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Enantioselective 1,3-Dipolar Cycloaddition of Azomethine Imines with Propioloylpyrazoles Induced by Chiral π–Cation Catalysts

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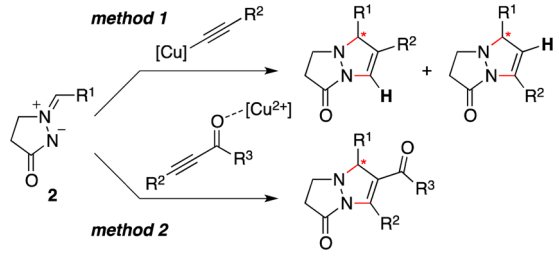
Supporting Information

ABSTRACT: We developed 1,3-dipolar cycloadditions of azomethine imines with propioloylpyrazoles catalyzed by a chiral copper(II) complex of 3-(2-naphthyl)-L-alanine amide. The asymmetric environment created by intramolecular π–cation interaction and the *N*-alkyl group of the chiral ligand 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 azomethine imines with internal alkyne derivatives to give fully substituted pyrazolines.

Nitrogen-containing five-membered heterocycles are core structures that are found in many bioactive compounds. For example, it has been reported that multisubstituted pyrazolines show various useful bioactivities.[1] Based on their biological significance and potential as chiral building blocks, the development of methods for the synthesis of these heterocycles is an important issue.[2] For the synthesis of chiral pyrazolines, asymmetric 1,3-dipolar cycloaddition of azomethine imines with alkynes is one of the most powerful methods.[3]

There are two methodologies for the 1,3-dipolar cycloaddition of azomethine imines with alkynes (Scheme 1): (1) copper(I) acetylide-mediated cycloaddition[4] and (2) Lewis acid-catalyzed cycloaddition. In 2003, Fu reported the first asymmetric CuI-catalyzed cycloaddition of azomethine imines with terminal alkynes (method 1).[4a] Recently, Arai,[4c,f] Kobayashi,[4d] and Maruoka[4e] also reported Cu(I) acetylide-mediated enantioselective cycloaddition of azomethine imines. Although these methods induce high enantioselectivity, dipolarophiles are limited to terminal alkynes. In contrast,

Scheme 1. 1,3-Dipolar Cycloaddition of Azomethine Imines with Alkynes



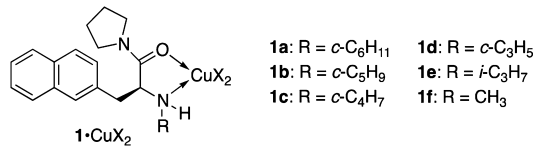


Figure 1. Chiral π–cation catalysts **1**·CuX_2.

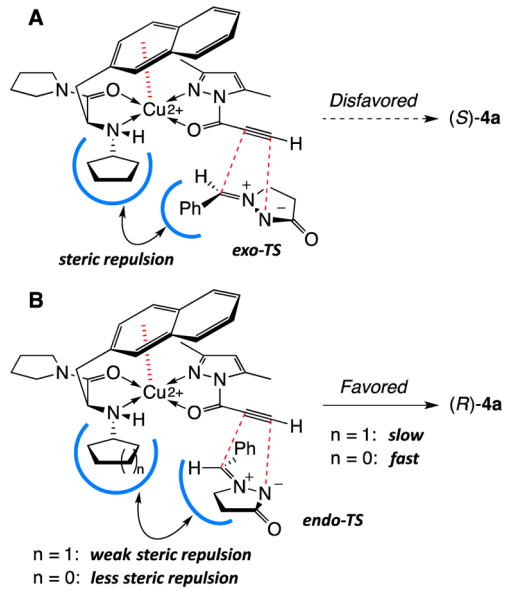


Figure 2. Proposed *exo*- and *endo*-transition-state assemblies for the reaction of **2a** with **3a**.

Lewis acid-catalyzed cycloaddition (method 2) could be applied to not only terminal alkynes but also to internal alkynes, in principal, so this method may be useful for the synthesis of fully substituted pyrazolines. However, there have been no reports on the asymmetric Lewis acid-catalyzed cycloaddition of azomethine imines with internal alkynes.

We previously reported that chiral π–cation catalyst **1b**·CuX_2 (Figure 1) effectively promoted enantioselective cycloadditions with propioloylpyrazoles **3**, such as the Diels–Alder reaction, [2 + 2] cycloaddition and the 1,3-dipolar cycloaddition of nitrones.[5−7] These cycloaddition reactions are

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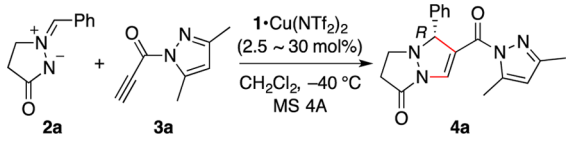
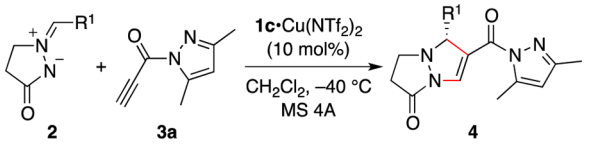
Table 1. 1,3-Dipolar Cycloaddition of 2a with 3a Catalyzed by 1·Cu(NTf$_2$)$_2$[a]



entry	1 (R)	time (h)	yield (%)	ee (%)
1	**1a** (*c*-C$_6$H$_{11}$)	26	73	54
2	**1b** (*c*-C$_5$H$_9$)	43	96	86
3	**1c** (*c*-C$_4$H$_7$)	2.5	95	95
4[b]	**1c** (*c*-C$_4$H$_7$)	24	94	95
5[c]	**1c** (*c*-C$_4$H$_7$)	192	98	94
6	**1d** (*c*-C$_3$H$_5$)	10	95	93
7	**1e** (*i*-C$_3$H$_7$)	43	92	60
8	**1f** (CH$_3$)	24	82	73

[a]Reaction of **2a** (1.1 equiv) with **3a** (0.1 mmol) was conducted in the presence of **1**·Cu(NTf$_2$)$_2$ (30 mol %) and MS 4A (100 mg) in CH$_2$Cl$_2$ (1.2 mL). [b]Reaction was conducted with **3a** (0.3 mmol) in the presence of **1c**·Cu(NTf$_2$)$_2$ (10 mol %). [c]Reaction was conducted with **3a** (0.6 mmol) in the presence of **1c**·Cu(NTf$_2$)$_2$ (2.5 mol %) in CH$_2$Cl$_2$ (7.5 mL).

Table 2. 1c·Cu(NTf$_2$)$_2$-Catalyzed 1,3-Dipolar Cycloaddition of 2 with 3a[a]



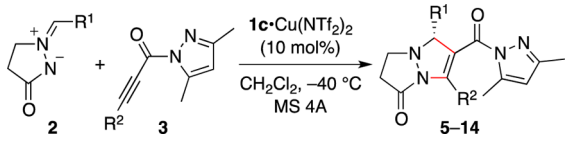
entry	2 (R^1)	4	time (h)	yield (%)	ee (%)
1	**2b** (2-MeOC$_6$H$_4$)	**4b**	69	80	88
2	**2c** (3-MeOC$_6$H$_4$)	**4c**	4	93	91
3[b]	**2c** (3-MeOC$_6$H$_4$)	**4c**	9	89	93
4	**2d** (4-MeOC$_6$H$_4$)	**4d**	24	87	90
5	**2e** (4-NO$_2$C$_6$H$_4$)	**4e**	66	94	90
6	**2f** (4-BrC$_6$H$_4$)	**4f**	21	91	93
7	**2g** (2-naphthyl)	**4g**	48	94	95
8	**2h** (3-furyl)	**4h**	122	83	87
9	**2i** (PhCH=CMe)	**4i**	25	98	90

[a]Reaction of **2** (1.1 equiv) with **3a** (0.3 mmol) was conducted in the presence of **1c**·Cu(NTf$_2$)$_2$ (10 mol %) and MS 4A (100 mg) in CH$_2$Cl$_2$ (1.2 mL). [b]Reaction of **2c** (1.1 equiv) with **3a** (3 mmol) was conducted in the presence of **1c**·Cu(NTf$_2$)$_2$ (10 mol %) and MS 4A (0.5 g) in CH$_2$Cl$_2$ (12 mL).

highly useful for the enantioselective synthesis of bicyclic 2,5-diene ligands, β-lactams, and so on. We report here a significant expansion of the scope of the enantioselective cycloadditions with alkynes: the 1,3-dipolar cycloaddition of azomethine imines **2** with propioloylpyrazoles **3**. To the best of our knowledge, this is the first enantioselective 1,3-dipolar cycloaddition of azomethine imines with internal alkynes.

In an initial investigation, we performed the enantioselective 1,3-dipolar cycloaddition of azomethine imine **2a** with propioloylpyrazole **3a** in CH$_2$Cl$_2$ at −40 °C in the presence of MS 4A.[8] However, the reaction required a long reaction time and showed unsatisfactory enantioselectivity, even when 30 mol % of **1b**·Cu(NTf$_2$)$_2$ was used as a catalyst (Table 1, entry 2). The absolute configuration of the major enantiomer of cycloadduct **4a** was determined to be *R*.[9] Based on the absolute configuration of **4a** and the previous results, the

Table 3. 1c·Cu(NTf$_2$)$_2$-Catalyzed 1,3-Dipolar Cycloaddition of 2 with β-Substituted Propiolamide 3[a]



entry	2	3 (R^2)	time (h)	yield (%)	ee (%)
1	**2a**	**3b** (ClCH$_2$)	88	**5**, 89	94
2	**2a**	**3c** (MeOCH$_2$)	300	**6**, 83	94
3[b]	**2d**	**3c** (MeOCH$_2$)	144	**7**, 79	87
4	**2a**	**3d** (MsOCH$_2$)	74	**8**, 92	92
5[c]	**2a**	**3d** (MsOCH$_2$)	48	**8**, 85	92
6	**2d**	**3d** (MsOCH$_2$)	72	**9**, 99	87
7	**2f**	**3d** (MsOCH$_2$)	48	**10**, 94	93
8	**2i**	**3d** (MsOCH$_2$)	24	**11**, 95	91
9	**2d**	**3e** (BzOCH$_2$)	120	**12**, 98	86
10	**2a**	**3f** [(CH$_2$O)$_2$CH]	48	**13**, 98	85
11[d]	**2a**	**3g** (PhthalNCH$_2$)	168	**14**, 70	80

[a]Reaction of **2** (1.1 equiv) with **3** (0.3 mmol) was conducted in the presence of **1c**·Cu(NTf$_2$)$_2$ (10 mol %) and MS 4A (100 mg) in CH$_2$Cl$_2$ (1.2 mL). [b]Reaction was conducted in the presence of **1c**·Cu(NTf$_2$)$_2$ (20 mol %). [c]The reaction of **2a** (1.1 equiv) with **3d** (3 mmol) was conducted in the presence of **1c**·Cu(NTf$_2$)$_2$ (10 mol %) and MS 4A (0.5 g) in CH$_2$Cl$_2$ (12 mL). [d]Reaction was conducted at −20 °C.

following transition-state assembly was proposed for the present 1,3-dipolar cycloaddition (Figure 2). An efficient asymmetric environment was created around the Cu(II) cation: a 2-naphthyl group in **1b** shielded the carbonyl *Re* face of coordinated **3a** through the intramolecular π−cation interaction that was supported by theoretical calculations.[5b,e,10,11] Azomethine imine **2a** would approach the *Si* face of the coordinated **3a** via the *endo*-TS (Figure 2B, *n* = 1), thus avoiding steric repulsion between the *N*-cyclopentyl group of **1b** and the phenyl group of **2a** in *exo*-TS (Figure 2A) to give (*R*)-**4a** as a major enantiomer. The steric interaction between the *N*-cyclopentyl group of **1b** and the ethylene group of **2a** may have decreased the reactivity.

Therefore, we next investigated the *N*-alkyl group of ligand **1** to improve the reactivity and enantioselectivity. When the reaction was conducted with **1a** bearing an *N*-cyclohexyl group, cycloadduct **4a** was obtained with poor enantioselectivity (entry 1). On the other hand, the use of *N*-cyclobutyl and *N*-cyclopropyl groups (ligands **1c** and **1d**) successfully improved both the reactivity and enantioselectivity (entries 3 and 5). Especially, the catalytic activity of **1c**·Cu(NTf$_2$)$_2$ was high enough to promote the reaction with a catalyst loading of 10 mol % (entry 4). Only 2.5 mol % of **1c**·Cu(NTf$_2$)$_2$ successfully promoted the reaction without any decrease of enantioselectivity, albeit the reaction required rather long reaction time (entry 5). The use of sterically less-hindered *N*-cycloalkyl groups would successfully avoid steric repulsion with the ethylene group of **2a** (Figure 2B, *n* = 0). The *N*-isopropyl group of **1e** has steric hindrance similar to the *N*-cyclohexyl group of **1a**, which may be the reason why **1e** showed low enantioselectivity (entry 7). Ligand **1f** bearing *N*-methyl group also showed poor enantioselectivity (entry 8), probably because steric repulsion between the *N*-methyl group and the phenyl group of **2a** in *exo*-TS was very weak, and the reaction proceeded via both *exo*- and *endo*-TS.

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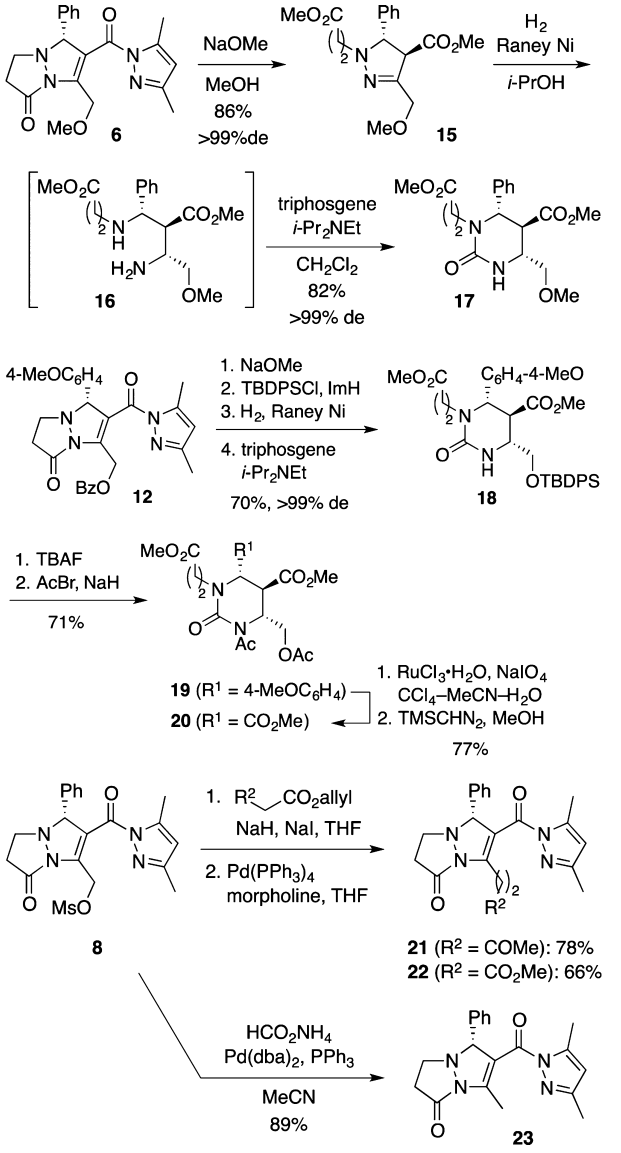
Scheme 2. Transformation of Cycloadducts 6 and 7



With the optimized π−cation catalyst in hand, we next examined the reactions of various azomethine imines to explore the generality and substrate scope of the present 1,3-dipolar cycloaddition (Table 2). The reactions were conducted in the presence of **1c**·$Cu(NTf_2)_2$ (10 mol %) at −40 °C to give the corresponding cycloadducts with high enantioselectivities. The reaction tolerated both electron-donating and -withdrawing groups on the phenyl, heteroaryl, and alkenyl groups (entries 1, 2 and 4−9). The large-scale reaction of **2c** with **3a** (3 mmol) also gave **4c** in 89% yield with 93% ee (entry 3).

The present cycloaddition was also effective for β-substituted propioloylpyrazoles **3**. The reaction of **2** with **3b**−**g** proceeded to give the corresponding fully substituted cycloadducts **5**−**14** in good to high yields with high enantioselectivity (Table 3). A large-scale reaction with **3d** (3 mmol) also gave **7** in 85% yield with 92% ee (entry 5).

The 1,3-dipolar cycloadducts **4**−**14** are useful compounds for the synthesis of various nitrogen-containing chiral compounds. For example, methanolysis of **6** gave the corresponding dimethyl ester **15** in 86% yield (Scheme 2). Raney Ni-catalyzed hydrogenation[12] of **15** gave the corresponding chiral 1,3-diamine **16** as a single diastereomer, which could be isolated as cyclic urea **17** after the reaction with triphosgene[13] (82% yield, 2 steps). The stereochemistry of three contiguous stereogenic centers of **18** was determined to be (4*R*,5*S*,6*S*) by ^{1}H NMR analysis. Cycloadduct **12** was also converted to the corresponding cyclic urea **18** (70% yield, 4 steps). Since the benzoyl group of **12** was removed by the methanolysis, the primary hydroxy group was protected by TBDPS group. Since the silyloxy and the urea groups of **18** were unstable under Ru-catalyzed oxidation, they were protected by acetyl group (71% yield, 2 steps). Oxidation of 4-methoxyphenyl group of **19**, followed by methyl esterification, gave the corresponding trimethyl ester **20** (77% yield, 2 steps). Since methoxycarbonyl and protected hydroxymethyl groups can be converted to various functional groups, cyclic ureas **17** and **20** should be useful building block.

Mesyloxymethyl group of **8** could be used for a carbon chain elongation. For example, nucleophilic substitution[14] of **8** with allyl acetoacetate and allyl methyl malonate, followed by decarboxylation,[15] gave methyl ketone **21** and methyl ester **22** in respective yields of 78 and 66%. In addition, the reduction of the mesyloxymethyl group of **8** gave **23** with the methyl group (89% yield).

In conclusion, we have developed a catalytic enantioselective 1,3-dipolar cycloaddition reaction of azomethine imines with propioloylpyrazoles using chiral π−cation catalysts. The reaction with β-substituted propioloylpyrazoles gave fully substituted pyrazolines in high yields with high enantioselectivities. The cycloadducts could be converted to 1,3-diamines with three contiguous stereogenic centers.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed 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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Notes

The authors declare no competing financial interest.

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