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GUANIDINE-CATALYZED ASYMMETRIC ADDITION REACTIONS: MICHAEL REACTION OF CYCLOPENTENONE WITH DIBENZYL MALONATES AND EPOXIDATION OF CHALCONE

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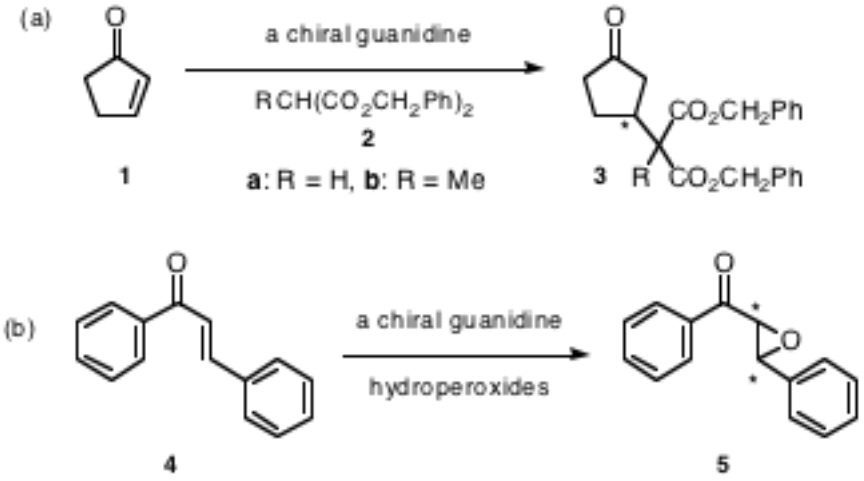
Abstract – Several kinds of modified guanidines designed by us were applied to two types of asymmetric synthesis as superbases: Michael reactions of cyclopentenone with dibenzyl malonates and epoxidation of chalcone. Good to moderate asymmetric inductions were observed in these guanidine-catalyzed reactions.

INTRODUCTION

Guanidines can be characterized as superbases[1] in organic synthesis due to their strong basicity.[2] We have explored the possibility of readily available modified guanidines[3] as re-useable chiral superbases in asymmetric synthesis.[4] Michael reaction is one of the most important organic reactions for C-C bond formation. Therefore, several chiral catalysts,[5] mainly metal bases, have been developed for asymmetric Michael reaction, but the use of guanidine-type catalysts[6] led to either ineffective or no chirality transfer from the guanidines. We have independently explored the possibility of modified guanidines[7] to organic synthesis as chiral auxiliaries and observed excellent asymmetric induction in the Michael reaction between activated vinyl compounds such as methyl vinyl ketone or acrylates with *tert*-butyl diphenyliminoacetate.[8] In this paper we present an alternative Michael reaction of cyclopentenone (**1**)

with dibenzyl malonates (**2**) (Scheme 1a) and epoxidation of chalcone (**4**) with hydroperoxides (Scheme 1b) catalyzed with chiral guanidines.



Scheme 1. Examined Guanidine-catalyzed Asymmetric Synthesis

RESULTS AND DISCUSSION

In these asymmetric syntheses total twenty-six guanidines (**6**, **7**-**8**,[3a] **9**-**12**,[4a] **13**,[3a] **14**,[4a] **15**-**20**,[3a] **21**-**22**,[3c] **23**-**26**,[3b] **27**-**28** and **29**-**31**[3b]) shown in Fig. 1 were screened. Acyclic guanidine (**6**) and cyclic guanidines (**27** and **28**) were prepared from carbodiimide (**32**[3c]) and carbamates (**33**[3c] and **34**[3c]), respectively, according to the reported procedures.[3b, c] In the former Michael reaction seventeen guanidines (**6**-**22**) and in the latter epoxidation thirteen guanidines (**10**, **14**, **17**-**18** and **23**-**31**) were examined, respectively.

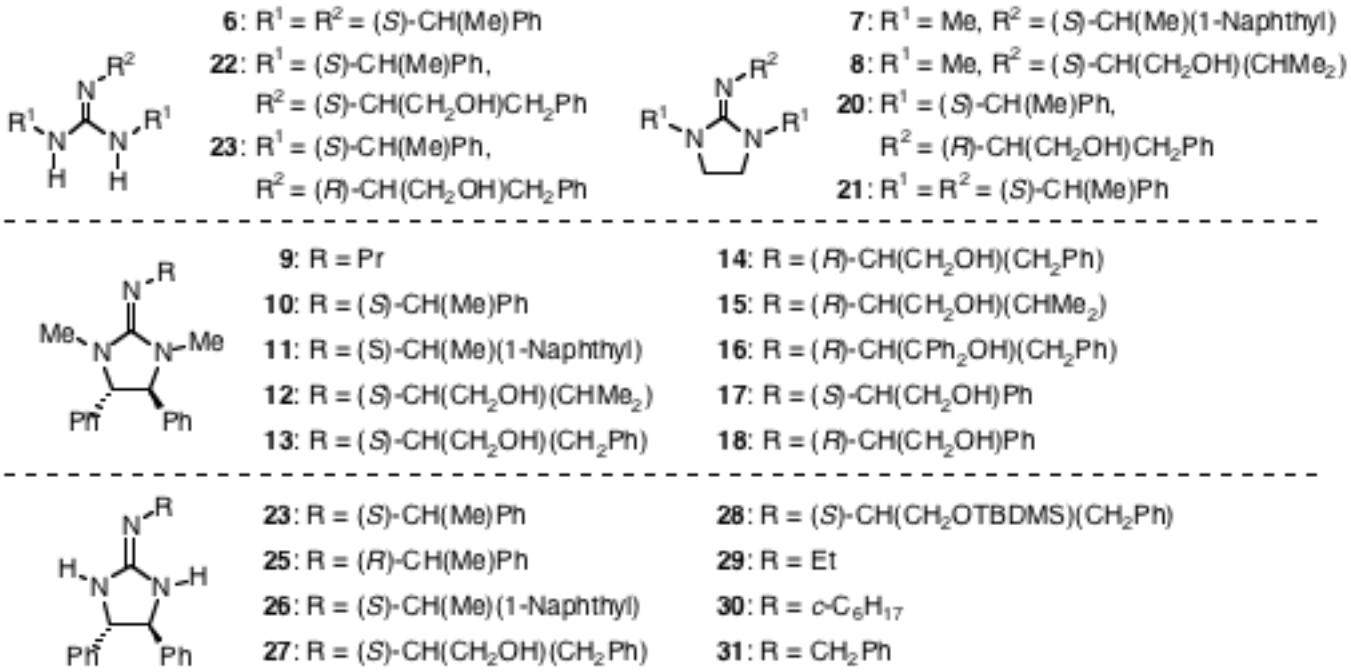


Figure 1. Modified Guanidines Examined as Chiral Auxiliaries

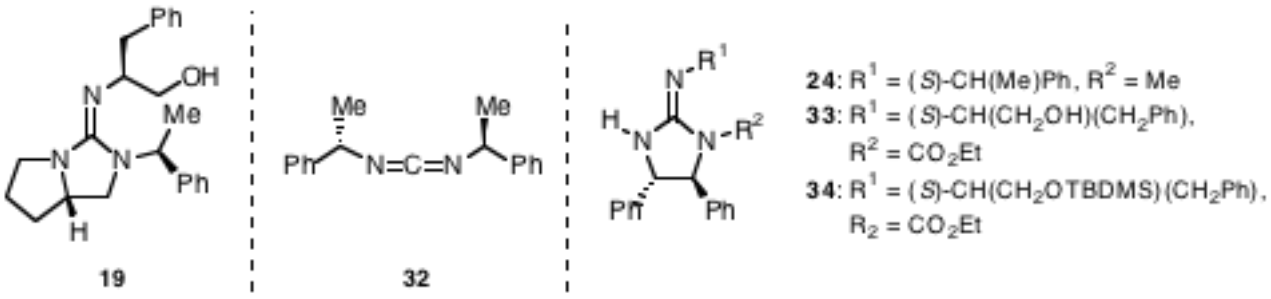
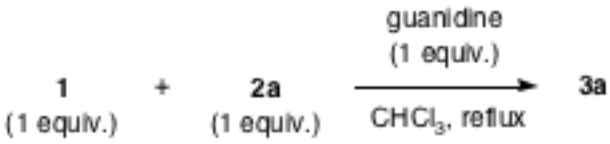


Figure 1. Modified Guanidines Examined as Chiral Auxiliaries (continued)

REACTION OF CYCLOPENTENONE (1) WITH DIBENZYL MALONATES (2)

Reaction of cyclopentenone (**1**) with dibenzyl malonate itself (**2a**) has been often used as a model reaction for asymmetric Michael reactions and successful results were reported in the uses of metal-BINOL complex[9] (93% yield; 91% ee), a quaternary ammonium salt[10] (62% yield; 58% ee) and metal-chiral aminodiol complex[11] (78% yield; 83% ee). Thus, we examined this reaction for screening the effect of modified guanidines as chiral superbases. The reaction was at first carried out in the presence of a stoichiometric amount of guanidines (Table 1).

Table 1. Preliminary Experiments for Asymmetric Michael Reaction of **1** with **2a** in the Presence of a Stoichiometric Amount of a Chiral Guanidine



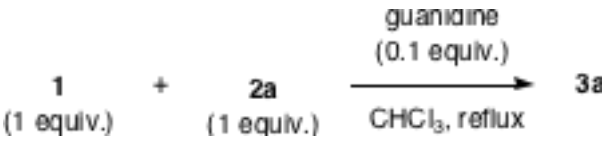
run	guanidine	time (d)	**3a**		
			yield [a] (%)	ee (%)	conf. [b]
1	**6**	9	80	12	*S*
2	**7**	14	47	0	-
3	**8**	10	36	0	-
4	**9**	20	45	8	*R*
5	**10**	10	98	15	*R*
6	**11**	20	51	11	*R*
7	**12**	16	57	19	*S*
8	**13**	14	61	28	*S*
9	**14**	21	65	43	*R*

[a] Isolated yields. [b] Configuration.

Cyclopentenone (**1**) was stoichiometrically treated with dibenzyl malonate (**2a**) in refluxed chloroform ($CHCl_3$) in the presence of nine different types of chiral guanidines (**6**-**14**) (see, Figure 1). Acyclic

guanidine (**6**) gave **3a** in 80% yield with only 12% enantiomer excess (ee) (run 1). Cyclic guanidines (**7** and **8**) without chiral center in the cyclic part gave racemic **3a** (runs 2 and 3). Next, we applied the cyclic guanidines with diphenyl groups at 4,5-positions of imidazolidine part, which had been reported to be good catalysts in the asymmetric Michael reaction of diphenyliminoacetate and α,β-unsaturated carbonyl compounds.[8] As expected, ee was slightly improved when this type of guanidines (**9**-**11**) were used (runs 4-6). Moderate asymmetric induction was observed with the 1,3-dimethylimidazolidine-type (NMe-type) guanidines (**12**-**14**) with a hydroxyethyl residue in a substituent on the external nitrogen function (runs 7-9), especially (*R*)-phenylalaninol derivative (**14**) gave **3a** in 65% yield with 43% ee, in which (*R*)-isomer was formed as a major enantiomer. An absolute configuration of **3a** was found to be controlled by the stereochemistry of the substituent on the external nitrogen when NMe-guanidines (**13** and **14**) with (2-hydroxy-1-benzyl)ethyl residue were used as chiral auxiliaries (runs 8 and 9). The guanidines used in this reaction were completely recovered as re-useable forms by acid-base extraction. The ee and the absolute configuration of an addition product (**3a**) were determined by chiral HPLC analysis followed by the procedure in the literature after conversion of **3a** into a dioxolane derivative.[9] The efficiency of a guanidine as a catalyst was evidenced because of no reaction in the absence of the guanidine.

Table 2. Trials for Michael Reaction of **1** with **2a** in the Presence of a Catalytic Amount of a Chiral Guanidine with a Hydroxyethyl Function



run	guanidine	time (d)	**3a**		
			yield [a] (%)	ee (%)	conf. [b]
1 [c]	**14**	12	65	43	*R*
2	**12**	10	30	12	*S*
3	**15**	22	16	20	*R*
4	**16**	23	59	0	-
5	**17**	26	NR [d]	-	-
6	**18**	6	NR [d]	-	-
7	**19**	25	13	21	*S*
8	**20**	12	51	12	*R*
9	**21**	12	8	8	*S*
10	**22**	12	17	20	*R*

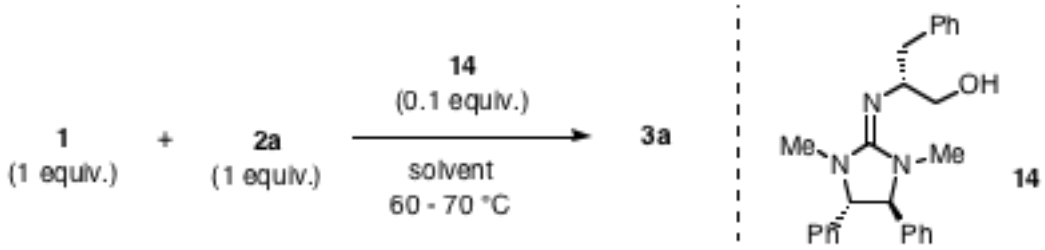
[a] Isolated yields. [b] Configuration. [c] The data of run 9 in Table 1. [d] No reaction.

In Michael reaction a base used should act in a catalytic amount. We next attempted the guanidine-

catalyzed (0.1 equiv.) Michael reaction of **1** with **2a** using ten types of guanidines (**12**, **14-22**) having a hydroxyethyl substituent under the same conditions that in Table 1 (Table 2). Phenylalaninol derivative (**14**) showed the highest asymmetric induction in this series, even in slow reactions (run 1). Varinol derivatives (**12** and **15**) gave lower ee (runs 2 and 3). Guanidine (**16**), in which two phenyl groups were introduced to the hydroxyethyl substituent of **14**, improved chemical yield, but showed no asymmetric induction (run 4). Phenylglycinol derivatives (**17** and **18**) gave no product (runs 5 and 6). Bicyclic (**19**), cyclic (**20**) without chiral center in the cyclic part, and acyclic guanidines (**21** and **22**) gave **3a** with low ee (runs 7-10).

The guanidine (**14**)-catalyzed reactions were further examined in different solvent systems at 60-70 °C (Table 3). In protic [ethanol (EtOH)] and non-protic polar [acetonitrile (MeCN)] solvents, reactions were accelerated but no chiral induction was observed (runs 2 and 3). Reaction in tetrahydrofuran (THF) gave no product (run 4). Reactions in aromatic solvents slightly improved ee but gave lowered chemical yields (runs 5-7). No acceleration of the reaction in toluene was observed even addition of *tert*-butyl alcohol as a proton source (run 8). Ee was improved to be 62% when the reaction in $CHCl_3$ was carried out at room temperature albeit low chemical yield (run 9).

Table 3. Solvent Effects in the Guanidine (**14**)-Catalyzed Reaction of **1** with **2a** at 60 - 70 °C

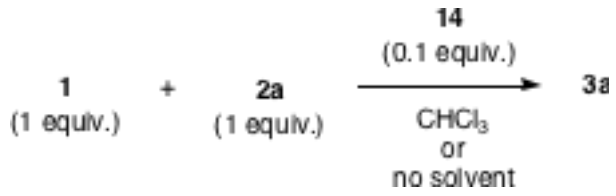


run	solvent	time (d)	**3a**		
			yield [a](%)	ee (%)	conf. [b]
1 [c]	$CHCl_3$	12	65	43	*R*
2	EtOH	1	55	0	-
3	MeCN	7	46	0	-
4	THF	7	NR [d]	-	-
5	toluene	7	17	48	*R*
6	$PhCF_3$	7	21	45	*R*
7	PhH	7	11	50	*R*
8	10% *t*-BuOH in toluene	7	11	47	*R*
9 [e]	$CHCl_3$	41	11	62	*R*

[a] Isolated yields. [b] Configuration. [c] The data of run 9 in Table 1. [d] No reaction.
[e] Reaction was carried out in rt.

Solvent-free reactions,[12] in which rate acceleration is generally observed, have attracted much attention from the ecological point of view. Thus, the Michael reaction was examined using the guanidine (**14**) as a catalyst under the condition without a solvent (Table 4). Stirring a heterogeneous mixture of **1** and **2a** containing 0.1 equivalent of **14** at 20 °C resulted in completion of the reaction within 19 h, but asymmetric induction was slightly lowered (run 2). No increase of ee was observed even in lower temperature (run 3).

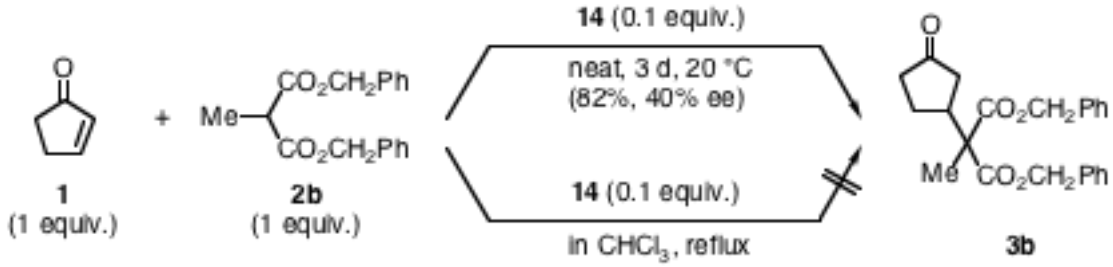
Table 4. A Guanidine (**14**)-catalyzed Asymmetric Michael Reaction of **1** with **2a** without Solvent



run	time	conditions	**3a**		
			yield [a] (%)	ee (%)	conf. [b]
1 [c]	12 d	refluxed in $CHCl_3$	65	43	*R*
2	19 h	neat, 20 °C	77	30	*R*
3	23 h	neat, 7-8 °C	75	31	*R*

[a] Isolated yields. [b] Configuration. [c] The data of run 9 in Table 1.

Similar rate-acceleration was observed when dibenzyl methylmalonate (**2b**) was used as Michael donor instead of **2a**, in which moderate ee was observed. On the other hand, no reaction was observed in chloroform solution (Scheme 2).



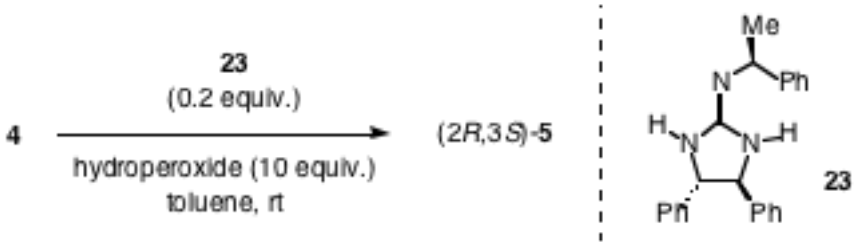
Scheme 2. A Guanidine (**14**)-catalyzed Michael Reaction of **1** with **2b**

EPOXIDATION OF CHALCONE (4)

Chalcone (**4**) is a common substrate for epoxidation trials of α,β-unsaturated ketones. Thus, good results were given in the use of poly-leucine,[13] quaternary quinine derivatives,[14] and metal complexes[15] as catalysts. Apart from these examples, there are no reports catalyzed with organic bases to our knowledge. We decided to explore the ability of our chiral guanidines as catalysts for this reaction. Several hydroperoxides were applied to the reaction in the presence of a catalytic amount (0.2 equiv.) of

guanidine (**23**) with an *N*-unsubstituted imidazolidine ring (NH-guanidine) (Table 5).

Table 5. Trials for Epoxidation of **4** Using Various Hydroperoxides in Toluene at Room Temperature in the Presence of a 0.2 Equivalent of **23**

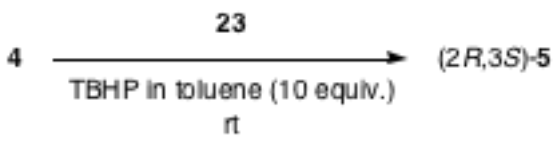


run	hydroperoxide	time (h)	**5**	
			yield [a] (%)	ee (%)
1	70% TBHP aq	24	43	30
2	CMHP	24	24	65
3	TBHP in toluene	24	33	49
4	CMHP in toluene	24	19	68
5	30% H_2O_2 aq	3	50	17
6	H_2O_2-urea complex	24	44	15
7	*m*CPBA	96	3	1

[a] Isolated yields.

Commercially available 70% *tert*-butyl hydroperoxide (TBHP) in water was added to the solution of chalcone (**4**) and guanidine (**23**) in toluene. After 24 h, the corresponding epoxide (**5**) was obtained in 43% yield (run 1). The ee (30%) and the (2*R*,3*S*)-configuration of product (**5**) were determined by chiral HPLC analysis.[16] Utilization of commercially available cumene hydroperoxide (CMHP) improved ee

Table 6. Trials for Optimization of the Guanidine (**23**)-catalyzed Epoxidation of **4** with TBHP in Toluene



run	**23** (equiv.)	time (d)	temp (°C)	**5**	
				yield [a] (%)	ee (%)
1[b]	0.2	1	rt	33	49
2	0.2	1	50	68	45
3	0.2	4	rt	67	45
4	1	1	rt	55	47

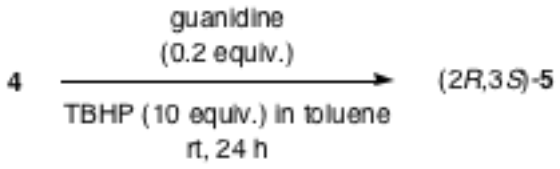
[a] Isolated yields. [b] The data of run 3 in Table 5.

(run 2). Purified hydroperoxides in toluene[16] were applied and the selectivities were further improved (runs 3 and 4). Hydrogen peroxides, both as an aqueous solution and as a complex with urea, lowered enantioselectivities (runs 5 and 6). The reaction was sluggish when *m*-chloroperoxybenzoic acid (*m*CPBA) was used (run 7). From these results, we chose TBHP in toluene as a standard oxidant and tried to optimize this epoxidation reaction (Table 6).

Elevating reaction temperature from rt to 50 °C, prolongation of reaction time, and increasing the amount of guanidine (**23)** led to increment of chemical yield, but did not affect to ee (runs 2-4). Thus, our attention was turned to the epoxidation using different kinds of chiral guanidines (Table 7).

Increasing number of methyl substituents on the imidazolidine nitrogens in guanidine (**23**) lowered not only reaction rate but also the selectivity (runs 2 and 3). Guanidine (**25**), a diastereomer of **23** with enantiomeric substituent on the external nitrogen of guanidine skeleton, gave **5** in the same asymmetric induction that **23** did (run 4). Interestingly, similar to Michael reaction discussed above, chirality of **5** was controlled by the absolute configuration of the imino substituent in the case of guanidines with hydroxyethyl moitey (**14**, **17** and **18**) (runs 5-7). Guanidine (**26**) with 1-naphthyl group instead of phenyl group showed almost same ee (run 8). Utilization of the NH-guanidines, which possess 2-hydroxyethyl (**27**), and 2-(*tert*-butyldimethylsilyloxy)ethyl moiety (**28**), ethyl (**29**), cyclohexyl (**30**), and benzyl functions (**31**), enhanced chemical yields; however improvement of ee was not observed in each case (runs 9-13).

Table 7. Trials for Epoxidation of **4** with TBHP in Toluene in the Presence of Various Types of Guanidines



run	guanidine	**5**		run	guanidine	**5**	
		yield [a] (%)	ee (%)			yield [a] (%)	ee (%)
1[b]	**23**	33	49	8	**26**	49	41
2	**24**	17	7	9	**27**	96	23
3	**10**	20	6	10	**28**	90	22
4	**25**	44	46	11	**29**	78	31
5	**14**	36	32 [c]	12	**30**	59	34
6	**17**	35	22	13	**31**	59	37
7	**18**	49	41 [c]				

[a] Isolated yield. [b] The data of run 3 in Table 5. [c] An enantiomer was formed.

MECHANISTIC CONSIDERATION FOR CHIRAL INDUCTIONS

It is found that the NMe-guanidine (**14**), which possesses a (2-hydroxy-1-benzyl)ethyl moiety, was suitable as a catalyst for enantioselective Michael reaction of cyclopentenone (**1**) with dibenzyl malonates (**2**), and that NH-guanidine (**23**) with 1-phenylethyl moiety was the best catalyst for epoxidation of chalcone (**4**). Simple MM2 calculation (Chem3D) approach to ureas (**35** and **36**), the precursors of these guanidines (**14** and **23**), allowed us to speculate possible transition states. Two phenyl groups located at 4 and 5 positions of imidazolidine ring share pseudoaxial positions each other because of steric repulsion between the phenyl and the N-Me groups in **35**. As a result, the two phenyl rings are perpendicular to the imidazolidine ring in **35**. On the other hand, no steric repulsion causes them to locate in pseudoequatrial positions in **36** which takes rather flat conformation than **35** (Figure 2). These situations can be supported by the difference of chemical shifts of phenyl group in the ^{1}H-NMR spectrum of each compound [7.12-7.15 (4H, m), 7.32-7.37 (6H, m) in **35**, 7.27-7.38 (10H, m) in **36**].[17]

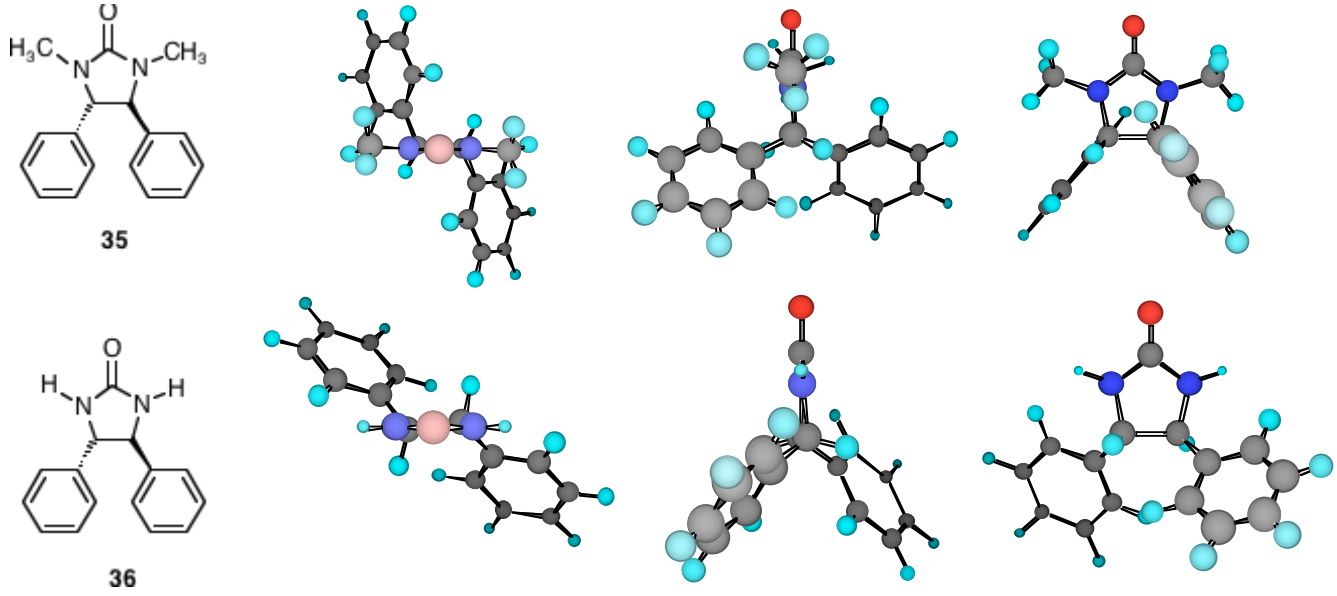


Figure 2. Optimized Structures of Ureas (**35** and **36**) by MM2 Calculation. From the Left, Top, Side, and Front Views.

From these results, mechanism of chiral induction in Michael reaction of **1** with **2a** catalyzed by **14** is considered as follows. Malonate anion would be tightly complexed with guanidinium salt *via* two hydrogen bonds between the carbonyl oxygen of **2a** and the hydroxy group of **14**, and between the enolate oxygen and the guanidinium proton. In addition each phenyl ring of **2a** and **14** could be interacted through π-π interaction (Figure 3). Under this situation *re*-face of **1** will approach from top side to the malonate unit of the complex by the aid of another hydrogen bond formation between the hydroxy group of **14** and the carbonyl oxygen of **1** to furnish (*R*)-**3a** as a major enantiomer.

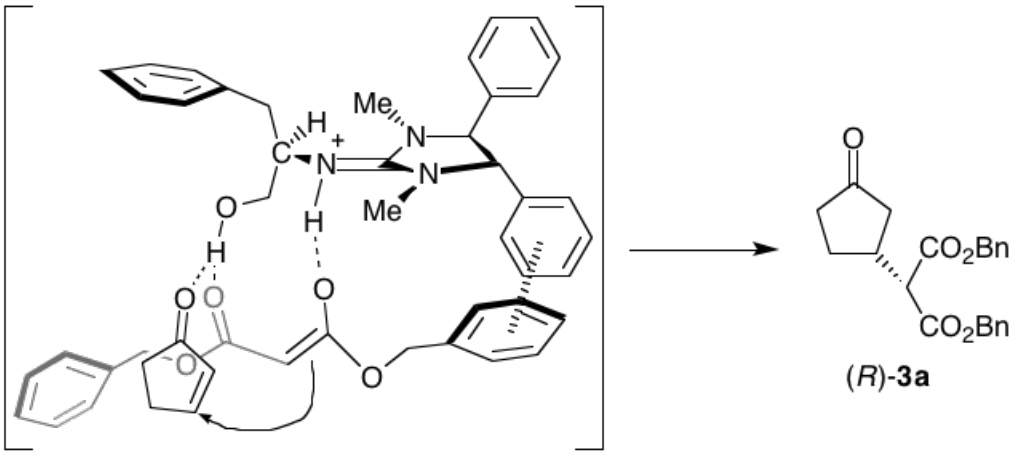


Figure 3. Proposed Mechanism for Chiral Induction of Cyclopentenone (**1**) with Dibenzyl Malonate (**2a**) Catalyzed by Guanidine (**14**).

In the case of the guanidine (**23**)-catalyzed epoxidation of chalcone (**4**) with TBHP, it could be reasonably supposed that the acid-base interaction between TBHP and **23** forms a seven-membered ring through two hydrogen bonds (Figure 4). The bottom side of the TBHP unit in the complex is shielded with the phenyl group of **23** close to the seven-membered ring. So, *si*-face at β position of **4** will approach from top side of this complex by the aid of hydrogen bond between the carbonyl oxygen of **4** and hydrogen on guanidine to furnish (2*R*,3*S*)-**5** as a major enantiomer.

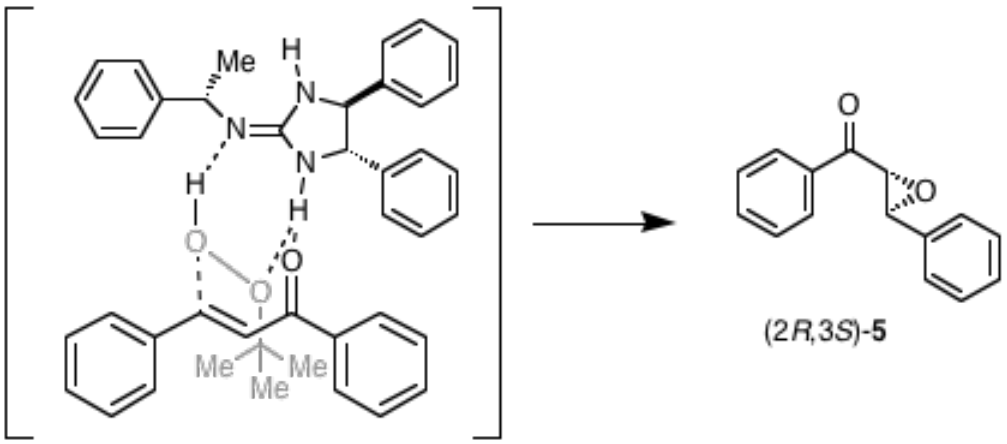


Figure 4. Proposed Mechanism for Chiral Induction of the Guanidine (**23**)-catalyzed Epoxidation of Chalcone (**4**) with TBHP

CONCLUSION

In summary, it was found that modified guanidines catalyzed the asymmetric Michael reaction of cyclopentenone (**1**) with dibenzyl malonates (**2**) and the epoxidation of chalcone (**4**) even not satisfactory results. Interestingly, in the former reaction, reaction was accelerated under solvent-less conditions.

These guanidine-catalyzed asymmetric synthesis could contribute to development of green chemistry,[14] because modified guanidines are considered to be re-useable (economically favored) and easily functionalizable (widely applicable) artificial organic bases.

EXPERIMENTAL

General Experimental Procedures. IR spectrum was recorded on a JASCO IR-700 Infrared Spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were recorded on a JEOL JNM GSX-300 spectrometer (300 MHz for ^{1}H, 75 MHz for ^{13}C) in $CDCl_3$. High resolution fast-atom bombardment mass (HRFABMS) spectrum was recorded on a JEOL JMS-HX110A mass spectrometer with a direct inlet system. Specific rotation, $[\alpha]_D$, was recorded on a JASCO DIP-140 digital polarometer in $CHCl_3$. High performance liquid chromatography (HPLC) was performed on a Shimadzu CLASS-LC-10/M10A. For column chromatography, silica gel 60 (Merck, 70-230 mesh) and FL-100D (Fuji Silysia) were used.

***N,N',N''*-Tris[(*S*)-1-phenylethyl]guanidine (6).** This compound was prepared from carbodiimide (**32**[3c]) and (*S*)-1-phenethylamine following the procedure reported in reference 3c. A colorless oil: IR (KBr) ν (cm^{-1}): 3430, 1635; ^{1}H-NMR δ (ppm): 1.31 (3H, d, *J* = 6.2 Hz), 1.41 (6H, d, *J* = 6.6 Hz), 4.51 (3H, brs), 6.75 (3H, brs), 7.15-7.26 (9H, m); ^{13}C-NMR δ (ppm): 25.12, 52.34, 125.98, 126.34, 128.23, 146.44, 149.31; HRFABMS *m/z*: 372.2407, calcd for $C_{25}H_{30}N_3$: 372.2440; $[\alpha]^{21}_D$ +209.5° (*c* 1.0).

(4*S*,5*S*)-2-[(1*S*)-1-Benzyl-2-(*tert*-butyldimethylsilyl)ethylimino]-4,5-diphenylimidazolidine (27) and (4*S*,5*S*)-2-[(1*S*)-1-Benzyl-2-hydroxyethylimino]-4,5-diphenylimidazolidine (28). These compounds were prepared by hydrolysis of carbamates (**33**[3c] and **34**[3c]) following the procedure reported in reference 3b. **27**: amorphous mass: IR (KBr) ν (cm^{-1}): 1620, 1550; ^{1}H-NMR δ (ppm): 0.05 (3H, s), 0.66 (3H, s), 0.92 (9H, s), 2.86 (1H, dd, *J* = 13.4, 7.5 Hz), 2.97 (1H, dd, *J* = 13.4, 6.2 Hz), 3.65 (1H, dd, *J* = 9.7, 3.7 Hz), 3.74 (1H, dd, *J* = 9.7, 4.4 Hz), 3.77 (3H, m), 4.44 (2H, br s), 7.17-7.30 (15H, m); ^{13}C-NMR δ (ppm): -5.40, -5.35, 18.35, 25.97, 38.45, 56.26, 64.66, 126.30, 126.52, 127.32, 128.46, 129.57, 139.04, 143.46, 159.83; HRFABMS 486.2925, calcd for $C_{30}H_{40}N_3OSi$: 486.2941; $[\alpha]^{21}_D$ –73.6° (*c* 1.0). **28**: amorphous mass; IR (KBr) ν (cm^{-1}): 3270, 1610; ^{1}H-NMR δ (ppm): 2.58 (1H, dd, *J* = 13.5, 8.6 Hz), 2.68 (1H, dd, *J* = 13.5, 5.5 Hz), 3.41 (1H, dd, *J* = 11.2, 6.8 Hz), 3.54 (1H, d, *J* = 11.2 Hz), 3.62-3.73 (1H, m), 4.24 (2H, m), 5.67 (3H, br s), 7.02-7.19 (15H, m); ^{13}C-NMR δ (ppm): 38.15, 56.93, 65.27, 72.13, 126.19, 126.29, 127.21, 128.32, 128.36, 129.18, 138.64, 142.97, 161.33; *Anal.* Calcd for $C_{24}H_{25}N_3O \cdot 1/3H_2O$: C, 76.36; H 6.85; N, 11.33. Found: C, 76.40; H; 6.80; N; 10.92; $[\alpha]^{21}_D$ –57.3° (*c* 1.0).

General procedure for Michael reaction of cyclopentenone (1) with dibenzyl malonate (2a) in the presence of chiral guanidine (14) (run 9 in Table 1). A mixture of **1** (70 mg, 0.86 mmol), **2a** (202 mg, 0.71 mmol) and **14** (201 mg, 0.50 mmol) in $CHCl_3$ (10 mL) was refluxed for 16 days. After cooling to rt, AcOEt was added and the whole was washed with 10% HCl and brine and dried over $MgSO_4$. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (SiO_2, hexane-Et_2O = 1 : 1) to give **3a** as a colorless oil (167 mg, 65%). **3a** was converted to corresponding dioxolane derivative,[9] which was subjected to chiral HPLC analysis (CHIRALCEL OD, hexane – 2-propanol = 40 : 1, 1.0 mL/min, 254 nm) to be 43% ee. The former peak, which was assigned as (*R*)-isomer, is major product.

General procedure for epoxidation of chalcone (4) and TBHP in toluene in the presence of chiral guanidine. To a toluene solution (0.2 mL) of chalcone (*ca.* 30 mg, 0.14 mmol) and chiral guanidine (0.2 equiv.), a toluene solution of TBHP (0.2 mL, 10 equiv.) was added at rt and the whole was stirred at rt for 24 h. The reaction was quenched with 10% aq. Na_2SO_3 and was extracted with AcOEt. Organic layer was washed with sat. aq. $NaHCO_3$, H_2O and brine and dried over $MgSO_4$. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (SiO_2, hexane – AcOEt = 10 : 1) to give **5** as colorless prisms which was subjected to chiral HPLC analysis (CHIRALCEL OD, hexane – 2-propanol = 40 : 1, 1.0 mL/min, 254 nm). The latter peak, which was assigned as (2*R*,3*S*)-isomer, is major product.

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REFERENCES AND NOTES

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1. M. Costa, G. P. Chiusoli, D. Taffurelli, and G. Dalmonego, *J. Chem. Soc., Perkin Trans. 1*, 1998, 1541.
2. Y. Yamamoto and S. Kojima, 'The Chemistry of Amidines and Imidates,' Vol. 2, ed. by S. Patai and Z. Rappoport, John Wiley & Sons Inc., New York, 1991. p. 485.
3. (a) T. Isobe, K. Fukuda, and T. Ishikawa, *J. Org. Chem.*, 2000, **65**, 7770; (b) T. Isobe, K. Fukuda, T. Tokunaga, H. Seki, K. Yamaguchi, and T. Ishikawa, *J. Org. Chem.*, 2000, **65**, 7774; (c) T. Isobe, K. Fukuda, K. Yamaguchi, H. Seki, T. Tokunaga, and T. Ishikawa, *J. Org. Chem.*, 2000, **65**, 7779.
4. T. Isobe, K. Fukuda, and T. Ishikawa, *Tetrahedron: Asymmetry,* 1998, **9**, 1729.

5. Recent reviews, see: M. Kanai and M. Shibasaki, 'Catalytic Asymmetric Synthesis,' 2nd ed., ed. by I. Ojima, Wiley, New York, 2000, p. 569; K. Tomioka and Y. Nagaoka, 'Comprehensive Asymmetric Catalysis,' ed. by E. N. Jacobsen, A. Pfaltz, and H. Yamamoto, Vol. 3, Chapter 31.1, Springer, Berlin, 1999.
6. (a) V. Alcázar, J. R. Morán, and J. de Mendoza, *Tetrahedron Lett*., 1995, **36**, 3941; (b) D. Ma and K. Cheng, *Tetrahedron: Asymmet*ry, 1999, **10**, 713; (c) A. Howard-Jones, P. J. Murphy, D. A. Thomas, and P. W. R. Caulkett, *J. Org, Chem*., 1999, **64**, 1039.
7. T. Ishikawa and T. Isobe, *Chem. Eur. J*., 2002, **8**, 552.
8. T. Ishikawa, Y. Araki, T. Kumamoto, H. Seki, K. Fukuda, and T. Isobe, *Chem. Commun*., 2001, 245.
9. Y. S. Kim, S. Matsunaga, J. Das, A. Sekine, T. Ohshima, and M. Shibasaki, *J. Am. Chem. Soc*., 2000, **122**, 6506.
10. A. Kawara and T. Taguchi, *Tetrahedron Lett*., 1994, **35**, 8805.
11. G. Manickam and G. Sundararajan, *Tetrahedron: Asymmetry*, 1997, **8**, 2271.
12. For examples, see (a) K. Tanaka and F. Toda, *Chem. Rev*., 2000, **100**, 1025; (b) V. K. Aggarwal and A. Mereu, *Chem. Commun*., 1999, 2311; (c) J. O. Metzger, *Angew. Chem., Int. Ed. Engl*., 1998, **37**, 2975.
13. (a) S. Juliá, J. Masana, and J. C. Vega, *Angew. Chem., Int. Ed. Engl*., 1980, **19**, 929; (b) for a review, see: C. Laurent and S. M. Roberts, *Aldrichimica Acta*, 2002, **35**, 47.
14. (a) R. Helder, J. C. Hummelen, R. W. P. M. Laane, J. S. Wiering, and H. Wynberg, *Tetrahedron Lett*., 1976, 1831; (b) B. Lygo and P. G. Wainwright, *Tetrahedron Lett*., 1998, **39**, 1599; (c) S. Arai, H. Tsuge, and T. Shioiri, *Tetrahedron Lett*., 1998, **39**, 7563; (d) E. J. Corey and F. Y. Zhang, *Org. Lett*., 1999, **1**, 1287; (e) T. Ooi, D. Ohara, M. Tamura, and K. Maruoka, *J. Am. Chem. Soc*., 2004, **126**, 6844.
15. (a) D. Enders, J. Zhu, and G. Rabbe, *Angew., Chem. Int. Ed. Engl*., 1996, **35**, 1725; (b) H.-B. Yu, X.-F. Zheng, Z.-M. Lin, Q.-S. Hu, W.-S. Huang, and L. Pu, *J. Org. Chem*., 1999, **64**, 8149; (c) C. L. Elston, R. F. W. Jackson, S. J. F. MacDonald, and P. J. Murray, *Angew. Chem., Int. Ed. Engl*., 1997, **36**, 410; (d) T. Nemoto, T. Ohshima, K. Yamaguchi, and M. Shibasaki, *J. Am. Chem. Soc*., 2001, **123**, 2725.
16. M. Bougauchi, S. Watanabe, T. Arai, H. Sasai, and M. Shibasaki, *J. Am. Chem. Soc*., 1997, **119**, 2329.
17. The difference of chemical shifts of phenyl group of **14** and **23** was not observed because of overlap of another phenyl group on imino substituent.
18. P. T. Anastas and J. C. Warner, '*Green Chemistry: Theory and Practice*,' Oxford University Press, Oxford, 1998.