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Catalytic Enantioselective 1,3-Dipolar Cycloadditions of Nitrones with Propioloylpyrazoles and Acryloylpyrazoles Induced by Chiral π-Cation Catalysts

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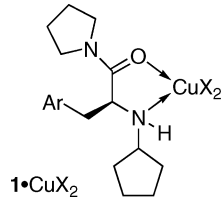
Abstract: A chiral copper(II) complex of 3-(2-naphthyl)-L-alanine amide successfully catalyzes the enantioselective 1,3-dipolar cycloaddition reaction of nitrones with propioloylpyrazole and acryloylpyrazole derivatives. The asymmetric environment created by intramolecular π−cation interaction gives the corresponding adducts in high yields with excellent enantioselectivity. This is the first successful method for the catalytic enantioselective 1,3-dipolar cycloaddition of nitrones with acetylene derivatives. The 1,3-dipolar cycloadducts can be stereoselectively converted to β-lactams via reductive cleavage of the N−O bond using SmI_2.

Despite recent advances with high-performance catalysts for use in asymmetric cycloaddition reactions, only a few successful examples of the catalytic enantioselective Diels−Alder reaction with acetylenic dienophiles have been reported.[1b,2] In general, acetylene derivatives with a linear sp−sp bond make asymmetric induction with a chiral Lewis acid difficult because the alkynyl moiety is far from the acidic metal center. Recently, we reported that Cu(II) complexes of 3-aryl-L-alanine amides (**1a** and **1b**, Chart 1) effectively promote the enantioselective Diels−Alder and [2 + 2] cycloaddition reactions with propioloylpyrazole derivatives **2** and acryloylpyrazole derivatives **3**.[1] Intramolecular π−cation attractive interaction between the electron-rich aromatic ring of **1** and the Cu(II) center creates an asymmetric environment to induce the enantioselective reaction. There have been no previous reports of the asymmetric 1,3-dipolar cycloaddition of nitrones with acetylene derivatives, although some achiral reactions have been reported.[3,4] The asymmetric 1,3-dipolar cycloaddition of nitrones has become one of the most prominent organic transformations.[5−7] We report here the first example of the catalytic and highly enantioselective 1,3-dipolar cycloaddition reactions of nitrones with **2** promoted by **1**•Cu(II) and the subsequent one-step transformation to *anti*-2,3-difunctionalized β-lactams.

Chart 1. Chiral Lewis Acid Catalysts **1**•CuX_2

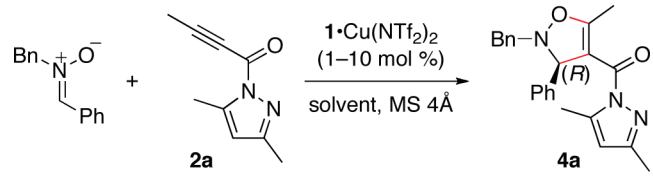


1•CuX_2

1a: Ar = 2-naphthyl
1b: Ar = 3,4-$(MeO)_2C_6H_3$

We began our studies by examining the 1,3-dipolar cycloaddition of *N*-benzylidenebenzylamine *N*-oxide with but-2-ynamide **2a** in the presence of **1**•$Cu(NTf_2)_2$ (5 mol %) and MS 4 Å[8] in CH_2Cl_2 (Table 1). As expected, **1a**•$Cu(NTf_2)_2$ effectively promoted the reaction at −40 °C and gave the corresponding adduct **4a** with high enantioselectivity (87% ee, entry 1). Complex **1b**•$Cu(NTf_2)_2$, which is also an effective catalyst for the Diels−Alder reaction with **2a**, showed slightly low enantioselectivity (84% ee, entry 2). The absolute configuration of the major enantiomer of **4a** was determined to be (3*R*).[9] Interestingly, the catalytic activity of **1a**•$Cu(NTf_2)_2$ was significantly higher than that of $Cu(NTf_2)_2$ itself (entry 1 versus entry 3). Only 1 mol % of **1a**•$Cu(NTf_2)_2$ successfully promoted the reaction to give **4a** in 97% yield with 87% ee (entry 4). The use of $EtNO_2$, MeCN, and toluene as solvents decreased the reactivity and enantioselectivity (entries 5−7).

Table 1. Enantioselective [3 + 2] Nitrone Cycloaddition with **2a**[a]



entry	**1** (mol %)	solvent	*T* (°C), *t* (h)	yield (%)	ee (%)
1	**1a**, 5	CH_2Cl_2	−40, 5	94	87 [*R*]
2	**1b**, 5	CH_2Cl_2	−40, 6	96	84 [*R*]
3	—	CH_2Cl_2	−40, 10	95	—
4[b]	**1a**, 1	CH_2Cl_2	−40, 48	97	87 [*R*]
5	**1a**, 10	$EtNO_2$	−20, 1	95	70 [*R*]
6	**1a**, 10	MeCN	−20, 2	96	48 [*R*]
7	**1a**, 10	toluene	−20, 23	88	81 [*R*]

[a] The reaction of a nitrone (1.1 equiv) with **2a** (0.3 mmol) was conducted in the presence of **1**•$Cu(NTf_2)_2$ (1−10 mol %) and MS 4 Å (100 mg) in solvent (1.2 mL). [b] The reaction of nitrone (1.1 equiv) with **2a** (1.5 mmol) was conducted in the presence of **1a**•$Cu(NTf_2)_2$ (1 mol %) and MS 4 Å (100 mg) in CH_2Cl_2 (6 mL).

To explore the scope and limitation of the present enantioselective cycloaddition reaction, several nitrones were examined under the optimized conditions (Table 2). The nitrone bearing a 1-naphthylmethyl (1-$NpCH_2$) group as an *N*-substituent (R^1) showed slightly higher enantioselectivity than those bearing benzyl and 3,4-dimethoxybenzyl (DMPM) groups (entries 3 and 4). In contrast, the use of methyl and phenyl groups as an R^1 group decreased the enantioselectivity (entries 1 and 2). *C*-(2-Naphthyl)-substituted nitrones gave the corresponding adducts **9a**−**c** with excellent enantioselectivities (entries 5, 8, and 10). Adduct **10** with a 3-methylfuran-2-yl (3-Me-furyl) group was obtained in 96% yield with 84% ee (entry 6). The ee of the adduct **10** could be upgraded to >99% ee by recrystallization from hexane-Et_2O. 3-Chlorobut-

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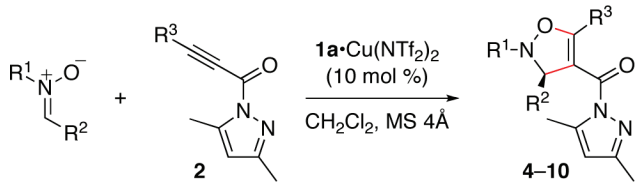
2-ynamide **2c** was also converted to the corresponding adducts bearing chloromethyl groups in high enantioselectivities (entries 9 and 10).

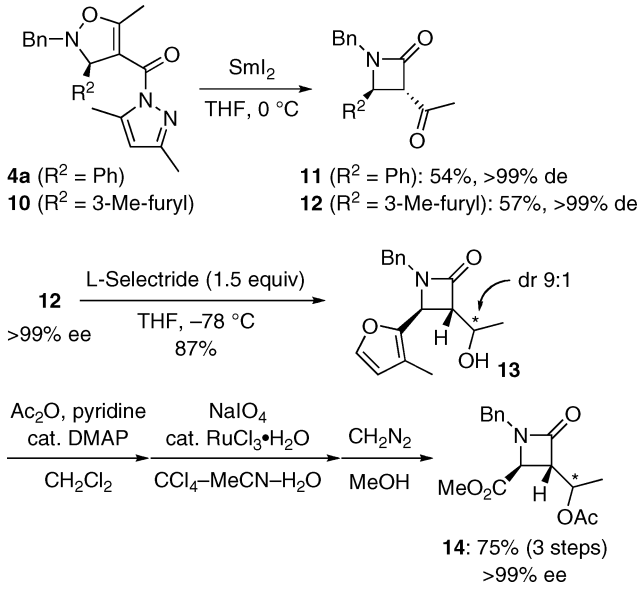
Table 2. Enantioselective 1,3-Dipolar Cycloaddition of Nitrones with Propioloylpyrazoles **2**[a]



entry	R^1	R^2	R^3 (**2**)	*T* (°C), *t* (h)	yield (%)	ee (%)
1	Me	Ph	Me (**2a**)	−20, 1.5	**5**, 81	74
2	Ph	Ph	Me (**2a**)	−20, 28	**6**, 39	80
3	DMPM[b]	Ph	Me (**2a**)	−40, 1	**7**, 82	87
4	1-NpCH$_2$[c]	Ph	Me (**2a**)	−40, 48	**8**, 91	91
5	Bn	2-Np[d]	Me (**2a**)	−40, 19	**9a**, 97	94
6	Bn	3-Me-furyl[e]	Me (**2a**)	−30, 61	**10**, 96	84
7	Bn	Ph	H (**2b**)	−40, 21	**4b**, 89	92
8	Bn	2-Np[d]	H (**2b**)	−40, 2	**9b**, 80	94
9	Bn	Ph	ClCH$_2$ (**2c**)	−40, 2	**4c**, 79	89
10	Bn	2-Np[d]	ClCH$_2$ (**2c**)	−40, 3.5	**9c**, 70	94

[a] The reaction of nitrone (1.1 equiv) with **2** (0.3 mmol) was conducted in the presence of **1a**•Cu(NTf$_2$)$_2$ (10 mol %) and MS 4 Å (100 mg) in CH$_2$Cl$_2$ (1.2 mL). [b] DMPM = 3,4-dimethoxybenzyl. [c] 1-NpCH$_2$ = 1-naphthylmethyl. [d] 2-Np = 2-naphthyl. [e] 3-Me-furyl = 3-methylfran-2-yl.

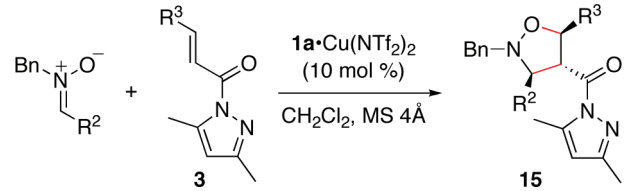
Scheme 1. Conversion of Cycloadducts **4a** and **10**



The 1,3-dipolar cycloadducts **4a** and **10** could be diastereoselectively converted to β-lactams **11** and **12** via reductive cleavage of the N−O bond using SmI$_2$[10] and subsequent cyclization without any loss of enantiomeric excess (Scheme 1). Diastereoselective reduction of the methylketone in **12** with L-Selectride[11] gave secondary alcohol **13** (87% yield, dr 9:1). The three-step transformation of **13** (acetylation of the hydroxy group, oxidative cleavage of the 3-methylfuran-2-yl group using NaIO$_4$ and RuCl$_3$,[12] and methyl esterification with CH$_2$N$_2$) gave methyl ester **14** (75% yield, 3 steps).

The 1,3-dipolar cycloaddition reaction of nitrones with acryloylpyrazole derivatives **3** was also effectively promoted by **1a**•Cu(NTf$_2$)$_2$ with high enantioselectivity (Table 3). The reaction of *N*-benzylnitrones with crotonamide **3a**, acrylamide **3b**, and fumarylamide **3c** gave the corresponding *endo*-adducts **15a**−**f** with high enantioselectivity (83−94% ee). The absolute configuration of the major enantiomer of **15a** was determined to be (3*S*,4*R*,5*S*).[9]

Table 3. Enantioselective 1,3-Dipolar Cycloaddition of Nitrones with Acryloylpyrazoles **3**[a]



entry	R^2	R^3 (**3**)	*T* (°C), *t* (h)	**15**, yield (%)	*endo*/*exo*	ee (%)
1	Ph	Me (**3a**)	0, 7	**15a**, 78	98:2	92
2	Ph	H (**3b**)	−20, 3.5	**15b**, 71	97:3	94
3	Ph	CO$_2$Et (**3c**)	rt, 49	**15c**, 41	73:27	83
4	2-Np[b]	Me (**3a**)	0, 13.5	**15d**, 82	>99:1	93
5	2-Np[b]	H (**3b**)	−20, 1	**15e**, 81	95:5	92
6	3-Me-furyl[c]	H (**3b**)	−10, 89	**15f**, 79	85:15	91

[a] The reaction of nitrone (1.1 equiv) with **3** (0.3 mmol) was conducted in the presence of **1a**•Cu(NTf$_2$)$_2$ (10 mol %) and MS 4 Å (100 mg) in CH$_2$Cl$_2$ (1.2 mL). [b] 2-Np = 2-naphthyl. [c] 3-Me-furyl = 3-methylfran-2-yl.

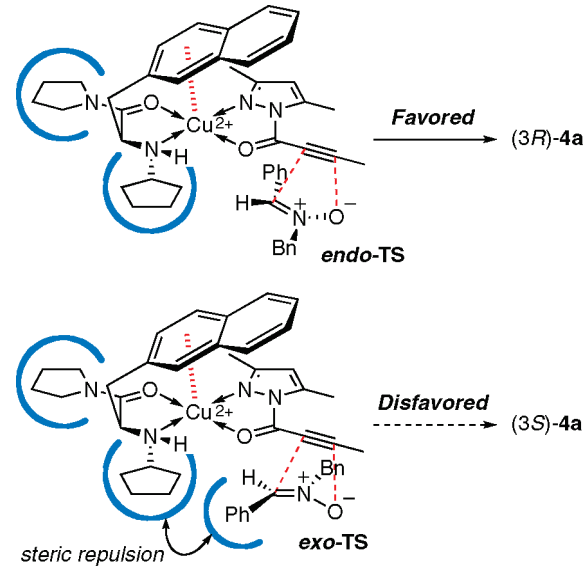


Figure 1. Proposed *endo*- and *exo*-transition-state assemblies for the 1,3-dipolar cycloaddition with **2a**.

Based on the previous results, the following reaction mechanism was proposed for the present nitrone cycloaddition: **2** and **3** would be predominantly *trans*-chelated with **1a**•Cu(NTf$_2$)$_2$, and the carbonyl *re* face of **2** and **3** would be shielded by the 2-naphthyl group in **1a** (Figure 1).[1] To avoid steric hindrance between the *N*-cyclopentyl group of **1a** and the phenyl group of nitrones in the *exo*-transition state (TS), nitrones would approach the *si* face of **2** and **3** via the *endo*-TS.[13] The finding that bulky *C*-(2-naphthyl)-substituted nitrones gave the adducts with excellent enantioselectivities can also be explained by these transition-state models.

In conclusion, we have developed catalytic enantioselective 1,3-dipolar cycloadditions of nitrones with propioloylpyrazole and acryloylpyrazole derivatives using chiral π−cation catalysts.[14] The cycloadducts of propioloylpyrazole derivatives could be stereoselectively converted to *anti*-2,3-difunctionalized β-lactams.

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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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