Rational Design of Minimal Artificial Diels–Alderases Based on the Copper(II) Cation–Aromatic π Attractive Interaction

KAZUAKI ISHIHARA,*,† MAKOTO FUSHIMI,† AND MATSUJIRO AKAKURA‡

Graduate School of Engineering, Nagoya University, Furo-cho, Chikusa, Nagoya 464-8603, Japan, and Department of Chemistry, Aichi University of Education, Igaya-cho, Kariya 448-8542, Japan

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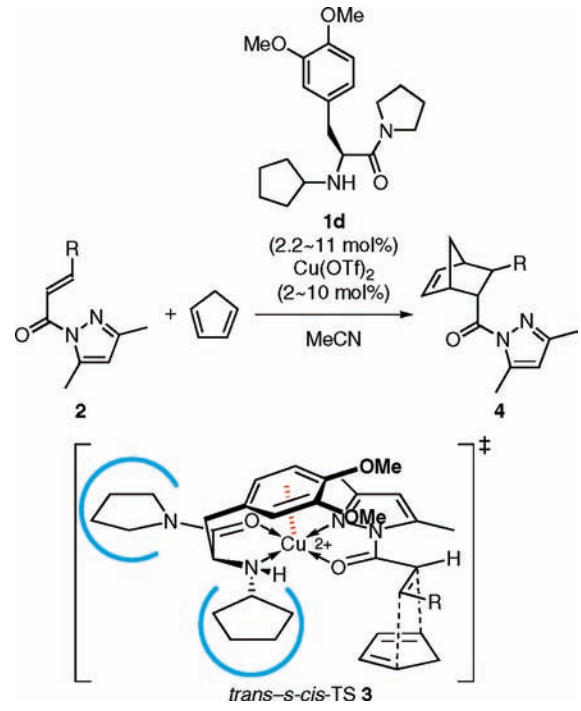
ABSTRACT

We have designed a minimal artificial metalloenzyme that is prepared *in situ* from $Cu(OTf)_2$ or $Cu(NTf_2)_2$ (1.0 equiv) and L-DOPA-derived monopeptide (1.1 equiv) based on the cation–π attractive interaction between copper(II) and the aromatic arm of the ligand, which is postulated on the basis of X-ray diffraction analysis and theoretical calculations. This catalyst (2–10 mol %) is highly effective for not only the enantioselective Diels–Alder reaction with α,β-unsaturated 1-acyl-3,5-dimethylpyrazoles but also the enantioselective Mukaiyama–Michael reaction with these compounds. Products bearing a 3,5-dimethylpyrazolyl auxiliary may be transformed into a range of carboxylic acid derivatives, such as the corresponding carboxylic acids, esters, amides, alcohols, aldehydes, ketones, and β-ketoesters, by known methods. The present results demonstrate that monopeptides are chirally economical and readily tunable ligands compared to bis(oxazoline)s, which have been reported to be notably useful ligands in various enantioselective reactions with bidentate electrophiles.

Introduction

The rational design of small-molecule asymmetric catalysts is an important subject in the development of economical and practical organic syntheses. We have been interested in designing minimal artificial enzymes from natural L-amino acids, which enantioselectively catalyze synthetically useful organic reactions.[1–3]

Scheme 1. Enantioselective DA Reaction Induced by 1d•Cu(OTf)$_2$ and Transition-State Assembly 3 Proposed on the Basis of the Cation–π Interaction



The existence of natural Diels–Alderases has been established by several research groups.[4] In 2003, Oikawa, Tanaka, and their co-workers reported the crystal structure of a Diels–Alderase, fungal macrophomate synthase (MPS), in complex with pyruvate.[5] MPS is a Mg^{II}-dependent enzyme with 399 amino acid residues [relative molecular mass (M_r) = 36 244].[5] Recently, we reported a small-molecule chiral catalyst, L-DOPA-derived monopeptide (**1d**)•copper(II) complex (M_w = 708), for the enantioselective Diels–Alder (DA) and Mukaiyama–Michael (MM) reactions with α,β-unsaturated 1-acyl-3,5-dimethylpyrazoles (**2**) (Scheme 1).[6] To the best of our knowledge, this may be the first example of the use of the intramolecular metal cation–aromatic π interaction in the design of chiral metal catalysts.[7] This Account summarizes the rational

* To whom corresdpondence should be addressed. Fax: +81-52-789-3222. E-mail: ishihara@cc.nagoya-u.ac.jp.
† Nagoya University.
‡ Aichi University of Education.

Kazuaki Ishihara was born in 1963 in Aichi, Japan, and received his Ph.D. degree from Nagoya University in 1991 under the direction of Professor Hisashi Yamamoto. He had worked under Professor Clayton H. Heathcock at the University of California, Berkeley, as a visiting graduate student for 3 months in 1988. He was a JSPS Fellow under the Japanese Junior Scientists Program from 1989 to 1991. After he completed his postdoctoral studies with Professor E. J. Corey at Harvard University for 15 months beginning in 1991, he returned to Japan and joined Professor Hisashi Yamamoto's group at Nagoya University as an Assistant Professor in 1992 and was made an Associate Professor in 1997. In 2002, he was appointed to his current position as a Full Professor at Nagoya University. He has received the Inoue Research Award for Young Scientists (1994), the Chemical Society of Japan Award for Young Chemists (1996), the Thieme Chemistry Journal Award (2001), the Green & Sustainable Chemistry Award from the Ministry of Education, Culture, Sports, Science, and Technology (2003), a JSPS Prize (2005), a BCSJ Award (2005), and the 0th International Conference on Cutting-Edge Organic Chemistry in Asia Lectureship Award (2006), and the Japan/UK GSC Symposium Lectureship Award (2007). His research interests include asymmetric catalysis, biomimetic catalysis induced by artificial enzymes, dehydrative condensation catalysis toward green and sustainable chemistry, and acid–base combination chemistry.

Makoto Fushimi was born in 1979 in Aichi, Japan. He received his Master of Engineering degree in chemistry from Nagoya University in 2005 under the direction of Professor Kazuaki Ishihara. He is currently carrying out his Ph.D. study in the same group. His Ph.D. research focuses on the design of artificial enzymes that are prepared from Lewis acids and amino-acid-derived monopeptides.

Matsujiro Akakura was born in 1968 in Osaka, Japan, and received his Ph.D. degree from Nagoya University in 1998 under the direction of Professor Hisashi Yamamoto. He worked under Professor Andrew R. Barron at Rice University as a visiting graduate student for 3 months in 1996. He became Assistant Professor in 1998 at Aichi University of Education and was made an Associate Professor in 2003. His current research interests include the design of reaction catalysis using computational calculation, the theoretical study of reaction mechanisms, and estimation of the chemical properties of new products.

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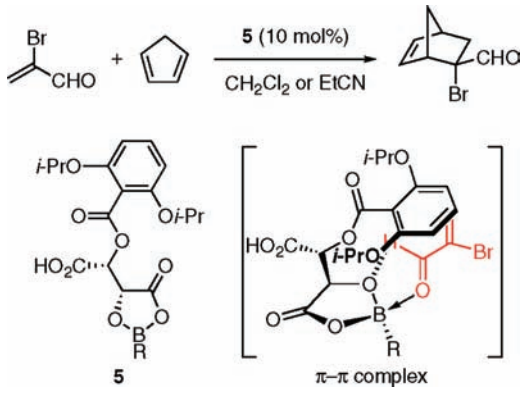
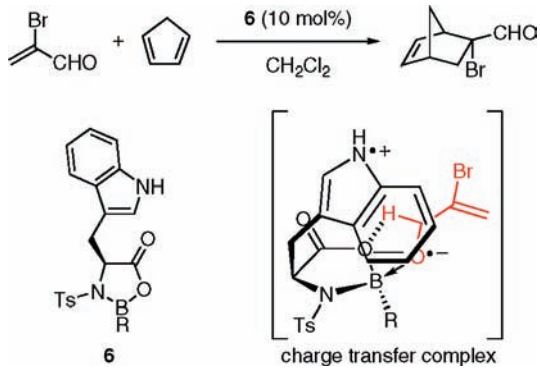
Scheme 2. Enantioselective DA Reaction Induced by 5



Scheme 3. Enantioselective DA Reaction Induced by 6



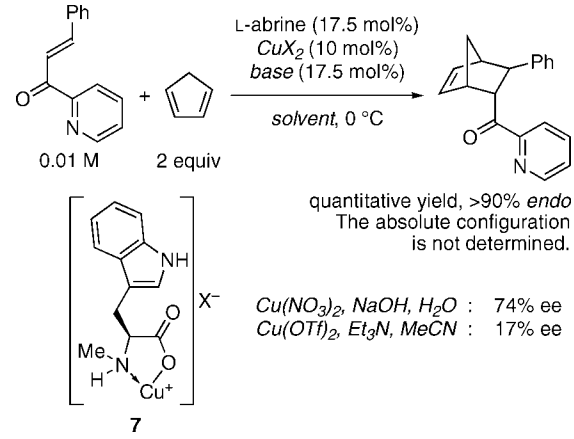
design of minimal DA catalysts based on the metal cation–π interaction. There is an emphasis on our own work because the space limitations of *Accounts of Chemical Research* prevent a comprehensive review. Similarly, we do not provide a detailed comparison with other asymmetric copper(II) catalysts, such as copper(II)•chiral bis(oxazoline)s.[8]

Design of Asymmetric Diels–Alder Catalysts Based on the π–π or Charge-Transfer Attractive Interaction

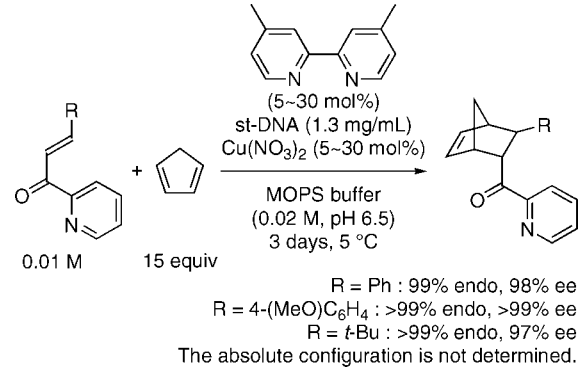
In 1988, Yamamoto's group developed chiral acyloxyborane (CAB) catalyst (**5**) derived from 2,6-di(isopropoxy)benzoyl L-tartaric acid and borane•tetrahydrofuran (THF) for the enantioselective DA reaction of dienes with acrylic acid.[9a] This catalyst is effective for not only acrylic acid but also α,β-alkenals[9b,d] and α,β-alkynals (Scheme 2).[9e] In 1993, Yamamoto and we established, by the use of the difference of nuclear Overhauser enhancement (NOE) measurements, that effective shielding of the *si* face of the **5**-coordinated α,β-alkenal arises from π–π stacking between the 2,6-diisopropoxybenzene ring and the coordinated aldehyde.[9c]

In 1991, Corey's group developed chiral oxazaborolidine catalyst **6** derived from *N*-(*p*-toluenesulfonyl)-L-tryptophan and borane•THF or butylboronic acid for the enantioselective DA reaction of α-bromoacrolein with dienes (Scheme 3).[10a] It has been ascertained by ^{1}H 2D nuclear Overhauser effect spectrometry (NOESY) studies that the high enantioselectivity is induced by the attractive interaction between the π-donor indole ring and the coordinated aldehyde.[10b] Judging from the bright orange–red color of the complex of **6** with methacrolein, this attractive interaction may originate because of charge-transfer complexation, which is stronger than the π–π attractive interaction.

Scheme 4. Enantioselective DA Reaction Induced by 7



Scheme 5. Enantioselective DA Reaction Induced by the DNA-Based Copper(II) Catalyst



In 1998, Engberts' group reported that the DA reaction of cyclopentadiene (CP) with 3-phenyl-1-(2-pyridinyl)-2-propen-1-one is enantioselectively induced by $Cu(NO_3)_2$ and the sodium salt of L-abrine (*N*-methyl-L-tryptophan) or *N*-methyl-L-tyrosine in water (Scheme 4).[11] In this reaction, water enhances the enantioselectivity up to 74% enantiomeric excess (ee). On the other hand, the enantioselectivity is reduced to ~17–44% ee in organic solvents, such as acetonitrile, THF, ethanol, and chloroform. The absolute configuration of the DA adduct has not yet been determined. Only one successful example is reported in the literature.[11] Their catalysts have not yet been shown to be synthetically useful with regard to enantioselectivity or the range of substrates. Their work focused on a proof of concept with enantioselectivity enhanced in water and was not intended to find the most selective catalyst. His group suggested that the π–π attractive interaction between the indole group in L-abrinate and the dienophile is important for asymmetric induction in their aqueous DA reaction catalyzed by [L-(abrinato)Cu^{II}]X (**7**).

On the basis of the reports by Engberts' group,[11] Roelfes and Feringa recently developed DNA-based copper(II) catalysts,[12] in which chirality is transferred directly from DNA to the catalyzed DA reactions of CP with 3-aryl- or

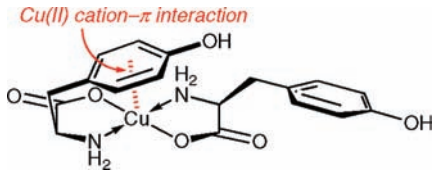


FIGURE 1. Crystal structure of the bis(L-tyrosinato)copper(II) complex.

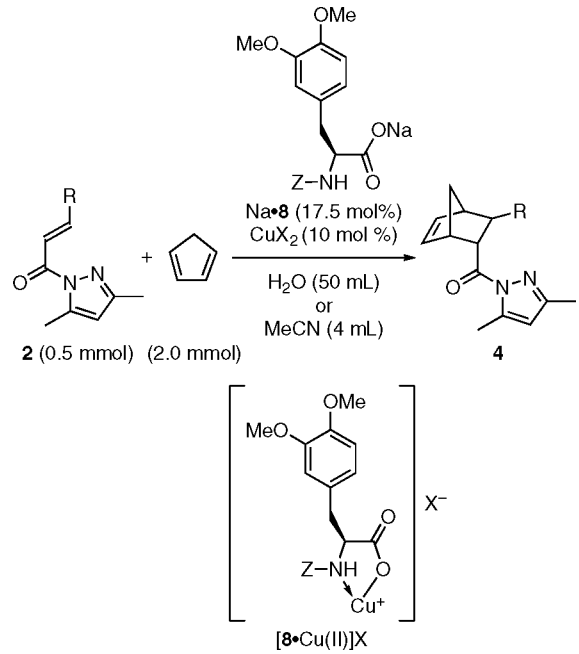
3-alkyl-1-(2-pyridinyl)-2-propen-1-ones (Scheme 5).[12b] The DNA-based catalyst consists of $Cu(NO_3)_2$ (~5–30 mol %), 4,4′-dimethyl-2,2′-bipyridine (~5–30 mol %), and salmon testes DNA (st-DNA) (1.3 mg/mL) in the presence of 3-(*N*-morpholino)propanesulfonic acid (MOPS) buffer (pH 6.5). *This means that 1300 mg of st-DNA and 100 mL of water are required for the DA reaction of 1 mmol of a dienophile (0.01 M).* The *endo*-adducts, which are produced almost exclusively, are obtained with ~97–99% ee. This is considerably higher than the results with L-(abrinato)copper(II) complexes.[10] Because the copper(II) complex with 4,4′-dimethyl-2,2′-bipyridine is achiral, this result demonstrates the direct transfer of chirality from DNA to the catalyzed DA reaction. As a result, the active copper(II) center is brought into the proximity of the chiral environment of the DNA double helix.

Design of Asymmetric Diels–Alder Catalysts Based on the Copper(II) Cation–π Attractive Interaction

Cation–π interactions between metal cations and aromatic arms of natural amino acids, such as L-phenylalanine, tyrosine, and tryptophan, are known to play an important role in biological systems.[13] The crystal structure of the bis(L-tyrosinato)copper(II) complex has been determined by van der Helm's group (Figure 1).[14a] They observed the intramolecular weak cation–π attractive interaction between the copper(II) ion and one of the phenolic rings of tyrosinates. The intermolecular cation–π interaction of the L-(trypthophyl-glycinato)copper(II) complex has also been reported.[15] Although Engberts' group suggested that the π–π attractive interaction between the indole group of L-abrinate and dienophile is important for asymmetric induction in their aqueous DA reaction catalyzed by **7**, we anticipated that the origin of the asymmetric induction might be the intramolecular cation–π interaction between the copper(II) cation and the indole ring. Although we can not completely exclude the possibility that distortions from rigorous square planarity may induce the π–π interaction, it seems that the cation–π interaction should be conformationally preferable in **7**, which is generally characterized by a square planar geometry. Thus, we studied the development of a new and minimal copper(II)–aromatic amino acid derivative catalyst, which induces enantioselectivity by the intramolecular cation–π interaction directed toward a practical synthetic methodology.

On the basis of the pioneering studies by Engberts' group,[11] we explored the enantioselective DA reaction of CP with α,β-unsaturated 1-acyl-3,5-dimethylpyrazoles **2**,[16] as more synthetically valuable dienophiles induced by

Table 1. [8•Cu^{II}]X-Induced DA Reaction of CP with 2



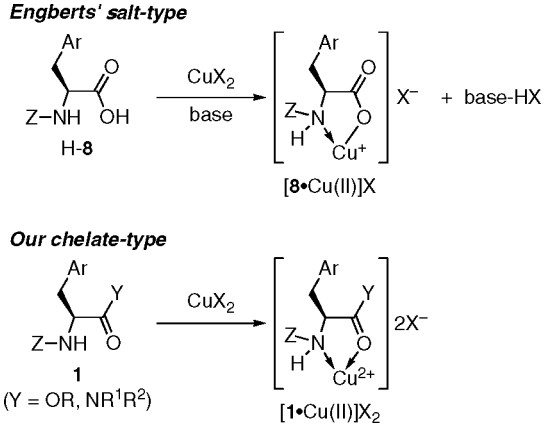
entry	**8** [Z]	**2** [R]	solvent	temperature (°C), time (h)	**4**,[a] yield (%)	ee (%)[b]
1[c]	**8a** [Pr]	**2a** [H]	H_2O	0, 2	**4a**, 88	85
2[c]	**8a** [Pr]	**2b** [Me]	H_2O	2, 3 + 8[d]	**4b**, 3[e]	72
3[f]	**8a** [Pr]	**2a** [H]	MeCN[g]	−40, 13	**4a**, >99	78
4[f]	**8b** [c-C_5H_9]	**2a** [H]	MeCN[g]	−40, 13	**4a**, >99	92
5[f]	**8b** [c-C_5H_9]	**2b** [Me]	MeCN[g]	3, 20	**4b**, 24[h]	76

[a] The *endo*/*exo* ratio was >90:10. [b] ee of *endo*-**4**. [c] H-**8**, 17.5 mol %; $Cu(NO_3)_2$•2.5H_2O, 10 mol %; NaOH, 7.5 mol %. [d] At 0 °C for 3 h and then at 23 °C for 8 h. [e] **2b** was hydrolyzed. [f] H-**8**, 15 mol %; $Cu(OTf)_2$, 10 mol %; Et_3N, 15 mol %. [g] MeCN (wet) was used. [h] **2b** remained.

[**8**•Cu^{II}]NO_3 in water (Table 1). The DA reaction was heterogeneously carried out under a high dilution condition ([**2**] = 0.01 M) because of the poor solubility of **2** in water. The *N*-alkyl substituent of L-DOPA as well as L-abrine was highly effective for increasing the enantioselectivity. The ee of *endo*-(2*S*)-**4a** was increased up to 85% ee with the use of [**8a**•Cu^{II}]NO_3 in water (entry 1). However, the DA reaction with 1-crotonoyl-3,5-dimethylpyrazole (**2b**) gave only a trace amount of *endo*-(2*S*)-**4b** with 72% ee because **2b** was predominantly hydrolyzed (entry 2).

In general, [L-(α-aminoacylato)Cu^{II}]X is insoluble in aprotic solvents and a high dilution condition is undesirable for scale-up, but {[α-(*N*-alkylamino)acylato]Cu^{II}}X was soluble in acetonitrile even at −40 °C. To prevent the hydrolysis of **2** and to concentrate the reaction mixture, the DA reaction with **2** was performed in the presence of 10 mol % of [**8**•Cu^{II}]OTf in wet acetonitrile ([**2**] = 0.125 M) at −40 °C. Fortunately, the DA reaction with **2a** proceeded quantitatively to give *endo*-(2*S*)-**4a** with 78% ee (entry 3). This enantioselectivity was comparable to the results achieved by Engberts in acetonitrile (17% ee, Scheme 4).[11] The use of *N*-cyclopentyl ligand Na•**8b** gave *endo*-(2*S*)-**3a** with 92% ee (entry 4). In contrast to entry 2, **2b** reacted to afford *endo*-(2*S*)-**3b** with 76% ee without hydrolysis, but its reactivity was still very low (entry 5).

Scheme 6. Rational Design of Copper(II)•L-Amino Acid Derivative Catalysts for the Enantioselective DA Reaction



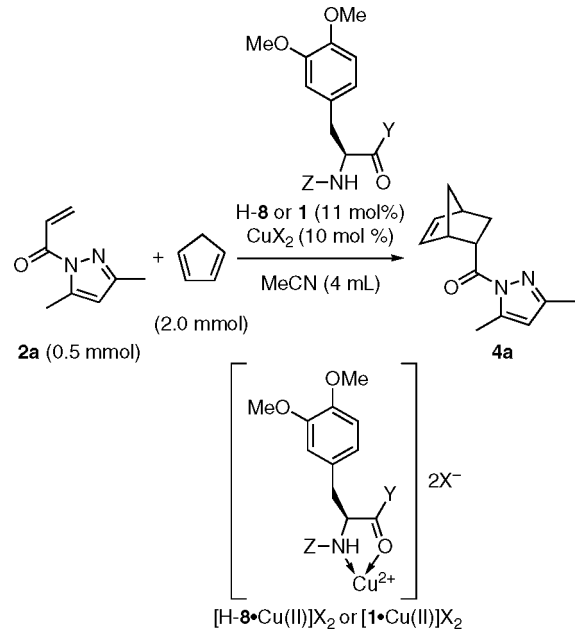
Engberts' salt-type catalyst [**8**•Cu^{II}]X is prepared from CuX_2 and the sodium salt of L-amino acid H-**8**. If a new chelate-type catalyst [**1**•Cu^{II}]X_2 is prepared from CuX_2 and L-amino ester or L-monopeptide **1** in place of H-**8** in the absence of base, the latter complex should be more enhanced than the former with regard to the catalytic activity and cation–π interaction, because of the more cationic nature of the copper(II) center in the latter complex (Scheme 6).

As expected, [H-**8b**•Cu^{II}]$(OTf)_2$ prepared from H-**8b** and $Cu(OTf)_2$ in the absence of Et_3N was more active than [**8b**•Cu^{II}]OTf (entry 4, Table 1) in acetonitrile and gave *endo*-(2*S*)-**4a** with 87% ee (entry 1, Table 2). Thus, Y of **1** was further screened to attain higher enantioselectivity under homogeneous conditions in acetonitrile (Table 2). Isopropyl ester **1c** was less effective than the corresponding acid H-**8b** with regard to enantioselectivity and catalytic activity (entry 2). On the other hand, pyrrolidine monopeptide **1d** was extremely effective and gave *endo*-(2*S*)-**4a** with 97% ee (entry 3). [**1d**•Cu^{II}]$(OTf)_2$ was sufficiently active even at −78 °C to give *endo*-(2*S*)-**4a** with 98% ee in quantitative yield (entry 4).

The generality and scope of the DA reaction with **2** induced by [**1d**•Cu^{II}]$(OTf)_2$ or more active [**1d**•Cu^{II}]$(NTf_2)_2$ (~2–10 mol %) were examined in acetonitrile (Table 3). The DA reaction with not only simple dienophiles **2a–c** but also β-functionalized dienophiles **2d–f**, which were synthetically valuable, gave the DA adducts with high enantioselectivities. More reactive **2d** reacted with high enantioselectivity with not only cyclic dienes but also acyclic dienes, such as 2-methoxybutadiene (MOB), 2-phenylbutadiene (PB), isoprene (IP), and 2,3-dimethylbutadiene (DMB).

The absolute stereochemical outcome in the DA reaction induced by [**1d**•Cu^{II}]$(OTf)_2$ can be understood through our proposed transition-state assembly, *trans–s-cis*-TS **3**, shown in Scheme 1. In addition, the *N*-cyclopentyl and pyrrolidinyl groups in **1d** would sterically assist the cation–π interaction. The 3- and 5-methyl groups of **2a** would sterically control the coordination environment around the copper(II) [*cis* (disfavored) or *trans* (favored)] and the conformation of **2a** [*s-cis* (favored) or *s-trans* (disfavored)], respectively.

Table 2. [1•Cu^{II}]$(OTf)_2$-Induced DA Reaction of CP with 2a



			4a		
entry	**1** [Y, Z]	temperature (°C), time (h)	yield (%)	*endo*/*exo*	ee (%)[a]
1[b]	H-**8b** [OH, *c*-C_5H_9]	−40, 7	>99	98:2	87
2[b]	**1c** [O*i*-Pr, *c*-C_5H_9]	−40, 3.5	30	98:2	66
3[b]	**1d** [$N(CH_2CH_2)_2$, *c*-C_5H_9]	−40, 0.7	97	98:2	97
4[c]	**1d** [$N(CH_2CH_2)_2$, *c*-C_5H_9]	−78, 7	99	99:1	98

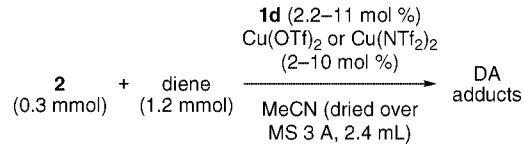
[a] ee of *endo*-**4a**. [b] MeCN (wet). [c] EtCN (dried over MS 3 A).

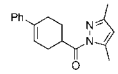
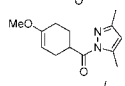
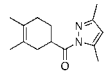
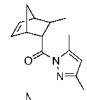
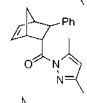
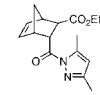
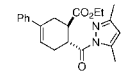
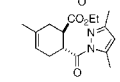
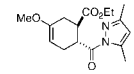
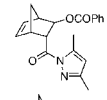
To ascertain experimentally the significance of the aromatic moiety in **1d** for asymmetric induction, the enantioselective DA reaction of DMB with 1-acryloyl-3,5-dimethylpyrazole was performed using pyrrolidine monopeptide of *N*-cyclopentyl-3-cyclohexyl-L-alanine in place of **1d** under the same conditions as entry 4 in Table 3 (Scheme 7). As expected, the enantioselectivity was diminished from 91 to 19% ee. These results also suggest that the copper(II) cation–aromatic π interaction plays an important role. Interestingly, the catalytic activity of [**1d**•Cu^{II}]OTf_2 was slightly higher than that of the control catalyst. The cationic character of Cu^{II} should be decreased because of the cation–π interaction but might be increased by releasing counter anions ($^-$OTf) from Cu^{II} at the same time. When these experimental results are taken into consideration, the cation–π interaction may contribute to the stabilization of a transition-state assembly including a diene.

Theoretical Calculations

To ascertain the possibility of the intramolecular cation–π interaction of [**1**•Cu^{II}]X_2, theoretical calculations for a 1:1:1 chelate complex of copper(II) cation, *O,N*-dimethyl-L-tyrosine *N,N*-dimethylamide, and *N*-formylpyrazole were performed using the Gaussian 98[16] and 03[17] programs. Optimization of the folded and extended geometries of the 1:1:1 complex was carried out using gradient-corrected

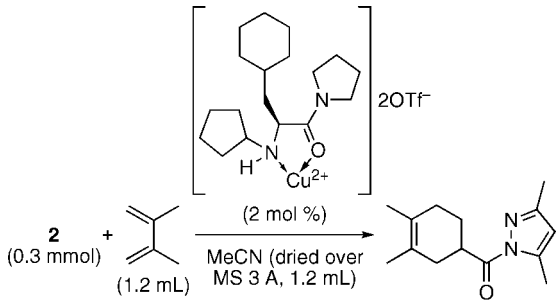
Table 3. [1d•Cu^{II}]X$_2$-Induced DA Reaction of Dienes with 2



Entry	2 [R]	diene[a]	temp. (°C), time (h)	DA adducts: major isomer	yield (%)	*endo*:*exo*	ee (%)[b] [config]
1[c]	**2a** [H]	CP	–40, 6		**4a**, >99	98 : 2	97 [2*S*]
2	**2a** [H]	PB	–40, 22		**9**, 88	>99 : 1[e]	97 [–]
3[d]	**2a** [H]	MOB	–40, 7		**10**, 85	>99 : 1[e]	97 [–]
4[f]	**2a** [H]	DMB	0, 49		**11**, 63	–	91 [–]
5[d,g]	**2b** [Me]	CP	–40, 24		**4b**, 95	97 : 3	97 [2*S*]
6[c]	**2b** [Me]	CP	0, 17.5		**4b**, 97	95 : 5	89 [2*S*]
7[d,g]	**2c** [Ph]	CP	0, 40		**4c**, 93	93 : 7	95 [–]
8[d]	**2d** [EtO$_2$C]	CP	–20, 7		**4d**, 97	91 : 9	98 [–]
9[c]	**2d** [EtO$_2$C]	CP	0, 10		**4d**, >99	88 : 12	95 [–]
10[d,g]	**2d** [EtO$_2$C]	PB	0, 39		**12**, 93	>99 : 1[e]	91 [–]
11[d,g,h]	**2d** [EtO$_2$C]	IP	23, 72		**13**, 83	93 : 7[e]	87 [–]
12[d,g]	**2d** [EtO$_2$C]	MOB	–20, 5		**14**, 96	>99 : 1[e]	97 [–]
13[d,g]	**2d** [EtO$_2$C]	DMB	0, 64		**15**, 76	–	93 [–]
14[d,g,i]	**2e** [OCOPh]	CP	23, 6		**4e**, 89	93 : 7	90 [–]
15[d,g]	**2f** [Cl]	CP	–20, 5		**4f**, 95	>99 : 1	97 [–]

[a] See the text. [b] ee of the major diastereomer. [c] **1d** (2.2 mol %)–Cu(OTf)$_2$ (2 mol %). [d] **1d** (11 mol %)–Cu(OTf)$_2$ (10 mol %). [e] The molar ratio of the four- and three-substituted diastereomers is shown. [f] DMB, 1.2 mL; MeCN, 1.2 mL. [g] Cu(NTf$_2$)$_2$ was used. [h] IP, 0.6 mL; MeCN, 0.6 mL. [i] MeCN (2.4 mL)–THF (1.2 mL).

Scheme 7. Enantioselective Diels–Alder Reaction Induced by the L-Aliphatic Monopeptide•Copper(II) Complex



density functional theory (DFT) calculations. Initially, geometrical optimization was carried out at the B3LYP level (Figure 2).[18] We chose the basis sets as follows: for Cu, Wachter's primitive set (14s9p5d),[19] supplemented with three f polarization functions[20] (Wachters+f), gave a final basis set of (14s9p5d3f)/[8s6p4d1f], and for C, N, O, and H, the standard 6–31G(d,p) basis set was used. After satisfactory geometry optimization, the vibrational spectrum of each species was calculated. As a result, the folded geometry is more stabilized than the extended one. The difference in free energy between the two geometries is 6.9 kJ/mol. The assumption that the stability of the folded geometry is due to the intramolecular cation–π interaction is reasonable, because the distance between Cu^{II} and C1 of the folded geometry and its Mulliken overlap population value are 2.860 Å and 0.114, respectively. These results strongly suggest that the enantioselective Diels–Alder reaction may proceed via a transition-state assembly including a diene, analogous to the folded geometry, which is shown by theoretical calculations.

Enantioselective Mukaiyama–Michael Reaction

A highly asymmetric induction of [**1d**•Cu^{II}](OTf)$_2$ was also observed in the enantioselective Mukaiyama–Michael reaction of silyl enol ethers (NuSiMe$_3$) with **2d**. Several examples are shown in Table 4.

Synthetic Transformation of Pyrazolyl Auxiliary

Interestingly, DA and MM adducts of **2** may be transformed into a range of carboxylic acid derivatives by treatment with appropriate nucleophiles (Scheme 8): hydrolysis,[22a] alcoholysis,[21a,c,d,21b,e] aminolysis,[21e,22a,c–e] reductive cleavage to aldehydes[22f–h] or alcohols,[2f] and alkylative cleavage to ketones[22i] or β-ketoesters.[22j]

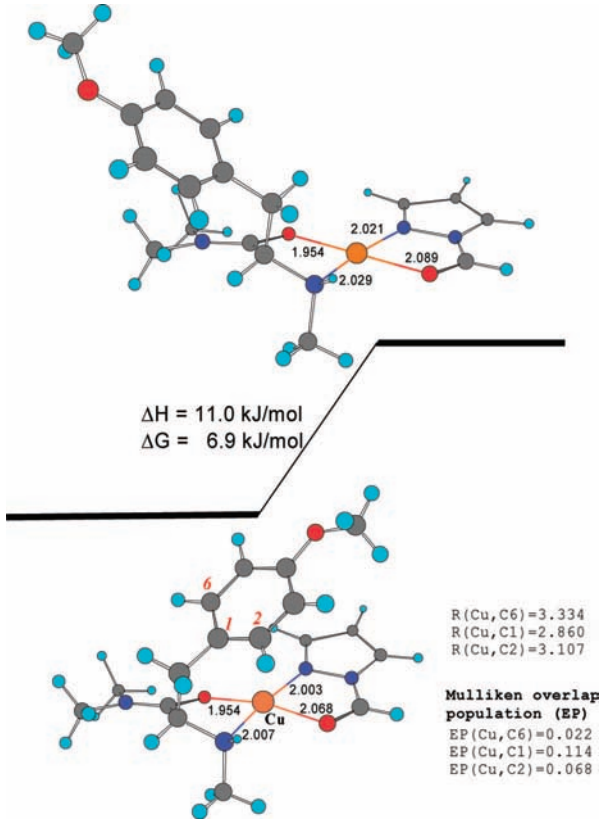
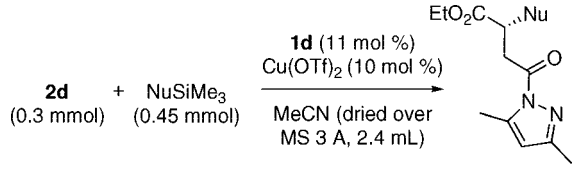
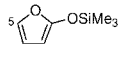


FIGURE 2. B3LYP-optimized geometries of the 1:1:1 chelate complex of copper(II) cation, *O*,*N*-dimethyl-L-tyrosine *N*,*N*-dimethylamide, and *N*-formylpyrazole. Distances are in angstroms.

Table 4. [1d•Cu^{II}](OTf)$_2$-Induced MM Reaction of NuSiMe$_3$ with 2d



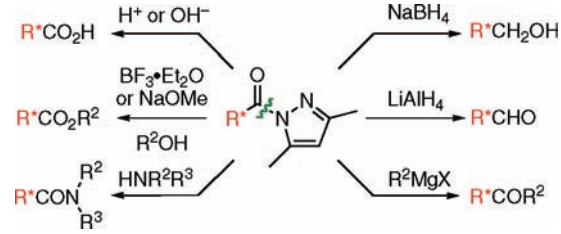
entry	NuSiMe$_3$	temp. (°C), time (h)	yield (%) of MM adducts	ee (%) [config]
1	$Me_2C{=}C(OMe)(OSiMe_3)$	−20, 13	**17**, 91	86 [–]
2	 **16**	−20, 2	**18**, 97[a,b]	98 [–][c]
3	$H_2C{=}CPh(OSiMe_3)$	23, 44.5	**19**, 70	96 [–]

[a] **16** reacted at its 5 position. [b] The diastereomeric ratio was 86:14. [c] ee of the major diastereomer.

Conclusion and Future Prospects

The present results demonstrate that the cation–π interaction can be used to control the conformation of an aromatic arm of chiral ligands, and monopeptides are readily tunable ligands that include only one chiral center compared to chiral bis(oxazoline)s, which have been reported to be useful ligands in various enantioselective reactions with bidentate electrophiles.[7] Further studies to obtain direct evidence to support the existence of the intramolecular cation–π interaction in [**1d**•Cu^{II}](OTf)$_2$ and its application to the design of chiral catalysts are currently under investigation in our laboratory.

Scheme 8. Synthetic Versatility of Pyrazolyl Auxiliary



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