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Chiral Biferrocene-based Bis(oxazolines): Ligands for Cu(I)-Catalyzed Asymmetric Cyclopropanations of Ene–Diazoacetates

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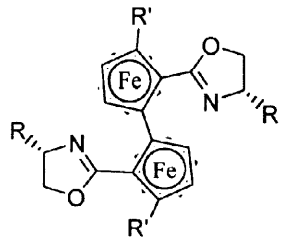
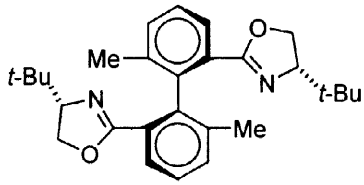
Abstract: *Chiral biferrocene-based bis(oxazoline) compounds, which have both planar and central chirality, are synthesized. The Cu(I)-complexes of the bis(oxazolinyl)biferrocenes were found to be conformationally flexible and have a wide bite angle (136°) by NMR and molecular modeling studies. The complexes catalyzed the intramolecular cyclopropanation reaction of ene–diazoacetates, and low to moderate enantioselectivities and decreased reactivity were observed, compared to known malonate-derived bis(oxazoline) systems.* © 1999 Elsevier Science Ltd. All rights reserved.

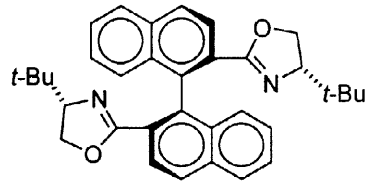
Recently we have communicated intermolecular asymmetric cyclopropanations between styrene and diazoacetates catalyzed by Cu(I)-complexes of biferrocene-based bis(oxazoline) ligands **1**[1]. The bis(oxazoline) ligands were expected to have a wide bite angle in the metal chelation as the bis(oxazolinyl)biaryl ligands **2** and **3** reported by Corey[2] and Hayashi[3], independently. Our ligands showed a similar enantioselectivity pattern in the Cu(I)-catalyzed cyclopropanation of styrene with diazoacetates as Hayashi's ligands. The ligands showed somewhat higher enantioselectivity for the *cis*-isomer than the *trans*-, while opposite trend was observed with the well-known malonate-derived bis(oxazolines) **4**. Since the Cu(I)-



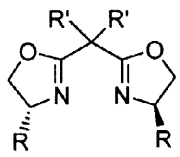
1, R = *t*-Bu, *i*-Pr;
R' = H, $SiMe_3$, $SiEt_3$



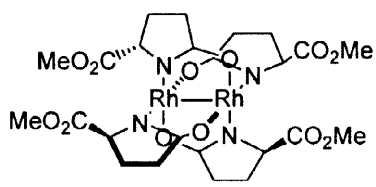
(*S,S,S*)-**2**



(*S,S,S*)-**3**



4, R = *i*-Pr, *t*-Bu, Ph;
R' = Me, H



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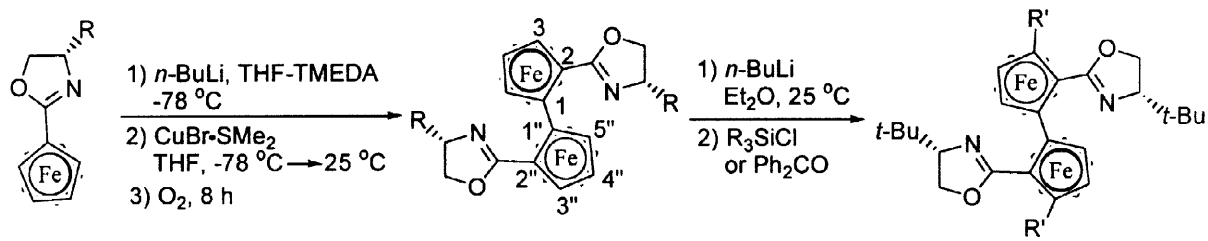
complex of **2** showed a pronounced enantioselectivity in an intramolecular cyclopropanation compared to bis(oxazolines) **4**, we were interested in the use of our ligands in the intramolecular cyclopropanation reaction. Compared to the intermolecular case, examples of the intramolecular cyclopropanation reaction are limited. The Doyle's pyroglutamate-derived Rh(I)-catalysts **5** have been shown to be effective for certain substrates in the intramolecular reactions[4]. Here we wish to report details of the synthesis of bis(oxazolinyl)biferrocenes **1** and their application to the Cu(I)-catalyzed intramolecular cyclopropanation of diazo–ene compounds.

Synthesis of the Ligands: Dimerization of Oxazolinylferrocenes 6.

Recently we and others[5] demonstrated that directed lithiation of oxazolinylferrocenes is an efficient way to the synthesis of chiral oxazolinylferrocene compounds. Applying this method we were able to prepare a variety of oxazolinylferrocene compounds which are potentially useful chiral ligands for asymmetric catalysts. We extended the protocol to the synthesis of the corresponding bis(oxazolinyl)biferrocene compounds through dimerization of the lithium intermediate. Dimerization of aryllithium species via organocopper complexes has been used to synthesize some natural biaryl products[6]. When bis(oxazolinyl)ferrocene **6a** was treated with *n*-BuLi in THF-TMEDA at -78 °C followed by a half-molar equivalent of CuCN to generate the corresponding "higher order" cuprate and then further reaction under an oxygen atmosphere, the desired bis(oxazolinyl)biferrocene **1a** was isolated in 41% yield. With an equimolar amount of $CuBr{\cdot}Me_2S$, instead of CuCN, the dimerization yield increased to 59%. Increasing the amount of CuCN to one molar equivalent or decreasing the amount of $CuBr{\cdot}Me_2S$ to a half-molar equivalent did not improve the yield. According to the established procedure, bis(oxazolinyl)biferrocene **1b** was similarly synthesized in 52% yield. Next, trialkylsilyl-substituted bis(oxazolinyl)biferrocenes **1c** and **1d** were synthesized by lithiation of bis(oxazolinyl)biferrocene **1b** with *n*-BuLi in Et_2O and subsequent treatment with the corresponding chlorotrialkylsilanes. The NMR data of the products were not informative on which position the substitution occurred. The oxazoline ring of (oxazolinyl)ferrocene **6** directs *n*-BuLi to one of the two α-protons adjacent to the oxazoline ring exclusively, due to otherwise the unfavorable steric strain between the alkyl substituent of the oxazoline ring and the solvent molecules bound to the lithium ion[5b], giving the corresponding lithiated

Scheme 1



6a, R = *i*-Pr
6b, R = *t*-Bu

1a, R = *i*-Pr
1b, R = *t*-Bu

1c, R' = $SiMe_3$
1d, R' = $SiEt_3$
1e, R' = $C(OH)Ph_2$

($S_p S$)-(oxazolinyl)ferrocene. Because this α-proton is already blocked in bis(oxazolinyl)biferrocene **1**, it was questionable whether the second deprotonation would occur at the remaining cyclopentadienyl (Cp) ring α-proton (C-3) or at the adjacent Cp ring proton (C-5"). Lithiation at the other ferrocene ring through remote lithiation seemed to be possible by molecular modeling and thus could not be excluded. All attempts to get single crystals of **1c** or **1c**–CuOTf complex were unsuccessful. Therefore, we synthesized **1e**, which readily crystallized to give single crystals suitable for the X-ray structure analysis. From the crystal structure of **1e** it was evident that the lithiation of **1b** occurred at the α-carbon adjacent to the oxazoline ring (Fig 1). Therefore, the substitution site of the silyl groups could be assigned. The X-ray crystal structure of **1e** shows that the oxazoline ring is in plane with the Cp ring and the hydroxyl group is oriented to the nitrogen atom[7]. The two ferrocene units are twisted 74 degree. Therefore, to form *N,N*-chelated metal complexes the two oxazoline rings should rotate significantly from the solid structure.

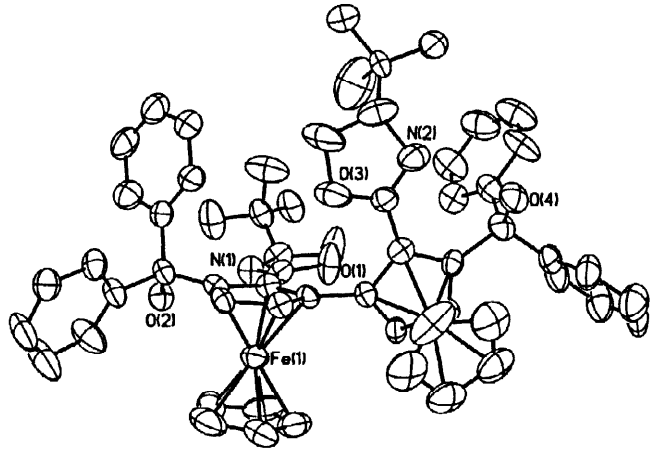


Figure 1. X-ray crystal structure of compound **1e**.

Structure of Bis(oxazolinyl)biferrocene 1–CuOTf Complexes.

Evans and co-workers obtained a polymeric crystal structure from the bis(oxazoline) **4**–CuOTf complex[8], while Corey and co-workers obtained a distinct monomeric crystal structure from the bis(oxazoline)biphenyl **2**–CuOTf complex[2]. The latter complex exhibited an enhanced chemical stability both in the solid state and in solution, compared to the former complex. The two ligands were different in the bite angles. Our effort to obtain the crystal structure of the **1b**–CuOTf complex was unsuccessful. Therefore, we carried out NMR and molecular modeling study to get information on the structure of the metal complexes. Comparing the ^{1}H NMR spectrum of the free ligand **1b** and that of the copper complex, downfield shifts, particularly for the oxazolinyl C-4 protons (0.08 ppm), were observed for the complex. The copper complex generated by mixing CuOTf·0.5C_6H_6 and bis(oxazoline) **1b** did not show any structural change at the temperature ranging from 20 to 60 °C. However, at lower temperature around 0 °C, there appeared some change on the ^{1}H NMR spectra (C-

-3 Cp ring proton shifted to upfield about 0.3 ppm and C-4 Cp ring proton splitted as doublet). We also observed that when the CuOTf–bis(oxazolinyl)biferrocene **1b** complex was preheated at 55 °C for 2 h, there was a consistent increase in the product yield (10-20%), even though the actual cyclopropanation reaction was carried out at 25 °C, relative to the case without warming the catalyst. In this case, there was no appreciable change in the enantioselectivity. The reason for the increased yield is not clear yet. As argued above, the two oxazoline rings in **1**, each of which is in plane with the adjacent Cp ring, should rotate in a considerable angle to form a chelated copper complex. According to Evans and co-workers, the bis(oxazoline) **4**–CuOTf complex is in a fast equilibrium between the complexed and uncomplexed ones at ambient temperature, faster than the NMR time scale[9]. We carried out molecular modeling for the copper complex of **1b** to figure out the most stable structure. Among various possible conformational isomers, two typical conformers **A** and **B** were chosen and subjected to energy minimization[10]. As the result, **B** or other intermediate conformers were readily converged into conformer **A** (Figure 2).

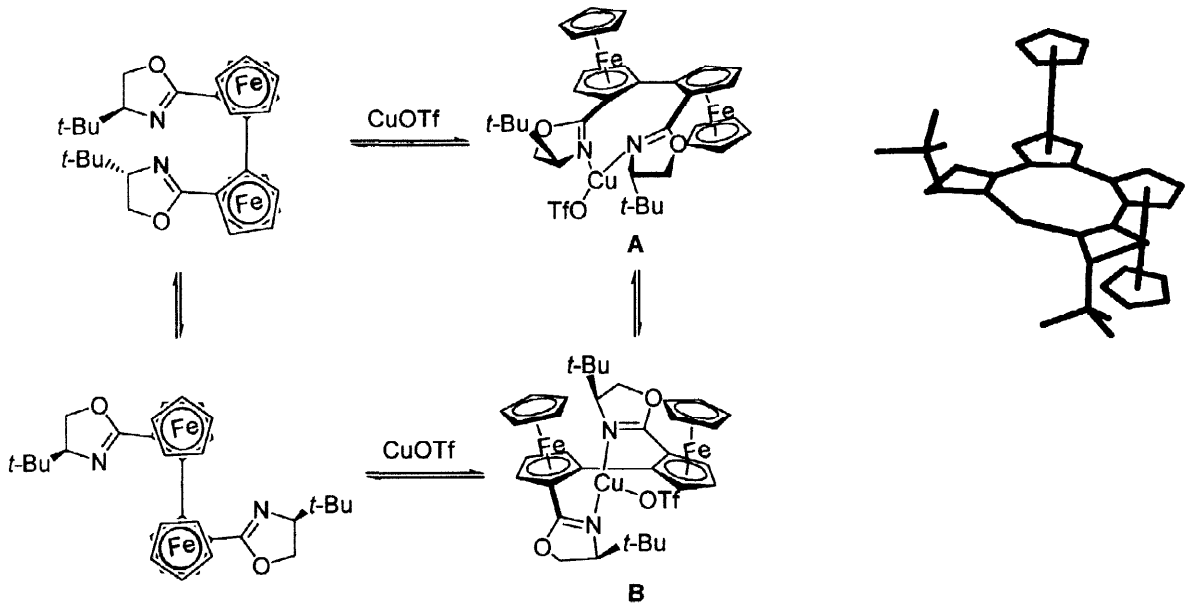


Figure 2.

This result corresponds to the result of the temperature variable NMR study for the complex that showed no change in the spectra at the temperature ranging from 20 to 60 °C. Therefore, the interplay of discrete copper complexes depending on the temperature could be excluded. The minimized molecular structure of the **1b**-Cu(I) complex **A**, showed C_2 symmetric environment around the metal center (The structure is given in the right side of Fig 2; the copper bound triflate was omitted for clarity). The bite angle in this structure was found to be 136°, which is similar to that of Corey's complex (*N*-Cu-*N* angle = 134°). The two ferrocene rings are positioned in the opposite direction and the two connected Cp rings are approximately in plane with a small dihedral angle (21°). Based on this complex structure, the observed *trans/cis*- and enantio-selectivity can be explained by the concerted mechanism proposed by Pfaltz[11], as depicted in Figure 3.

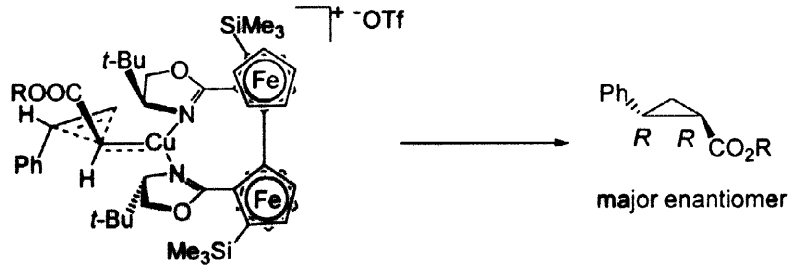
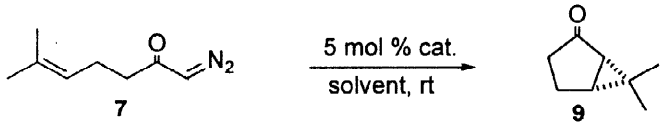


Figure 3.

Intramolecular Cyclopropanation of Diazo–Alkenes. Generally, the enantioselectivity of the catalytic asymmetric cyclopropanation reactions of alkenes with diazoacetates depends greatly on the substrates used[2,12]. The copper complexes of our bis(oxazolinyl)biferrocenes exhibited up to 90% ee for the *trans*- and 99% ee for the *cis*-product in the cyclopropanation of styrene with diazoacetates. Encouraged by these and the promising results of Corey and co-workers mentioned before, we studied the intramolecular cyclopropanation of diazo–alkenes using the **1**–CuOTf complexes. We chose 1-diazo-6-methyl-5-hepten-2-one as a standard substrate, which was prepared according to the literature procedure[13]. The copper catalyst was prepared by mixing equimolar amounts of bis(oxazolinyl)biferrocene **1** and CuOTf·0.5C_6H_6 in a halogenated solvent at 25 °C. In this study the catalyst was not pre-warmed. The results are summarized in Table 1. As observed in the intermolecular cyclopropanations, bis(oxazolinyl)biferrocene **1b** produced better enantioselective catalysts than **1a**. Also, the copper complexes of silyl-substituted ligands **1c** and **1d** produced better selectivities than those without the substituents. The trimethylsilyl-substituted **1c** gave the best results, producing 63% ee[14]. In addition to the moderate enantioselectivity, the reaction underwent slowly. This low reactivity was manifested for the less reactive substrate, 1-diazo-7-methyl-6-octen-2-one, for which lower conversion (12% yield) was observed even after several days, although there was a little change in the enantioselectivity. The enantioselectivity was shown to be very dependent on the substrate used, as observed in the case of 1-diazo-5-hexen-2-one (25% ee)[15]. The lower reactivity may be due to the conformational

Table 1. Enantioselective Intramolecular cyclopropanation catalyzed by **1**-CuOTf complexes



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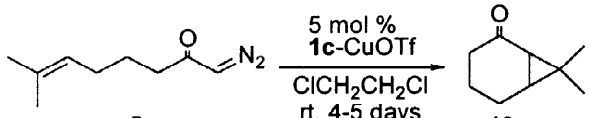
Ligand	Time (h)	Solent	Yield (%)	ee (%)
1a	48	$ClCH_2CH_2Cl$	37	16
1b	8	$ClCH_2CH_2Cl$	50	37
1b	18	CH_2Cl_2	50	47
1c	24	$ClCH_2CH_2Cl$	51	63
1c	24	CH_2Cl_2	42	55
1d	36	$ClCH_2CH_2Cl$	44	50
1d	36	CH_2Cl_2	43	57



8 **10** 64% ee

flexibility of our biferrocene-based complexes.

Summary

Biferrocene-based bis(oxazoline) compounds, which have both planar and central chirality and also can have a wide bite angle in the metal chelation, were synthesized. A crystal structure for a derivative was obtained. The bis(oxazolinyl)biferrocene compounds were used as the chiral ligands in the copper catalyzed intramolecular cyclopropanation reaction of ene–diazoacetates. Low to moderate enantioselectivities were observed, depending on the substrates used. The catalytic system showed decreased reactivity, compared to the malonate-derived bis(oxazoline) systems.

Experimental

Melting points are uncorrected ones. Optical rotation was recorded at wavelength of 589 nm. ^{1}H NMR spectra are reported as follows: chemical shift in ppm from internal tetramethylsilane on the delta scale, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), integration, and coupling constant (in Hertz). Mass spectra and elemental analyses were performed by Seoul Branch Analytical Laboratory of Korea Basic Science Institute. Chromatography means flash column chromatography which was carried out on Merck silica gel 60 (230-400 mesh). All reactions were run under an atmosphere of argon. THF and diethyl ether were distilled from sodium–benzophenone ketyl under argon. Triethylamine, dichloromethane, and 1.2-dichloroethane were distilled from calcium hydride under argon. TMEDA was distilled from sodium under argon. *n*-BuLi was titrated with diphenylacetic acid prior to use. CuOTf·0.5C_6H_6 was purchased from Aldrich Co. and was handled in a glove bag under argon. 1-Diazo-6-methyl-5-hepten-2-one, 1-diazo-7-methyl-6-octen-2-one, and 1-diazo-5-hexen-2-one were synthesized according to the literature procedures[13]. The compounds **1a-1d** were fully characterized and their physical and spectroscopic data were given in the reference 1.

(*S*,*S*$_p$,*S*,*S*$_p$)-2,2"-Bis(4-*tert*-butyl-2-oxazolin-2-yl)-1,1"-biferrocene (1b). *n*-BuLi (1.65 ml, 2.14 M in hexanes) was added dropwise to a solution of [4(*S*)-*tert*-butyl-2-oxazolin-2-yl]ferrocene **6b** (1.00 g, 3.22 mmol) in THF (16 ml) containing TMEDA (1.94 ml, 12.8 mmol) at -78 °C. The reaction mixture was allowed to stir at -78 °C for 2 h, then the reaction mixture was placed in an ice-water bath and stirred for 5 min. This lithiated solution was transferred dropwise to a suspension of CuBr·Me_2S (782 mg, 3.54 mmol) in THF (8 ml) at -78 °C through a cannula, and the resulting mixture was stirred at -78 °C for 2 h and then at room temperature for 2 h. The argon flow was then stopped, and oxygen was bubbled into the reaction mixture for 8 h. The reaction was quenched with a saturated NH_4Cl-NH_4OH solution (9:1), and the resulting mixture was stirred for 3 h. The mixture was extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. Purification of the residue by chromatography (eluent : 20% diethyl ether in hexanes) gave **1b** in 59% yield (589 mg): R_f = 0.51 (70% diethyl ether in hexanes).

(*S*,*S*$_p$,*S*,*S*$_p$)-2,2"-Bis(4-isopropyl-2-oxazolin-2-yl)-1,1"-biferrocene (1a). A similar procedure as for **1b** gave

7a in 52% yield (1.0 g scale): R_f = 0.35 (70% diethyl ether in hexanes).

(*S*,*S*$_p$,*S*,*S*$_p$)-2,2"-Bis(4-*tert*-butyl-2-oxazolin-2-yl)-3,3"-bis(trimethylsilyl)-1,1"-biferrocene (1c). *n*-BuLi (0.849 ml, 2.09M in hexane) was added dropwise to a solution of oxazoline **1b** (500 mg, 0.806 mmol) in Et_2O (8 ml) at room temperature. The reaction mixture was stirred for 2 h and then treated with TMSCl (1.93 mmol, 0.245 ml). After being stirred for 30 min, the mixture was treated with a saturated aqueous $NaHCO_3$ solution. The organic layer was separated and the aqueous layer was extracted twice with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification of the residue by chromatography (eluent : 5% diethyl ether in hexanes) gave **1c** in 58% yield (357 mg): R_f = 0.25 (10% diethyl ether in hexanes).

(*S*,*S*$_p$,*S*,*S*$_p$)-2,2"-Bis(4-*tert*-butyl-2-oxazolin-2-yl)-3,3"-bis(triethylsilyl)-1,1"-biferrocene (1d) A similar procedure as for **1c** gave **1d** in 46% yield (200 mg scale): R_f = 0.39 (70% diethyl ether in hexanes).

(*S*,*S*$_p$,*S*,*S*$_p$)-2,2"-Bis(4-*tert*-butyl-2-oxazolin-2-yl)-3,3"-bis(diphenylhydroxymethyl)-1,1"-biferrocene (1e) A similar procedure as for **1c** gave **1e** in 59% yield (200 mg scale): R_f = 0.55 (30% diethyl ether in hexanes); mp 204-206°C (dec); $[\alpha]^{27}_D$ = -230.9 (*c* 0.865, $CHCl_3$); IR($CHCl_3$, cm^{-1}) 3020, 2401, 1638, 1480, 1427, 1216, 1039; ^1H NMR (300 MHz, $CDCl_3$) δ 9.91 (s, 2H), 7.06-7.40 (m, 20H), 5.29 (d, 2H, *J*=2.5 Hz), 4.62 (d, 2H, *J*=2.5 Hz), 4.41 (s, 10H), 4.06 (t, 2H, *J*=11.3 Hz), 3.77 (d, 4H, *J*=11.3 Hz), 0.34 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.29, 150.28, 147.46, 128.53, 128.18, 127.56, 127.46, 126.96, 126.81, 126.29, 100.69, 88.13, 74.84, 74.76, 73.25, 71.72, 68.98, 68.91, 33.50, 25.40; MS (FAB) *m/z* 985 (M); Anal. Calcd for $C_{60}H_{60}Fe_2N_2O_4$: C, 73.18; H, 6.14; N, 2.84. Found: C, 72.78; H, 6.21; N, 2.51.

General Procedure for Intramolecular Cyclopropanation. To a suspension of $CuOTf{\cdot}0.5C_6H_6$ (0.050 mmol) in 1.0 ml of a given solvent, was added a solution of ligand **1c** (0.052 mmol) in 1.0 ml of the solvent at room temperature. After 2 h, the mixture was filtered through a filter-cannula, which was comprised of a needle with the hub packed with glass wool. To this solution was added dropwise a diazo compound (1.0 mmol) dissolved in the solvent. The reaction mixture was stirred until the diazo compound could no longer be detected by TLC. The mixture was concentrated *in vacuo*, and the crude residue was purified by chromatography to give the corresponding cyclic ketone. The enantioselectivity was determined by GC analysis (30 m Chiraldex® G-TA capillary column; oven temp: 110 °C; injection temp: 200 °C; detection temp: 250 °C; flow rate: 1 ml/min): t_R: **9**: 9.89 min (2*R*,3*S*-isomer, minor), 11.7 min (2*S*,3*R*-isomer, major); **10**: 17.5 min (major), 18.8 min (minor). The absolute stereochemistry of 6,6-dimethyl[3.1.0]bicyclohexan-2-one (**9**) was determined by CD spectra according to the literature[16]. As reported (2*S*,3*R*)-configuration was assigned to the major isomer that exhibited (+) CE. (2*S*,3*R*)-**9** that has optical purity of 63% ee exhibited $[\alpha]_D^{25}$ = -34.3 (*c* 1.0, $CHCl_3$). (2*R*,3*S*)-**9** that has optical purity of 68% ee $[\alpha]_D^{25}$ = +38.2 (*c* 2.2, $CHCl_3$), which was prepared independently, exhibited exactly the opposite Cotton effect: (-)-CE. For intermolecular reactions, a similar reaction procedure was employed, except for the addition of diazoacetates by a syringe pump for 6 h.

Acknowledgment. Financial support by Center for Biofunctional Molecules is gratefully acknowledged.

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