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Asymmetric Synthesis and Characterization of Chiral 2,2′-Diamino-3,3′-diethoxycarbonyl-8,8′-diphenyl-1,1′-biazulene

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Abstract: rac-2,2′-Diamino-3,3′-diethoxycarbonyl-8,8′-diphenyl-1,1′-biazulene was synthesized from diethyl 2-aminoazulene-1,3-dicarboxylate and was optically resolved into two enantiomers of S-form and R-form. The enantioselective oxidative couplings with two chiral amines [(−)-sparteine and (R)-(+)-α-methylbenzylamine] and ferric chloride catalyst, and the asymmetric couplings with two chiral oxovanadium(IV) complexes of ethyl 2-amino-4-phenylazulene-1-carboxylate, easily yielded chiral 2,2′-diamino-3,3′-diethoxycarbonyl-8,8′-diphenyl-1,1′-biazulene. Therefore, the introduction of two phenyl groups at the 8- and 8′-postions of each azulene ring using phenyl magnesium bromide via an addition–oxidation–decarboxylation mechanism resulted in 1,1′-biazulene forming a chiral C_2 axis.

Keywords: asymmetric couplings with chiral oxovanadium(IV) complexes, CD, chiral 1,1′-biazulene, enantioselective oxidative couplings

INTRODUCTION

Although azulenoids were found to be a class of nonbenzenoid hydrocarbons in essential oils more than a century ago, they are still the subject of much study in the field of organic chemistry. The study of azulenoid chemistry, in

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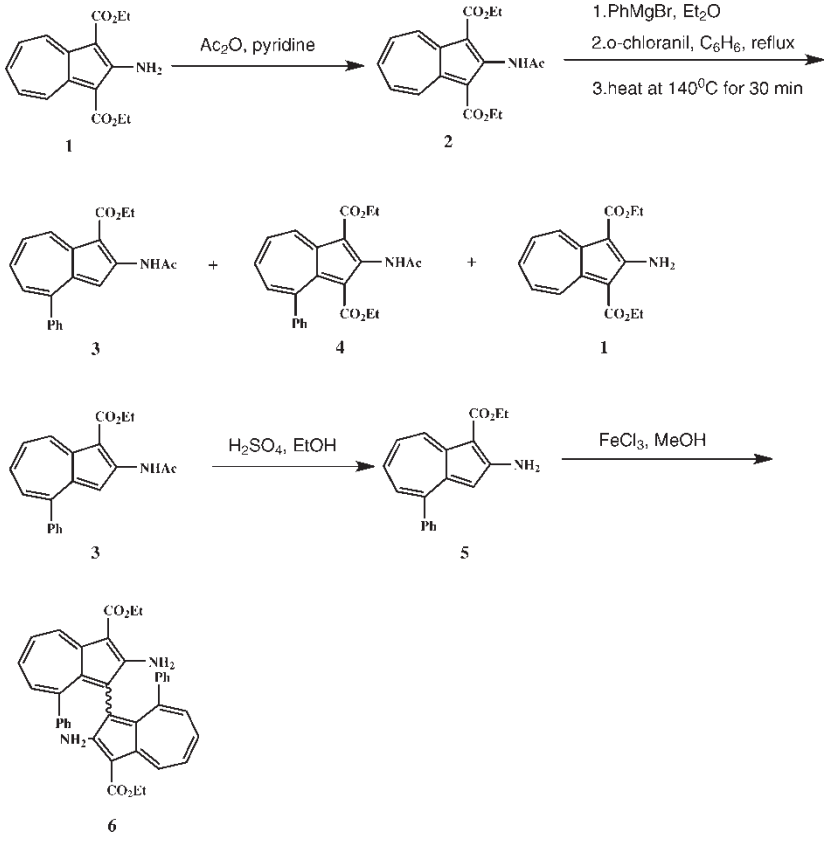
particular, has received great interest because of its many important applications such as in dyestuffs, liquid crystals, and the medical treatment of inflammation and hypertension.[1] Azuloquinones have antibacterial, antifungal, and antitumor properties, and they likewise play important roles photosynthesis, the respiratory electron-transport chain, and solid-state electroconductivity.[2] Recently, Tajiri et al. reported that rac-2,2′-dimethyl-1,1′-biazulene could be resolved into R(−) and S(+) forms with the aid of high-performance liquid chromatography (HPLC) using a (+)-polytriphenylmethyl methacrylate column, but rac-2,2′-dimethoxy-1,1′-biazulene could not be resolved.[3] We have found that 3,3′-diethylcarbonyl-2,2′-dihydroxy-1,1′-biazulene was not resolved using HPLC with a Chiralcel OD column, but the chemical shift of both 2- and 2′-hydroxy protons shifted the down field of 0.43 ppm from 300 K to 210 K in a low-temperate ^{1}HNMR.[4] To investigate the chirality of biazulenoids, in this article we discuss the asymmetric synthesis and characterization of chiral 2,2′-diamino-3,3′-diethoxycarbonyl-8,8′-diphenyl-1,1′-biazulene through the introduction of two phenyl groups at the 8- and 8′-postions of each azulene ring.

RESULTS AND DISCUSSION

To protect the amino group of diethyl 2-aminoazulene-1,3-dicarboxylate (**1**) reacted with phenyl magnesium bromide, it was acetylated with acetic anhydride in the presence of pyridine to give diethyl 2-acetamidoazulene-1,3-dicarboxylate (**2**) in a yield of 72%. Diethyl 2-acetamidoazulene-1,3-dicarboxylate (**2**) was reacted with phenyl magnesium bromide, oxidized with o-chloranil, and then heated at 140°C for 30 min to yield ethyl 2-acetamido-4-phenylazulene-1-carboxylate (**3**) (20%), diethyl 2-acetamido-4-phenylazulene-1,3-dicarboxylate (**4**) (22%),[4c,5] and diethyl 2-aminolazulene-1,3-dicarboxylate (**1**) (25%) (Scheme 1). After reaction of diethyl 2-acetamidoazulene-1,3-dicarboxylate (**2**) with phenyl magnesium bromide and oxidization with o-chloranil, the reaction mixture was found to have diethyl 2-acetamido-4-phenylazulene-1,3-dicarboxylate (**4**), but no ethyl 2-acetamido-4-phenylazulene-1-carboxylate (**3**). Diethyl 2-acetamido-4-phenylazulene-1,3-dicarboxylate (**4**), however, might be followed with the intramolecular Friedel–Crafts cyclization to form 7H-naphth[3,2,1-cd]azulen-7-one derivative by heating in the acidic media.[6a] The formation of ethyl 2-acetamido-4-phenylazulene-1-carboxylate (**3**) might be attributed to the addition of diethyl 2-acetamidoazulene-1,3-dicarboxylate (**2**) with phenyl magnesium bromide, and the protonation produced a 4-phenyl-3,4-dihydroazulene intermediate; then the intermediate followed oxidation and decarboxylation at the 3-ethoxycarbonyl group, which was more crowded with a 4-phenyl group than the 1-ethoxycarbonyl group.[6b] The structure of ethyl 2-acetamido-4-phenylazulene-1-carboxylate (**3**) was determined using spin decoupling and nuclear Overhauser effect difference spectrometry.



1 2 3 4 1 3 5 6

Scheme 1.

Ethyl 2-acetamido-4-phenylazulene-1-carboxylate (**3**) was deacetylated with treatment of sulfuric acid in ethanol to give ethyl 2-amino-4-phenylazulene-1-carboxylate (**5**) in a yield of 91%. Finally, several mild oxidants such as Fe^{3+}, Cu^{2+}, Cu^{+}, and Sn^{4+} salts and cerium ammonium nitrate (CAN)

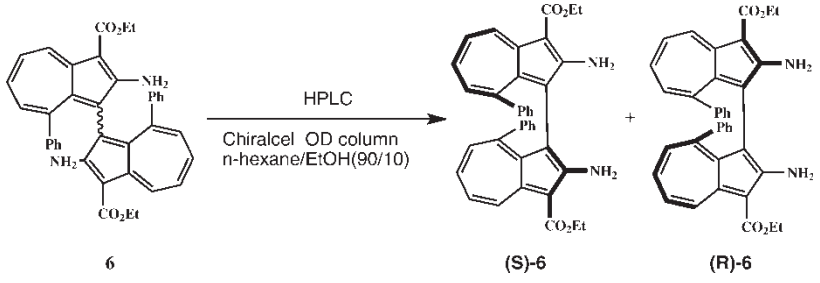
Table 1. NOE enhancement (%) of ethyl 2-acetamido-4-phenylazulene-1-carboxylate (**3**)

Chemical shift of irradiation	CO_2CH_2-CH_3	CO_2CH_2-CH_3	4-Ph[a]	5-H, 7-H	6-H	8-H
δ 1.5 (CH_2-CH_3)	15.8					8.3
δ 4.5 (CH_2-CH_3)		10.2				4.3
δ 7.6 (6-H)			7.7	12.0		1.6
δ 7.8 (3-H)				4.0		
δ 9.3 (8-H)	1.2	1.6		16.0	6.6	

[a] 2′,6′-H_2 of 4-phenyl group.

were tried for investigation of the oxidative self-coupling of ethyl 2-amino-4-phenylazulene-1-carboxylate (**5**). However, only the treatment of ferric chloride in methanol of ethyl 2-amino-4-phenylazulene-1-carboxylate (**5**) was easily coupled to afford rac-2,2′-diamino-3,3′-diethoxycarbonyl-8,8′-diphenyl-1,1′-biazulene (**6**) in a yield of 56%.

Although the racemic mixtures of 1,1′-bi-2-naphthol (BINOL) and its derivatives can be separated into their enantiomers using the precipitate of an inclusion complex with N-benzylcinchonidium chloride[7] or reaction with (1S)-(+)-camphor-10-sulfonyl chloride[8a] or (−)-menthyl chloroformate,[8b] rac-2,2′-diamino-3,3′-diethoxycarbonyl-8,8′-diphenyl-1,1′-biazulene (**6**) could not form the precipitate of an inclusion complex with N-benzylcinchonidium chloride and failed to afford its diastereomers upon treatment with (1S)-(+)-camphor-10-sulfonyl chloride or (−)-menthyl chloroformate for the resolution of its enantiomers. Fortunately, rac-2,2′-diamino-3,3′-diethoxycarbonyl-8,8′-diphenyl-1,1′-biazulene (**6**) was found to be optically resolved into two enantiomers of S-form ((**S**)-**6**) and R-form ((**R**)-**6**) with the retention times of 7.30 and 12.10 min, respectively, using HPLC with a chiralcel OD column, a UV detector at 320 nm, and an eluent of n-hexane/ethanol (v/v = 90/10) on a flow rate of 1 mL/min (Scheme 2). The specific rotations of S-form ((**S**)-**6**) and R-form ((**R**)-**6**) were measured at 589 nm and 25°C in the degrees of $+1.73 \times 10^3$ (c = 0.027 g/100 mL, MeOH) and -1.86×10^3 (c = 0.030 g/100 mL, MeOH), respectively. The chiral exciton coupling of circular dichroism (CD) was used to assign the absolute stereochemistry of biaryl compounds.[9] The CD spectra of these two fractions, S-form ((**S**)-**6**) and R-form ((**R**)-**6**), measured in MeOH at 25°C under a nitrogen atmosphere, are shown in Fig. 1, A and B curves, respectively. In comparison with the CD spectra of S- and R-forms of rac-2,2′-dimethyl-1,1′-biazulene,[3] the first fraction, S-form ((**S**)-**6**), had positive chirality with Cotton effects at 341 nm ($\Delta\varepsilon$ +23.9) and 318 nm ($\Delta\varepsilon$ −35.4), respectively (A curve in Fig. 1), whereas the second fraction, R-form ((**R**)-**6**), gave negative chirality with Cotton effects at 342 nm ($\Delta\varepsilon$ −28.5) and 318 nm ($\Delta\varepsilon$ +42.9) respectively (B curve in Fig. 1). Therefore, 1,1′- biazulene introduced with two phenyl groups at the 8- and 8′-postions of each azulene ring using phenyl



Scheme 2.

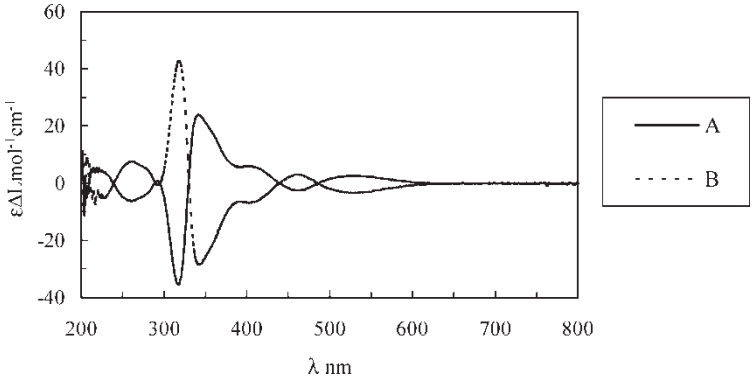


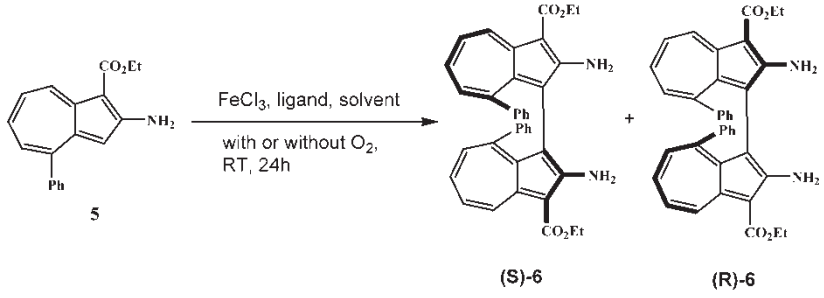
Figure 1. CD spectra of S-form ((**S**)-**6**) (A curve) and R-form ((**R**)-**6**) (B curve) of rac-2,2′-diamino-3,3′-diethoxycarbonyl-8,8′-diphenyl-1,1′-biazulene (**6**) in MeOH at 25°C.

magnesium bromide via an addition–oxidation–decarboxylation mechanism resulted in the formation of a chiral C_2 axis.

Because of the unsuccessful resolution of rac- 2,2′-diamino-3,3′-diethoxycarbonyl-8,8′-diphenyl-1,1′-biazulene (**6**) by forming the precipitate of inclusion complex or the diastereomers, it was discovered to be formed using the enantioselective oxidative coupling of ethyl 2-amino-4-phenylazulene-1-carboxylate (**5**) with chiral amines and metal sources, with or without oxygen.[10] To demonstrate further utility, two chiral amines, (−)-sparteine and (R)-(+)-α-methylbenzylamine, were used as the ligands. As shown in Table 2, the $FeCl_3$/two chiral amines–mediated oxidative couplings in methanol with or without oxygen provided some level of enantioselectivity in this reaction, for example, in the reactions of 1/10/15 molar ratio of substrate (**5**)/(−)-sparteine/$FeCl_3$ and 1/10/15 molar ratio of substrate(**5**)/(+)-PhCH(NH_2)Me/$FeCl_3$ in methanol with oxygen to give the enantiomeric excess of 13.7% and 14.3%, respectively (entries 2 and 8 in Table 2). However, this reaction with these two chiral amines in two solvents of acetonitrile and dichloromethane with or without oxygen could not afford this enantioselective oxidative coupling. At the same time, the $CuCl_2$, CuCl, and CuI catalysts with these two chiral amines in a series of solvents (methanol, acetonitrile, dichloromethane, and isopropanol) failed in the enantioselective oxidative coupling reactions.

Recently, in addition to using the metal complexes of chiral amines for the enantioselective oxidative couplings of 2-naphthols, the oxovanadium(IV) complexes of chiral Schiff bases were developed for the asymmetric couplings of 2-naphthols to optically active 1,1′-bi-nahthol (BINOL) and its derivatives, which have been extensively used as chiral auxiliaries and ligands in asymmetric synthesis.[11] Two oxovanadium(IV) complexes of chiral Schiff bases, **7** and **8,** prepared from 2-hydrox-1-naphhthaldehyde and L-valine or L-phenylalanine, respectively, with vanadyl sulfate, were further investigated

Table 2. Enantioselective oxidative couplings of ethyl 2-amino-4-phenylazulene-1-carboxylate (**5**) with the $FeCl_3$/chiral amine–mediated oxidants

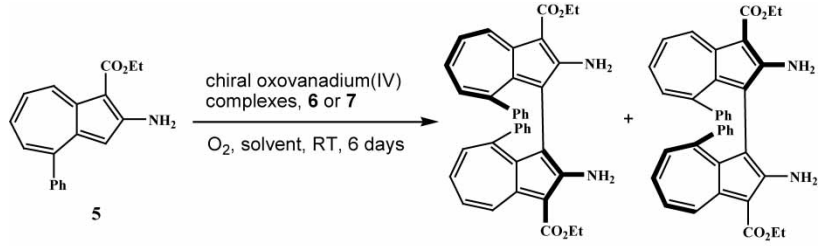


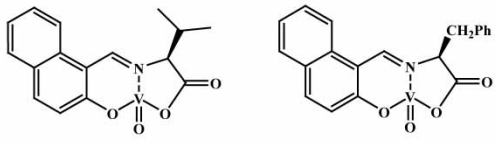
Entry	Ligand	molar ratio of substrate (**5**)/ ligand metal	Reaction condition	Yield (%)	ee (%)[a]
1	(−)-sparteine	1:3.75:15	$CH_3OH + O_2$	33	12.6
2	(−)-sparteine	1:10:15	$CH_3OH + O_2$	21	13.7
3	(−)-sparteine	1:3.75:15	$CH_3OH + N_2$	27	2.5
4	(−)-sparteine	1:5:15	$CH_3OH + N_2$	55	6.6
5	(−)-sparteine	1:10:15	$CH_3OH + N_2$	12	8.3
6	(+)-PhCH(NH_2)Me	1:3.75:15	$CH_3OH + O_2$	38	3.4
7	(+)-PhCH(NH_2)Me	1:5:15	$CH_3OH + O_2$	15	9.5
8	(+)-PhCH(NH_2)Me	1:10:15	$CH_3OH + O_2$	19	14.3

[a]The enantiomeric excess (ee%) determined by chiral HPLC (Chiralcel OD column) with an eluent of n-hexane/ethanol (90/10, v/v) and calculated with (%R − %S/ %R + %S) × 100.

for the asymmetric couplings of ethyl 2-amino-4-phenylazulene-1-carboxylate (**5**). As shown in Table 3, these two chiral oxovanadium(IV) complexes, **7** and **8,** produced enantiomeric excess from 9.9% to 17.9% with chemical yields from 10% to 80% in two solvents of chloroform and dichloromethane. However, carbon tetrachloride is not a suitable solvent, despite its wide use as a solvent in the asymmetric coupling of 2-naphthols by chiral tridenate oxovanadium(IV) complexes.[11] The asymmetric couplings, using the chiral oxovanadium(IV) complexes, **7** in two solvents of chloroform and dichloromethane and **8** in a solvent of chloroform, showed a high recovery of substrate from 47% to 78% by stirring for 6 days at room temperature. The enantiomeric excess of both oxovanadium(IV) complexes of chiral Schiff bases, **7** and **8,** for the asymmetric couplings of ethyl 2-amino-4-phenylazulene-1-carboxylate (**5**) in chloroform and dichloromethane solvents was different, one R and the other S, respectively.

Table 3. Asymmetric couplings of ethyl 2-amino-4-phenylazulene-1-carboxylate (**5**) with chiral oxovanadium(IV) complexes **6** and **7**





Entry	Catalyst	Molar ratio of substrate(**5**)/ catalyst	Solvent	Yield (%)	ee (%)[a]
1	**7**	1:0.5	$CHCl_3$	43	9.9
2	**7**	1:1	$CHCl_3$	64	14.3
3	**7**	1:2	$CHCl_3$	59	11.4
4	**7**	1:1	CH_2Cl_2	14	−12.5
5	**7**	1:2	CH_2Cl_2	10	−11.0
6	**8**	1:0.5	$CHCl_3$	48	17.9
7	**8**	1:1	$CHCl_3$	80	17.9
8	**8**	1:0.5	CH_2Cl_2	10	−16.1
9	**8**	1:1	CH_2Cl_2	43	−15.9
10	**8**	1:2	CH_2Cl_2	20	−12.2

[a]The enantiomeric excess (ee%) determined by chiral HPLC (Chiralcel OD column) with an eluent of n-hexane/ethanol (90/10, v/v) and calculated with (%R − %S/ %R + %S) × 100.

CONCLUSION

2,2′-Diamino-3,3′-diethoxycarbonyl-8,8′-diphenyl-1,1′-biazulene (**6**) was synthesized from diethyl 2-aminoazulene-1,3-dicarboxylate and was optically resolved into two enantiomers of S-form ((**S**)-**6**) and R-form ((**R**)-**6**). The enantioselective oxidative coupling with two chiral amines, (−)-sparteine and (R)-(+)-α-methylbenzylamine, and ferric chloride catalyst, and the asymmetric couplings with two chiral oxovanadium(IV) complexes,

7 and **8**, of ethyl 2-amino-4-phenylazulene-1-carboxylate (**5**) were shown to easily produce chiral 2,2′-diamino-3,3′-diethoxycarbonyl-8,8′-diphenyl-1,1′-biazulene, **(S)-6** and **(R)-6.** Therefore, by introducing two phenyl groups at 8- and 8′-postions of each azulene ring using phenyl magnesium bromide via an addition–oxidation–decarboxylation mechanism, 1,1′-biazulene resulted in the formation of a chiral C_2 axis. Further studies to address application of the target as a chiral auxiliary in asymmetric synthesis are under way.

EXPERIMENTAL

General

The melting points were determined without correction on a Yanagimoto micromelting-point apparatus. ^{1}H and ^{13}C nuclear magnetic resonance, (NMR) spectra were measured on a Varian Inova-500 spectrometer. Mass spectra were determined on a VG Quattro GC/MS/MS DS spectrometer. Elemental analyses were measured on a Heraeus CHN-O-Rapid Analyzer. Meanwhile, specific rotations were determined on a Horiba SEPA-300 polarimeter, and CD spectra were measured on a Jasco J-810 spectropolarimeter. Lastly, HPLC analyses were performed on a Waters Multisolvent Delivery System 600E with a Waters Tunable Absorbance Detector 486, equipped with a SISC chromatography data system.

Synthesis of rea-2,2′-diamino-3,3′-diethoxycarbonyl-8,8′-diphenyl-1,1′-biazulene (6)

Diethyl 2-Acetamidoazulene-1,3-dicarboxylate **(2)**

A solution of diethyl 2-aminooazulene-1,3-dicarboxylate (**1**) (27.22 g, 0.094 mol) and acetic anhydride (200 mL) was refluxed in an oil bath at 140°C overnight. The reaction mixture was adjusted with 2N aqueous sodium hydroxide to pH 5–6 and then was extracted with ethyl acetate. The organic layer was washed with a saturated sodium bicarbonate solution and a brine solution and then dried over sodium sulfate. After this, the organic solution was evaporated to remove the solvent under reduced pressure. The residue was chromatographed on silica gel and eluted with n-hexane–ethyl acetate (v/v = 3/1) to give diethyl 2-acetamidoazulene-1,3-dicarboxylate (**2**) (22.57 g, 72%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.38 (t, J = 7.5 Hz, 6H), 2.30 (s, 3H), 4.39 (q, J = 7.5 Hz, 4H), 7.85 (t, J = 10.0 Hz, 2H), 8.06 (t, J = 10.0 Hz, 1H), 9.90 (d, J = 10.0 Hz, 2H), 10.58 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): 14.32, 26.63, 60.55, 113.21, 130.65, 131.60, 136.06, 137.68, 140.69, 141.42, 141.89, 142.44, 149.03, 163.75, 172.32; MS (EI, m/z, %): 169 (100.0), 196 (33.7),

287 (35.6), 329 (M, 10.6), 330 (M + 1, 2.5). Anal. found: C, 65.47%; H, 5.76%; N, 4.15%; calcd. for $C_{18}H_{19}N_{O5}$: C, 65.64%; H, 5.81%; N, 4.25%.

Ethyl 2-Acetamido-4-phenylazulene-1-carboxylate **(3)**

Under a nitrogen atmosphere, a solution of diethyl 2-acetamidoazulene-1,3-dicarboxylate (**2**) (1.64 g, 5.00 mmol) in a dry diethyl ether (260 mL) on an ice bath was added to an ether solution of phenyl magnesium bromide (25 mL of 1.0 M solution, 25.0 mmol); this was stirred continuously for 10 min on an ice bath and for another 10 min at room temperature. The reaction mixture was cooled on an ice bath, methanol (20 mL), was added and it was then stirred for 10 min. The reaction mixture was then poured into 6N HCl (10 mL) and then extracted with diethyl ether. The extract was washed with a saturated sodium bicarbonate solution, dried over anhydrous magnesium sulfate, and then evaporated under reduced pressure to remove the solvent. The residue was dissolved in dry benzene (20 mL), o-chloranil (2.54 g, 10.0 mmol) was added, and then it was refluxed in an oil bath overnight. The reaction mixture was evaporated to remove benzene under reduced pressure. Then the residue was heated in an oil bath at 140°C for 30 min. The reaction mixture was dissolved in benzene and flowed through a column of alumina to remove excess o-chloranil. The benzene elution was evaporated to remove benzene under reduced pressure. The residue was chromatographed again on silica gel and eluted with n-hexane–ethyl acetate (v/v = 5/1) to give ethyl 2-acetamido-4-phenylazulene-1-carboxylate (**3**) (327 mg, 20%), diethyl 2-acetamido-4-phenylazulene-1,3-dicarboxylate (**4**) (456 mg, 22%), and diethyl 2-aminolazulene-1,3-dicarboxylate (**1**) (366 mg, 25%). Ethyl 2-acetamido-4-phenylazulene-1-carboxylate (**3**): ^{1}H NMR ($CDCl_3$, 500 MHz): 1.54 (t, J = 7.0 Hz, 3H), 2.25 (s, 3H), 4.53 (q, J = 7.0 Hz, 2H), 7.43–7.54 (m, 7H), 7.63 (t, J = 9.5 Hz, 1H), 7.84 (s, 1H), 9.37 (d, J = 9.5 Hz, 1H), 10.92 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): 14.60, 24.93, 60.38, 102.43, 109.66, 127.72, 128.52, 128.41, 128.98, 131.39, 134.49, 134.88, 140.39, 142.65, 143.33, 149.14, 149.61, 167.47, 168.69; MS (EI, m/z, %): 189 (100.0), 217 (66.1), 245 (60.9), 272 (72.5), 287 (18.7), 333 (M, 30.0), 334 (M + 1, 6.7). Anal. found: C, 75.47%; H, 5.80%; N, 4.15%; calcd. for $C_{21}H_{19}NO_3$: C, 75.66%; H, 5.74%; N, 4.20%.

Ethyl 2-Amino-4-phenylazulene-1-carboxylate **(5)**

A solution of ethyl 2-acetamido-4-phenylazulene-1-carboxylate (**3**) (50 mg, 0.15 mmol) and 6N sulfuric acid (2 mL) in ethanol (10 mL) was refluxed for 40 min. Water (10 mL) was added to the reaction mixture and extracted with ethyl acetate; the mixture was washed with a saturated sodium bicarbonate solution and a brine solution and then dried over sodium sulfate. The ethyl acetate solution was evaporated to remove the solvent under reduced pressure. The residue was chromatographed on silica gel and eluted with

n-hexane–ethyl acetate (v/v = 3/1) to give ethyl 2-amino-4-phenylazulene-1-carboxylate (**5**) (40 mg, 91%). ^{1}H NMR ($CDCl_3$, 500 MHz): 1.48 (t, J = 7.0 Hz, 3H), 4.63 (q, J = 7.0 Hz, 2H), 5.40 (br, 2H), 7.22–7.51 (m, 9H), 9.04 (d, J = 9.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): 14.70, 59.71, 108.62, 127.27, 127.49, 127.73, 128.16, 128.33, 128.47, 128.88, 129.38, 130.18, 130.98, 135.84, 136.30, 143.69, 166.57; MS (EI, m/z, %): 217 (49.3), 245 (100.0), 291 (M, 86.2), 292 (M + 1, 18.1). Anal. found: C, 78.02%; H, 5.60%; N, 4.55%; calcd. for $C_{19}H_{17}NO_2$: C, 78.33%; H, 5.88%; N, 4.81%.

Typical Coupling Reaction of Ethyl 2-Amino-4-phenylazulene-1-carboxylate (5)

A solution of ethyl 2-amino-4-phenylazulene-1-carboxylate (**5**) (286 mg, 0.96 mmol) and ferric chloride (796 mg, 4.90 mmol) in methanol was stirred at room temperature overnight. The reaction mixture was evaporated to remove the solvent under reduced pressure. The residue was extracted with ethyl acetate, washed with a brine solution, dried over sodium sulfate, and evaporated to remove the solvent under reduced pressure. The residue was chromatographed on silica gel and eluted with n-hexane–ethyl acetate (v/v = 5/1) to give rac-2,2′-diamino-3,3′-diethoxycarbonyl-8,8′-diphenyl-1,1′-biazulene (**6**) (133 mg, 54%). ^{1}H NMR ($CDCl_3$, 500 MHz): 1.50 (t, J = 7.0 Hz, 6H), 4.49 (q, J = 7.0 Hz, 4H), 4.80 (br, 4H), 6.53–6.60 (m, 8H), 6.86 (d, J = 7.5 Hz, 2H), 6.91 (d, J = 9.0 Hz, 2H), 7.17–7.26 (m, 4H), 8.75 (d, J = 10.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): 14.83, 59.42, 97.89, 110.55, 125.22, 125.32, 125.89, 126.32, 127.71, 129.83, 133.55, 141.06, 143.27, 144.21, 145.71, 158.07, 166.53; MS (EI, m/z, %): 411 (60.7), 445 (13.0), 472 (13.8), 506 (10.2), 538 (12.1), 580 (M, 100.0), 582 (M + 1, 35.5). Anal. found: C, 78.32%; H, 5.70%; N, 4.68%; calcd. for $C_{38}H_{32}N2O_4$: C, 78.60%; H, 5.55%; N, 4.82%.

Typical Enantioselective Oxidative Couplings of Ethyl 2-Amino-4-phenylazulene-1-carboxylate (5) with the $FeCl_3$/Chiral Amine–Mediated Oxidants

Under an oxygen atmosphere, (−)-sparteine (64.2 mg, 0.274 mmol) was added to a 3-mL methanol solution of ferric chloride (296.4 mg, 1.09 mmol), and the mixture was stirred for 10 min at room temperature. A 3-mL methanol solution of ethyl 2-amino-4-phenylazulene-1-carboxylate (**5**) (21.3 mg, 0.073 mmol) was added to the mixture. This was then stirred for 24 h at room temperature. The reaction mixture was poured in 10 mL of water and then extracted with ethyl acetate. The extract was washed with a brine solution and dried over anhydrous magnesium sulfate, and then the solvent was evaporated under reduced pressure. The residue was separated on a thin-layer chromatography

(TLC) plate of silica gel with a developing solvent of n-hexane/toluene (v/v = 1/20) to give rac-2,2′-diamino-3,3′-diethoxycarbonyl-8,8′-diphenyl-1,1′-biazulene (**6**) (5.4 mg, 25%). The enantiomeric excess (ee) was determined by the chiral HPLC method (Chiralcel OD column, 4.6 cm ID × 25 cm) with an eluent of n-hexane/ethanol (90/10, v/v).

Typical Asymmetric Couplings of Ethyl 2-Amino-4-phenylazulene-1-carboxylate (5) with Chiral Oxovanadium(IV) Complexes

In a 50-mL, two-necked, round-bottomed flask, L-phenylalanine (2.0 g, 12.1 mmol) and NaOAc (1.98 g, 24.2 mmol) were placed in 20 mL of degassed H_2O. After completely dissolving the reaction mixture by stirring at 60°C, the reaction mixture was added dropwise to a solution of 2-hydroxy-1-naphthaldehyde (2.08 g, 12.1 mmol) in 10 mL of degassed EtOH. The reaction mixture became slightly yellow in color by heating at 80°C for 10 min and was gradually cooled to ambient temperature for 2 h. A solution of vanadyl sulfate hydrate (1.97 g, 12.1 mmol) in 15 mL of degassed water was added to the resultant Schiff base. The reaction mixture was stirred for 2 h and then concentrated to half of the original solvent volume. The precipitate of vanadyl complex (**8**) was collected by filtration to provide 3.02 g of **8** (65%) as a dark green solid.

Under an oxygen atmosphere, vanadyl complex (**8**) (11.8 mg, 0.03 mmol) was dissolved in 2 mL of anhydrous CH_2Cl_2, and the solution was stirred for 15 min at room temperature. Ethyl 2-amino-4-phenylazulene-1-carboxylate (**5**) (9.0 mg, 0.03 mmol) and methanol (3 mL) were added to the solution, and the reaction mixture was stirred for 6 days at room temperature. The reaction mixture was evaporated to remove the solvent under reduced pressure. The residue was extracted with ethyl acetate, washed with a brine solution, dried over sodium sulfate, and evaporated to remove the solvent under reduced pressure. The residue was chromatographed on silica gel and eluted with ethyl acetate–toluene (v/v = 1/20) to give rac-2,2′-diamino-3,3′-diethoxycarbonyl-8,8′-diphenyl-1,1′-biazulene (**6**) (3.8 mg, 43%). The enantiomeric excess (ee) was determined by the chiral HPLC method (Chiralcel OD column, 4.6 cm ID × 25 cm) with an eluent of n-hexane/ethanol (90/10, v/v).

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