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Design of a Small-Molecule Catalyst Using Intramolecular Cation–π Interactions for Enantioselective Diels–Alder and Mukaiyama–Michael Reactions: L-DOPA-Derived Monopeptide·Cu(II) Complex

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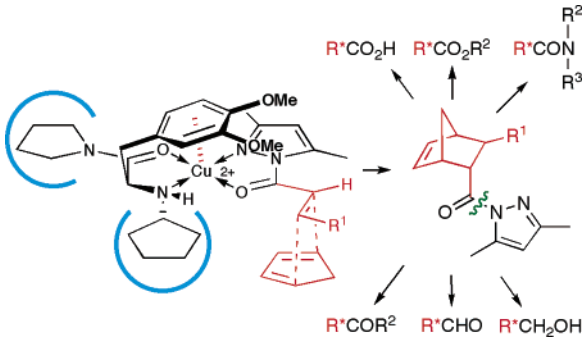
ABSTRACT



We have designed a small-molecule 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). This catalyst (2–10 mol %) is highly effective for the enantioselective Diels–Alder (DA) and Mukaiyama–Michael (MM) reactions with α,β-unsaturated 1-acyl-3,5-dimethylpyrazoles. The present results demonstrate that cation–π interactions may be available for controlling the conformation of sidearms of chiral ligands, and monopeptides are readily tunable ligands that include only one chiral center.

The rational design of small-molecule asymmetric catalysts is an important subject toward the development of economical and practical organic synthesis. We have been interested in designing minimal artificial enzymes from natural L-amino acids which enantioselectively catalyze synthetically useful organic reactions.[1] We report here a small-molecule chiral catalyst, L-DOPA-derived monopeptide (**1**, Y = NR_2)·Cu(II) complex (**type I**), for the enantioselective Diels−Alder (DA) and Mukaiyama−Michael (MM) reactions with α,β-unsaturated 1-acyl-3,5-dimethylpyrazoles (**2**) (Scheme 1). To the best of our knowledge, this may be the first example of the use of an intramolecular cation−π interaction in the design of chiral catalysts.[2]

According to the pioneering studies by Engberts et al., 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 L-abrine (*N*-methyl-L-tryptophane) or *N*-methyl-L-tyrosine in water.[3] In this reaction, water enhances the enantioselectivity up to 74% ee. Their catalysts (**type II**) have not yet been shown to be a synthetically useful with regard to enantioselectivity or the range of substrates.[4]

(1) (a) Ishihara, K.; Kosugi, Y.; Akakura, M. *J. Am. Chem. Soc.* **2004**, *126*, 12212−12213. (b) Ishihara, K.; Nakano, K. *J. Am. Chem. Soc.* **2005**, *127*, 10504−10505.

(2) For typical examples of asymmetric induction by $\pi-\pi$ attractive interaction between a catalyst and a dienophile, see: (a) Corey, E. J.; Loh, T.-P. *J. Am. Chem. Soc.* **1991**, *113*, 8966−8967. (b) Ishihara, K.; Gao, Q.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 10412−10413.

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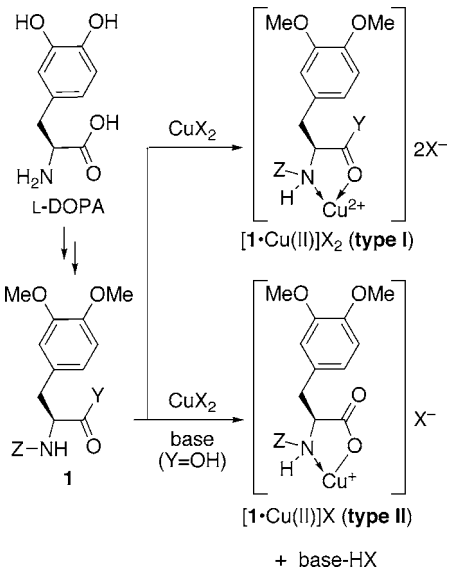
Scheme 1. Design of l-DOPA Derivatives **1**•Cu(II) Complexes



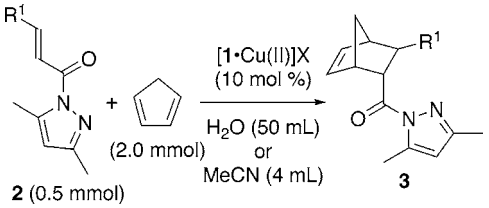
The focus of Engberts' work[3] was proof of concept with the enantioselectivity enhanced in water and not a study to find the most selective catalyst.

Based on Engberts' results,[3] we explored the enantioselective DA reaction of CP with **2**[5] as more synthetically valuable dienophiles induced by [**1**•Cu(II)]NO_3 (**type II**) in water (Table 1). The DA reaction was heterogeneously carried out under a high dilution condition ([**2**] = 0.01 M) due to the poor solubility of **2** in water. The *N*-alkyl substituent of L-DOPA as well as L-abrine were highly effective for increasing the enantioselectivity. The ee of *endo*-(2*S*)-**3a** was increased up to 85% ee with the use of [**1a**•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*)-**3b** with 72% ee because **2b** was predominantly hydrolyzed (entry 2). In general, [L-amino acid•Cu(II)]X is insoluble in aprotic solvents and a high dilution condition is undesirable for scale-up, but [*N*-alkyl-L-amino acid•Cu(II)]X was soluble in acetonitrile even at −40 °C. To prevent the hydrolysis of **2** and concentrate the reaction mixture, the DA reaction with **2** was performed in the presence of 10 mol % of [**1**•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*)-**3a** with 78% ee (entry 3). This enantioselectivity was comparable to the results achieved by Engberts in acetonitrile (17% ee).[3] The use of *N*-cyclopentyl ligand **1b** 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).

Surprisingly, [**1b**•Cu(II)]$(OTf)_2$ (**type I**) prepared from **1b** and $Cu(OTf)_2$ in the absence of Et_3N was more active than [**1b**•Cu(II)]OTf (**type II**; entry 4, Table 1) in acetonitrile and gave *endo*-(2*S*)-**3a** 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 **1b** with regard to enantioselectivity and catalytic activity (entry 2). On the other hand, pyrrolidine monopeptide **1d** was extremely effective, and gave *endo*-(2*S*)-**3a** with 97% ee (entry 3). [**1d**•Cu(II)]$(OTf)_2$ was sufficiently active even at −78 °C to give *endo*-(2*S*)-**3a** 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**

Table 1. [**1**•Cu(II)]X (Type II)-Induced DA Reaction of CP with **2**

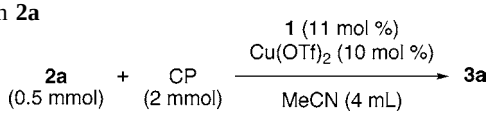


2 (0.5 mmol) **3**

entry	**1** [Y, Z]	**2** [R^1]	solvent	T (°C), time (h)	**3**,[a] yield (%)	ee[b] (%)
1[c]	**1a** [OH, Pr]	**2a** [H]	H_2O	0, 2	**3a**, 88	85
2[c]	**1a** [OH, Pr]	**2b** [Me]	H_2O	0, 3 to 23, 8[d]	**3b**, 3[e]	72
3[f]	**1a** [OH, Pr]	**2a** [H]	MeCN[g]	−40, 13	**3a**, >99	78
4[f]	**1b** [OH, *c*-C_5H_9]	**2a** [H]	MeCN[g]	−40, 13	**3a**, >99	92
5[f]	**1b** [OH, *c*-C_5H_9]	**2b** [Me]	MeCN[g]	23, 20	**3b**, 24[h]	76

[a] *Endo/exo* ratio was >90:10. [b] Ee of *endo*-**3**. [c] **1** (17.5 mol %), $Cu(NO_3)_2$•$2.5H_2O$ (10 mol %), NaOH (17.5 mol %). [d] 0 °C, 3 h, and then 23 °C, 8 h. [e] **2b** was hydrolyzed. [f] **1** (15 mol %), $Cu(OTf)_2$ (10 mol %), Et_3N (15 mol %). [g] MeCN (wet) was used. [h] **2b** was remained.

Table 2. [**1**•Cu(II)]$(OTf)_2$ (Type I)-Induced DA Reaction of CP with **2a**



			3a		
entry	**1** [Y, Z]	T (°C), time (h)	yield (%)	*endo*/*exo*	ee[a] (%)
1[b]	**1b** [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

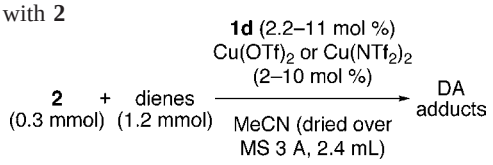
[a] Ee of *endo*-**3a**. [b] MeCN (wet). [c] EtCN (dried over MS 3 A).

(3) (a) Otto, S.; Boccaletti, G.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1998**, *120*, 4238−4239. (b) Otto, S.; Engberts, J. B. F. N. *J. Am. Chem. Soc.* **1999**, *121*, 6798−6806.

(4) Only one successful example is shown in ref 3. The absolute configuration of the DA adduct has not yet been determined.

(5) For reactions with 1-acryloylpyrazoles, see: (a) Kashima, C.; Fukusaka, K.; Takahashi, K.; Yokoyama, Y. *J. Org. Chem.* **1999**, *64*, 1108−1114. (b) Gelbert, M.; Lüning, U. *Supramolecular Chem.* **2001**, *12*, 435−444. (c) Kashima, C.; Miwa, Y.; Shibata, S.; Nakazono, H. *J. Heterocycl. Chem.* **2003**, *40*, 681−688. (d) Kashima, C.; Shibata, S.; Yokoyama, H.; Nishio, T. *J. Heterocycl. Chem.* **2003**, *40*, 773−782. (e) Itoh, K.; Kanemasa, S. *J. Am. Chem. Soc.* **2002**, *124*, 13394−13395. (f) Sibi, M. P.; Itoh, K.; Jasperse, C. P. *J. Am. Chem. Soc.* **2004**, *126*, 5366−5367.

Table 3. [**1d**·Cu(II)]X_2 (Type I)-Induced DA Reaction of Dienes with **2**



				DA adducts		
entry	**2** [R^1]	diene[a]	*T* (°C), time (h)	yield (%)	*endo*/*exo*	ee[b] (%) [config]
1[c]	**2a** [H]	CP	−40, 6	**3a**, >99	98:2	97 [2*S*]
2	**2a** [H]	PB	−40, 22	**4**, 88	>99:1[e]	97 [−]
3[d]	**2a** [H]	MOB	−40, 7	**5**, 85	>99:1[e]	97 [−]
4[f]	**2a** [H]	DMB	0, 49	**6**, 63		91 [−]
5[d,g]	**2b** [Me]	CP	−40, 24	**3b**, 95	97:3	97 [2*S*]
6[c]	**2b** [Me]	CP	0, 17.5	**3b**, 97	95:5	89 [2*S*]
7[d,g]	**2c** [Ph]	CP	0, 40	**3c**, 93	93:7	95 [−]
8[d]	**2d** [EtO_2C]	CP	−20, 7	**3d**, 97	91:9	98 [−]
9[c]	**2d** [EtO_2C]	CP	0, 10	**3d**, >99	88:12	95 [−]
10[d,g]	**2d** [EtO_2C]	PB	0, 39	**7**, 93	>99:1[e]	91 [−]
11[d,g,h]	**2d** [EtO_2C]	IP	23, 72	**8**, 83	93:7[e]	87 [−]
12[d,g]	**2d** [EtO_2C]	MOB	−20, 5	**9**, 96	>99:1[e]	97 [−]
13[d,g]	**2d** [EtO_2C]	DMB	0, 64	**10**, 76		93 [−]
14[d,g,i]	**2e** [OCOPh]	CP	23, 6	**3e**, 89	93:7	90 [−]
15[d,g]	**2f** [Cl]	CP	−20, 5	**3f**, 95	>99:1	97 [−]

[a] See 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 4- and 3-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).

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 not only with cyclic dienes but also acyclic dienes such as 2-methoxybutadiene (MOB), 2-phenylbutadiene (PB), isoprene (IP), and 2,3-dimethylbutadiene (DMB).

The crystal structure of bis(L-tyrosinato)Cu(II) complex has been determined by van der Helm et al. (Figure 1).[6] They observed a weak cation−π attractive interaction[7] between the Cu(II) ion and one of the phenolic rings of tyrosinates. On the basis of this significant observation, 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 **11**, shown in Figure 1. The cation−π interaction in [**1**·Cu(II)]$(OTf)_2$ (**type I**) would be stronger than that in [**1**·Cu(II)]OTf (**type II**). 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 Cu(II) [*cis* (disfavored) or *trans* (favored)] and the conformation of **2a** [*s-cis* (favored) or *s-trans* (disfavored)], respectively. In contrast, Engberts et al. suggest that π−π attractive interaction[2] between the indole group in L-abrine and the dienophile is important for asymmetric induction in their aqueous DA reaction catalyzed by [L-abrine·Cu(II)]NO_3.[3] Although it cannot be absolutely

(6) (a) van der Helm, D.; Lawson, M. B.; Enwall, E. L. *Acta Crystallogr.* **1972**, *B28*, 2307−2312. (b) Muhonen, H.; Hämäläinen, R. *Finn. Chem. Lett.* **1983**, 120−124.

(7) For cation−π interaction between Cu(II) and α-amino acids, see: (a) Tao, W. A.; Zhang, D.; Nikolaev, E. N.; Cooks, R. G. *J. Am. Chem. Soc.* **2000**, *122*, 10598. (b) Wu, L.; Tao, W. A.; Cooks, R. G. *Anal. Bioanal. Chem.* **2002**, *373*, 618−627.

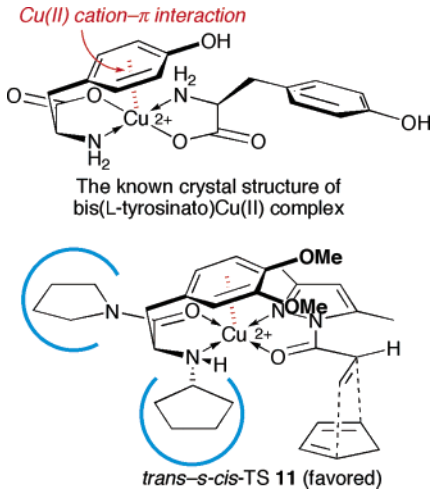


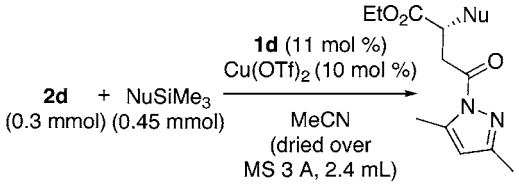
Figure 1. Transition-state assembly **11** proposed based on the crystal structure of bis(L-tyrosinato)Cu(II) complex.[6a]

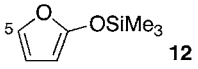
denied that distortions from rigorous square planarity may induce such a π−π interaction between **1d** and **2a**, it seems that the cation−π interaction between the Cu(II) ion and **1d** should be conformationally preferable in [**1d**·Cu(II)·**2a**]$(OTf)_2$ which is generally characterized by a square planar geometry.

Interestingly, DA adducts of **2** may be transformed into a range of carboxylic acid derivatives by treatment with appropriate nucleophiles: hydrolysis,[8a] alcoholysis,[5a,c,d,8b,e] aminolysis,[5e,8a,c−e] reductive cleavage to aldehydes[8f−h] or alcohols,[5f] and alkylative cleavage to ketones[8i] or β-ketoesters.[8j]

A highly asymmetric induction of [**1d**·Cu(II)]$(OTf)_2$ was also observed in the enantioselective Mukaiyama−Michael (MM) reaction of silyl enol ethers ($NuSiMe_3$) with **2d**. Several examples are shown in Table 4.

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	**13**, 91	86 [−]
2	 **12**	−20, 2	**14**, 97[a,b]	98 [−][c]
3	$H_2C{=}CPh(OSiMe_3)$	23, 44.5	**15**, 70	96 [−]

[a] **12** reacted at its 5-position. [b] The diastereomeric ratio was 86:14. [c] ee of the major diastereomer.

The present results demonstrate that cation−π interaction is available for controlling the conformation of a sidearm 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.[9] Further studies toward direct evidence to support the existence of intramolecular cation−π interaction in [**1d**·Cu(II)](OTf)$_2$ and its application to the design of chiral catalysts is currently under investigation in our laboratory.

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Supporting Information Available: Experimental procedures; full characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) For hydrolysis, see: (a) Kahima, C.; Fukusaka, K.; Takahashi, K. *J. Heterocycl. Chem.* **1997**, *34*, 1559−1565. For alcoholysis, see: (b) Kashima, C.; Harada, H.; Kita, I.; Fukuchi, I.; Hosomi, A. *Synthesis* **1994**, 61−65. For aminolysis, see: (c) Ried, W.; Schleimer, B. *Liebigs Ann. Chem.* **1959**, *626*, 98−105. (d) Kashima, C.; Fukuchi, I.; Takahashi, K.; Hosomi, A. *Heterocycles* **1994**, *38*, 1407−1412. (e) Kashima, C.; Fukuchi, I.; Takahashi, K.; Hosomi, A. *Tetrahedron* **1996**, *52*, 10335−10346. For reductive cleavage to aldehydes with $LiAlH_4$, see: (f) Ried, W.; Königstein, F.-J. *Angew. Chem.* **1958**, *70*, 165. (g) Ried, W.; Königstin, F.-J. *Liebigs Ann. Chem.* **1959**, *622*, 37−42. (h) Ried, W.; Deuschel, G.; Kotelko, A. *Liebigs Ann. Chem.* **1961**, *642*, 121−127. For Grignard reaction, see: (i) Kashima, C.; Kita, I.; Takahashi, K.; Hosomi, A. *J. Heterocycl. Chem.* **1995**, *32*, 25−27. For Reformatsky reaction, see: (j) Kashima, C.; Kita, I.; Takahashi, K.; Hosomi, A. *J. Heterocycl. Chem.* **1995**, *32*, 723−725.

(9) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325−335.