ethyl-3-pyrazolidinone (**5c**),[e] 1-benzyl-2-[(*E*)-crotonoyl]-5,5-dimethyl-3-pyrazolidinone (**8a**),[6b] 1-benzyl-5,5-dimethyl-2-[(*E*)-2-pentenoyl]-3-pyrazolidinone (**10a**),[6b] and 1-benzyl-5,5-dimethyl-2-[(*E*)-3-(ethoxycarbonyl)propenoyl]-3-pyrazolidinone (**12a**)[9a] were prepared by the procedure reported in the literature. Ethyl diazoacetate (**1a**),[19] ethyl diazophenylacetate (**1b**),[20] and 2-diazo-3-phenylpropanoic acid esters **1c**,[21] **16c**,[21] and **17c**[21] were prepared by the procedure reported in the literature. Powdered 4 Å molecular sieves (MS 4 Å) is commercially available (Aldrich) and dried in vacuo at 200 °C for 12 h before use. $Ni(ClO_4)_2 \cdot 6H_2O$ and $Ni(BF_4)_2 \cdot 6H_2O$ are commercially available and used without further purification. CH_2Cl_2 was purified by distillation first from $CaCl_2$ and then CaH_2 under argon before use.

General Procedure for the (*R*)-BINIM−Ni (II)-Catalyzed Reaction Was Exemplified in the Reaction of Ethyl Diazoacetate (1a) with 3-Acryloyl-2-oxazolidinone (2a). A suspension of (*R*)-BINIM-4Ph-2QN (37.5 mg, 0.05 mmol), powdered MS 4 Å (127 mg), and $Ni(ClO_4)_2 \cdot 6H_2O$ (18.3 mg, 0.05 mmol) in CH_2Cl_2 (2.5 mL) was stirred for 6 h at room temperature. 3-Acryloyl-2-oxazolidinone (**2a**) (70.6 mg, 0.50 mmol) in CH_2Cl_2 (1.0 mL) and ethyl diazoacetate (**1a**) (85.6 mg, 0.75 mmol) in CH_2Cl_2 (1.0 mL) were successively added to the catalyst suspension. After being stirred at room temperature for 24 h, the mixture was filtered through Celite−silica gel using AcOEt (50 mL) as an eluent. The solvent was evaporated in vacuo, and then the residue was chromatographed on silica gel (15 g) with hexane−ethyl acetate (7:3 v/v) as an eluent to give cycloadduct **3aa** and **4aa** (118 mg, 93%). The **3aa**/**4aa** ratio was determined to be 72:28 by ^{1}H NMR analysis (400 Mz). The enantiomeric excesses of **3aa** and **4aa** were determined by HPLC analysis (Daicel Chiralpak AD-H, *i*-PrOH−hexane (1:2 vol/vol), detector: UV 254 nm, flow rate =0.5 mL/min, 35 °C). **3aa**: t_{major} = 39.8 min, t_{minor} = 61.7 min. **4aa**: t_{major} = 31.2 min, t_{minor} = 43.7 min.

A 72:28 mixture of 5-[(2-oxo-3-oxazolidinyl)carbonyl]-3-(2-pyrazoline)carboxylic acid ethyl ester (**3aa**) and 3-[(2-oxo-3-oxazolidinyl)-carbonyl]-5-(2-pyrazoline)carboxylic acid ethyl ester (**4aa**): Yellow viscous oil, $[\alpha]^{25}_D$ = +12.9 (*c* 0.3, $CHCl_3$, **3aa**:**4aa** = 72:28, 90% ee (**3aa**)); IR ($CHCl_3$) 3382, 3000, 2927, 2341, 1758, 1712, 1473, 1384, 1276, 1234, 1195, 1118 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.35 (3H × 72/100, t, *J* = 7.1 Hz, **3aa**), 3.29 (1H × 72/100, dd, *J* = 12.4, 18.1 Hz, **3aa**), 3.41 (1H × 72/100, dd, *J* = 8.1, 18.1, Hz, **3aa**), 4.04−4.08 (2H × 72/100, m, **3aa**), 4.31 (2H × 72/100, q, *J* = 7.1 Hz, **3aa**), 4.50−4.55 (2H × 72/100, m, **3aa**), 5.25 (1H × 72/100, ddd, *J* = 2.7, 8.1, 12.4 Hz, **3aa**), 6.87 (1H × 72/100, bs, **3aa**), 1.30 (3H × 28/100, t, *J* = 7.1 Hz, **4aa**), 3.29 (1H × 28/100, m, **4aa**), 3.41 (1H × 28/100, m, **4aa**), 4.03−4.21 (2H × 28/100, m, **4aa**), 4.24 (2H × 28/100, q, *J* = 7.1 Hz, **4aa**), 4.39−4.56 (3H × 28/100, m, **4aa**), 6.77 (1H × 28/100, bs, **4aa**); ^{13}C NMR ($CDCl_3$) δ 14.2 (CH_3, **3aa**), 34.6 (CH_2, **3aa**), 42.6 (CH_2, **3aa**), 61.1 (CH_2, **3aa**), 62.6 (CH, **3aa**), 62.9 (CH_2, **3aa**), 142.8 (C, **3aa**), 153.2 (C, **3aa**), 161.6 (C, **3aa**), 169.7 (C, **3aa**); MS (EI) *m*/*z* 255 (M^+), 149, 87, 69, 55, 38, 26, 15; HRMS (EI) Calcd for $C_{10}H_{13}N_3O_5$ (M^+): 255.0854. Found: 255.0853.

A 85:15 mixture of 5-[(4,4-dimethyl-2-oxo-3-oxazolidinyl)carbonyl]-3-(2-pyrazoline)carboxylic acid ethyl ester (**3ab**) and 3-[(4,4-dimethyl-2-oxo-3-oxazolidinyl)carbonyl]-5-(2-pyrazoline)carboxylic acid ethyl ester (**4ab**): Yellow viscous oil, $[\alpha]^{25}_D$ = +3.2 (*c* 1.0, $CHCl_3$, **3ab**:**4ab** = 85:15, 28% ee (**3ab**)); IR (KBr) 3378, 2977, 2938, 1778, 1704, 1550, 1380, 1311, 1234, 1184, 1095, 1029, 968 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.35 (3H × 85/100, t, *J* = 7.1 Hz, **3ab**), 1.59 (6H × 85/100, s, **3ab**), 3.21 - 3.40 (2H × 85/100, m, **3ab**), 4.05 - 4.13 (2H × 85/100, m, **3ab**), 4.31 (2H × 85/100, q, *J* = 7.1 Hz, **3ab**), 5.23 (1H × 85/100, ddd, *J* = 2.7, 8.3, 12.4 Hz, **3ab**), 6.85 (1H × 85/100, bs, **3ab**), 1.30 (3H 15/100, t, *J* = 7.1 Hz, **4ab**), 1.60 (6H 15/100, s, **4ab**), 3.20−3.39 (2H × 15/100, m, **4ab**), 4.07 (2H × 15/100, s, **4ab**), 4.24 (2H × 15/100, q, *J* = 7.1 Hz, **4ab**), 4.44 (1H × 15/100, dd, *J* = 5.4, 11.9 Hz, **4ab**), 6.68 (1H × 15/100, bs, **4ab**); ^{13}C NMR ($CDCl_3$) δ 14.3 (CH_3, **3ab**), 24.5 (CH_3, **3ab**), 24.53 (CH_3, **3ab**), 35.8 (CH_2, **3ab**), 60.2 (C, **3ab**), 60.7 (CH_2, **3ab**), 63.5 (CH_2, **3ab**), 66.7 (CH, **3ab**), 135.6 (C, **3ab**), 153.2 (C, **3ab**), 161.6 (C, **3ab**), 170.1 (C, **3ab**); MS (EI) *m*/*z* 283 (M^+), 264, 238, 210, 195, 170, 141, 116, 95, 69, 54, 39; HRMS (EI) Calcd for $C_{12}H_{17}N_3O_5$ (M^+): 283.1167. Found: 283.1158. The enantiomeric excesses were determined by HPLC analysis (Daicel Chiralpak AD-H, *i*-PrOH:hexane = 1:9, detector: UV 254 nm, flow rate =1.0 mL/min, 35 °C). **3ab**: t_{major} = 57.9 min, t_{minor} = 104.7 min. **4ab**: t_{major} = 30.7 min, t_{minor} = 42.8 min.

5-[(5,5-Dimethyl-2-oxo-3-oxazolidinyl)carbonyl]-3-(2-pyrazoline)carboxylic Acid Ethyl Ester (3ac). Colorless plates, mp 114−116 °C (CH_2Cl_2−hexane); $[\alpha]^{25}_D$ = +33.1 (*c* 0.2, $CHCl_3$, 90% ee); IR (KBr) 3370, 2958, 2341, 1762, 1724, 1693, 1380, 1334, 1292, 1214, 1172, 1110, 1029 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.35 (3H, t, *J* = 7.1 Hz), 1.54 (3H, s), 1.55 (3H, s), 3.28 (1H, dd, *J* = 12.4, 18.0 Hz), 3.41 (1H, dd, *J* = 8.1, 18.0, Hz), 3.77 (2H, s), 4.31 (2H, q, *J* = 7.1 Hz), 5.25 (1H, ddd, *J* = 2.7, 8.1, 12.4 Hz), 6.09 (1H, bs); ^{13}C NMR ($CDCl_3$) δ 14.3 (CH_3), 27.3 (CH_3), 27.4 (CH_3), 34.6 (CH_2), 54.4 (CH_2), 61.3 (CH_2), 62.9 (CH), 80.1 (C), 143.2 (C), 152.4 (C), 161.7 (C) 169.9 (C); MS (EI) *m*/*z* 283 (M^+), 237, 167, 141, 116, 95, 69, 56, 35, 26, 16. Anal. Calcd for $C_{12}H_{17}N_3O_5$: C, 50.88; H, 6.05; N, 14.83%. Found: C, 50.99; H, 6.29; N, 14.48%. The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak AD-H, *i*-PrOH:hexane = 1:9,

detector: UV 254 nm, flow rate = 0.5 mL/min, 35 °C). t_{major} = 53.8 min, t_{minor} = 80.3 min.

A 70:30 mixture of 5-[(5,5-dimethyl-2-oxo-3-oxazolidinyl)carbonyl]-3-(2-pyrazoline)carboxylic acid ethyl ester (**3ac**) and 3-[(5,5-dimethyl-2-oxo-3-oxazolidinyl)carbonyl]-5-(2-pyrazoline)carboxylic acid ethyl ester (**4ac**): Although **4ac** could not be separated by chromatography from a mixture with major **3ac**, it could be characterized by ^{1}H NMR. $[\alpha]^{25}_D$ = +28.9 (*c* 1.0, $CHCl_3$, **3ac**:**4ac** = 70:30, 92% ee (**3ac**)); ^{1}H NMR ($CDCl_3$) δ 1.35 (3H × 70/100, t, *J* = 7.1 Hz, **3ac**), 1.54 (3H × 70/100, s, **3ac**), 1.55 (3H × 70/100, s, **3ac**), 3.28 (1H × 70/100, dd, *J* = 12.4, 18.0 Hz, **3ac**), 3.41 (1H × 70/100, dd, *J* = 8.1, 18.0, Hz, **3ac**), 3.77 (2H × 70/100, s, **3ac**), 4.31 (2H × 70/100, q, *J* = 7.1 Hz, **3ac**), 5.25 (1H × 70/100, ddd, *J* = 2.7, 8.1, 12.4 Hz, **3ac**), 6.09 (1H × 70/100, bs, **3ac**), 1.30 (3H × 30/100, t, *J* = 7.1 Hz, **4ac**), 1.51 (6H × 30/100, s, **4ac**), 3.23−3.51 (2H × 30/100, m, **4ac**), 3.89 (2H × 30/100, s, **4ac**), 4.23 (2H × 30/100, q, *J* = 7.1 Hz, **4ac**), 4.43 (1H × 30/100, m, **4ac**), 6.75 (1H × 30/100, bs, **4ac**). The enantiomeric excesses were determined by HPLC analysis (Daicel Chiralpak AD-H, *i*-PrOH:hexane = 1:9, detector: UV 254 nm, flow rate = 0.5 mL/min, 35 °C). **3ac**: t_{major} = 53.8 min, t_{minor} = 80.3 min. **4ac**: t_{major} = 75.0 min, t_{minor} = 120.1 min.

(5*S*)-5-[(1-Benzyl-5,5-dimethyl-3-oxo-2-pyrazolidinyl)-carbonyl]-3-(2-pyrazoline)carboxylic Acid Ethyl Ester (6aa):[6b] Colorless plates; mp 42−43 °C (CH_2Cl_2−hexane); $[\alpha]^{25}_D$ = +106.7 (*c* 0.5, $CHCl_3$, 92% ee); IR (KBr) 3356, 3062, 2982, 2937, 1756, 1716, 1576, 1351, 1060, 737 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.29 (3H, s), 1.31 (3H, s), 1.36 (3H, t, *J* = 7.0 Hz), 2.58 (1H, d, *J* = 17.3 Hz), 2.65 (1H, d, *J* = 17.3 Hz), 3.20 (2H, d, *J* = 10.2 Hz), 4.03 (1H, d, *J* = 13.5 Hz), 4.10 (1H, d, *J* = 13.5 Hz), 4.30 (2H, q, *J* = 7.0 Hz), 5.01 (1H, bt, *J* = 10.2 Hz), 6.71 (1H, bs), 7.22−7.32 (3H, m), 7.36−7.41 (2H, m); MS (EI) *m*/*z* 372 (M^+), 358, 327, 318, 308, 294, 279, 268, 250, 231, 216, 204, 190, 187, 174, 162, 152, 121, 109, 99, 81, 51, 23, 12; HRMS (EI) Calcd for $C_{19}H_{24}N_4O_4$ (M^+): 372.1796. Found: 372.1812. The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak AD-H, *i*-PrOH:hexane = 1:19, detector: UV 254 nm, flow rate = 1.0 mL/min, 35 °C). t_{major} = 103.9 min, t_{minor} = 125.6 min. The absolute configuration of 2-pyrazoline **6aa** was assigned based on the optical rotation previously reported.[6b]

A 85:15 mixture of 5-[(1-Benzyl-5,5-dimethyl-3-oxo-2-pyrazolidinyl)-carbonyl]-3-(2-pyrazoline)carboxylic acid ethyl ester (**6aa**) and 3-[(1-Benzyl-5,5-dimethyl-3-oxo-2-pyrazolidinyl)carbonyl]-5-(2-pyrazoline) carboxylic acid ethyl ester (**7aa**): Although **7aa** could not be separated by chromatography from a mixture with major **6aa**, it could be characterized by ^{1}H NMR. $[\alpha]^{25}_D$ = +114.9 (*c* 1.0, $CHCl_3$, **6aa**:**7aa** = 85:15, 97% ee (**6aa**)); ^{1}H NMR ($CDCl_3$) δ 1.29 (3H × 85/100, s, **6aa**), 1.31 (3H × 85/100, s, **6aa**), 1.36 (3H × 85/100, t, *J* = 7.0 Hz, **6aa**), 2.58 (1H × 85/100, d, *J* = 17.3 Hz, **6aa**), 2.65 (1H × 85/100, d, *J* = 17.3 Hz, **6aa**), 3.20 (2H × 85/100, d, *J* = 10.2 Hz, **6aa**), 4.03 (1H × 85/100, d, *J* = 13.5 Hz, **6aa**), 4.10 (1H × 85/100, d, *J* = 13.5 Hz, **6aa**), 4.30 (2H × 85/100, q, *J* = 7.0 Hz, **6aa**), 5.01 (1H × 85/100, bt, *J* = 10.2 Hz, **6aa**), 6.71 (1H × 85/100, bs, **6aa**), 7.22−7.32 (3H × 85/100, m, **6aa**), 7.36−7.41 (2H × 85/100, m, **6aa**), 1.29 (3H × 15/100, t, *J* = 7.1 Hz, **7aa**), 1.32 (3H × 15/100, s, **7aa**), 1.36 (3H × 15/100, s, **7aa**), 2.54 (2H × 15/100, s, **7aa**), 2.97 (1H × 15/100, dd, *J* = 12.2, 17.1 Hz, **7aa**), 3.14 (1H × 15/100, d, *J* = 4.88, 17.1 Hz, **7aa**), 4.01 (1H × 15/100, d, *J* = 12.9 Hz, **7aa**), 4.11 (1H × 15/100, d, *J* = 12.9 Hz, **7aa**), 4.23 (2H × 15/100, q, *J* = 7.1 Hz, **7aa**), 4.32 (1H × 15/100, dd, *J* = 4.88, 12.2 Hz, **7aa**), 6.62 (1H × 15/100, bs, **7aa**), 7.21−7.39 (5H × 15/100, m, **7aa**). The enantiomeric excesses were determined by HPLC analysis (Daicel Chiralpak AD-H, *i*-PrOH:hexane = 1:19, detector: UV 254 nm, flow rate = 0.5 mL/min, 35 °C). **6aa**: t_{major} = 103.9 min, t_{minor} = 125.6 min. **7aa**: t_{major} = 131.5 min, t_{minor} = 135.8 min (partly overlap).

(5*S*)-5-[(5,5-Dimethyl-1-(1-naphthylmethyl)-3-oxo-2-pyrazolidinyl)carbonyl]-3-(2-pyrazoline)carboxylic Acid Ethyl Ester (6ab). Colorless plates; mp 167−168 °C (CH_2Cl_2−hexane); $[\alpha]^{25}_D$ = +166.8 (*c* 0.5, $CHCl_3$, 95% ee); IR (KBr) 3359, 2981, 2931, 2854, 1712, 1577, 1508, 1423, 1384, 1338, 1307, 1234, 1153, 1118, 1025, 744 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.34 (3H, t, *J* = 7.1 Hz), 1.34 (3H, s), 1.40 (3H, s), 2.75 (1H, d, *J* = 17.3 Hz), 2.84 (1H, d, *J* = 17.3 Hz), 3.01 (2H, m), 4.28 (2H, m), 4.39 (1H, d, *J* = 12.9 Hz), 4.51 (1H, d, *J* = 12.9 Hz), 4.74 (1H, bs), 6.41 (1H, bs), 7.34 (1H, m), 7.47−7.58 (3H, m), 7.75 (1H, m), 7.84 (1H, m), 8.22 (1H, m); ^{13}C NMR ($CDCl_3$) δ 14.4 (CH_3), 25.9 (CH_3), 26.3 (CH_3), 35.1 (CH_2), 42.9 (CH_2), 55.0 (CH_2), 61.2 (CH_2), 61.7 (C), 63.1 (CH), 123.2 (CH), 124.9 (CH), 125.7 (CH), 126.2 (CH), 127.9 (CH), 128.5 (CH), 128.6 (CH), 131.7 (C), 131.8 (C), 133.4 (C), 142.7 (C), 161.8 (C), 167.3 (C), 174.6 (C); MS (EI) *m*/*z* 422 (M^+), 393, 376, 348, 281, 266, 253, 238, 210, 197, 182, 167, 154, 142, 127, 115, 95, 83, 69, 56, 35, 24, 13. Anal. Calcd for $C_{23}H_{26}N_4O_4$: C, 65.39; H, 6.20; N, 13.26%. Found: C, 65.35; H, 6.23; N, 13.27%. The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak OD-H, *i*-PrOH:hexane = 1:7, detector: UV 254 nm, flow rate = 0.5 mL/min, 35 °C). t_{minor} = 119.7, t_{major} = 132.1 min. The absolute configuration of 2-pyrazoline **6ab** was assigned similar to **6aa**.

A 84:16 mixture of 5-[(5,5-dimethyl-1-(1-naphthylmethyl)-3-oxo-2-pyrazolidinyl)carbonyl]-3-(2-pyrazoline)carboxylic acid ethyl ester (**6ab**) and 3-[(5,5-dimethyl-1-(1-naphthylmethyl)-3-oxo-2-pyrazolidinyl)carbonyl]-5-(2-pyrazoline)carboxylic acid ethyl ester (**7ab**): Although **7ab** could not be separated by chromatography from a mixture with major **6ab**, it could be characterized by ^{1}H NMR. $[\alpha]^{25}_D$ = +147.1 (*c* 1.0, $CHCl_3$, **6ab**:**7ab** = 84:16, 95% ee (**6ab**)); ^{1}H NMR ($CDCl_3$) δ 1.34 (3H × 84/100, t, *J* = 7.1 Hz, **6ab**), 1.34 (3H × 84/100, s, **6ab**), 1.40 (3H × 84/100, s, **6ab**), 2.75 (1H × 84/100, d, *J* = 17.3 Hz, **6ab**), 2.84 (1H × 84/100, d, *J* = 17.3 Hz, **6ab**), 3.01 (2H × 84/100, m, **6ab**), 4.28 (2H × 84/100, m, **6ab**), 4.39 (1H × 84/100, d, *J* = 12.9 Hz, **6ab**), 4.51 (1H × 84/100, d, *J* = 12.9 Hz, **6ab**), 4.74 (1H × 84/100, bs, **6ab**), 6.41 (1H × 84/100, bs, **6ab**), 7.34 (1H × 84/100, m, **6ab**), 7.47−7.58 (3H × 84/100, m, **6ab**), 7.75 (1H × 84/100, m, **6ab**), 7.84 (1H × 84/100, m, **6ab**), 8.22 (1H × 84/100, m, **6ab**), 1.23 (3H × 16/100, t, *J* = 7.1 Hz, **7ab**), 1.44 (6H × 16/100, s, **7ab**), 2.59−2.89 (4H × 16/100, m, **7ab**), 3.70 (1H × 16/100, dd, *J* = 6.3, 12.2 Hz, **7ab**), 4.26 (2H × 16/100, m, **7ab**), 4.35 (1H × 16/100, d, *J* = 12.9 Hz, **7ab**), 4.54 (1H × 16/100, d, *J* = 12.9 Hz, **7ab**), 6.20 (1H × 16/100, bs, **7ab**), 7.32−7.58 (7H × 16/100, m, **7ab**). The enantiomeric excesses were determined by HPLC analysis (Daicel Chiralpak OD-H, *i*-PrOH:hexane = 1:7, detector: UV 254 nm, flow rate = 0.5 mL/min, 35 °C). **7ab**: t_{major} = 100.0 min, t_{minor} = 106.9 min (partly overlap). **6ab**: t_{major} = 117.1 min, t_{minor} = 133.9 min.

A 79:21 mixture of 5-[(5,5-dimethyl-1-ethyl-3-oxo-2-pyrazolidinyl)-carbonyl]-3-(2-pyrazoline)carboxylic acid ethyl ester (**6ac**) and 3-[(5,5-dimethyl-1-ethyl-3-oxo-2-pyrazolidinyl)carbonyl]-5-(2-pyrazoline)carboxylic acid ethyl ester (**7ac**): Yellow viscous oil; $[\alpha]^{25}_D$ = +8.5 (*c* 1.0, $CHCl_3$, **6ac**:**7ac** = 79:21, 8% ee (**6ac**), 3% ee (**7ac**)); IR (KBr) 3262, 3058, 2981, 1689, 1596, 1442, 1373, 1330, 1241, 1160, 1114, 1029, 744 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.05 (3H × 79/100, t, *J* = 7.3 Hz, **6ac**), 1.33 (3H × 79/100, s, **6ac**), 1.34 (3H × 79/100, s, **6ac**), 1.35 (3H × 79/100, t, *J* = 7.1 Hz, **6ac**), 2.61 (1H × 79/100, d, *J* = 17.3 Hz, **6ac**), 2.66 (1H × 79/100, d, *J* = 17.3 Hz, **6ac**), 3.02 (2H × 79/100, m, **6ac**), 3.29 (1H × 79/100, dd, *J* = 12.5, 18.3 Hz, **6ac**), 3.39 (1H × 79/100, dd, *J* = 8.0, 18.3 Hz, **6ac**), 4.31 (2H × 79/100, q, *J* = 7.1 Hz, **6ac**), 5.16 (1H × 79/100, ddd, *J* = 2.4, 8.0, 12.5 Hz, **6ac**), 6.89 (1H × 79/100, bs, **6ac**), 1.10 (3H × 21/100, t, *J* = 7.1 Hz, **7ac**), 1.31 (3H × 21/100, t, *J* = 7.1 Hz, **7ac**), 1.33 (3H × 21/100, s, **7ac**), 1.35 (3H × 21/100, s, **7ac**), 2.65 (2H × 21/100, s, **7ac**), 2.96−3.02 (2H × 21/100, m, **7ac**), 3.23−3.43 (2H × 21/100, m, **7ac**), 4.23 (2H × 21/100, q, *J* = 7.1 Hz, **7ac**), 4.44 (2H × 21/100, dd, *J* = 5.4, 12.2 Hz, **7ac**), 6.71 (1H × 21/100, bs, **7ac**); ^{13}C NMR ($CDCl_3$) δ 12.9 (CH_3, **6ac**), 14.3 (CH_3, **6ac**), 25.2 (CH_3, **6ac**), 25.5 (CH_3, **6ac**), 34.7 (CH_2, **6ac**), 42.7 (CH_2, **6ac**), 43.7 (CH_2, **6ac**), 46.9 (CH_2, **6ac**), 61.2 (CH, **6ac**), 63.1 (C, **6ac**), 149.3 (C, **6ac**), 161.8 (C, **6ac**), 169.7 (C, **6ac**), 174.8 (C, **6ac**); MS (EI) *m*/*z* 310 (M^+), 288, 279, 264, 255, 236, 226, 212, 199, 186, 173, 166, 152, 126, 114, 98, 84, 72, 60, 51, 23, 14; Anal. Calcd for $C_{14}H_{22}N_4O_4$: C, 54.18; H, 7.15; N, 18.05%. Found: C,

54.10; H, 7.44; N, 17.84%. The enantiomeric excesses were determined by HPLC analysis (Daicel Chiralpak AD-H, *i*-PrOH:hexane = 1:9, detector: UV 254 nm, flow rate = 1.0 mL/min, 35 °C). **6ac**: t_{major} = 30.2, t_{minor} = 42.1 min. **7ac**: t_{major} = 33.9, t_{minor} = 37.7 min.

(4*S*,5*S*)-5-[(1-Benzyl-5,5-dimethyl-3-oxo-2-pyrazolidinyl)-carbonyl]-4-methyl-3-(2-pyrazoline)carboxylic Acid Ethyl Ester (9aa):[6b] Colorless plates; mp 117−119 °C (CH_2Cl_2−hexane); $[\alpha]^{25}_D$ = +171.2 (*c* 1.0, $CHCl_3$, 93% ee); IR (KBr) 3349, 2979, 2933, 1748, 1700, 1588, 1453, 1369, 1327, 1093, 771 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (3H, s), 1.32 (3H, s), 1.36 (3H, t, *J* = 7.1 Hz), 1.36 (3H, d, *J* = 7.1 Hz), 2.58 (1H, d, *J* = 17.3 Hz,), 2.68 (1H, d, *J* = 17.3 Hz), 3.41 (1H, dq, *J* = 4.6, 7.1 Hz), 3.99 (1H, d, *J* = 13.4 Hz), 4.09 (1H, d, *J* = 13.4 Hz), 4.24−4.36 (2H, m), 4.57 (1H, bd, *J* = 4.6 Hz), 6.61 (1H, bs), 7.22−7.32 (3H, m), 7.36−7.41 (2H, m); ^{13}C NMR ($CDCl_3$) δ 14.4 (CH_3), 17.1 (CH_3), 26.1 (CH_3), 26.3 (CH_3), 43.2 (CH_2), 43.3 (CH), 56.9 (CH_2), 61.0 (CH_2), 61.6 (C), 70.9 (CH), 127.5 (CH), 128.2 (CH), 129.1 (CH), 136.4 (C), 146.6 (C), 161.5 (C), 167.3 (C), 174.8 (C); MS (EI) *m*/*z* 386 (M^+), 358, 276, 203,190, 155, 114, 90, 78, 51, 24, 14. Anal. Calcd for $C_{20}H_{26}N_4O_4$: C, 62.16; H, 6.78; N, 14.50%. Found: C, 62.17; H, 7.06; N, 14.29%. The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak AD-H, *i*-PrOH:hexane = 1:9, detector: UV 254 nm, flow rate = 1.0 mL/min, 35 °C). t_{major} = 38.8, t_{minor} = 51.2 min. The absolute configuration of 2-pyrazoline **9aa** was assigned based on the optical rotation previously reported.[6b]

(4*S*,5*S*)-5-[(1-Benzyl-5,5-dimethyl-3-oxo-2-pyrazolidinyl)-carbonyl]-4-ethyl-3-(2-pyrazoline)carboxylic Acid Ethyl Ester (11aa):[6b] Colorless plates; mp 41−42 °C (CH_2Cl_2−hexane); $[\alpha]^{25}_D$ = +194.9 (*c* 1.0, $CHCl_3$, 86% ee); IR (KBr) 3356, 2972, 2934, 1750, 1701, 1568, 1349, 1233, 1103, 733 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (3H, t, *J* = 7.6 Hz), 1.29 (3H, s), 1.30 (3H, s), 1.32−1.36 (3H, m), 1.74 (1H, m), 1.90 (1H, m), 2.60 (1H, d, *J* = 17.3 Hz), 2.67 (1H, d, *J* = 17.3 Hz), 3.57 (1H, m), 4.03 (1H, d, *J* = 13.4 Hz), 4.08 (1H, d, *J* = 13.4 Hz), 4.24−4.33 (2H, m), 4.68 (1H, bs), 6.69 (1H, bs), 7.17−7.44 (5H, m); ^{13}C NMR ($CDCl_3$) δ 10.1 (CH_3), 14.2 (CH_3), 24.1 (CH_2), 26.0 (CH_3), 26.3 (CH_3), 43.2 (CH_2), 48.3 (CH), 56.7 (CH_2), 60.8 (CH_2), 61.4 (C), 68.1 (CH), 127.4 (CH), 128.1 (CH), 129.0 (CH), 136.4 (C), 144.8 (C), 161.7 (C), 166.9 (C), 174.7 (C); MS (EI) *m*/*z* 400 (M^+), 355, 189, 123, 92, 65, 39, 15. Anal. Calcd for $C_{21}H_{28}N_4O_4$: C, 62.98; H, 7.05; N, 13.99%. Found: C, 62.95; H, 7.08; N, 13.76%. The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak AD-H, *i*-PrOH:hexane = 1:9, detector: UV 254 nm, flow rate = 1.0 mL/min, 35 °C). t_{major} = 41.1, t_{minor} = 46.9 min. The absolute configuration of 2-pyrazoline **11aa** was assigned based on the optical rotation previously reported.[6b]

(4*S*,5*S*)-5-[(1-Benzyl-5,5-dimethyl-3-oxo-2-pyrazolidinyl)-carbonyl]-4-ethoxycarbonyl-3-(2-pyrazoline)carboxylic Acid Ethyl Ester (13aa). Colorless plates; mp 38−40 °C (CH_2Cl_2−hexane); $[\alpha]^{25}_D$ = +226.7 (*c* 1.0, $CHCl_3$, 85% ee); IR (KBr) 3351, 2981, 1735, 1565, 1376, 1230, 1118, 732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.29 (3H, t, *J* = 7.1 Hz), 1.30 (3H, s), 1.31 (3H, s), 1.34 (3H, t, *J* = 7.1 Hz), 2.62 (2H, s), 4.04 (1H, d, *J* = 13.7 Hz), 4.09 (1H, d, *J* = 13.7 Hz), 4.13−4.36 (4H, m), 4.49 (1H, d, *J* = 8.1 Hz), 5.25 (1H, bs), 6.84 (1H, bs), 7.22−7.32 (3H, m), 7.36−7.41 (2H, m); ^{13}C NMR ($CDCl_3$) δ 14.2 (CH_3), 14.4 (CH_3), 26.0 (CH_3), 26.6 (CH_3) 43.3 (CH_2), 51.9 (CH), 56.8 (CH_2), 61.4 (CH_2), 61.6 (C), 61.9 (CH_2), 68.5 (CH), 127.6 (CH), 128.4 (CH), 129.2 (CH), 136.3 (C), 140.0 (C), 160.9 (C), 164.5 (C), 169.3 (C), 175.0 (C); MS (EI) *m*/*z* 444 (M^+), 398, 370, 294, 258, 204, 188, 166, 140, 127, 84, 66, 52, 34, 10. Anal. Calcd for $C_{22}H_{28}N_4O_6$: C, 59.45; H,6.35; N, 12.60%. Found: C, 59.42; H, 6.31; N, 12.46%. The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak AD-H, *i*-PrOH:hexane = 1:12, detector: UV 254 nm, flow rate = 1.0 mL/min, 35 °C). t_{major} = 104.0, t_{minor} = 116.1 min. The absolute configuration of 2-pyrazoline **13aa** was assigned similar to **11aa**.

3-[(1-Benzyl-5,5-dimethyl-3-oxo-2-pyrazolidinyl)carbonyl]-5-phenyl-5-(2-pyrazoline)carboxylic Acid Ethyl Ester (7ba). Colorless plates; mp 159−160 °C (CH_2Cl_2−hexane); $[\alpha]^{25}_D$ = −50.9 (*c* 0.10, $CHCl_3$, 43%ee); IR (KBr) 3459, 3278, 3058, 2973, 2931, 1739, 1673, 1569, 1434, 1376, 1299, 1245, 1141, 1087, 1041, 998, 848, 821, 767, 690, 501, 466 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (3H, t, *J* = 7.3 Hz), 1.34 (3H, s), 1.35 (3H, s), 2.57 (1H, d, *J* = 16.8 Hz), 2.63 (1H, d, *J* = 16.8 Hz), 2.94 (1H, d, *J* = 17.1 Hz), 3.82 (1H, d, *J* = 17.1 Hz), 4.04 (1H, d, *J* = 12.9 Hz), 4.09 (1H, d, *J* = 12.9 Hz), 4.22 (2H, q, *J* = 7.3 Hz), 7.16 (1H, bs), 7.18−7.25 (3H, m), 7.28−7.43 (7H, m); ^{13}C NMR (100 MHz) δ 14.0 (CH_3), 26.0 (CH_3), 26.2 (CH_3), 42.8 (CH_2), 43.1 (CH_2), 57.7 (CH_2), 61.8 (C), 62.4 (CH_2), 75.1 (C), 125.5 (CH), 127.4 (CH), 127.9 (CH), 128.0 (CH), 128.5 (CH), 129.7 (CH), 136.1 (C), 139.4 (C), 144.2 (C), 160.5 (C), 172.3 (C), 173.4 (C); MS (EI) *m*/*z* 448 (M^+), 419, 374, 332, 316, 283, 260, 245, 232, 217, 203, 188, 172, 159, 144, 127, 106, 90, 76, 63, 47, 23, 10. Anal. Calcd for $C_{25}H_{28}N_4O_4$: C, 66.95; H, 6.29; N, 12.49%. Found: C, 66.92; H, 6.32; N, 12.49%. The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak AD-H, *i*-PrOH:hexane = 1:6, detector: UV 254 nm, flow rate = 0.5 mL/min, 35 °C). t_{minor} = 97.1, t_{major} = 129.4 min.

Although cyclopropane **14** and alkene **15** could not be separated completely by chromatography, these could be characterized by ^1H NMR or ^{13}C NMR. A 78:22 mixture of 2-[(1-benzyl-5,5-dimethyl-3-oxo-2-pyrazolidinyl)carbonyl]-1-phenyl-1-cyclopropane carboxylic acid ethyl ester (**14**) and 4-[(1-benzyl-5,5-dimethyl-3-oxo-2-pyrazolidinyl)-carbonyl]-2-phenyl-2-butenoic acid ethyl ester (**15**): ^1H NMR ($CDCl_3$) δ 1.01 (3H × 78/100, s, **14**), 1.21 (3H × 78/100, t, *J* = 7.1 Hz, **14**), 1.25 (3H × 78/100, s, **14**), 1.84 (1H × 78/100, dd, *J* = 4.6, 8.1 Hz, **14**), 2.26 (1H × 78/100, dd, *J* = 4.6, 6.8 Hz, **14**), 2.60 (2H × 78/100, s, **14**), 3.60 (1H × 78/100, dd, *J* = 6.8, 8.1 Hz, **14**), 3.70 (1H 78/100, d, *J* = 13.9 Hz, **14**), 3.78 (1H × 78/100, d, *J* = 13.9 Hz, **14**), 4.12−4.25 (2H × 78/100, m, **14**), 7.14−7.26 (8H × 78/100, m, **14**) 7.32−7.34 (2H × 78/100, m, **14**), 1.22 (6H × 22/100, s, **15**), 1.27 (3H × 22/100, t, *J* = 7.1 Hz, **15**), 2.52 (2H × 22/100, s, **15**), 3.42 (2H × 22/100, brd, *J* = 7.1 Hz, **15**), 3.99 (2H × 22/100, s, **15**), 4.21 (2H × 22/100, q, *J* = 7.1 Hz, **15**), 7.08 (1H × 22/100, t, *J* = 7.1 Hz, **15**), 7.12−7.17 (2H × 22/100, m, **15**), 7.19−7.39 (8H × 22/100, m, **15**); ^{13}C NMR ($CDCl_3$) δ 14.3 (CH_3, **15**), 18.0 (CH_2, **15**), 26.2 (CH_3, **15**), 26.3 (CH_3, **15**), 32.7 (CH, **15**), 43.6 (CH_2, **15**), 56.5 (CH_2, **15**), 60.7 (CH_2, **15**), 61.7 (CH_2, **15**), 127.1 (CH, **15**), 127.4 (CH, **15**), 127.8 (CH, **15**), 128.1 (CH, **15**), 128.6 (CH, **15**), 130.5 (CH, **15**), 133.7 (C, **15**), 137.6 (C, **15**), 164.1 (C, **15**), 171.8 (C, **15**), 174.0 (C, **15**).

5-Benzyl-3-[(1-benzyl-5,5-dimethyl-3-oxo-2-pyrazolidinyl)-carbonyl]-5-(2-pyrazoline)carboxylic Acid Ethyl Ester (7ca). Colorless amorphous; $[\alpha]^{25}_D$ = −106.4 (*c* 0.40, $CHCl_3$, 75% ee); IR (KBr) 3357, 2979, 1735, 1681, 1496, 1455, 1373, 1302, 1232, 1033, 702 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.19 (3H, t, *J* = 7.1 Hz), 1.32 (3H, s), 1.34 (3H, s), 2.55 (1H, d, *J* = 16.8 Hz), 2.63 (1H, d, *J* = 16.8 Hz), 2.78 (1H, d, *J* = 17.1 Hz), 3.04 (1H, d, *J* = 13.4 Hz), 3.19 (1H, d, *J* = 13.4 Hz), 3.24 (1H, d, *J* = 17.1 Hz), 4.00 (1H, d, *J* = 12.7 Hz), 4.07 (1H, d, *J* = 12.7 Hz), 4.12 (2H, q, *J* = 7.1 Hz), 6.60 (1H, bs), 7.10−7.38 (10H, m); ^{13}C NMR ($CDCl_3$) 14.0 (CH_3), 25.9 (CH_3), 26.3 (CH_3), 41.0 (CH_2), 42.9 (CH_2), 43.4 (CH_2), 57.7 (CH_2), 61.79 (C), 61.82 (CH_2), 73.5 (C), 127.1 (CH), 127.4 (CH), 128.0 (CH), 128.3 (CH), 129.5 (CH), 129.8 (CH), 134.9 (C), 136.1 (C), 144.2 (C), 160.7 (C), 172.6 (C), 173.6 (C); MS (EI) *m*/*z* 462 (M^+), 231, 204, 189, 157, 129, 113, 91, 69, 55, 41, 28, 3. Anal. Calcd for $C_{26}H_{30}N_4O_4$: C, 67.51; H, 6.54; N, 12.11%. Found: C, 67.62; H, 6.49; N, 12.05%. The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak OZ-3, *i*-PrOH: hexane = 50:50, detector: UV 254 nm, flow rate = 0.5 mL/min, 35 °C). t_{major} =20.3, t_{minor} = 27.6 min.

3-[(1-Benzyl-5,5-dimethyl-3-oxo-2-pyrazolidinyl)carbonyl]-5-naphthylmethyl-5-(2-pyrazoline)carboxylic Acid Ethyl Ester (7cb). Colorless amorphous; $[\alpha]^{25}_D$ = −142.3 (*c* 0.40, $CHCl_3$, 77% ee); IR (KBr) 3340, 2978, 2360, 1735, 1373, 1303, 1227, 1032, 797, 776, 702, 418 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10 (3H, t, *J* = 7.1 Hz), 1.47 (3H, s), 1.50 (3H, s), 2.04 (1H, d, *J* = 17.1 Hz), 2.52 (1H, d, *J* = 13.4 Hz), 2.68 (1H,

d, J = 16.8 Hz), 2.80 (1H, d, J = 16.8 Hz), 2.86 (1H, d, J = 17.1 Hz), 2.87 (1H, d, J = 13.4 Hz), 3.96−4.04 (2H, m), 4.38 (1H, d, J = 12.2 Hz), 4.52 (1H, d, J = 12.2 Hz), 6.24 (1H, bs), 6.96−8.27 (12H, m); ^{13}C NMR ($CDCl_3$) 13.7 (CH_3), 25.5 (CH_3), 26.3 (CH_3), 40.4 (CH_2), 42.2 (CH_2), 42.9 (CH_2), 55.6 (CH_2), 61.3 (CH_2), 61.6 (C), 72.9 (C), 123.7 (CH), 124.8 (CH), 125.2 (CH), 125.9 (CH), 126.7 (CH), 127.9 (CH), 128.1 (CH), 128.5 (CH), 128.9 (CH), 129.6 (CH), 130.7 (C), 131.7 (C), 133.2 (C), 134.8 (C), 143.3 (C), 160.0 (C), 172.1 (C), 173.1 (C); MS (EI) m/z 512 (M^+), 282, 254, 231, 211, 185, 157, 141, 115, 91, 77, 55, 28, 3; HRMS (EI) Calcd for $C_{30}H_{32}N_4O_4$ (M^+): 512.2422. Found: 512.2449. The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak OZ-3, i-PrOH:hexane = 65:35, detector: UV 254 nm, flow rate = 0.5 mL/min, 35 °C). t_{minor} = 22.1, t_{major} = 33.8 min.

3-[(1-Benzyl-5,5-dimethyl-3-oxo-2-pyrazolidinyl)carbonyl]-5-naphthylmethyl-5-(2-pyrazoline)carboxylic Acid Methyl Ester (18cb). Colorless amorphous; $[\alpha]^{25}_D$ = −114.2 (c 0.40, $CHCl_3$, 77% ee); IR (KBr) 3341, 2972, 2359, 1739, 1439, 1303, 1228, 797, 703 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.47 (3H, s), 1.50 (3H, s), 2.06 (1H, d, J = 17.0 Hz), 2.51 (1H, d, J = 13.4 Hz), 2.67 (1H, d, J = 16.8 Hz), 2.80 (1H, d, J = 16.8 Hz), 2.84 (1H, d, J = 17.0 Hz), 2.87 (1H, d, J = 13.4 Hz), 3.56 (3H, s), 4.37 (1H, d, J = 12.2 Hz), 4.51 (1H, d, J = 12.2 Hz), 6.21 (1H, s), 6.91−8.27 (12H, m); ^{13}C NMR ($CDCl_3$) 25.6 (CH_3), 26.3 (CH_3), 40.4 (CH_2), 42.2 (CH_2), 42.9 (CH_2), 52.2 (CH_3), 55.7 (CH_2), 61.7 (C), 73.1 (C), 123.7 (CH), 124.9 (CH), 125.3 (CH), 125.9 (CH), 126.9 (CH), 128.0 (CH), 128.2 (CH), 128.6 (CH), 128.9 (CH), 129.7 (CH), 130.7 (C), 131.7 (C), 133.2 (C), 134.7 (C), 143.4 (C), 159.9 (C), 172.6 (C), 173.3 (C); MS (EI) m/z 498 (M^+), 254, 217, 185, 157, 141, 115, 91, 77, 55, 28, 3; HRMS (EI) Calcd for $C_{29}H_{30}N_4O_4$ (M^+): 498.2265. Found: 498.2267. The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak OZ-3, i-PrOH:hexane = 65:35, detector: UV 254 nm, flow rate = 0.5 mL/min, 35 °C). t_{minor} = 23.2, t_{major} = 37.1 min.

3-[(1-Benzyl-5,5-dimethyl-3-oxo-2-pyrazolidinyl)carbonyl]-5-naphthylmethyl-5-(2-pyrazoline)carboxylic Acid *tert*-Butyl Ester (19ca). Colorless amorphous; $[\alpha]^{25}_D$ = −69.6 (c 0.40, $CHCl_3$, 44% ee); IR (KBr) 3327, 2977, 1756, 1728, 1689, 1496, 1424, 1370, 1306, 1254, 1153, 843, 772, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.32 (3H, s), 1.35 (3H, s), 1.38 (9H, s), 2.55 (1H, d, J = 16.9 Hz), 2.64 (1H, d, J = 16.9 Hz), 2.74 (1H, d, J = 17.1 Hz), 3.03 (1H, d, J = 13.4 Hz), 3.16 (1H, d, J = 13.4 Hz), 3.24 (1H, d, J = 17.1 Hz), 4.03 (1H, d, J = 12.8 Hz), 4.10 (1H, d, J = 12.8 Hz), 6.57 (1H, s), 7.18−7.42 (11H, m); ^{13}C NMR ($CDCl_3$) δ 25.9 (CH_3), 26.4 (CH_3), 27.9 (CH_3), 41.1 (CH_2), 42.9 (CH_2), 43.4 (CH_2), 57.7 (CH_2), 61.8 (C), 73.6 (C), 82.7 (C), 127.0 (CH), 127.4 (CH), 128.0 (CH), 128.2 (CH), 129.8 (CH), 129.8 (CH), 135.1 (C), 136.2 (C), 144.0 (C), 160.9 (C), 171.6 (C), 173.5 (C); MS (EI) m/z 490 (M^+), 231, 204, 189, 157, 129, 113, 91, 71, 57, 41, 28, 2; HRMS (EI) Calcd for $C_{28}H_{34}N_4O_4$ (M^+): 490.2578. Found: 490.2569. Anal. Calcd for $C_{28}H_{34}N_4O_4$: C, 68.55; H, 6.99; N, 11.42%. Found: C, 68.30; H, 6.93; N, 11.72%. The enantiomeric excess was determined by HPLC analysis (Daicel Chiralpak OZ-3, i-PrOH:hexane = 1:1, detector: UV 254 nm, flow rate = 0.5 mL/min, 35 °C). t_{minor} =13.9, t_{major} = 20.8 min.

Reductive Conversion of 2-Pyrazoline 9aa to Alcohol 20 by $NaBH_4$. Sodium borohydride (19.7 mg, 0.52 mmol) was added to a solution of **9aa** (50.0 mg, 0.13 mmol) in THF (1.6 mL) at −40 °C and stirred for 24 h. After completion, a saturated solution of ammonium chloride (2 mL) and water (2 mL) was added to the reaction mixture at −40 °C and then allowed to warm to room temperature with vigorous stirring. The mixture was extracted with ethyl acetate (4 mL × 5). The combined extracts were washed with brine, dried over magnesium sulfate, and evaporated in vacuo, and then the residue was chromatographed on silica gel (5 g) with hexane−ethyl acetate (1:1 v/v) as an eluent to give the alcohol (16.8 mg, 69%). The enantiomeric excess of alcohol **20** was determined by HPLC analysis (Daicel Chiralpak AD-H, i-PrOH−hexane 1:9, detector: UV 254 nm, flow rate = 1 mL/min, 35 °C), t_{major} = 10.1, t_{minor} = 11.3 min.

(4*S*,5*S*)-4,5-Dihydro-3-ethoxycarbonyl-5-hydroxymethyl-4-methyl-1*H*-pyrazole. Colorless oil; $[\alpha]^{25}_D$ = +25.9 (c 0.17, $CHCl_3$, 96% ee), IR (neat) 3358, 2929, 1708, 1555, 1453, 1377, 1241, 1101 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.28 (3H, d, J = 6.8 Hz), 1.35 (3H, t, J = 7.2 Hz), 2.35 (1H, bs), 3.04 (1H, quint, J = 6.8 Hz), 3.61−3.68 (3H, m), 4.23−4.35 (2H, m); ^{13}C NMR ($CDCl_3$) 14.4 (CH_3), 16.9 (CH_3), 40.5 (CH), 61.0 (CH_2), 63.2 (CH_2), 70.2 (CH), 146.1 (C), 162.3 (C); MS (EI) m/z 186 (M^+), 155, 141, 109, 91, 83, 71, 65, 55, 39, 29, 15; HRMS (EI) Calcd for $C_8H_{14}N_2O_3$ (M^+): 186.1004. Found: 186.1032.

Preparation of (*R*)-BINIM-4(3,5-TFXylyl)-2QN by the Reaction of (*R*)-1,1′-Binaphthyl-2,2′-diamine with 4-[3,5-Bis(trifluoromethyl)phenyl]-2-quinolinecarbaldehyde. A suspension of (*R*)-1,1′-binaphthyl-2,2′-diamine (0.427 g, 1.5 mmol), 4-[3,5-bis(trifluoromethyl)phenyl]-2-quinolinecarbaldehyde (1.10 g, 3.0 mmol), and MS 4 Å (9.0 g) in benzene (25 mL) was heated under reflux for 6 h. After removal of MS 4 Å by filtration, the solvent was evaporated in vacuo. The residual solid was recrystallized from diethyl ether to give the corresponding (*R*)-BINIM-4(3,5-CF_3Ph)-2QN (0.829 g, 56%).

(*R*)-*N*,*N*′-Bis{4-[3,5-bis(trifluoromethyl)phenyl]-2-quinolylmethylene}-1,1′-binaphthyl-2,2′-diamine. Yellow powder; mp 142−145 °C (diethyl ether); $[\alpha]^{25}_D$ = −135.7 (c 1.0, $CHCl_3$); IR (KBr) 1335, 1281, 1182, 1138 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.23−7.27 (4H, m), 7.32−7.36 (2H, m), 7.43 (2H, bd, J = 8.3 Hz), 7.52−7.58 (4H, m), 7.63−7.65 (2H, m), 7.69−7.73 (6H, m), 7.84 (2H, bd, J = 8.0 Hz), 7.97−8.04 (6H, m), 8.69 (2H, s); ^{13}C NMR ($CDCl_3$) δ 116.7 (CH), 118.5 (CH), 122.0 (CH, m), 122.9 (C, q, J_{C-F} = 272.2 Hz), 124.2 (CH), 125.2 (CH), 125.9 (C), 126.3 (CH), 126.9 (CH), 127.5 (CH), 128.1 (CH), 129.1 (CH), 129.2 (CH, d, J_{C-F} = 3.1 Hz), 129.5 (C), 129.7 (CH), 130.0 (CH), 131.7 (C, q, J_{C-F} = 33.6 Hz), 132.1 (C), 133.2 (C), 139.6 (C), 144.6 (C), 145.4 (C), 147.8 (C), 154.2 (C), 158.5 (CH). Anal. Calcd for $C_{56}H_{30}F_{12}N_4$: C, 68.16; H, 3.06; N, 5.68%. Found: C, 68.32; H, 3.06; N, 5.52%.

3-Acryloyl-5,5-dimethyl-2-oxazolidinone (**2c**)[9e] was prepared according to the procedure reported by Evans.[17]

3-Acryloyl-5,5-dimethyl-2-oxazolidinone (2c). Colorless prisms; mp 83−85 °C (diethyl ether−hexane); IR (KBr) 1767, 1678 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.53 (6H, s), 3.81 (2H, s), 5.90 (1H, dd, J = 1.9, 10.5 Hz), 6.55 (1H, dd, J = 1.9, 17.1 Hz), 7.52 (1H, dd, J = 10.5, 17.1 Hz); ^{13}C NMR ($CDCl_3$) δ 27.3 (CH_3), 54.4 (CH_2), 78.7 (C), 127.1 (CH), 131.4 (CH_2), 152.3 (C), 165.0 (C); MS (EI) m/z 169 (M^+), 125, 97, 82, 67, 55, 43, 27, 18, 15. Anal. Calcd for $C_8H_{11}NO_3$: C, 56.80; H, 6.55; N, 8.28%. Found: C, 56.75; H, 6.85; N, 8.21%.

■ ASSOCIATED CONTENT

Supporting Information. Spectroscopic data of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*Phone: +81-26-269-5392. Fax: +81-26-269-5424. E-mail: sugahio@shinshu-u.ac.jp.

■ ACKNOWLEDGMENT

This work was supported in part by a Grant-in-Aid for Scientific Research (nos. 17550097, 20550094, and 20200052) from the Ministry of Education, Science and Culture, Japan.

REFERENCES

(1) (a) *1,3-Dipolar Cycloaddition Chemistry; General Heterocyclic Chemistry Series*; Padwa, A., Ed.; John Wiley and Sons: New York, 1984. (b) Torsell, K. B. G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*; VCH: Weinheim, 1988. (c) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863. (d) *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A.; Pearson, W. H., Eds.; Wiley: Chichester, 2002. (e) Pellissier, H. *Tetrahedron* **2007**, *63*, 3235.

(2) (a) Gothelf, K. V.; Jørgensen, K. A. *Chem. Commun.* **2000**, 1449. (b) Stanley, L. M.; Sibi, M. P. *Chem. Rev.* **2008**, *108*, 2887.

(3) For representative examples: (a) Gothelf, K. V.; Thomsen, I.; Jørgensen, K. A. *J. Am. Chem. Soc.* **1996**, *118*, 59. (b) Kobayashi, S.; Kawamura, M. *J. Am. Chem. Soc.* **1998**, *120*, 5840. (c) Kanemasa, S.; Oderaotoshi, Y.; Tanaka, J.; Wada, E. *J. Am. Chem. Soc.* **1998**, *120*, 12355. (d) Simonsen, K. B.; Rita, P. B.; Hazell, G.; Gothelf, K. V.; Jørgensen, K. A. *J. Am. Chem. Soc.* **1999**, *121*, 3845. (e) Desimoni, G.; Faita, G.; Mortoni, A.; Righetti, P. *Tetrahedron Lett.* **1999**, *40*, 2001. (f) Iwasa, S.; Tsushima, S.; Shimada, T.; Nishiyama, H. *Tetrahedron* **2002**, *58*, 227. (g) Hori, K.; Kodama, H.; Ohta, T.; Furukawa, I. *J. Org. Chem.* **1999**, *64*, 5017. (h) Sibi, M. P.; Ma, Z.; Jasperse, C. P. *J. Am. Chem. Soc.* **2004**, *126*, 718. (i) Suga, H.; Nakajima, T.; Itoh, K.; Kakehi, A. *Org. Lett.* **2005**, *7*, 1431.

(4) For reactions with α,β-unsaturated aldehydes, see: (a) Viton, F.; Bernardinelli, G.; Kündig, E. P. *J. Am. Chem. Soc.* **2002**, *124*, 4968. (b) Mita, T.; Ohtsuki, N.; Ikeno, T.; Yamada, T. *Org. Lett.* **2002**, *4*, 2457. (c) Shirahase, M.; Kamenasa, S.; Oderaotoshi, Y. *Org. Lett.* **2004**, *6*, 675. (d) Carmona, D.; Lamata, M. P.; Viguri, F.; Rodriguez, R.; Oro, L. A.; Balana, A. I.; Lahoz, F. J.; Tejero, T.; Merino, P.; Franco, S.; Montesa, I. *J. Am. Chem. Soc.* **2004**, *126*, 2716. (e) Kano, T.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2005**, *127*, 11926.

(5) Kanemasa, S.; Kanai, T. *J. Am. Chem. Soc.* **2000**, *122*, 10710.

(6) (a) Kano, T.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2006**, *128*, 2174. (b) Sibi, M. P.; Stanley, L. M.; Soeta, T. *Org. Lett.* **2007**, *9*, 1553.

(7) (a) Suga, H.; Funyu, A.; Kakehi, A. *Org. Lett.* **2007**, *9*, 97. (b) Sibi, M. P.; Rane, D.; Stanley, L. M.; Soeta, T. *Org. Lett.* **2008**, *10*, 2971.

(8) Recently, Maruoka reported the asymmetric cycloadditions of azomethine imines including unstable substrates: Hashimoto, T.; Maeda, Y.; Omote, M.; Nakatsu, H.; Maruoka, K. *J. Am. Chem. Soc.* **2010**, *132*, 4076.

(9) (a) Sibi, M. P.; Itoh, K.; Jasperse, C. P. *J. Am. Chem. Soc.* **2004**, *126*, 5366. (b) Sibi, M. P.; Ma, Z.; Itoh, K.; Prabagaran, N.; Jasperse, C. P. *Org. Lett.* **2005**, *7*, 2349. (c) Yamamoto, H.; Hayashi, S.; Kubo, M.; Harada, M.; Hasegawa, M.; Noguchi, M.; Sumimoto, M.; Hori, K. *Eur. J. Org. Chem.* **2007**, 2859. (d) Brinkmann, Y.; Madhushaw, R. J.; Jazzar, R.; Bernardinelli, G.; Kündig, E. P. *Tetrahedron* **2007**, *63*, 8413. (e) Suga, H.; Adachi, Y.; Fujimoto, K.; Furihata, Y.; Tsuchida, T.; Kakehi, A.; Baba, T. *J. Org. Chem.* **2009**, *74*, 1099.

(10) Sibi, M. P.; Stanley, L. M.; Jasperse, C. P. *J. Am. Chem. Soc.* **2005**, *127*, 8276.

(11) (a) Suga, H.; Inoue, K.; Inoue, S.; Kakehi, A. *J. Am. Chem. Soc.* **2002**, *124*, 14836. (b) Suga, H.; Inoue, K.; Inoue, S.; Kakehi, A.; Shiro, M. *J. Org. Chem.* **2005**, *70*, 47. (c) Suga, H.; Suzuki, T.; Inoue, K.; Kakehi A. *Tetrahedron* **2006**, *62*, 9218. (d) Suga, H.; Ishimoto, D.; Higuchi, S.; Ohtsuka, M.; Arikawa, T.; Tsuchida, T.; Kakehi, A.; Baba, T. *Org. Lett.* **2007**, *9*, 4359. (e) Suga, H.; Higuchi, S.; Ohtsuka, M.; Ishimoto, D.; Arikawa, T.; Hashimoto, Y.; Misawa, S.; Tsuchida, T.; Kakehi, A.; Baba, T. *Tetrahedron* **2010**, *66*, 3070.

(12) (a) Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 9874. (b) Karlsson, S.; Högberg, H.-E. *Eur. J. Org. Chem.* **2003**, 2782. (c) Chow, S. S.; Nevalainen, M.; Evans, C. A.; Johannes, C. W. *Tetrahedron Lett.* **2007**, *48*, 277. (d) Vicario, J. L.; Reboredo, S.; Badia, D.; Carrillo, L. *Angew. Chem., Int. Ed.* **2007**, *46*, 5168. (e) Xue, M.-X.; Zang, X.-M.; Gong, L.-Z. *Synlett* **2008**, 691. (f) Du, W.; Liu, Y.-K.; Chen, Y.-C. *Synlett* **2008**, 2997. (g) Weselinski, L.; Stepniak, P.; Jurczak, J. *Synlett* **2009**, 2261.

(13) (a) Chen, W.; Yuan, X.-H.; Li, R.; Du, W.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *Adv. Synth. Catal.* **2006**, *348*, 1818. (b) Chen, W.; Du, W.; Duan, Y.-Z.; Wu, Y.; Yang, S.-Y.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2007**, *46*, 7667. (c) Suga, H.; Arikawa, T.; Itoh, K.; Okumura, Y.; Kakehi, A.; Shiro, M. *Heterocycles* **2010**, *81*, 1669.

(14) (a) Sibi, M. P.; Stanley, L. M.; Nie, X.; Venkatraman, L.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **2007**, *129*, 395. (b) Sibi, M. P.; Venkatraman, L.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **2001**, *123*, 8444. (c) Sibi, M. P.; Liu, M. *Org. Lett.* **2001**, *3*, 4181. (d) Sibi, M. P.; Prabagaran, N. *Synlett* **2004**, 2421.

(15) The structure of the complex was optimized by PM3 calculations (Spartan 08).

(16) (a) Suga, H.; Kakehi, A.; Mitsuda, M. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 561. (b) Suga, H.; Kitamura, T.; Kakehi, A.; Baba, T. *Chem. Commun.* **2004**, 1414.

(17) (a) Evans, D. A.; Miller, S. J.; Lectka, T.; von Matt, P. *J. Am. Chem. Soc.* **1999**, *121*, 7559. (b) Evans, D. A.; Schejdt, K. A.; Johnston, J. N.; Willis, M. C. *J. Am. Chem. Soc.* **2001**, *123*, 4480.

(18) Ho., G.-J.; David, J.; Mathre, D. J. *J. Org. Chem.* **1995**, *60*, 2271.

(19) Searle, N. E. Organic Syntheses; Wiley: New York, 1963; Collect. Vol. 4, p 424

(20) Deng, Q.-H.; Xu, H.-W.; Yuen, A. W.-H.; Xu, Z.-J.; Che, C.-M. *Org. Lett.* **2008**, *10*, 1529.

(21) Taber, D. F.; Sheth, R. B.; Joshi, P. V. *J. Org. Chem.* **2005**, *70*, 2851.

(22) Chapuis, C.; Jurczak, J. *Helv. Chim. Acta* **1987**, *70*, 436.