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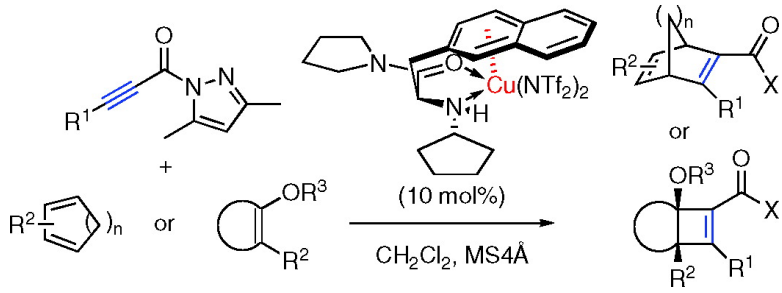

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Catalytic Enantioselective [2 + 4] and [2 + 2] Cycloaddition Reactions with Propiolamides

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Although several examples of the catalytic enantioselective Diels−Alder (DA) reaction of dienes with acetylenic dienophiles have been reported,[1] the enantioselectivity and chemical yield of the adducts have never been high, and the range of suitable substrates is quite narrow. In general, acetylene derivatives are less reactive than the corresponding ethylene derivatives as electron-deficient dienophiles. Acetylene derivatives with a linear sp−sp bond make the asymmetric induction with chiral Lewis acid difficult because the alkynyl moiety is far from the acidic metal center. Therefore, a more conformationally rigid and larger chiral substituent is needed around the metal center. We report here the catalytic and highly enantioselective DA and [2 + 2] cycloaddition reactions with propiolamide derivatives (**2**) induced by the Cu(II)•3-(2-naphthyl)-L-alanine amide (**1a**) complex (Chart 1). To the best of our knowledge, there have been only three examples of catalytic enantioselective [2 + 2] cycloaddition reactions with alkynes.[2]

We previously reported that Cu(II)•L-DOPA amide (**1b**) complex was highly effective for the enantioselective DA reaction of dienes with 1-(3,5-dimethyl-1*H*-pyrazol-1-yl)prop-2-en-1-ones (**3**).[3,4] An asymmetric environment to induce the enantioselective reaction was constructed around the metal center of Cu(II)•**1b** through intramolecular cation−π attractive interaction between the Cu(II) center and the 3,4-dimethoxyphenyl group of **1b**.[3b] On the basis of the previous results, the DA reaction of cyclopentadiene (CP) with **2a** was examined in the presence of 10 mol % of Cu(II)•**1b** in MeCN. Fortunately, bicycloadduct **4a** was obtained in 94% yield with 77% ee (entry 1, Table 1). The absolute configuration of the major enantiomer of **4a** was determined to be (1*R*,4*S*) (see Supporting Information). Next, to expand the asymmetric environment of the catalyst, **1a** was used instead of **1b**. Although the catalytic activity of Cu(II)•**1a** was lower than that of Cu(II)•**1b**, the enantioselectivity was increased to 83% ee (entry 2) and further to 87% ee in CH_2Cl_2 (entry 3).[5] The addition of molecular sieves 4 Å was effective for activating Cu(II)•**1a** and preventing the hydrolysis of **2a** (entry 4).[5,6]

To explore the scope and limitations of the present enantioselective DA reaction, several cyclic dienes and β-substituted propiolamides **2** were examined under the optimized conditions shown for entry 4 of Table 1. Representative results are shown in Table 2. The reaction of CP with **2a** at −78 °C gave **4a** with 93% ee in 50% yield (entry 1). When the reaction was carried out at −40 °C, **4a** was obtained with 88% ee in 91% yield (entry 2). Although more electron-rich but-2-ynamide (**2b**) was a less reactive dienophile, the enantioselectivity was still high under the reaction conditions at −20 °C (entry 3). Fortunately, more electron-deficient 3-iodopropiolamide (**2c**) reacted with CP at −40 °C to give 3-iodo adduct **4c** with 89% ee in 82% yield (entry 4). **4c** can be transformed to 3-nonsubstituted derivative and 3-alkyl derivative by known methods.[1a] Therefore, **2c** is an outstanding dienophile as a synthetic equivalent of **2a** and **2b**. The DA reaction of 1,3-cyclohexadiene gave bicycloadduct **5a** with up to 96% ee, although the chemical yield of **5a** was still moderate (entries 5−7). The absolute configuration of **5a** was (1*R*,4*S*), as seen for **4a**. The DA reaction of cyclohexadiene with **2c** gave **5c** in up to 89% yield and up to 98% ee (entries 8−10). Several 2- and 1-substituted 1,3-cyclohexadienes could also be used as DA dienes, and 5- and 1-substituted bicyclo[2.2.2]octadienyl-2-carboxamides (**6**−**8**) were obtained with 87−96% ee without the production of any 6- and 4-substituted regioisomers, respectively (entries 11−15).[7]

Chart 1. Chiral Lewis Acid Catalysts **1** and Dienophiles **2** and **3**

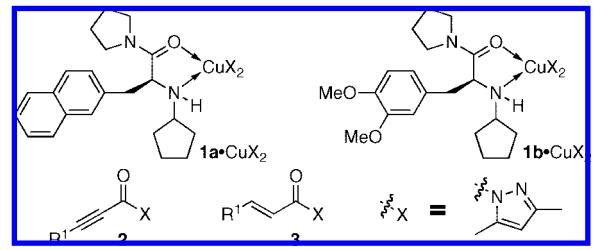
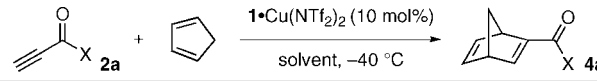


Table 1. Enantioselective DA Reaction of CP with **2a**[a]



entry	1	solvent	additive	time (h)	yield (%)	ee (%)
1	**1b**	MeCN		7	94	77 (1*R*,4*S*)
2	**1a**	MeCN		21	91	83 (1*R*,4*S*)
3	**1a**	CH_2Cl_2		7	85	87 (1*R*,4*S*)
4	**1a**	CH_2Cl_2	MS 4 Å[b]	7	91	88 (1*R*,4*S*)

[a] The DA reaction of CP (4 equiv) with **2a** (0.3 mmol) was conducted in the presence of **1**•$Cu(NTf_2)_2$ (10 mol %) in solvent (1.2 mL). [b] MS 4 Å (100 mg) was added.

Recently, impressive progress has been made in the development of chiral diene ligands for the asymmetric catalysis of Rh and Ir.[8,9] The DA reaction of cyclic dienes with acetylenic dienophiles may provide a concise method for the preparation of chiral bicyclic 2,5-diene ligand candidates.

Unexpectedly, [2 + 2] cycloadduct **9** was obtained with 80% ee in 65% yield in the reaction of 2-methoxy-5,5-dimethylcyclohexadiene with **2a** catalyzed by **1a**•$Cu(NTf_2)_2$ (10 mol %) (Table 3, entry 1). No corresponding DA adducts were obtained. 5,5-Dimethyl substituents of the diene might sterically suppress the DA reaction. 1-Trialkylsilyloxy-1-cyclopentenes and its 2-methyl analogue also reacted with **2a** to give cyclobutenecarboxamides **10**−**12** in higher yields with 81−83% ee (entries 2−4). Interestingly, Michael adduct **13** was enantioselectively obtained along with **12** when the [2 + 2] cycloaddition was conducted by using 1 equiv of the silyl enol ether in the presence of **1b**•$Cu(NTf_2)_2$ (10 mol %) (entry 5).[7]

The bicyclic [2 + 2] adducts shown in Table 3 are very useful chiral intermediates for further synthetic elaboration. For instance, the adduct **12** was transformed efficiently into the known (*S*)-bicyclo[4.3.0]nonenone (**15**)[10] as shown in Scheme 1.[11] Thus, the absolute configuration of **12** was established.

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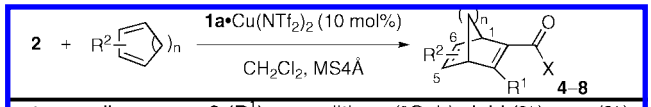
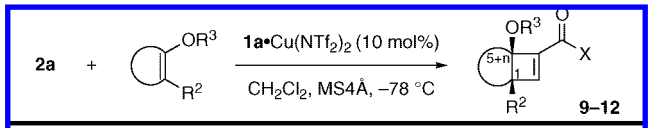
Table 2. Enantioselective DA Reaction of Cyclic Dienes with **2**[a]



entry	diene	2 (R^1)	conditions (°C, h)	yield (%)	ee (%)
1		**2a** (H)	–78, 36	**4a**, 50	93 (1*R*,4*S*)
2		**2a** (H)	–40, 7	**4a**, 91	88 (1*R*,4*S*)
3		**2b** (Me)	–20, 45	**4b**, 22	89
4[b]		**2c** (I)	–78 to –40, 4	**4c**, 82	89
5		**2a** (H)	–20, 48	**5a**, 48	93 (1*R*,4*S*)
6[c]		**2a** (H)	–20, 48	**5a**, 52	94 (1*R*,4*S*)
7[c,d]		**2a** (H)	–20, 28	**5a**, 68	96 (1*R*,4*S*)
8		**2c** (I)	–78, 1 to –40, 64	**5c**, 57	98
9		**2c** (I)	–10, 21	**5c**, 70	96
10[c]		**2c** (I)	–20, 47	**5c**, 89	97
11[e]	Ph	**2a** (H)	–78, 3 to –40, 42	**6a**, 50[f]	87
12[g]	Ph	**2c** (I)	–20, 3	**6c**, 83[f]	95
13	Bn	**2a** (H)	–78, 17 to –20, 168	**7a**, 69[f]	89
14	Bn	**2c** (I)	–40, 17 to –20, 25	**7c**, 83[f]	96
15	OMe	**2c** (I)	–40, 1	**8c**, 84[h]	96

[a] The reaction was conducted under the same conditions as entry 4 in Table 1. [b] CP (2 equiv) was used. [c] $Cu(NTf_2)_2$ (20 mol %) and **1a** (22 mol %) were used. [d] Cyclohexadiene (0.6 mL) was used. [e] CH_2Cl_2 (0.6 mL) was used. [f] Only 5-substituted isomer was obtained. [g] CH_2Cl_2 (1.6 mL) was used. [h] Only 1-substituted isomer was obtained.

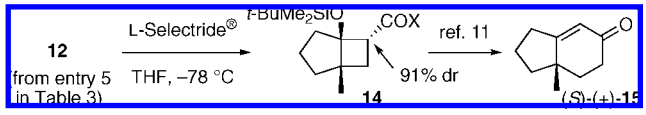
Table 3. Enantioselective [2 + 2] Cycloaddition of Enes with **2a**[a]



entry	ene	time (h)	Yield (%)	ee (%)
1[b]	OMe	5	**9**, 65[c]	80
2	OR^3 R^3=Si*i*-Pr_3	32	**10**, 79[c]	81
3	OR^3 R^3=Si*t*-$BuMe_2$	0.5	**11**, 79[c]	82
4	$OSiMe_2$*t*-Bu	0.75	**12**, 93[c]	83 (1*S*,5*R*)
5[c]	$OSiMe_2$*t*-Bu	2.7	**12**, 80 [**13**, 3][d]	73 (1*S*,5*R*) [81][e]

[a] The reaction was conducted under the same conditions as entry 4 in Table 1. [b] The ene (2 equiv) was used. [c] Only (5+*n*)-R^3O substituted regioisomeric adduct was obtained. The reaction of the ene (1.0 equiv) with **2a** (1.74 mmol) was conducted in the presence of **1b** instead of **1a**. [d] The yield and ee of the Michael adduct **13** are shown in brackets. For the chemical structure of **13**, see Supporting Information.

Scheme 1. Conversion of (1*S*,5*R*)-**12** to (*S*)-(+)-**15**



On the basis of our previous experimental results with the DA reaction of dienes with **3** catalyzed by **1b**•Cu(II),[3] we propose the following reaction mechanism: **2a** would be predominantly *trans*-chelated with **1a**•Cu(II) due to steric hindrance between the *N*-cyclopentyl group of **1a** and the pyrazolyl moiety of **2a**, and then the carbonyl *re* face of **2a** would be preferentially shielded by the 2-naphthyl face of **1a**, which would be conformationally folded through cation−π interaction with Cu(II). CP would predominantly approach the *si* face side of **2a** to give (1*R*,4*S*)-**4a** through *exo*-transition-state (TS) assembly **16** (Figure 1). The frontier molecular orbital theory also explains the predominance

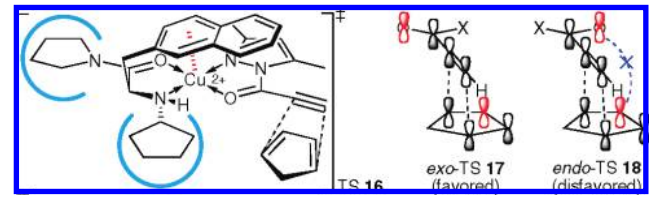


Figure 1. Proposed *exo*,*trans*-chelated TS **16** and the frontier molecular orbital explanation of *exo*-TS **17** and *endo*-TS **18**.

of *exo*-TS **17** in terms of secondary antibonding interaction[12] between the lobes on the C-2 position of cyclopentadiene (HOMO) and the carbonyl oxygen of **2a** (LUMO) in *endo*-TS **18**.

For the [2 + 2] cycloaddition, a stepwise mechanism through Michael aldol reactions might be reasonable, judging from the experimental results shown in entry 5 in Table 3.[13] According to the observed absolute configuration of cycloadduct **12**, the Michael reaction should occur through the enantiofacial approach of **2a** to the *re* face of the silyl enol ether.

In summary, we have developed the catalytic enantioselective [2 + 4] and [2 + 2] cycloadditions of electron-rich dienes or silyl enol ethers with electron-deficient propiolamide derivatives.

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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.

References

(1) (a) Ishihara, K.; Kondo, S.; Yamamoto, H.; Ohashi, H.; Inagaki, S. *J. Org. Chem.* **1997**, *62*, 3026. (b) Corey, E. J.; Lee, T. W. *Tetrahedron Lett.* **1997**, *38*, 5755. (c) Maruoka, K.; Concepcion, A. B.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 3501. (d) Evans, D. A.; Miller, S. J.; Lectka, T.; von Matt, P. *J. Am. Chem. Soc.* **1999**, *121*, 7559. (e) Hilt, G.; Hess, W.; Harms, K. *Org. Lett.* **2006**, *8*, 3287.
(2) (a) Narasaka, K.; Hayashi, Y.; Shimadzu, H.; Niihata, S. *J. Am. Chem. Soc.* **1992**, *114*, 8869. (b) Ito, H.; Hasegawa, M.; Takenaka, Y.; Kobayashi, T.; Iguchi, K. *J. Am. Chem. Soc.* **2004**, *126*, 4520. (c) Takenaka, Y.; Ito, H.; Hasegawa, M.; Iguchi, K. *Tetrahedron* **2006**, *62*, 3380. (d) Takenaka, Y.; Ito, H.; Iguchi, K. *Tetrahedron* **2007**, *63*, 510. (e) Shibata, T.; Takami, K.; Kawachi, A. *Org. Lett.* **2006**, *8*, 1343.
(3) (a) Ishihara, K.; Fushimi, M. *Org. Lett.* **2006**, *8*, 1921. (b) Ishihara, K.; Fushimi, M.; Akakura, M. *Acc. Chem. Res.* **2007**, *40*, 1049.
(4) For a recent review of copper Lewis acid catalysis, see: Stanley, L. M.; Sibi, M. P. In *Acid Catalysis in Modern Organic Synthesis*; Yamamoto, H., Ishihara, K., Eds.; Wiley-VCH: Weinheim, Germany, 2008; Vol. 2, pp 903−985.
(5) Cu(II)•**1a** could not be prepared in CH_2Cl_2 because of the poor solubility of **1a**. Cu(II)•**1a** was prepared in MeCN, and then the solvent was exchanged to CH_2Cl_2 before adding CP and **2a**. A trace amount of MeCN remained in the reaction mixture.
(6) A trace amount of MeCN in the reaction mixture might also be removed by molecular sieves 4 Å.
(7) Acyclic dienes and acyclic silyl enol ethers were not suitable as reactants. .
(8) For a mini review, see: Glorius, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 3364.
(9) (a) Hayashi, T.; Ueyama, K.; Tokunaga, N.; Yoshida, K. *J. Am. Chem. Soc.* **2003**, *125*, 11508. (b) Tokunaga, N.; Otomaru, Y.; Okamoto, K.; Ueyama, K.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, *26*, 13584. (c) Otomaru, Y.; Okamoto, K.; Shintani, R.; Hayashi, T. *J. Org. Chem.* **2005**, *70*, 2503. (d) Fischer, C.; Defieber, C.; Suzuki, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2004**, *126*, 1628. (e) Paquin, J.-F.; Defieber, C.; Stephenson, C. R. J.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 10850.
(10) (a) Pfau, M.; Revial, G.; Guigant, A.; Angelo, J. *J. Am. Chem. Soc.* **1985**, *107*, 273.
(11) Canales, E.; Corey, E. J. *J. Am. Chem. Soc.* **2007**, *129*, 12686.
(12) For secondary antibonding interaction, see: (a) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; John Wiley & Sons, Ltd.: New York, 1976; pp 106−109. (b) See ref 1a.
(13) Ishihara, K.; Nakano, K. *J. Am. Chem. Soc.* **2007**, *129*, 8930.

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