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Rational Design of Highly Effective Asymmetric Diels−Alder Catalysts Bearing 4,4′-Sulfonamidomethyl Groups

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Although numerous chiral Lewis acid catalysts have been reported for the asymmetric Diels−Alder (DA) reaction,[1,2] there are still some drawbacks with regard to catalytic activity, enantioselectivity, and the range of substrates. For example, $M(SbF_6)_n$ is often used with chiral chelating ligands to increase the catalytic activity, counteranions of which are thought to be completely liberated from the catalyst.[2e] However, labile cationic catalysts often cause the decomposition of catalyst, product inhibition and an undesired side reaction.[3] To overcome these problems, the rational design of a chiral cationic catalyst using weak secondary interactions might be essential for the stabilization of cation species and the construction of a rather flexible but highly efficient asymmetric environment around the metal center.

We previously reported that Cu(II)•3-aryl-L-alanine amide complexes were highly effective for the asymmetric DA reaction.[4] An asymmetric environment for induction of the enantioselective reaction was constructed around the metal center through intramolecular π-cation attractive interaction between the aromatic ring of the ligands and the Cu(II) center. In this context, intramolecular n-cation interaction between heteroatoms (Y:) of a ligand and a metal cation is one of the most promising candidates for obtaining higher enantioselectivity and a broader range of substrates (Scheme 1). In general, coordination of a Lewis basic site to a metal cation decreases its Lewis acidity. However, rationally designed additional Lewis basic sites are expected to increase the Lewis acidity by displacing counteranions.[5] In this case there is an equilibrium between complexes **A** and **B**. To overcome this equilibrium, we envisioned that chiral bis(oxazoline)s bearing 4,4′-protic substituents (HZ:) would predominantly stabilize n-cation complex **C**, since released counteranions may interact with HZ through hydrogen bonding.[6] We report here the rational design of bis(oxazoline)-copper(II) catalysts[7−9] based on intramolecular secondary n-cation interaction for the highly enantioselective DA reaction.

Scheme 1. Working Hypothesis: Chiral Catalysts Based on Intramolecular Secondary *n*-Cation Interaction

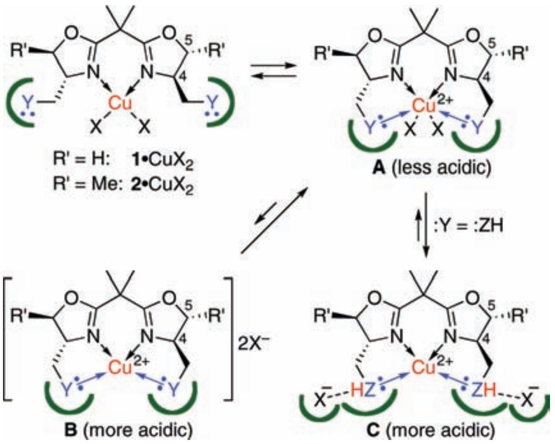
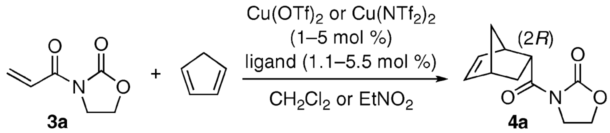


Table 1. DA Reaction of CP with **3a** Catalyzed by **2**•CuX_2[a]



3a

4a

entry	ligand [Y or ZH]	conditions (°C, h)	conv (%)[b]	*endo*/*exo*	ee (%)[b] [config]
1	**2a** [OMe]	−20, 12	63	90:10	8 [2*R*]
2	**2b** [OAc]	−40, 23	99	98:2	24 [2*R*]
3	**2c** [OMs]	−72, 21	18	98:2	84 [2*R*]
4	**2d** [NHMs]	−72, 16	97	99:1	93 [2*R*]
5[c]	**2d** [NHMs]	−72, 9	99	99:1	91 [2*R*]
6[c,d]	**2d** [NHMs]	−72, 1	95	99:1	98 [2*R*]
7[e]	**2d** [NHMs]	−72, 9	97 [94[f]]	99:1	98 [2*R*]
8	**2e** [NHTf]	−72, 8.5	99	98:2	80 [2*R*]
9[c,d]	**2e** [NHTf]	−72, 1.5	97	98:2	96 [2*R*]
10[g]	**2e** [NHTf]	−72, 8.5	96	98:2	92 [2*R*]
11[c,g]	**2e** [NHTf]	−72, 20	73	99:1	96 [2*R*]
12[c,d]	*ent*-**1d** [NHMs]	−72, 6	92	99:1	91 [2*S*]
13[c,d]	*ent*-**1f** [*i*-Pr]	−72, 6	33	97:3	86 [2*S*]
14[c,d]	none	−72, 1.5	86	98:2	−

[a] The reaction of CP (3 equiv) with **3a** (0.2 mmol) was conducted in the presence of $Cu(OTf)_2$ (5 mol %) and a ligand (5.5 mol %) in CH_2Cl_2 (1 mL). [b] Ee of *endo*-**4a**. [c] $EtNO_2$ was used instead of CH_2Cl_2. [d] $Cu(NTf_2)_2$ was used instead of $Cu(OTf)_2$. [e] The reaction of CP (3 equiv) with **3a** (1 mmol) was conducted in the presence of **2d**•$Cu(NTf_2)_2$ (1 mol %) in $EtNO_2$ (1 mL). [f] Isolated yield. [g] $Cu(SbF_6)_2$ was used instead of $Cu(OTf)_2$.

We first examined the catalytic activities of $Cu(OTf)_2$ complexes with **2** bearing Lewis basic sites at the 4,4′-substituents[10] in the reaction of cyclopentadiene (CP, 3 equiv) with **3a** in CH_2Cl_2, according to the conditions reported by Evans and co-workers[2e] (Table 1). When the reaction was conducted with **2a** (Y = OMe) or **2b** (Y = OAc), DA adduct **4a** was obtained with poor enantioselectivity (8 and 24% ee, entries 1 and 2). The use of **2c** (Y = OMs) also gave excellent enantioselectivity although reactivity was low[11] (entry 3). The use of ligands **2d** (ZH = NHMs) and **2e** (ZH = NHTf) successfully gave excellent enantioselectivities and reactivities (93 and 80% ees, entries 4 and 8). These results suggest that the sulfonamido groups of **2d** and **2e** may play a key role in the construction of an efficient asymmetric environment. The use of $EtNO_2$ instead of CH_2Cl_2 significantly increased the reactivity as reported by Jørgensen and co-workers,[12] while the enantioselectivity was not improved (entry 5). The use of $EtNO_2$ and $Cu(NTf_2)_2$ instead of CH_2Cl_2 and $Cu(OTf)_2$ successfully improved

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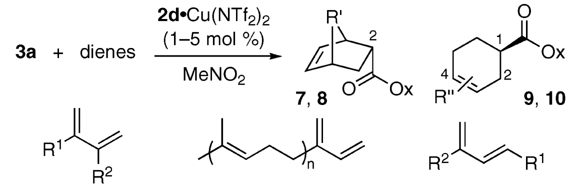
Table 2. **2d•**$Cu(NTf_2)_2$-Catalyzed DA Reaction with **3a**[a]

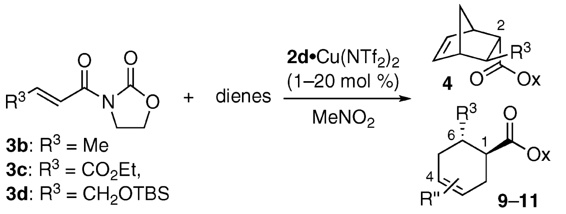


5a: $R^1 = CH_3$, $R^2 = H$
5b: $R^1 = R^2 = CH_3$
5c: $R^1 = Ph$, $R^2 = H$
5d: $R^1 = OMe$, $R^2 = H$
5e: n = 1
5f: n = 2
6a: $R^1 = CH_3$, $R^2 = H$
6b: $R^1 = OAc$, $R^2 = CH_3$

entry	diene	conditions (°C, h)	isolated yield (%)	isomer ratio	ee (%)[b] [config][c]
1	CH	0, 30	**7**, 95	99:1[d]	92 [2*R*]
2[e,f]	CH	−20, 25	**7**, 57	99:1[d]	86 [2*R*]
3[e,f]	furan[g]	−72, 72	**8**, 92[h]	76:24[d]	98 [2*R*]
4	**5a**	−20, 24	**9a**, 93	>99:1[i]	99 [1*R*]
5[j]	**5a**	0, 44	**9a**, 91	>99:1[i]	98 [1*R*]
6	**5b**	−20, 52	**9b**, 83	−	95 [1*R*]
7	**5c**	−20, 6	**9c**, 91	>99:1[i]	91 [1*R*]
8[e]	**5d**	−40, 7.5	**9d**, 68	>99:1[i]	86 [1*R*]
9[e,f]	**5e**	−20, 24	**9e**, 67	>99:1[i]	94 [1*R*]
10[f]	**5f**	−20, 24	**9f**, 76	>99:1[i]	98 [1*R*]
11	**6a**	0, 72	**10a**, 92	85:9:6[d,i]	92 [1*R*,2*S*]
12[e,f]	**6b**	−20, 12	**10b**, 96	52:48[d]	99 [1*R*,2*S*][k]

[a] The reaction of a diene (3 equiv) with **3a** (0.2 mmol) was conducted in the presence of **2d•**$Cu(NTf_2)_2$ (5 mol %) in $MeNO_2$ (1 mL). [b] Ee of major isomer. [c] See Supporting Information (SI). [d] Diastereomer. [e] $EtNO_2$ was used instead of $MeNO_2$. [f] **2e** was used instead of **2d**. [g] 10 equiv of furan were used. [h] Conversion yield determined by ^1H NMR analysis. [i] Regioisomer. [j] The reaction of **5a** (3 equiv) with **3a** (1 mmol) was conducted in the presence of **2d•**$Cu(NTf_2)_2$ (1 mol %) in $MeNO_2$ (1 mL). [k] Minor diastereomer was 91% ee [1*R*,2*R*].

Table 3. Catalytic DA Reaction with *β*-Substituted Dienophiles **3**[a]



3b: $R^3 = Me$
3c: $R^3 = CO_2Et$,
3d: $R^3 = CH_2OTBS$

entry	3	diene	conditions (°C, h)	isolated yield (%)	isomer ratio	ee (%)[b] [config][c]
1[d,e]	**3b**	CP	−20, 7	**4b**, 58[f]	93:7[g]	95 [2*R*]
2[d,e]	**3c**	CP	−72, 19	**4c**, 99	95:5[g]	94 [2*S*]
3[h]	**3c**	CP	−40, 21	**4c**, 99	89:11[g]	89 [2*S*]
4	**3c**	**5a**	rt, 60	**11**, 87	94:6[i]	90 [1*R*,6*S*]
5	**3c**	**5b**	0, 48	**12**, 68	−	81 [1*R*,6*S*]
6[j]	**3d**	**5a**	rt, 66	**13**, 76	>99:1[i]	95 [1*S*,6*S*]

[a] The reaction of a diene (3 equiv) with **3** (0.2 mmol) was conducted in the presence of **2d•**$Cu(NTf_2)_2$ (5 mol %) in $MeNO_2$ (1 mL). [b] Ee of major isomer. [c] See SI. [d] $EtNO_2$ was used instead of $MeNO_2$. [e] **2e** was used instead of **2d**. [f] Conversion yield determined by ^1H NMR analysis. [g] Diastereomer. [h] The reaction of CP (10 equiv) with **3c** (1 mmol) was conducted in the presence of **2d•**$Cu(NTf_2)_2$ (1 mol %) in $MeNO_2$ (1 mL). [i] Regioisomer. [j] The reaction of isoprene (10 equiv) was conducted in the presence of **2d•**$Cu(NTf_2)_2$ (20 mol %).

the reactivity and the enantioselectivity (entries 6 and 9). Only 1 mol % of **2d•**$Cu(NTf_2)_2$ efficiently promoted the reaction to give **4a** in 94% isolated yield with 98% ee (entry 7). When a labile catalyst, **2e•**$Cu(SbF_6)_2$, was used,[2e] the chemical yield of **4a** was less reproducible although the enantioselectivity was constantly high (entries 10 and 11).[3,13] The catalytic activity of *ent*-**1f•**$Cu(NTf_2)_2$ was much lower than that of $Cu(NTf_2)_2$ itself (entries 13 versus 14). In contrast, the use of **2d**, **2e**, and **1d** bearing 4,4′-sulfonamide groups significantly increased the catalytic activities and enantioselectivities (entries 6, 9, and 12 versus 13). In particular, the catalytic activities of **2d•**$Cu(NTf_2)_2$ and **2e•**$Cu(NTf_2)_2$ were higher than that of $Cu(NTf_2)_2$ itself (entries 6 and 9 versus 14).

To explore the generality and scope of the present enantioselective DA reaction, the reactions of various dienes were examined under optimized conditions (Table 2). For the reaction at −20 °C or higher, the use of $MeNO_2$ instead of $EtNO_2$ improved the reactivity. The DA reaction of cyclic dienes such as cyclohexadiene (CH) and furan also gave the corresponding *endo* adducts **7** and **8** with high enantioselectivities (entries 1−3).[14] For the reaction of CH, **2d** gave higher enantioselectivity than **2e**, while **2e** gave higher catalytic activity than **2d**. Evans and co-workers reported that the *t*-Bu-bis(oxazoline)•$Cu(OTf)_2$-catalyzed DA reaction of isoprene (**5a**) with **3a** gave **9a** with 59% ee.[2e,5] In contrast, the present DA reactions using **2d•**$Cu(NTf_2)_2$ and **2e•**$Cu(NTf_2)_2$ were highly effective for a series of 2-substituted butadienes and gave the corresponding 4-substituted adducts **9** with excellent regio- and enantioselectivities (>99:1 dr, 86−99% ee, entries 4−10). The reaction of **5a** was also successfully promoted by 1 mol % of **2d•**$Cu(NTf_2)_2$ (entry 5). 1-Substituted butadienes such as **6a** and **6b** were also suitable substrates for the present DA reaction and gave the corresponding 2-substituted adducts **10a** and **10b** with high enantioselectivities (92 and 99% ee), albeit the reactivities and diastereoselectivities were moderate (entries 11 and 12).

The present DA reaction was also effective for *β*-substituted dienophiles (Table 3). The reaction of CP with **3b** ($R^3 = Me$) and **3c** ($R^3 = CO_2Et$) proceeded smoothly to give the corresponding adducts **4b** and **4c** with high enantioselectivities, even when the reaction was conducted in the presence of 1 mol % of **2d•**$Cu(NTf_2)_2$ (89−95% ees, entries 1−3). The DA reaction of acyclic dienes with *β*-substituted dienophiles, which was one of the most challenging sets, gave the corresponding adducts **11**−**13** with high enantioselectivities (81−95% ees) albeit the reactivities were moderate (entries 4−6). The absolute configuration of **13** was determined to be (1*S*,6*S*) after conversion to the corresponding benzyl ester (BnOLi, THF, rt).[15] Sorensen and co-workers synthesized the benzyl ester as a key intermediate for the synthesis of the decahydrofluorene core of hirsutellones via the diastereoselective DA reaction using the chiral auxiliary.[15]

The postulated intramolecular secondary *n*-cation interaction of sulfonyl oxygens was considered based on theoretical calculations[5] for a **2d•**$Cu(NTf_2)_2$−**3a** complex. As shown in Figure 1, the sulfonyl oxygens coordinate with the Cu(II) cation (*n*-cation interaction), where counteranions (Tf_2N^-) do not coordinate to the Cu(II) cation but rather to protons of sulfonamido groups, as expected.[12] It is conceivable that dienes predominantly approach the *si*-face side of *s-cis* acrylimides, since a sulfomanide group and a Tf_2N^- preferentially shielded the *re*-face of the acrylimide moiety (Figure 1, right).

In conclusion, we have designed a new class of bis(oxazoline) ligands bearing 4,4′-sulfonamidomethyl groups for the DA reaction with **3**. A theoretical calculation suggested that the sulfonamide groups successfully interact with the Cu(II) cation and that the counteranions with protons of sulfonamido groups. These weak secondary interactions might contribute to the high catalytic activity, the broad range of substrates, and the high level of induction of the enantioselectivity. The present DA reaction gave the best results among those previously reported.

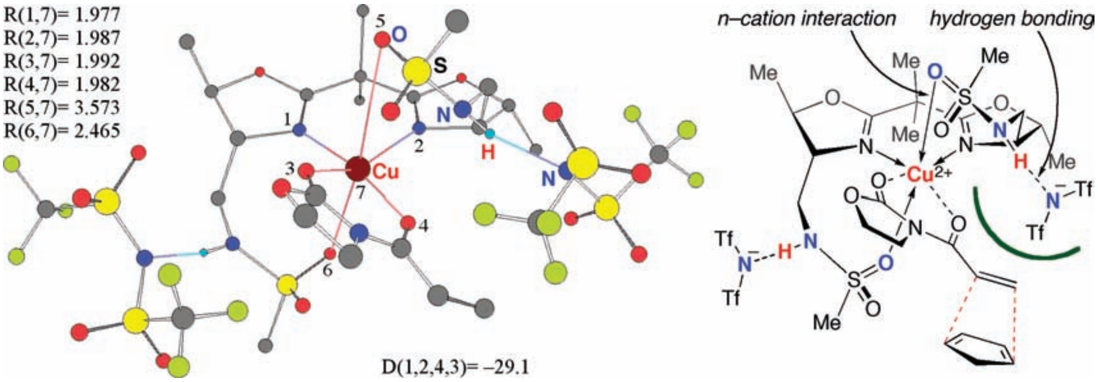


Figure 1. B3LYP/6-31G(d) optimized geometry of **2d**•Cu(NTf$_2$)$_2$−**3a** (left) and proposed transition-state assembly (right). Hydrogen atoms, except for protons of sulfonamido groups, are omitted for clarity.

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

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