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Diastereoselective cycloaddition of chiral 1-acryloyl-2-imidazolidinone and *o*-quinodimethane generated by reduction of 1,2-bis(bromomethyl)benzene with zinc

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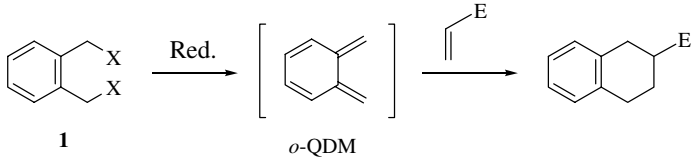
Abstract—The reduction of 1,2-bis(bromomethyl)benzene with zinc powder followed by cycloaddition with the chiral dienophile (4*R*,5*S*)-1-acryloyl-3,4-dimethyl-5-phenyl-2-imidazolidinone in the presence of $BF_3{\cdot}Et_2O$ under ultrasound irradiation gave the corresponding Diels–Alder cycloadduct in high yield (90%) and high diastereoselectivity (*R*:*S* = 87:13).

1. Introduction

o-Quinodimethanes (*o*-QDMs) are useful intermediates for the construction of 1,2,3,4-tetrahydronaphthalenes by their cycloaddition with dienophiles.[1] To generate *o*-QDMs, the reductive dehalogenation of 1,2-bis(halomethyl)benzenes **1** seems to be the most convenient and simplest method (Scheme 1). In fact, a number of reducing agents such as Zn,[2] Fe,[3] Cu,[4] Cr^{II},[5] Ni,[6] NaI,[7] $Me_3SiSnBu_3$-CsF,[8] and tetrakis(dimethylamino)ethylene,[9] and electrochemical reduction[10] have been reported for this purpose. On the other hand, several examples for the stereoselective cycloaddition of chiral *o*-QDMs with achiral dienophiles[11] and that of achiral *o*-QDMs with chiral dienophiles[12] have been explored in order to obtain chiral cycloadducts. However, the cycloaddition of *o*-QDMs generated reductively from **1** with chiral dienophiles has not so far been published. We therefore investigated the cycloaddition of *o*-QDM generated by the reduction of 1,2-bis(bromomethyl)benzenes **1a** with chiral acrylic acid derivatives. Herein we report that (4*R*,5*S*)-1-acryloyl-3,4-dimethyl-5-phenyl-2-imidazolidinone **2** was an efficient chiral dienophile for the diastereoselective cycloaddition with *o*-QDM generated from **1a** by the reduction with zinc powder. We found that the diastereoselectivity of cycloadduct **3** increased by the addition of $BF_3{\cdot}Et_2O$ to the reaction mixture. In addition, the transition states have been calculated by a DFT method to clarify the diastereoselectivity.

2. Results and discussion

In the preliminary experiments, it was found that the cycloaddition of chiral acrylic acid esters prepared from (−)-menthol, (−)-*endo*-borneol, and methyl (−)-lactate with *o*-QDM resulted in poor diastereoselectivity of the cycloadducts (<20% de). Next, (4*R*,5*S*)-3,4-dimethyl-5-phenyl-2-imidazolodinone was selected as a chiral auxiliary. The



Scheme 1.

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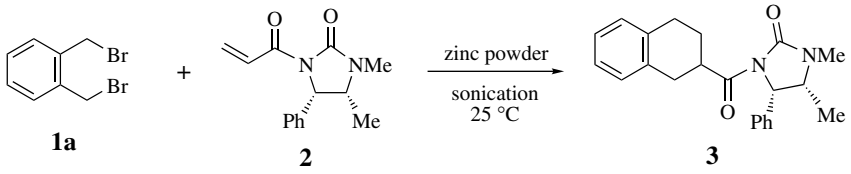
Table 1. Reduction of **1a** and **2**[a]



Run	Solvent	Additive (equiv)	Yield[b] (%) of **3**	*R*:*S*[c] in **3**
1	THF	None	95	67:33
2	Dioxane	None	93	63:37
3	Toluene	None	70	62:38
4	DMF	None	68	50:50
5	THF	$BF_3{\cdot}Et_2O$ (1)	92	82:18
6	THF	$BF_3{\cdot}Et_2O$ (2)	90	87:13
7	THF	$BF_3{\cdot}Et_2O$ (3)	85	87:13
8	THF	$MgBr_2{\cdot}Et_2O$ (2)	93	77:23
9	THF	$CeCl_3$ (2)	69	71:29
10	THF	$AlCl_3$ (2)	38	56:44
11	MeOH[d]		76	59:41

[a] Reduction with zinc (runs 1–10) was carried out using 1.5 mmol of **1a**, 0.5 mmol of **2**, 3.0 mmol of zinc, and 5 mL of solvent under sonication at 25 °C for 1 h.
[b] Isolated yields.
[c] Determined by ^{1}H NMR spectra.
[d] Electroreduction (run 11) was carried out using 1.5 mmol of **1a** and 0.5 mmol of **2** in 20 mL of 0.2 M NH_4NO_3–MeOH (Ref. 10c).

reduction of **1a** (3 equiv) followed by cycloaddition with chiral 1-acryloyl-2-imidazolidinone **2** (1 equiv) was carried out using zinc powder (5 equiv) as reducing agent under ultrasonic irradiation at 25 °C and the results are summarized in Table 1. Initially, we surveyed several solvents (runs 1–4) and found that THF was the most favorable solvent; 95% yield, *R*:*S* = 67:33 (run 1). When the reaction was performed in the presence of $BF_3{\cdot}Et_2O$ (1–3 equiv) as an additive (runs 5–7), the diastereoselectivity in **3** increased up to 87:13. As evidenced by the results, 2 equiv of $BF_3{\cdot}Et_2O$ was sufficient to provide the highest diastereomeric ratio (run 6). The addition of $MgBr_2{\cdot}Et_2O$ or $CeCl_3$ slightly increased the diastereoselectivity (runs 8 and 9), but the addition of $AlCl_3$ brought about poor results in both yield and diastereoselectivity (run 10). The electroreduction[10c] in NH_4NO_3–MeOH also gave the cycloadduct **3** in 76% yield and *R*:*S* = 59:41 (run 11).

The diastereomeric mixture of **3** (87:13 dr) was transformed to the (*R*)-form of carboxylic acid **4** in 76% yield by treatment with LiOH in THF–H_2O, and its enantiomeric excess was determined to be 75% by its specific rotation (Scheme 2). Therefore, an (*R*)-configuration for the major isomer was assigned. Fortunately, the major diastereomer of **3** could be isolated by column chromatography on silica gel and crystallized. Thus, the stereostructure of the major isomer of **3** was undoubtedly determined to be (*R*) by X-ray crystallography (Fig. 1). The hydrolysis of pure (*R*)-**3** gave enantiomerically pure (*R*)-**4** (>99% ee).

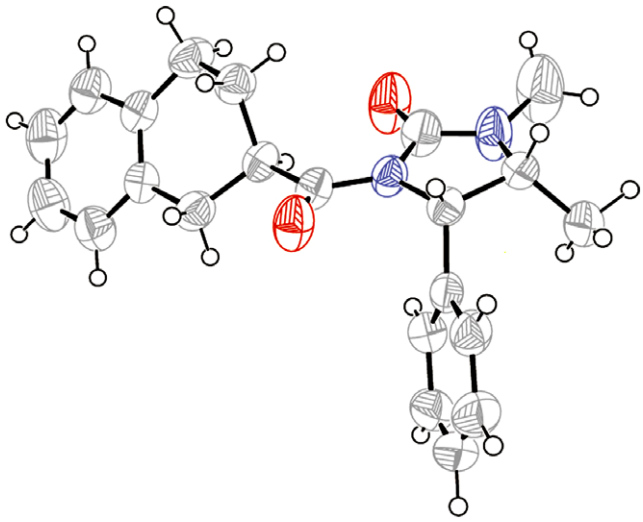
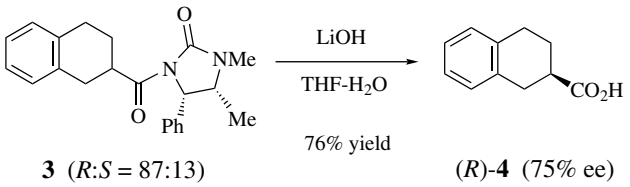


Figure 1. X-ray crystal structure of (*R*)-**3**.



Scheme 2.

To elucidate the (*R*)-selectivity in the cycloaddition of *o*-QDM with **2**, we optimized the structures of the transition states (**TSA**) for the cycloaddition by the DFT method at the B3LYP/6-31+G** level and calculated their energies using the PCM model for the THF solvent at the same level.[13] As shown in Figure 2, ***syn*-TSAs** (**TSA5-8**) are much higher in energy (>4 kcal/mol) than ***anti*-TSAs** (**TSA1-4**).

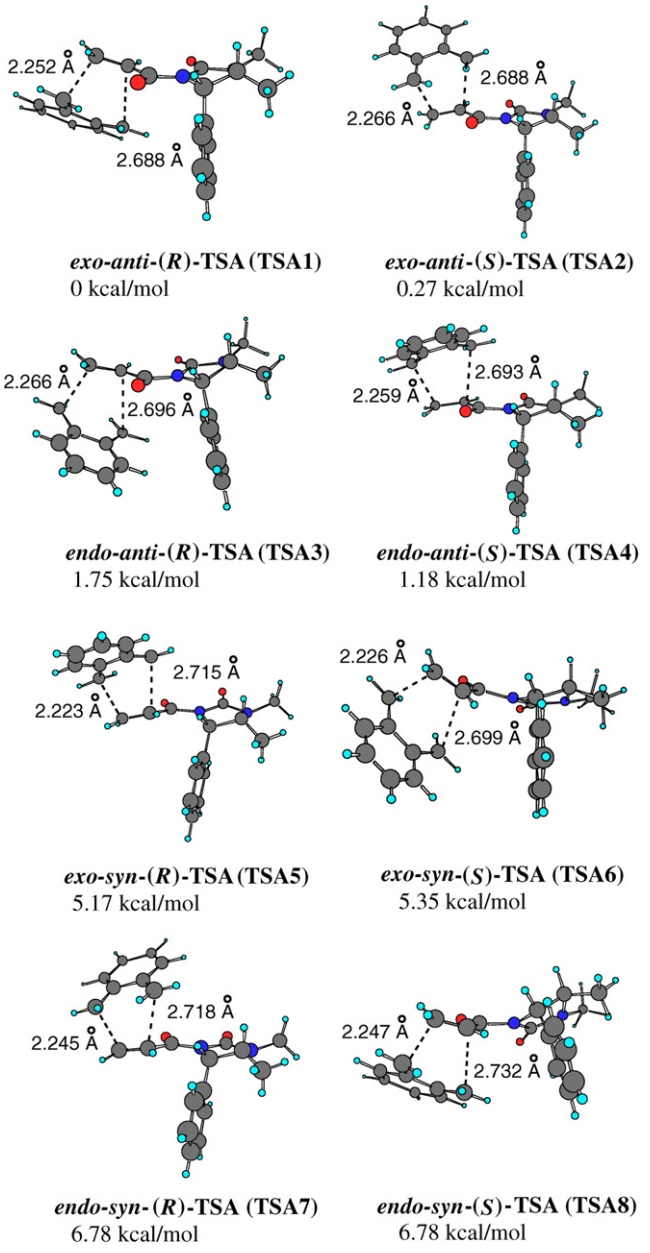


Figure 2. Optimized structures (B3LYP/6-31+G**) and relative energies using the IEFPCM model (THF) of transition states **TSA** for the cycloaddition of *o*-QDM with **2.**

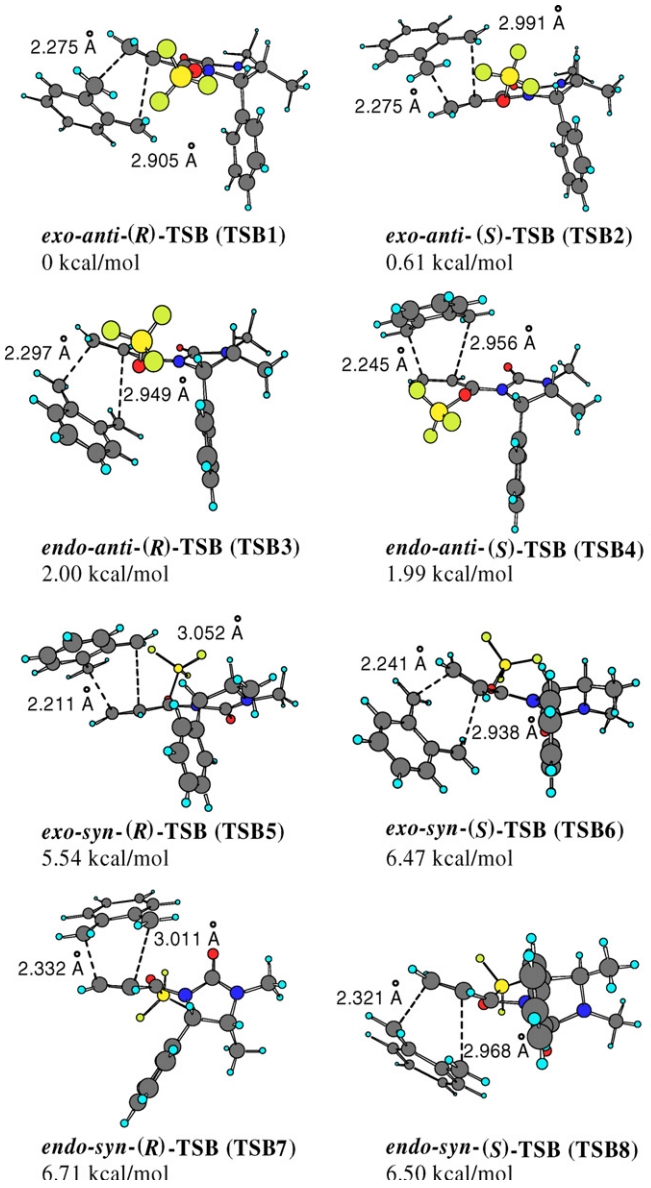
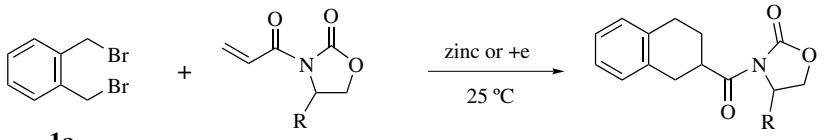


Figure 3. Optimized structures (B3LYP/6-31+G**) and relative energies using the IEFPCM model (THF) of transition states (**TSB**) for the cycloaddition of *o*-QDM with **2** coordinated by BF_3.

Of the ***anti*-TSA**s, ***endo–anti*-TSA**s (**TSA3** and **TSA4**) are higher in energy (ca. 1 kcal/mol) than ***exo–anti*-TSA**s (**TSA1** and **TSA2**). Among the ***exo–anti*-TSA**s, ***exo–anti*-(*R*)-TSA** (**TSA1**) is lower in energy (0.27 kcal/mol corresponding to $R{:}S = 61{:}39$) than ***exo–anti*-(*S*)-TSA** (**TSA2**). These calculations are consistent with the (*R*)-selectivity in the formation of **3**. Although the effect of the addition of $BF_3{\cdot}Et_2O$ is currently not clear, it is supposed that the coordination of BF_3 to **2** enlarges the energy difference between ***exo–anti*(*R*)-TSA** and ***exo–anti*(*S*)-TSA**. Therefore, we also calculated the transition states (**TSB**) for the cycloaddition of *o*-QDM with **2** coordinated by BF_3 in the same way as that employed in Figure 2. The results shown in Figure 3 indicate that ***exo–anti*-TSB**s (**TSB1** and **TSB2**) are lower in energy than the other **TSB**s (**TSB3-8**), and ***exo–anti*(*R*)-TSB** (**TSB1**) is lower in energy (0.61 kcal/mol corresponding to $R{:}S = 74{:}26$) than ***exo–anti*(*S*)-TSB** (**TSB2**). These computational results well agree with the increase of the (*R*)-selectivity by the addition of $BF_3{\cdot}Et_2O$.

As chiral dienophiles, 1-acryloyl-2-oxazolidinones **5** were also employed for the reduction with **1a** under the same conditions as in runs 1, 6, and 11 in Table 1. As can be seen from Table 2, the diastereomeric ratios of adducts **6** were lower than the highest ratio (87:13) of **3** in Table 1. In addition, the *R*:*S* ratios in **6a** and **6b** were almost the same, irrespective of the reduction conditions. The diastereomeric mixtures of **6a** and **6b** were converted to (*R*)-**4** and (*S*)-**4**,

Table 2. Reduction of **1a** and **5**[a,b]



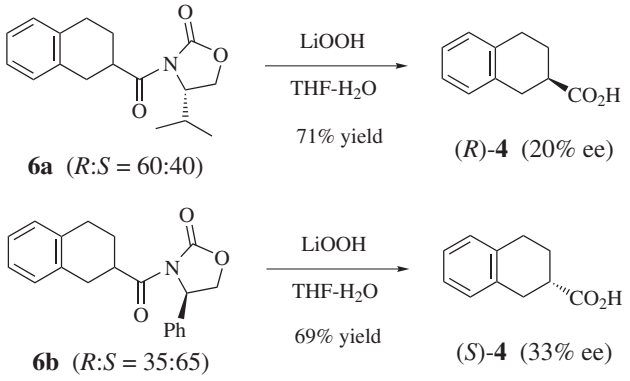
5a: R = (*S*)-*i*-Pr
5b: R = (*R*)-Ph

6a: R = (*S*)-*i*-Pr
6b: R = (*R*)-Ph

Run	5	Solvent	Additive (equiv)	Yield[c] (%) of 6	*R*:*S*[d] in 6
1	**5a**	THF[a]	None	68	59:41
2	**5a**	THF[a]	$BF_3{\cdot}Et_2O$ (2)	91	60:40
3	**5a**	MeOH[b]		56	58:42
4	**5b**	THF[a]	None	95	38:62
5	**5b**	THF[a]	$BF_3{\cdot}Et_2O$ (2)	94	36:64
6	**5b**	MeOH[b]		66	35:65

[a] Reduction with zinc (runs 1, 2, 4, and 5) was carried out using 1.5 mmol of **1a**, 0.5 mmol of **5**, 2.5 mmol of zinc powder, and 5 mL of THF under sonication at 25 °C for 1 h.
[b] Electroreduction (runs 3 and 6) was carried out using 1.5 mmol of **1a** and 0.5 mmol of **2** in 20 mL of 0.2 M NH_4NO_3–MeOH (Ref. 10c).
[c] Isolated yields.
[d] Determined by ^1H NMR spectra.

respectively, by treatment with LiOOH in THF–H_2O (Scheme 3).



6a (*R*:*S* = 60:40) (*R*)-**4** (20% ee)

6b (*R*:*S* = 35:65) (*S*)-**4** (33% ee)

Scheme 3.

3. Conclusion

The reduction of 1,2-bis(bromomethyl)benzenes **1a** with zinc powder followed by cycloaddition with (4*R*,5*S*)-1-acryloyl-3,4-dimethyl-5-phenyl-2-imidazolidinone **2** in the presence of $BF_3{\cdot}Et_2O$ under ultrasonic irradiation gave cycloadduct **3** in high yield (90%) and high diastereomeric ratio (*R*:*S* = 87:13). It was disclosed that chiral 1-acryloyl-2-imidazolidinone **2** was an efficient chiral dienophile for the cycloaddition with *o*-QDM generated by the reduction of **1a**. The major (*R*)-isomer of **3** was isolated and its stereoconfiguration was confirmed by X-ray crystallographic analysis. The (*R*)-selectivity in the formation of **3** is well explained by the DFT calculations of the transition states of the cycloaddition. The diastereoselectivity in **6** obtained from chiral 1-acryloyl-2-oxazolidinones **5** was lower than that of **3**.

4. Experimental

4.1. General

All ^1H and ^{13}C NMR spectra were measured on a JEOL GX-270 or GMX-500 spectrometer with tetramethylsilane (TMS) as an internal standard. Optical rotations were obtained on a Jasco DIP-360 digital polarimeter. Column chromatography was performed on silica gel 60. THF was distilled from sodium benzophenone ketyl. DMF was distilled from CaH_2. MsOH was distilled from P_2O_5. Zinc powder was treated with 1 M HCl, washed successively with H_2O, EtOH, and Et_2O, and dried in vacuo.

4.2. Chiral dienophiles

Chiral dienophiles **2**, **5a**, and **5b** were synthesized by treatment of (4*R*,5*S*)-3,4-dimethyl-5-phenylimidazolodin-2-one, (*S*)-4-isopropyloxazolidin-2-one, and (*R*)-4-phenyloxazolidin-2-one, respectively, with acryloyl chloride according to the reported methods.[14,15]

4.2.1. (4*R*,5*S*)-1-Acryloyl-3,4-dimethyl-5-phenylimidazolidin-2-one 2. White solid. Mp 150–152 °C. $[\alpha]_D^{20} = 132$ (*c* 1.00, $CHCl_3$). ^1H NMR (270 MHz, $CDCl_3$): δ 0.82 (d, 3H, $J = 6.9$ Hz), 2.85 (s, 3H), 3.88–3.99 (m, 1H), 5.36 (d, 1H, $J = 8.6$ Hz), 5.76 (dd, 1H, $J = 2.0$, 10.6 Hz), 6.39 (dd, 1H, $J = 2.0$, 17.2 Hz), 7.14–7.19 (m, 1H), 7.26–7.36 (m, 3H), 7.71 (dd, 1H, $J = 10.6$, 17.2 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.8 (q), 28.1 (q), 53.9 (d), 59.3 (d), 126.9 (d), 128.0 (d), 128.4 (d), 128.7 (d), 129.6 (t), 136.4 (s), 155.6(s), 164.4 (s).

4.2.2. (*S*)-3-Acryloyl-4-isopropyloxazolidin-2-one 5a. White solid. Mp 44–45 °C. $[\alpha]_D^{20} = +120$ (*c* 1.18, $CHCl_3$). ^1H NMR (270 MHz, $CDCl_3$): δ 0.90 (d, 3H, $J = 6.9$ Hz), 0.94 (d, 3H, $J = 6.9$ Hz), 2.34–2.52 (m, 1H), 4.24 (dd, 1H, $J = 3.3$, 9.2 Hz), 4.31 (t, 1H, $J = 8.2$ Hz), 4.47–4.53 (m, 1H), 5.89 (dd, 1H, $J = 2.0$, 10.6 Hz), 6.54 (dd, 1H, $J = 2.0$,

16.8 Hz), 7.52 (dd, 1H, $J = 10.6$, 16.8 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.6 (q), 17.9 (q), 20.4 (d), 58.4 (d), 63.4 (t), 127.2 (d), 131.2 (t), 153.7 (s), 164.5 (s).

4.2.3. (*R*)-3-Acryloyl-4-phenyloxazolidin-2-one 5b. White solid. Mp 89–90 °C. $[\alpha]_D^{20} = -147$ (c 1.17, $CHCl_3$). ^{1}H NMR (270 MHz, $CDCl_3$): δ 4.31 (dd, 1H, $J = 4.0$, 8.9 Hz), 4.72 (t, 1H, $J = 8.9$ Hz), 5.49 (dd, 1H, $J = 4.0$, 8.9 Hz), 5.88 (dd, 1H, $J = 1.7$, 10.2 Hz), 6.48 (dd, 1H, $J = 1.7$, 17.2 Hz), 7.29–7.43 (m, 5H), 7.52 (dd, 1H, $J = 10.2$, 17.2 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 57.6 (d), 70.0 (t), 125.8 (d), 127.0 (d), 128.5 (d), 129.0 (d), 131.8 (t), 138.6 (s), 153.4 (s), 164.1 (s).

4.3. Typical procedure for the reduction with zinc powder (run 6, Table 1)

A suspension of **1a** (0.40 g, 1.5 mmol), **2** (122 mg, 0.5 mmol), zinc powder (0.16 g, 2.5 mmol), and $BF_3{\cdot}Et_2O$ (0.13 mL, 1.0 mmol) in THF (5 mL) was placed in an ultrasound bath (38 kHz, 200 W) at 25 °C for 1 h. The mixture was diluted with 1 M HCl (15 mL) and extracted with ethyl acetate. Product **3** was isolated by column chromatography on silica gel (hexanes/ethyl acetate). The major isomer of **3** [(*R*)-**3**] was separated, crystallized from hexanes/ethyl acetate = 2:1, and gave satisfactory spectroscopic and X-ray crystallographic data.

4.3.1. (4*S*,5*R*)-1,5-Dimethyl-4-phenyl-3-((*R*)-1,2,3,4-tetrahydronaphthalene-2-carbonyl)imidazolidin-2-one (*R*)-3. White solid. Mp 146–147 °C (recryst. from hexanes/ethyl acetate = 2:1). $[\alpha]_D^{24} = -41.2$ (c 1.05, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.82 (d, 3H, $J = 6.9$ Hz), 1.79–1.89 (m, 1H), 2.09–2.15 (m, 1H), 2.80–3.03 (m, 4H), 2.84 (s, 3H), 3.89–3.95 (m, 1H), 4.06–4.13 (m, 1H), 5.33 (d, 1H, $J = 8.7$ Hz), 7.03–7.09 (m, 4H), 7.15–7.19 (m, 2H), 7.27–7.37 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.9 (q), 26.1 (t), 28.1 (q), 28.7 (t), 31.7 (t), 39.3 (d), 53.7 (d), 59.4 (d), 125.46 (d), 125.51 (d), 126.7 (d), 128.0 (d), 128.5 (d), 128.6 (d), 128.9 (d), 135.4 (s), 135.9 (s), 136.7 (s), 155.5 (s), 175.2 (s). Anal. Calcd for $C_{22}H_{24}N_2O_2$: C, 75.83; H, 6.94; N, 8.04. Found: C, 75.78; H, 6.95; N, 7.94.

4.3.2. Diastereomeric mixture of 3 (*R*:*S* = 67:33). White solid. R_f 0.65 (hexanes/ethyl acetate = 2:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.79 (d, 3H, $J = 6.6$ Hz), 1.63–1.73 (m, 0.33H), 1.79–1.90 (m, 0.67H), 2.08–2.16 (m, 0.67H), 2.18–2.26 (m, 0.33H), 2.77–3.11 (m, 4H), 2.82 (s, 3H), 3.86–3.93 (m, 1H), 4.07–4.14 (m, 1H), 5.32 (d, 0.67H, $J = 8.8$ Hz), 5.34 (d, 0.33H, $J = 8.8$ Hz), 7.03–7.09 (m, 4H), 7.14–7.19 (m, 2H), 7.26–7.37 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.90 (q), 14.93 (q), 26.1 (t), 26.8 (t), 28.1 (q), 28.7 (t), 28.8 (t), 31.0 (t), 31.7 (t), 39.1 (d), 39.3 (d), 53.76 (d), 53.78 (d), 59.2 (d), 59.4 (d), 125.46 (d), 125.52 (d), 126.8 (d), 128.0 (d), 128.5 (d), 128.61 (d), 128.64 (d), 128.93 (d), 128.97 (d), 135.4 (s), 135.5 (s), 135.92 (s), 135.94 (s), 136.75 (s), 136.77 (s), 155.5 (s), 175.1 (s), 175.2 (s).

4.3.3. Diastereomeric mixture of (4*S*)-4-isopropyl-3-(1,2,3,4-tetrahydronaphthalene-2-carbonyl)oxazolidin-2-one 6a (*R*:*S* = 60:40). White solid. R_f 0.3 (hexanes/ethyl acetate = 5/1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.906 (d, 1.2H, $J = 7.0$ Hz), 0.911 (d, 1.8H, $J = 7.0$ Hz), 0.928 (d, 1.2H, $J = 7.0$ Hz), 0.931 (d, 1.8H, $J = 7.0$ Hz), 1.78–1.92 (m, 1H), 2.07–2.14 (m, 0.6H), 2.21–2.28 (m, 0.4H), 2.34–2.44 (m, 1H), 2.83–3.15 (m, 4H), 3.90–4.00 (m, 1H), 4.23 (dd, 1H, $J = 3.2$, 9.2 Hz), 4.29 (dt, 1H, $J = 2.8$, 8.4 Hz), 4.46–4.51 (m, 1H), 7.06–7.13 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.6 (q), 17.80 (q), 17.82 (q), 25.7 (t), 27.0 (t), 28.28 (d), 28.32 (d), 28.4 (t), 28.6 (t), 30.7 (t), 31.9 (t), 38.9 (d), 39.0 (d), 58.2 (d), 58.4 (d), 63.2 (t), 125.62 (d), 125.63 (d), 125.7 (d), 125.8 (d), 128.7 (d), 128.8 (d), 128.9 (d), 134.7 (s), 134.9 (s), 135.6 (s), 135.7 (s), 153.56 (s), 153.58 (s), 175.6 (s), 175.7 (s). Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87. Found: C, 70.93; H, 7.39; N, 4.66.

4.3.4. Diastereomeric mixture of (4*R*)-4-phenyl-3-(1,2,3,4-tetrahydronaphthalene-2-carbonyl)oxazolidin-2-one 6b (*R*:*S* = 35:65). White solid. R_f 0.55 (hexanes/ethyl acetate = 2:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.65–1.75 (m, 0.35H), 1.78–1.88 (m, 0.65H), 2.12–2.21 (m, 1H), 2.75–3.09 (m, 4H), 3.92–3.99 (m, 1H), 4.27–4.32 (m, 1H), 4.69–4.75 (m, 1H), 5.44–5.50 (m, 1H), 7.03–7.14 (m, 4H), 7.30–7.43 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.7 (t), 26.4 (t), 28.35 (t), 28.41 (t), 30.6 (t), 31.4 (t), 34.0 (t), 38.9 (d), 39.0 (d), 57.5 (d), 57.6 (d), 69.7 (t), 125.55 (d), 125.60 (d), 125.64 (d), 125.7 (d), 126.1 (d), 128.5 (d), 128.6 (d), 128.8 (d), 128.9 (d), 129.0 (d), 134.6 (s), 134.7 (s), 135.50 (s), 135.55 (s), 139.0 (s), 139.1 (s), 153.2 (s), 175.0 (s), 175.1 (s). Anal. Calcd for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36. Found: C, 74.82; H, 6.05; N, 4.21.

4.4. X-ray crystallographic analysis of (*R*)-3

All measurements were made on a Rigaku RAXIS imaging plate area detector with graphite monochromated Mo Kα radiation. The structure was solved by direct methods with SIR-97 and refined with SHELXL-97. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined isotropically. All calculations were performed using the YADOKARI-XG software package.

4.4.1. Crystal data of (*R*)-3. $C_{22}H_{24}N_2O_3$, FW = 348.43, mp 146–147 °C, orthorhombic, $P2_12_12_1$ (no 19), colorless block, $a = 8.1139(11)$ Å, $b = 9.1221(16)$ Å, $c = 25.827(4)$ Å, $V = 1911.6(5)$ Å^3, $T = 298$ K, $Z = 4$, $D_{calcd} = 1.211$ g/cm^3, $\mu = 0.78$ cm^{-1}, GOF = 1.005. CCDC 640624 contains the supplementary crystallographic data for (*R*)-**3**. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.

4.5. Typical procedure for electroreduction (run 11 in Table 1)

A solution of 0.2 M NH_4NO_3 in MeOH (20 mL) was placed into a divided cell of a 40 mL beaker (3 cm diameter, 6 cm height) equipped with a Pb cathode (5 × 5 cm^2), a Pt anode (2 × 1 cm^2), and a cylindrical ceramic diaphragm (1.8 cm diameter, 7.5 cm height). To the catholyte (outside the diaphragm) were added **1a** (0.40 g, 1.5 mmol) and **2** (122 mg, 0.5 mmol). Electroreduction was carried

out at a constant current of 0.05 A at 25 °C until 600 C of electricity had passed. The catholyte was poured into water (50 mL) and extracted with ethyl acetate. Product **3** was isolated by column chromatography on silica gel (hexanes/ethyl acetate).

4.6. Typical procedure for hydrolysis of 3 to 4

A solution of an 87:13 diastereomeric mixture of **3** (167 mg, 0.5 mmol) and $LiOH{\cdot}H_2O$ (0.21 g, 5 mmol) in THF (5 mL) and H_2O (5 mL) was stirred at 50 °C for 24 h. After being allowed to return to room temperature, the mixture was diluted with 1 M HCl (20 mL) and extracted with ethyl acetate. Product **4** was isolated by column chromatography on silica gel (hexanes/ethyl acetate). Compound **4**: $[\alpha]_D^{22} = +41.6$ (*c* 1.1, $CHCl_3$). Lit.[16] for enantiomerically pure (*R*)-**4**: $[\alpha]_D^{22} = +55.5$ (*c* 1.4, $CHCl_3$).

4.7. General procedure for hydrolysis of 6 to 4

A solution of **6** (0.5 mmol) and $LiOH{\cdot}H_2O$ (0.21 g, 5 mmol) in THF (5 mL) and 15% H_2O_2 aq (2 mL) was stirred at 25 °C for 24 h. The mixture was diluted with 1 M HCl (20 mL) and extracted with ethyl acetate. Product **4** was isolated by column chromatography on silica gel (hexanes/ethyl acetate).

4.8. Computational methodology

All calculations were carried out with the GAUSSIAN 03 program.[13] Geometry optimization was performed by the B3LYP/6-31+G** method throughout. All optimized geometries were verified by the vibrational analysis and their energies were thermally corrected to 298 K based on the frequencies. As for the transition states, it was confirmed that these structures had only one imaginary frequency. The imaginary frequency was ascertained to be consistent with the cycloaddition by displaying the vibrational mode using the GAUSS VIEW program. In addition, single point calculations were carried out for all optimized transition states using the IEFPCM model for THF solvent at the same level as the geometry optimization (B3LYP/6-31+G**) to take the solvent effect into consideration.

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