HETEROCYCLES, Vol. 76, No. 1, 2008, pp. 801 - 810. © The Japan Institute of Heterocyclic Chemistry
Received, 7th April, 2008, Accepted, 28th April, 2008, Published online, 1st May, 2008. COM-08-S(N)98

DEVELOPMENT OF BIFUNCTIONAL ACYCLIC HYDROXYL-GUANIDINE ORGANOCATALYST: APPLICATION TO ASYMMETRIC NUCLEOPHILIC EPOXIDATION†

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Abstract – Asymmetric epoxidation of α,β-unsaturated ketones using acyclic **3a** as a new bifunctional organocatalyst is described. The hydroxyl-guanidine **3a** promoted the reaction to give the corresponding epoxy ketones in good yields (up to 99% yield) and enantioselectivities (up to 73% *ee*).

The development of asymmetric reactions with metal-free organocatalyst[1] is an important and challenging issue in synthetic organic chemistry. Recently, we reported the cyclic guanidines[2] as chiral PTCs,[3] which promoted the asymmetric epoxidation of α,β-unsaturated ketones with moderate enantioselectivities.[6e] Encouraged with these preliminary results, we planned to design a new type of guanidine compounds to improve the catalytic activity. Herein we wish to describe the synthesis of chiral acyclic guanidine **3a** as a new bifunctional organocatalyst, and its application to asymmetric epoxidation of α,β-unsaturated ketones of chalcone derivatives.[4-6]

During our studies to develop new organocatalysts, we found that the bifunctional organocatalyst having octadecyl-substituted guanidine and thiourea groups linked with a chiral spacer notably promoted asymmetric direct nitroaldol reaction (Henry reaction) of aldehydes and nitroalkanes.[7] In this reaction,

selective recognition of guanidine and thiourea groups with nitroalkanes and aldehyde is realized to be significant for obtaining high stereoselectivities. Based upon these results, we decided to develop a new bifunctional organocatalyst for the asymmetric nucleophilic epoxidation to α,β-unsaturated ketones. Thus, the catalyst was designed to connect guanidine and hydroxyl group with the chiral spacer, and these functional groups were expected to interact with carbonyl group and oxidant of TBHP (*tert*-butyl hydroperoxide), respectively (Figure 1).

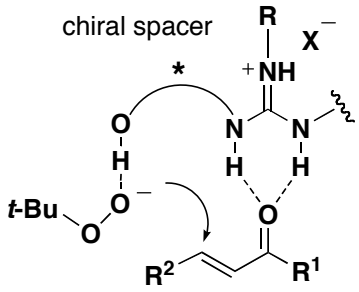
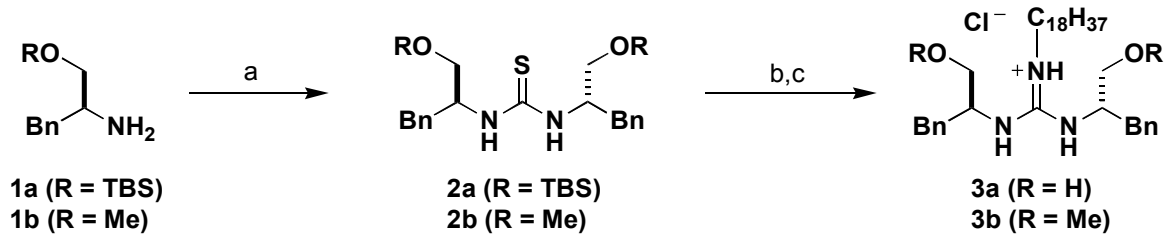


Figure 1. Design of hydroxy-guanidine bifunctional organocatalyst for nucleophilic epoxidation reaction.

The chiral hydroxy-guanidine **3a** was readily prepared from L-Phe (Scheme 1). The amine **1a**,[8] which was obtained from L-Phe, was converted into the thiourea **2a** with carbon disulfide in 57% yield. The thiourea **2a** was reacted with octadecylamine using mercury (II) chloride to give acyclic guanidine. Finally, **3a** was completed by removing TBS group under acidic conditions in 80%. The guanidine **3b**, which has methyl ether instead of hydroxyl group, was synthesized from **1b**[9] by a similar way.



1a (R = TBS)
1b (R = Me)

2a (R = TBS)
2b (R = Me)

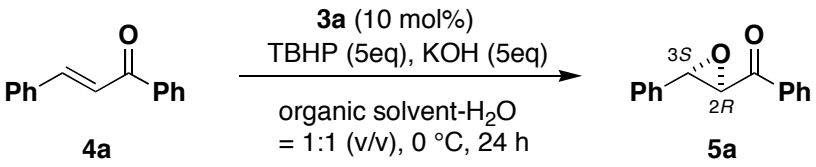
3a (R = H)
3b (R = Me)

Scheme 1. Synthesis of chiral hydroxyl-guanidine **3**. (a) CS_2, EtOH, reflux, (**2a**: 57%, **2b**: 90%); (b) $C_{18}H_{37}NH_2$, $HgCl_2$, Et_3N, MeCN, 80 °C (**3b**: 83% from **2b**); (c) HCl-MeOH, (**3a**: 69% from **2a**).

The optically active hydroxyl-guanidine compounds in hand, we examined the catalytic asymmetric epoxidation of *trans*-chalcone **4a** by the use of **3a**. We firstly examined the epoxidation reaction of **4a** using TBHP (5 equiv) and KOH (5 equiv) in the presence of **3a** (10 mol%) at 0 °C under biphasic conditions (organic solvent-H_2O = 1:1 (v/v)), and some organic solvents were screened in Table 1. The

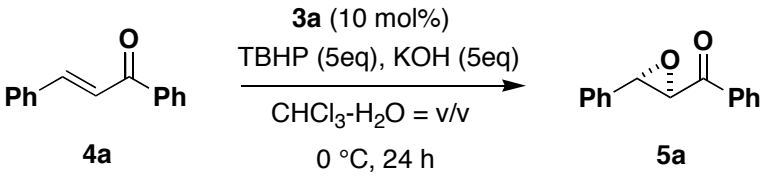
reaction in dichloromethane, chloroform or toluene gave the (2*R*,3*S*)-epoxy ketone **5a** with moderate yields and enantioselectivities (entries 1-3). In case of diethyl ether and methanol, **5a** was obtained almost quantitatively, but enantioselectivity was poor or not observed (entries 4 and 5).

Table 1. Solvent effects in epoxidation of *trans*-chalcone **4a** catalysed by **3a**.



Entry	Solvent	Yield (%)	ee (%)
1	CH_2Cl_2	52	27
2	$CHCl_3$	36	38
3	toluene	58	33
4	Et_2O	90	16
5	MeOH	99	1

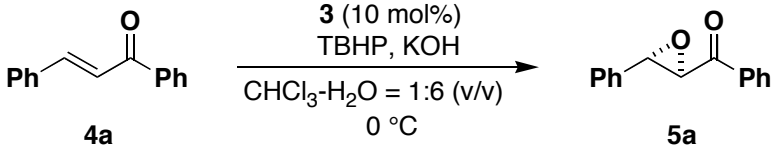
Table 2. Solvent ratios in epoxidation of *trans*-chalcone **4a** catalysed by **3a**.



Entry	$CHCl_3$-H_2O	Yield (%)	ee (%)
1	10 : 1	76	0
2	1 : 1	36	38
3	1 : 2	50	54
4	1 : 4	50	55
5	1 : 6	58	60
6	1 : 8	50	60

As chloroform gave the best result (38% *ee*) among the solvents examined, we next investigated the ratio of the solvents in biphasic system (Table 2). Excess amount of chloroform (10:1) increased the chemical yield of **5a**, however, no enantioselectivity was observed (entry 1). On the other hand, the enantiomeric excess of **5a** increased up to 60% *ee* when the ratio of chloroform-water was changed from 1:1 to 1:2-8 (entries 3-6). With these results, we next investigated the amounts of oxidant (TBHP) and base (KOH) using the biphasic conditions of entry 5 in Table 2 (Table3). When the equivalents of KOH were changed from 5 equiv to 25 equiv, the enantiomeric excess of **5a** increased to 70% *ee*, however, chemical yield was dropped to 25% (entries 1-4). Thus, the reaction was conducted using 20 equiv of TBHP, and **5a** was obtained in 54% yield without loosing enantioselectivity by using 80 equiv of KOH (entry 5).[10] Finally, **5a** was obtained with 94% yield with 70% *ee* using 30 equiv of TBHP by the divided addition into 2 times (entry 6, see experimental section). We next examined the property of hydroxyl group in **3a** by changing the catalyst to **3b**. When the reaction was employed under the optimal conditions in entry 6 (Table 3) in the presence of catalyst **3b** (10 mol%), the yield and enantioselectivity significantly dropped, and **5a** was obtained in 24% yield with 2% *ee* (entry 7). These results revealed that the hydroxyl group in **3a** was indispensable for the highly asymmetric induction for epoxidation, and crucial interactions between hydroxyl group in **3a** and oxidant of TBHP were strongly suggested.

Table 3. Optimization of nucleophilic epoxidation of **4a** in the presence of **3**.



Entry	Cat.	TBHP (eq.)	KOH (eq.)	Time (h)	Yield (%)	ee (%)
1	**3a**	5	5	24	58	60
2	**3a**	5	10	24	40	63
3	**3a**	5	20	24	27	70
4	**3a**	5	25	24	25	70
5	**3a**	20	80	24	54	70
6	**3a**	30[a]	80	48	94	70
7	**3b**	30[a]	80	48	24	2

[a]15 Equivalents of TBHP was added first , and another 15equiv was added after 24 h.

Since (2*R*,3*S*)-**5a** was preferentially obtained in the presence of **3a**, we proposed a plausible transition state for the asymmetric nucleophilic epoxidation of **4a** (Figure 2). Carbonyl group in **4a** coordinates with guanidine in **3a** through hydrogen bonding, and two conformers of **3a**, i.e., **I** and **II** can be considered at this stage.[11,5j] In these cases, conformer-**I** is more favorable than **II** since the bulky benzyl group locates at equatorial position against the guanidine planer. From the conformer-**I**, nucleophilic attack of TBHP anion takes place by interacting with hydroxyl group in **3a**, and generates (2*R*,3*S*)-**5a** as a major product.

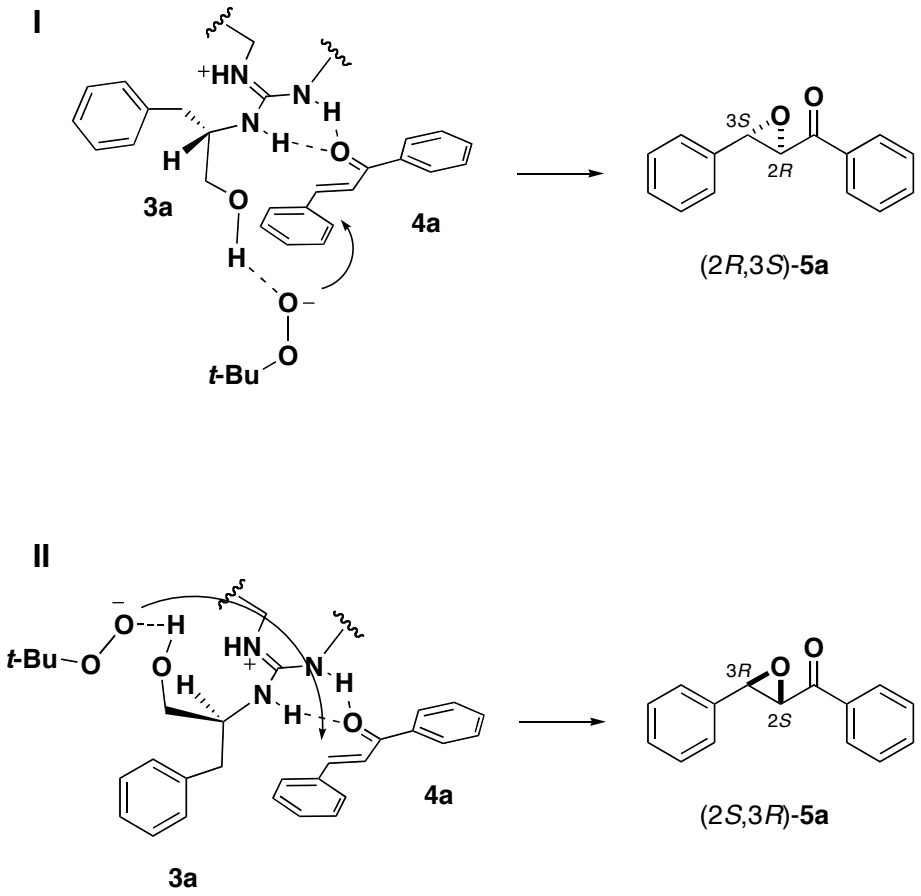
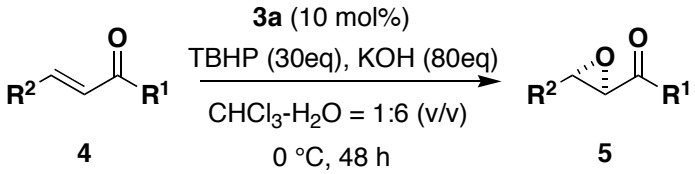


Figure 2. Plausible transition states of epoxidation for **4a** in the presence of bifunctional guanidine **3a**.

Finally, epoxidation reaction of chalcones **4b**-**f** was explored under the optimal reaction conditions, i.e., entry 6 in Table 3, and results were summarized in Table 4. In all cases, the corresponding (2*R*,3*S*)-epoxy ketones were obtained with moderate to good yields and enantioselectivities (56-99% yield, 62-73% *ee*).



Entry	4	R^1	R^2	Product	Yield (%)	ee (%)
1	**4b**	Ph	2-naphthyl	**5b**	84	73
2	**4c**	Ph	4-Me-C_6H_4	**5c**	74	62
3	**4d**	Ph	4-Cl-C_6H_4	**5d**	99	65
4	**4e**	4-Br-C_6H_4	Ph	**5e**	98	65
5	**4f**	4-MeO-C_6H_4	Ph	**5f**	56	60

Table 4. Asymmetric epoxidation of chalcones **4b**-**f** under the optimal conditions.

In conclusion, acyclic hydroxyl-guanidine bifunctional organocatalyst **3a** was developed for the nucleophilic asymmetric epoxidation of α,β-unsaturated ketones. The hydroxyl group in **3a** was realized to play a critical role for the good enantioselectivities. Further studies for the development more efficient organocatalyst for nucleophilic epoxidation are currently in progress.

EXPREMENTAL

General

Optical rotations were measured with a JASCO DIP 1000 polarimeter. ^{1}H and ^{13}C NMR spectra were recorded on JEOL JNM-AL300 or JEOL JMN-ECX400. Mass spectra were recorded on JEOL JMS-T100X spectrometer with ESI-MS mode. TBHP 5 M in decane solution was purchased from Aldrich.

Synthesis of acyclic hydrokyl-guanidine 3a.

To a solution of amine **1a** (1.58 g, 5.96 mmol) in EtOH (40 mL) was added CS_2 (355 μL, 5.96 mmol) at rt, and the resulting mixture was stirred at 90 °C for 14 h. The reaction mixture was concentrated *in vacuo* and the residue was purified by column chromatography on silica gel (hexane-EtOAc, 40:1 to 20:1) to give thiourea **2a** (977 mg, 1.70 mmol, 57%). To a mixture of **2a** (427 mg, 0.75 mmol), octadecylamine (305 mg, 1.12 mmol) and Et_3N (310 μL, 2.24 mmol) in MeCN (10 mL) was added $HgCl_2$ (304 mg, 1.12 mmol) at rt, and the resulting mixture was stirred at 80 °C for 20 h. The reaction mixture was concentrated *in vacuo* and the residue was purified by column chromatography on silica gel

(hexane-EtOAc, 1:1 to 1:3) to give bis-TBS guanidine (516 mg, 0.64 mmol, 86%). The bis-TBS guanidine (463 mg, 0.57 mmol) was dissolved in HCl-MeOH solution (6 mL) at 0 °C. The mixture was stirred at rt for 4 h, and the resulting mixture was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane-EtOAc, 60:1 to 10:1) to give **3a** (283 mg, 0.46 mmol, 80%).
Spectral data for **2a** and **3a**. **2a**: $[\alpha]_D^{22}$ −55 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.16 (m, 10H), 5.93 (s, 2H), 3.65-3.41 (m, 5H), 2.98-2.62 (m, 5H), 0.93 (s, 18H), 0.07 (s, 6H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.48, 137.84, 129.36, 128.54, 126.55, 62.48, 56.74, 36.90, 25.89, 18.23, -5.40, -5.48; HRMS (ESI, M+Na) calcd for $C_{31}H_{52}N_2NaO_2SSi_2$ 595.3186, found 595.3230. **3a**: $[\alpha]_D^{22}$ −98 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50-6.86 (m, 12H), 5.86 (s, 2H), 3.96-3.50 (m, 5H), 3.06-2.50 (m, 5H), 2.16-2.00 (s, 1H), 1.54-0.80 (m, 37H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.65, 137.17, 129.00, 128.52, 126.61, 66.10, 57.13, 42.47, 36.71, 36.66, 31.85, 29.67, 29.59, 29.52, 29.29, 29.07, 28.74, 26.47, 22.61, 14.05; HRMS (ESI, M+H) calcd for $C_{37}H_{62}N_3O_2$ 580.4842, found 580.4802.
With the same procedure, **3b** were obtained from **1b**. Spectral data for **3b**: $[\alpha]_D^{25}$ −200 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-6.94 (m, 13H), 3.66-3.25 (m, 12H), 3.00-2.80 (m, 4H), 1.33-1.08 (m, 34H), 0.87 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.95, 137.12, 129.24, 128.52, 126.72, 77.21, 59.04, 55.37, 42.64, 31.87, 29.66, 29.61, 29.58, 29.55, 29.31, 29.12, 28.78, 26.56, 22.64, 14.08; HRMS (ESI, M+H) calcd for $C_{39}H_{66}N_3O_2$ 608.5155, found 608.5122.

Typical procedure for the asymmetric epoxidation of *trans*-chalcone 4a in the presence of 3a.
A mixture of *trans*-chalcone **4a** (10.5 mg, 0.05 mmol) and **3a** (3.1 mg, 0.005 mmol) in $CHCl_3$ (0.25 mL) and aqueous KOH (1.50 mL, 4.00 mmol) was cooled at 0 °C. To the mixture was added TBHP (5 M decane solution, 0.15 mL, 0.75 mmol), and the resulting mixture was stirred vigorously at 0 °C for 24 h, and then additional TBHP (5 M decane solution, 0.15 mL, 0.75 mmol) was added. The mixture was stirred vigorously at 0 °C for another 24 h. To the reaction mixture was added saturated aqueous NH_4Cl, and extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane-EtOAc, 100:1 to 30:1) to give **5a** (10.5 mg, 0.047 mmol, 94 %, 70 % *ee*). Spectral data for **5a-f** were as follows.[5]
trans-(2*R*,3*S*)-Epoxy-1,3-diphenylpropan-1-one (**5a**)[5h]: The enantiomeric excess of **5a** (70% *ee*) was determined by HPLC analysis, using DAICEL Chiralcel OD-H column, 0.46 cm (ϕ) x 25 cm (*L*), hexane/2-propanol = 98/2, 1.00 mL/min; t_{minor} = 18.4 min, t_{major} = 19.7 min; $[\alpha]_D^{24}$ −112 (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04-7.98 (m, 2H), 7.66-7.59 (m, 1H), 7.49 (t, *J* = 7.8 Hz, 2H), 7.45-7.34 (m, 5H), 4.31 (d, *J* = 1.8 Hz, 1H), 4.08 (d, *J* = 1.8 Hz, 1H).
trans-(2*R*,3*S*)-Epoxy-3-(2-naphthyl)-1-phenylpropan-1-one (**5b**)[5b]: The enantiomeric excess of **5b** (73%

ee) was determined by HPLC analysis, using DAICEL Chiralcel OD-H column, 0.46 cm (ϕ) x 25 cm (*L*), hexane/2-propanol = 98/2, 1.00 mL/min; t_{minor} = 34.9 min, t_{major} = 40.6 min; $[\alpha]_D^{23}$ −108 (*c* 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05-8.00 (m, 2H), 7.92-7.82 (m, 4H), 7.66-7.40 (m, 6H), 4.41 (d, *J* = 1.8 Hz, 1H), 4.25 (d, *J* = 1.8 Hz, 1H).

trans-(2*R*,3*S*)-Epoxy-3-(4-methylphenyl)-1-phenylpropan-1-one (**5c**)[5j]: The enantiomeric excess of **5c** (62% *ee*) was determined by HPLC analysis, using DAICEL Chiralcel OD-H column, 0.46 cm (ϕ) x 25 cm (*L*), hexane/2-propanol = 90/10, 1.00 mL/min; t_{minor} = 8.6 min, t_{major} = 9.6 min; $[\alpha]_D^{23}$ −121 (*c* 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, *J* = 7.3 Hz, 2H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 2H), 7.24 (dd, *J* = 7.8, 2.1 Hz, 4H), 4.30 (d, *J* = 1.8 Hz, 1H), 4.04 (d, *J* = 1.9 Hz, 1H), 2.38 (s, 1H).

trans-(2*R*,3*S*)-Epoxy-3-(4-chlorophenyl)-1-phenylpropan-1-one (**5d**)[5a]: The enantiomeric excess of **5d** (65% *ee*) was determined by HPLC analysis, using DAICEL Chiralpak AD-H column, 0.46 cm (ϕ) x 25 cm (*L*), hexane/2-propanol = 100/1, 1.00 mL/min; t_{minor} = 47.3 min, t_{major} = 54.8; $[\alpha]_D^{23}$ −127 (*c* 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04-7.96 (m, 2H), 7.68-7.28 (m, 7H), 4.26 (d, *J* = 1.8 Hz, 1H), 4.07 (d, *J* = 1.8 Hz, 1H).

trans-(2*R*,3*S*)-Epoxy-3-phenyl-1-(4-bromophenyl)propan-1-one (**5e**)[5h]: The enantiomeric excess of **5e** (65% *ee*) was determined by HPLC analysis, using DAICEL Chiralcel OD-H column, 0.46 cm (ϕ) x 25 cm (*L*), hexane/2-propanol = 95/5, 0.8 mL/min; t_{major} = 20.5 min, t_{minor} = 22.2 min; $[\alpha]_D^{24}$ −90 (*c* 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.6 Hz, 2H), 7.64 (d, *J* = 8.6 Hz, 2H), 7.46-7.32 (m, 5H), 4.23 (d, *J* = 1.7 Hz, 1H), 4.07 (d, *J* = 1.5 Hz, 1H).

trans-(2*R*,3*S*)-Epoxy-3-phenyl-1-(4-methoxyphenyl)propan-1-one (**5f**)[5j]: The enantiomeric excess of **5f** (60% *ee*) was determined by HPLC analysis, using DAICEL Chiralpak AD-H column, 0.46 cm (ϕ) x 25 cm (*L*), hexane/2-propanol = 100/1, 1.00 mL/min, 1.00 mL/min; t_{minor} = 36.9 min, t_{major} = 42.4; $[\alpha]_D^{23}$ −65 (*c* 0.6, $CHCl_3$); ^{1}H NMR (300 Hz, $CDCl_3$) δ 8.05-7.97 (m, 2H), 7.45-7.32 (m, 5H), 6.99-6.91 (m, 2H), 4.26 (d, *J* = 2.0 Hz, 1H), 4.07 (d, *J* = 1.8 Hz, 1H), 3.88 (s, 3H).

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†This paper is dedicated to Professor Dr. Ryoji Noyori on the occasion of his 70th birthday.

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