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Trisoxazoline/Cu(II)-Promoted Kinugasa Reaction. Enantioselective Synthesis of β-Lactams

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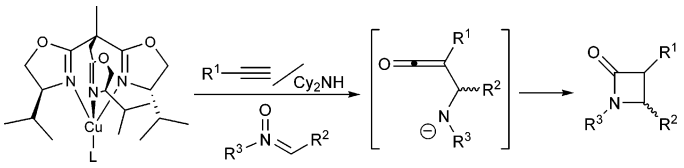

The reactions of nitrones with terminal alkynes, catalyzed by chiral ^{i}Pr-trisoxazoline **2a**/Cu(ClO_4)$_2$·6H_2O under air atmosphere, afforded β-lactams in moderate to good yields with up to 85% ee. The diastereoselectivity depends on the alkyne. Propiolate gives the trans-isomer as a major product, while the other alkynes afford cis-disubstituted lactams predominantly. Copper(II) salt proved to be an efficient catalyst precursor for the first time in the Kinugasa reaction, and this allowed the reaction to be performed under a practical and convenient condition. An appropriate base used in this reaction was essential to control both diastereoselectivity and enantioselectivity. Compared with primary and tertiary amines, secondary amines gave higher enantioselectivities. The reaction scope and limitation as well as the mechanism were also studied.

Introduction

β-Lactam is a core structure of many natural and synthetic β-lactam antibiotics,[1] such as penicillin, cephalosporin, thienamycin, and monocyclic β-lactams, as well as a useful synthetic intermediate[2] in organic synthesis. Although many synthetic methods have been developed, most of them are based on the use of chiral precursors.[1,3] Of the direct catalytic enantioselective approaches,[4] the most successful is the asymmetric Staudinger condensation of ketenes with imines, developed by Lectka et al.[4h] Asymmetric Kinugasa reaction[5] also provides an easy access to optically pure β-lactams with different structures due to its appealing virtues, such as readily available starting materials, high functional-group tolerance, and atom-economical character.

Kinugasa and Hashimoto first reported the reaction of copper(I) phenylacetylide with nitrone in dry pyridine, providing an atom-economical and a facile way to synthesize β-lactams in 1972.[5b] Later on, Miura and co-workers developed the first catalytic version of this reaction and found that the coupling reactions between phenylacetylene **4a** and a series of C,N-diarylnitrones could be accomplished well directly in the presence of substoichiometric CuI.[5c] They also pioneered the asymmetric reaction of phenylacetylene **4a** with diphenylnitrone **5a** using chiral ligands **1a**−**1c** (Figure 1).

With 10 mol % of CuI and 20 mol % of bisoxazoline **1a** in the presence of K_2CO_3, the reaction provided β-lactams in 57% ee and in 30% de. Recently, great progress was made by Fu and and Lo.[5d] They found that 1 mol % of bis(azaferrocenes) **3**/CuCl (Figure 1) could catalyze intermolecular Kinugasa reaction very well to afford the desired products with good to high enantioselectivities (up to 93% ee) and with high cis diastereoselections. By a similar strategy, they demonstrated that an intramolecular Kinugasa reaction could be used to construct fused tricyclic ring systems efficiently with good enantioselectivities.[5e]As described above, Cu(I) is always used as the catalyst for the Kinugasa reaction. Thus, this reaction gets to be

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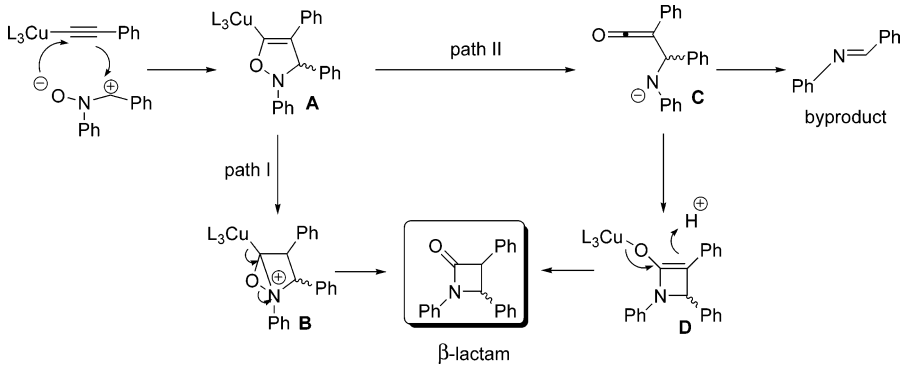
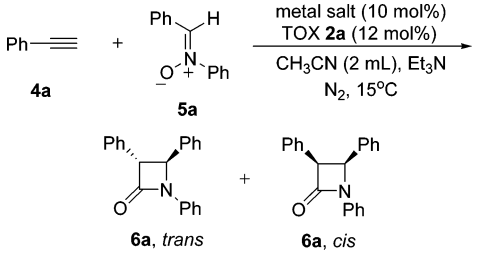
SCHEME 1. Plausible Mechanism



performed strictly under nitrogen to mitigate the Glaser oxidative coupling. In our efforts to develop superior catalysts that are cheap, easy to access, air-stable, and water-tolerant, we designed a pseudo C_3-symmetric trisoxazoline (TOX) **2a**[6,7] (Scheme 1) by sidearm approach and found that TOX **2a**/Cu(II) was an efficient catalyst for the asymmetric Friedel−Crafts reaction of indole with alkylidene malonate,[7] asymmetric 1,3-cycloaddition,[8a] and Diels−Alder reaction.[8b] Recently, we extended the TOX

TABLE 1. Effect of Copper Salt on the Kinugasa Reaction[a]



entry	metal salt	Et_3N (equiv)	time (h)	yield (%)[b]	cis/trans[c]	ee (%)[d]
1	CuCl	2.0	7	42	13/1	33
2	CuBr	2.0	96	30	11/1	49
3	CuI	2.0	16	46	12/1	51
4	CuOTf·1/2C_6H_6	2.0	40	36	11/1	5
5	$Cu(ClO_4)_2$·$6H_2O$	2.0	12	42	10/1	56
6	$Cu(OTf)_2$	2.0	6	60	11/1	3
7	$Cu(BF_4)_2$·xH_2O	2.0	42	53	13/1	56
8	$Cu(ClO_4)_2$·$6H_2O$	1.5	19	50	11/1	61
9	$Cu(ClO_4)_2$·$6H_2O$	1.0	19	56	11/1	61
10[e]	$Cu(ClO_4)_2$·$6H_2O$	1.0	18	45	12/1	63
11	$Cu(ClO_4)_2$·$6H_2O$	0.5	19	43	11/1	63

[a] Reactions were run at 15 °C using 12 mol % of TOX **2a** and 10 mol % of $Cu(ClO_4)_2$·$6H_2O$ under N_2 on 0.25 mmol scale. [b] Total isolated yield of cis- and trans-isomers. [c] Determined by ^1H NMR. [d] The enantiomeric excess of the cis-isomer was determined by chiral HPLC. [e] Under air atmosphere.

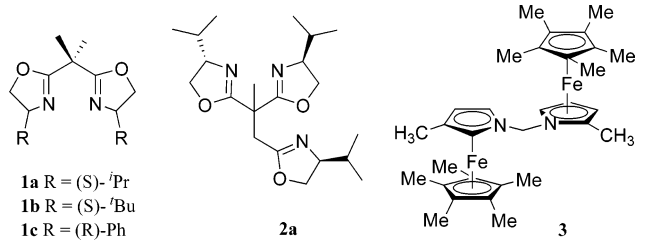


FIGURE 1. Chiral ligands for the asymmetric Kinugasa reaction.

2a/Cu(I or II) system to the Kinugasa reaction and found that, in the presence of a catalytic amount of TOX **2a**, $Cu(ClO_4)_2$·$6H_2O$ could be used directly instead of Cu(I) salt to catalyze the Kinugasa reaction between alkynes **4** and nitrones **5** very well to provide the desired β-lactams **6** in moderate to good enantioselectivities.[9] In this article, we wish to report the reaction modification, the scope and limitation in detail, and the mechanistic studies.

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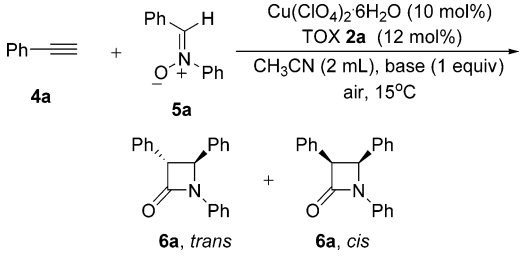
TABLE 2. Effect of Base[a]



entry	base	yield (%)[b]	cis/trans[c]	ee (%)[d]	entry	base	yield (%)[b]	cis/trans[c]	ee (%)[d]
1	Et_3N	45	12/1	63	12	*n*-octyl$_2$NH	59	6/1	80
2	*i*-Pr_2NEt	51	>99/1	55	13	Et_2NH	61	6/1	82
3	$CyNEt_2$	56	11/1	56	14	Cy_2NH	63	13/1	79
4	Cy_2NMe	45	23/1	58	15	*c*-amyl$_2$NH	65	16/1	76
5	PMP[e]	41	>99/1	58	16	*n*-octylNHCy	66	7/1	77
6	NMO	12	20/1	55	17	TMP[f]	54	>99/1	55
7	Proton Sponge	41	5/1	56	18	morpholine	16	5/1	52
8	*i*-Pr_2NH	61	9/1	72	19	*i*-$PrNH_2$	39	5/1	59
9	*s*-Bu_2NH	62	15/1	73	20	*t*-$BuNH_2$	53	9/1	51
10	*i*-Bu_2NH	52	9/1	68	21	*i*-$BuNH_2$	28	4/1	52
11	*i*-amyl$_2$NH	55	6/1	79	22	cinchonidine	14	12/1	62

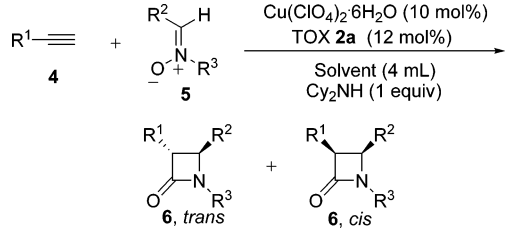
[a] Reactions were run at 15 °C using 12 mol % of TOX **2a** and 10 mol % of $Cu(ClO_4)_2 \cdot 6H_2O$ under air atmosphere on 0.25 mmol scale. [b] Total isolated yield of cis- and trans-isomers. [c] Determined by ^1H NMR. [d] The enantiomeric excess of the cis-isomer was determined by chiral HPLC. [e] 1,2,2,6,6-Pentamethylpiperidine. [f] 2,2,6,6-Tetramethylpiperidine.

Results and Discussion

Preliminary Results. Initially, we tried the reaction of phenylacetylene **4a** with nitrone **5a** using TOX **2a**/CuCl as a catalyst under conditions similar to Fu's conditions,[5d] but triethylamine instead of dicyclohexylmethylamine at 15 °C and only 33% ee was obtained (Table 1, entry 1). Other copper(I) salts were also examined (entries 2−4). As shown in Table 1, CuI gave the best enantioselectivity (51% ee) but CuOTf·1/2C_6H_6 afforded a very low enantioselectivity (5% ee) in the same conditions (entries 3 and 4). CuBr was less active, and the corresponding reaction could not be complete even when the reaction time was prolonged to 96 h (entry 2). Gratifyingly, copper(II) salts were found to be good catalysts for this reaction and usually gave better enantioselectivities than copper(I) salts under the same conditions (entries 1−3 versus entries 7−11) except that $Cu(OTf)_2$ only gave 3% ee (entry 6). The results suggested that the counterion of the copper salts played an important role in the enantiofacial differentiation of this reaction. We also examined other metal salts, such as $Zn(ClO_4)_2 \cdot 6H_2O$, $Co(ClO_4)_2 \cdot 6H_2O$, $Ni(ClO_4)_2 \cdot 6H_2O$, $PtCl_2$, and $Ag(ClO_4)_2 \cdot xH_2O$, but no desired product was obtained. The reduction of triethylamine from 2.0 equiv to 0.5 equiv did not influence enantioselectivity of the predominant cis product but lowered the yield slightly (entries 8−11). When triethylamine was reduced to 0.1 equiv, only a trace amount of lactam was detected. Noticeably, it was found that TOX **2a**/$Cu(ClO_4)_2 \cdot 6H_2O$ was air-stable and water-tolerant, which allowed the Kinugasa reaction to be performed under air atmosphere for the first time without loss of enantiomeric excess (entry 10). This modification simplified greatly the reaction operation.

Effect of Base. Further studies showed that the amines strongly influenced diastereoselectivity, enantioselectivity, and reaction rate. Bulkier amines always gave better diastereoselection. As summarized in Table 2, generally tertiary amines provided higher diastereoselectivity than secondary ones, and the latter were better than primary ones. For example, both 1,2,2,6,6-pentamethylpiperidine and diisopropylethylamine gave almost a single cis-isomer, but *iso*-butylamine only gave the product with moderate diastereoselectivity (entries 2, 5, and 21). Compared with tertiary and primary amines, secondary ones afforded the desired products with higher enantioselectivity but lower diastereoselectivity (entries 8−16). To obtain better diastereoselectivity as well as enantioselectivity, we investigated a variety of secondary amines (entries 14−16) and found that the dicyclohexylamine gave the most satisfactory result (entry 14). In this case, the reaction of phenylacetylene **4a** with nitrone **5a** gave 79% ee, comparable to the result reported by Fu with the use of **3**/CuCl as a chiral catalyst.[5d] These results suggested that the amine might coordinate to the copper center and relay the chirality to the product. Compared with alkylamines, the aromatic amines, such as *N*,*N*-dimethylaniline and aniline, did

TABLE 3. Effect of Solvent and Temperature[a]



entry	solvent	T (°C)	time (h)	yield (%)[b]	cis/trans[c]	ee (%)[d]
1	$PhCH_3$	15	18	44	4/1	72
2	Et_2O	15	18	40	6/1	74
3	THF	15	18	44	13/1	78
4	EtOAc	15	18	42	11/1	77
5	acetone	15	18	35	16/1	74
6	DMF	15	40	39	8/1	63
7	CH_3CN	15	16	63	13/1	79
8	CH_3CN	30	14	47	14/1	76
9	CH_3CN	0	38	60	15/1	82
10	CH_3CN	−10	52	64	27/1	83

[a] Reactions were run using 12 mol % of TOX **2a** and 10 mol % of $Cu(ClO_4)_2 \cdot 6H_2O$ in air on 0.25 mmol scale. [b] Total isolated yield of cis- and trans-isomers. [c] Determined by ^1H NMR. [d] Determined by chiral HPLC for the cis-isomer.

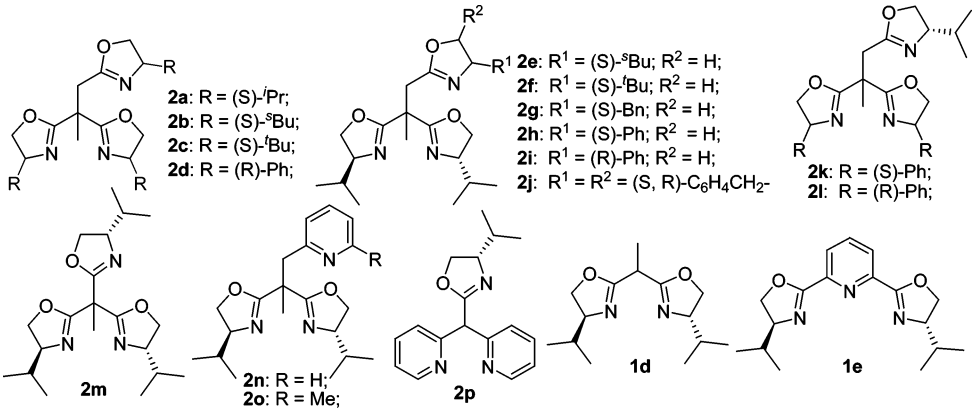


FIGURE 2. Chiral oxazoline ligands.

not catalyze this reaction at all. However, Proton Sponge (entry 7) promoted the reaction well (56% ee and 5/1 diastereomer ratio). Noticeably, cinchonine could not promote this reaction, and cinchonidine gave moderate enantioselectivity (entry 22).

Effects of Solvent and Temperature. We also examined the effects of solvents and temperature on this reaction using dicyclohexylamine as the optimal base.

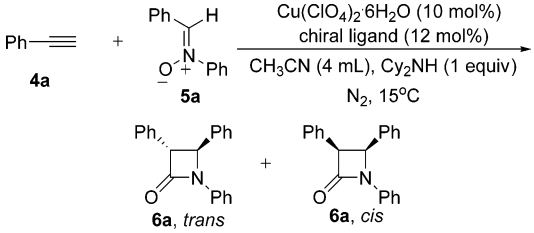
As shown in Table 3, the reaction of phenylacetylene **4a** with nitrone **5a** proceeded well in a number of solvents, providing cis-isomer as the major product. However, in methanol, no reaction was observed. In our screened conditions, acetonitrile was the optimal solvent. In addition, we found that lowering the temperature increased both the yield and the cis-selectivity slightly in CH_3CN (entries 7−10).

Effect of Ligand. Usually, the cooperation effects between metal and ligands influence strongly the enantioselectivity and yield.[10] To further improve the asymmetric induction, we synthesized a variety of trisoxazolines based on the frameworks of bisoxazolines (Figure 2) to study the effect of ligand on the reaction.

As shown in Table 4, bisoxazolines gave lower reaction rates and enantioselectivities than trisoxazolines (entries 1−3 versus entries 5−16). The reason, we proposed, is that trisoxazolines provided stronger chelation with copper center than bisoxazaolines to prevent effectively phenylethynylcopper from its coordination polymerization.[11] During the experiments, we did observe a small amount of yellow precipitation formed in the bisoxazolines/Cu(II) reaction system, but a clear solution occurred in the case of trisoxazolines. Generally, the pendant oxazoline rarely influences the enantoselectivity of the Kinugasa reaction (entries 5 and 8−13). For example, trisoxazolines **2h** and **2i**, with opposite chiral center in the pendant oxazoline, gave similar enantioselectivities (entries 11 and 12). Increasing the steric hindrance decreased the reaction rate greatly (entry 7), and thus trisoxazoline **2c** did not give the desired β-lactam.

Bisoxazaoline backbone proved to be essential to the reaction. For instance, two trisoxazolines (**2k**, **2l**) derived from (*S*)-Ph-bisoxazoline and (*R*)-Ph-bisoxazoline, respectively, provided β-lactams with opposite absolute configurations (entries 14 and 15). C_3-symmetric trisoxazoline **2m** reported by Gade and coworkers,[12] afforded moderate ee (entry 16). Considering that pyridine is in favor of the formation of β-lactams in the Kinugasa reaction,[5c] we designed and synthesized pyridinyl- and 2-methylpyridinyl-derived ^{i}Pr-bisoxazoline **2n** and **2o**, which proved to catalyze the Kinugasa reaction well but only gave 71 and 73% ee, respectively (entries 17 and 18). In addition, a bipyridine ligand **2p** was synthesized but gave a poor result (entry 19). In our screening conditions, the best result was achieved by using TOX **2a** as the ligand.

TABLE 4. Effect of Chiral Ligand[a]



entry	ligand	time (h)	yield (%)[b]	cis/trans[c]	ee (%)[d]
1	**1b**	7 days	31	9/1	60
2	**1c**	7 days	25	20/1	54
3	**1d**	6 days	33	43/1	36
4	**1e**	19	40	10/1	54
5	**2a**	15	60	13/1	80
6	**2b**	11	71	20/1	80
7	**2d**	6 days	47	13/1	−70
8	**2e**	15	51	9/1	66
9	**2f**	14	51	10/1	75
10	**2g**	11	56	9/1	58
11	**2h**	12	56	9/1	61
12	**2i**	15	60	10/1	56
13	**2j**	11	56	10/1	61
14	**2k**	32	52	9/1	58
15	**2l**	80	51	10/1	−52
16	**2m**	25	47	12/1	49
17	**2n**	10	49	17/1	71
18	**2o**	26	62	6/1	73
19	**2p**	5 days	14	9/1	2

[a] Reactions were run at 15 °C using 12 mol % of chiral ligand and 10 mol % of $Cu(ClO_4)_2 \cdot 6H_2O$ under N_2 on 0.25 mmol scale. [b] Total isolated yield of cis- and trans-isomers. [c] Determined by ^{1}H NMR. [d] The enantiomeric excess of the cis-isomer was determined by chiral HPLC.

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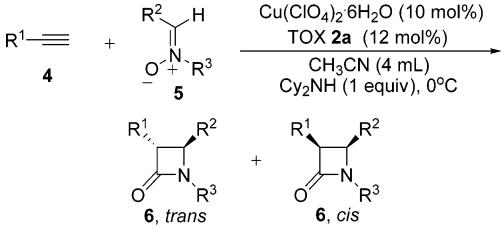
TABLE 5. Aymmetric Synthesis of β-Lactams[a]



entry	R^1	R^2	R^3	lactam	yield (%)[b]	cis/trans[c]	ee (%)[d]
1	C_6H_5	C_6H_5	C_6H_5	**6a**	56	15/1	82
2	C_6H_5	C_6H_5	*p*-MeC_6H_4	**6b**	36	19/1	82
3	C_6H_5	C_6H_5	*p*-$MeOC_6H_4$	**6c**	36	31/1	84
4	C_6H_5	C_6H_5	*p*-BrC_6H_4	**6d**	70	13/1	74
5	C_6H_5	C_6H_5	*p*-$EtO_2CC_6H_4$	**6e**	98	10/1	70
6	C_6H_5	*p*-MeC_6H_4	C_6H_5	**6f**	50	18/1	82
7	C_6H_5	*p*-$MeOC_6H_4$	C_6H_5	**6g**	58	18/1	83
8	C_6H_5	*p*-$F_3CC_6H_4$	C_6H_5	**6h**	75	14/1	82
9	C_6H_5	α-furyl	C_6H_5	**6i**	56	2/1	85
10	C_6H_5	*p*-$F_3CC_6H_4$	*p*-$MeOC_6H_4$	**6j**	35	25/1	84
11	C_6H_5	cyclohexyl	C_6H_5	no reaction			
12	C_6H_5	C_6H_5	$C_6H_5CH_2$	no reaction			
13	*p*-$F_3CC_6H_4$	C_6H_5	C_6H_5	**6k**	65	3/1	73
14	1-cyclohexenyl	C_6H_5	C_6H_5	**6l**	33	13/1	72
15	Me_3Si	C_6H_5	C_6H_5	no reaction			
16	EtO_2C	C_6H_5	C_6H_5	**6m**	25	1/6	46[e]
17[f]	EtO_2C	C_6H_5	C_6H_5	**6m**	45	1/5	48[e]
18[g]	EtO_2C	C_6H_5	C_6H_5	**6m**	67	1/6	50[e]
19[g]	EtO_2C	C_6H_5	*p*-$EtO_2CC_6H_4$	**6n**	80	1/4	51[e]
20[g]	EtO_2C	α-furyl	C_6H_5	**6o**	78	1/8	45[e]

[a] Reactions were run at 0 °C using 12 mol % of TOX **2a** and 10 mol % of $Cu(ClO_4)_2 \cdot 6H_2O$ under air atmosphere on 0.25 mmol scale. [b] Total isolated yield of cis- and trans-isomers. [c] Determined by ^1H NMR. [d] ee of the cis-isomer determined by chiral HPLC. [e] ee of the trans-isomer determined by chiral HPLC. [f] Using 6 mol % of TOX **2a**, 5 mol % of $Cu(ClO_4)_2 \cdot 6H_2O$, and 20 mol % of $^iPr_2NEt$. [g] Using 6 mol % of BOX **1b**, 5 mol % of $Cu(ClO_4)_2 \cdot 6H_2O$, and 20 mol % of $^iPr_2NEt$.

Reaction Scope. Under the optimal reaction conditions, we examined the generality of the current reaction by employing a variety of structurally different nitrones and alkynes. As shown in Table 5, the electronic character of aromatic groups on carbons of nitrones affected both the yields and the stereoselections. Electron-rich aromatic groups increased enantioselectivities but decreased the yields (entries 1−3). Electron-deficient ones slightly decreased enantioselectivities but increased the reaction rates (entries 4 and 5).[13] The electronic properties of the N-bound aromatic groups of nitrones had almost no obvious impact on the enantioselections (entries 6−10). Both electron-deficient and electron-rich aromatic groups afforded good enantioselectivities and diastereoselectivities. Nitrone with N-bound furyl group furnished the best ee but lowest diastereoselectivity in moderate yield (entry 9). Neither α-alkyl nor *N*-alkyl nitrone gave the desired product (entries 11 and 12). Noticeably, both aryl and alkyl alkynes worked well to provide the desired β-lactams (entries 13 and 14). For example, 1-cyclohexenyl acetylene gave 72% ee with high diastereoselectivity (entry 14).

We also investigated the reactions of ethyl propiolate with nitrones.[5j] As shown in Table 5, ethyl propiolate was a good substrate for the synthesis of desired β-lactam even in the presence of 5 mol % of Cu(II)/TOX **2a** (entries 16 and 17). Noticeably, compared with Cu(II)/TOX **2a**, Cu(II)/BOX **1b** gave better yield with comparable enantiomeric excess (entry 17 versus entry 18).

Mechanism Discussion. The classical Kinugasa reaction is catalyzed by Cu(I); however, in our case, Cu(II) was used as the promoter. To understand the mechanism, it is very important to clarify that the catalytic species is Cu(I) or Cu(II). In literature, Cu(II) could be reduced into Cu(I) through a radical process.[14,15] We also isolated a small amount (8.2 mg) of the coupling product diphenylbutadiyne in the reaction of phenyl acetylene **4a** (0.375 mmol) with nitrone **5a** (0.25 mmol) in the presence of 10 mol % of TOX **2a**/$Cu(ClO_4)_2 \cdot 6H_2O$ and 1.0 equiv of Cy_2NH under nitrogen atmosphere. Therefore, we proposed that the Cu(II) was reduced in situ into Cu(I) by phenylacetylene in the aforementioned Kinugasa reactions and the catalytic species is still Cu(I). This is also consistent with the following experimental phenomenon: a small amount of yellow precipitate (a probable coordination polymer of copper(I) phenylacetylide[11]) was observed in the reaction using bisoxazolines as ligands.

In literature, the Kinugasa reaction was proposed to proceed via a [3 + 2] cycloaddition reaction, followed by a rearrangement to give the β-lactam (path I in Scheme 1). Considering that imine was found as a byproduct in some reactions described above[16] and the nitrones with N-bound electron-withdrawing substituents gave better yields than those with N-bound electron-rich substituents (Table 5, entries 4 and 5 versus entries 1−3),

(13) Please see the Supporting Information.

(14) Recently, Carreira and Knopfel used $Cu(OAc)_2$ instead of Cu(I) to produce copper acetylide in the presence of sodium ascorbate. See: Knopfel, T. F.; Carreira, E. M. *J. Am. Chem. Soc.* **2003**, *125*, 6054.

(15) For Glaser coupling, see: (a) Glaser, C. *Ber. Dtsch. Chem. Ges.* **1869**, *2*, 422. (b) Youngblood, W. J.; Gryko, D. T.; Lammi, R. K.; Bocian, D. F.; Holten, D.; Lindsey, J. S. *J. Org. Chem.* **2002**, *67*, 2111. (c) Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2632. For Eglinton coupling, see: (d) Eglinton, G.; Galbraith, A. R. *Chem. Ind.* **1956**, 737. (e) Inouchi, K.; Kabashi, S.; Takimiya, K.; Aso, Y.; Otsubo, T. *Org. Lett.* **2002**, *4*, 2533. (f) Fabian, K. H. H.; Lindner, H.-J.; Nimmerfroh, N.; Hafner, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 3402.

we proposed another rationale, path II as shown in Scheme 1. In path II, cycloaddition adduct **A** decomposed into intermediate ketene **C**,[17] followed by an intramolecular nucleophilic cyclization to give enolate **D**, as in the Stauginger reaction. The enolate was protonated to afford the desired β-lactam. This mechanism is more reasonably than that in path I for the following observation: *N*-(4-carboethoxyphenyl)-α-phenylnitrone gave much higher yield than diphenylnitrone. The reason is probably that the N-bound electron-withdrawing group stabilized immediate **C** and prevented immediate **C** from its decomposition into the corresponding imine. An attempt to trap intermediate **C** failed. A clear mechanism awaits further study.

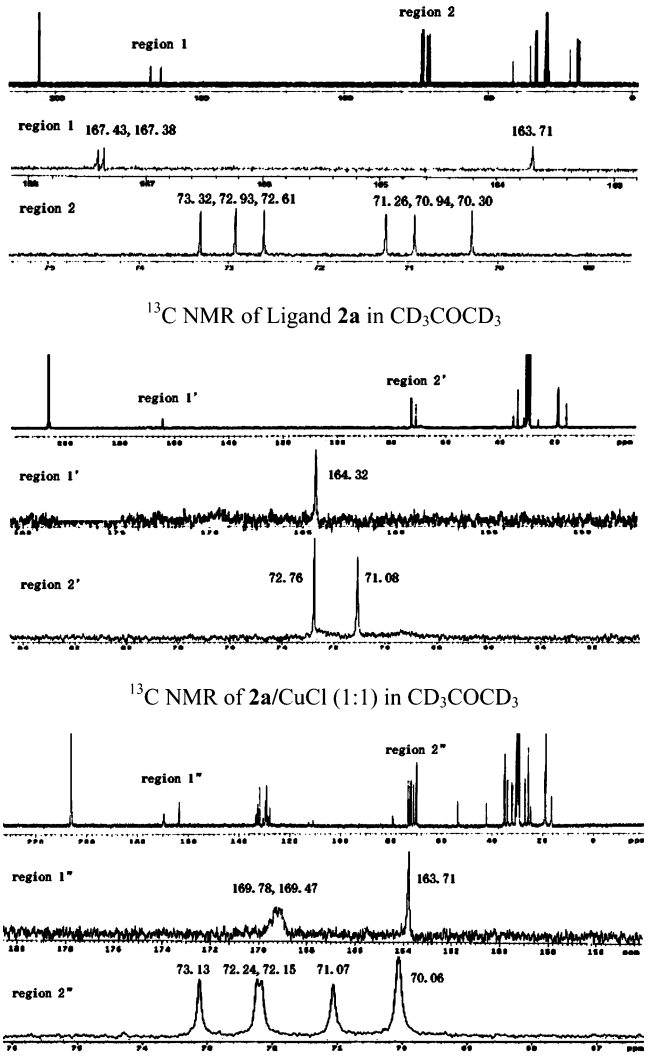
Stereochemical Model. Very recently, Gade and co-workers found that the pendant oxazoline of bisoxazoline-based tridentate ligand was dynamically coordinated to Cu(II), stabilized the catalytic species, and improved the catalytic efficiency greatly.[18] To further understand the role of the sidearm oxazoline in **2a** in the present reaction, the ^{13}C NMR technique was used for our study. Considering that Cu(II) is paramagnetic and Cu(I) was the possible catalytic species in our reaction, we chose CuCl instead of $Cu(ClO_4)\cdot 6H_2O$ for the ^{13}C NMR study. As shown in Figure 3, without CuCl, the ^{13}C chemical shifts of the three sp^2 carbon of oxazolines in TOX **2a** appeared at δ 163.71, 167.38, and 167.43 ppm (region 1, Figure 3). However, in the presence of equimolar CuCl, the ^{13}C signals merged at δ 164.32 ppm (region 1′, Figure 3). The ^{13}C signals merging were also observed for both the O- and N-bound sp^3 carbons (regions 2 and 2′, Figure 3). These results suggested that all three nitrogen atoms of TOX **2a** might coordinate to copper, as shown in Scheme 2.

With the addition of equimolar phenylacetylene **4a** and Cy_2NH, the single peak of the three sp^2 carbon of oxazolines split again into three peaks at δ 169.78, 169.47, and 163.71 ppm (region 1″, Figure 3). Compared with ligand **2a**, one peak at 163.71 ppm was identical and the other two shifted to downfield (167.38 and 167.43 versus 169.78 and 169.47). Similar shifts were observed in ^{13}C signals of the O- and N-bound sp^3 carbons (region 2″, Figure 3). These facts suggested that decoordination of the pendant oxazoline might occur when copper(I) phenylacetylide formed (Scheme 2), consistent with the coordination/decoordination equilibrium[18] proposed by Gade et al. in the trisoxazoline/Cu(II) catalytic system.

On the basis of these studies as well as the experimental results, we developed a stereochemical model in Scheme 2 to account for the enantioselection. Owing to the steric hindrance between the nitrone and isopropyl group, cuprous phenylacetylide approached the *Si*-face of nitrone to afford the (4*S*)-enantiomer of β-lactam.

Conclusions

In summary, the air-stable and water-tolerant TOX **2a**/$Cu(ClO_4)_2\cdot 6H_2O$ complex proved to be a good catalyst in the asymmetric Kinugasa reaction. This method provided a facile access to β-lactams in moderate to good yield and in moderate to good diastereo- and enantioselectivity. Noticeably, Cu(II) salt proved to be an efficient catalyst precursor for the first time in the Kinugasa reaction. It is significant that this modification allowed the Kinugasa reaction to be performed under air atmosphere, whereas all documented protocols were run under inert atmosphere. In addition, organic bases were found to influence both the selectivity and the reactivity strongly, and this provides probably some information for the catalyst design to further improve the selectivity and reactivity in this reaction.



^{13}C NMR of Ligand **2a** in CD_3COCD_3

^{13}C NMR of **2a**/CuCl (1:1) in CD_3COCD_3

^{13}C NMR of **2a**/CuCl/**4a**/Cy_2NH (1:1:1:1) in CD_3COCD_3

FIGURE 3. ^{13}C NMR study.

Experimental Section

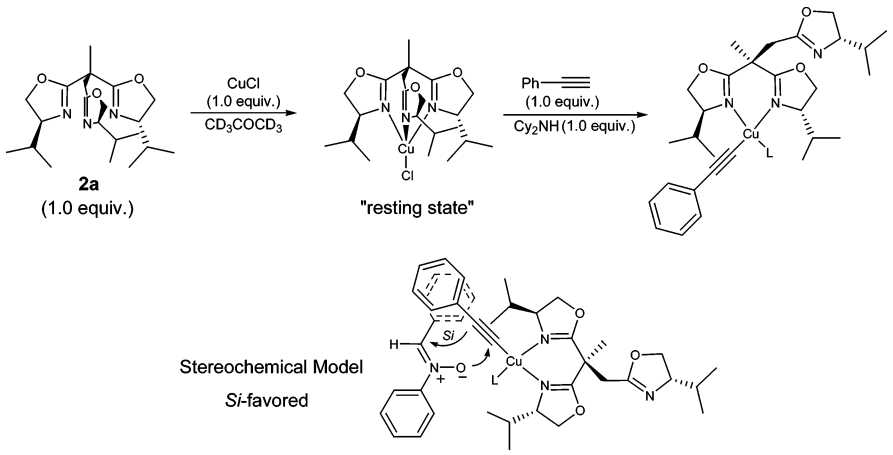
The Synthesis of Chiral Ligand 2p. To a solution of dipyridin-2-ylmethane (272 mg, 1.6 mmol) in dried THF (30 mL) was added dropwise *t*-BuLi (0.95 mL, 1.7 M in hexanes, 1.6 mmol) within 15−20 min at −78 °C under nitrogen. The resulting yellow solution was stirred for an additional hour at this temperature. Then a solution of (4*S*)-2-bromo-4-isopropyl-4,5-dihydrooxazole (357 mg, 1.9 mmol) in THF (10 mL) was added dropwise at −78 °C over 10 min. The solution was slowly warmed to room temperature, was stirred for an hour, and then refluxed for 6 h. The mixture was diluted with CH_2Cl_2 (30 mL) and was washed with H_2O (5

(16) From β-lactam **6a** to **6e**, the ratios of corresponding imines to lactams were 1/2.8, 1/1.4, 1.4/1, 1/7, 1/21, respectively, determined by ^1H NMR sepectroscopic analysis of the corresponding crude products. Also, 15% yield of (E)-*N*-benzylidenebenzeneamine was isolated in the reaction of **4a** and **5a**.

(17) For similar ketene intermediate, see: Ahn, C.; Kennington, J. W., Jr.; DeSheong, P. *J. Org. Chem.* **1994**, *59*, 6282. In addition, Fu also indicated this processes; see ref 5e.

(18) Foltz, C.; Stecker, B.; Marconi, G.; Bellemin-Laponnaz, S.; Wadepohl, H.; Gade, L. H. *Chem. Commun.* **2005**, 5115.

SCHEME 2



mL). The aqueous layer was extracted with CH_2Cl_2 (10 mL), and the combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (EtOAc/Et_3N = 200/1) to give the desired product 257 mg (syrup, 57%). $[\alpha]^{20}_D$ −37.0 (*c* 0.75, $CHCl_3$); IR (neat) 2961, 2891, 1671, 1586, 1567, 1467, 1432, 1356, 997, 989 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.57−8.54 (m, 2H), 7.64−7.60 (m, 2H), 7.48−7.42 (m, 2H), 7.18−7.15 (m, 2H), 5.46 (s, 1H), 4.30−4.22 (m, 1H), 4.05−3.97 (m, 2H), 1.84−1.76 (m, 1H), 0.93 (d, J = 6.9 Hz, 3H), 0.85 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.4, 158.1, 158.0, 149.4, 149.4, 136.6, 123.7, 123.6, 122.2, 122.2, 72.0, 70.0, 56.2, 32.4, 18.9, 17.7; LRMS-EI(*m*/*z*): 281 (M^+), 169 (100); HRMS-ESI (*m*/*z*): $[M + H]^+$ calcd for $C_{17}H_{19}N_3O$, 282.1601; found, 282.1617.

General Procedures for Catalytic Asymmetric Synthesis of *β*-Lactams. Procedure A. A mixture of $Cu(ClO_4)_2 \cdot 6H_2O$ (9.3 mg, 0.025 mmol) and (*S*)-isopropyl trisoxazoline **2a** (11.3 mg, 0.03 mmol) in CH_3CN (4 mL) was stirred under air atmosphere at 15 °C for 2 h. The solution was cooled to 0 °C, and then Cy_2NH (50 μL, 0.25 mmol) was added. After 10 min, alkyne (0.375 mmol) was added. When the color of the resulting mixture turned light yellow, we added nitrone (0.25 mmol) to the solution. After the reaction was complete (monitored by TLC), the mixture was passed through a short silica gel column (neat CH_2Cl_2 as the eluent). The filtrate was concentrated, and the residue was purified by flash chromatography (PE/CH_2Cl_2) to afford the product. The diastereoselectivity was determined by ^1H NMR sepectroscopic analysis of crude product. The determination of enantioselective excess of the cis-isomer was performed by chiral HPLC with a Daicel Chiralcel OD-H column (eluent: hexane/^{i}PrOH 80/20, flow rate: 0.7 mL/min).

Procedure B. A mixture of $Cu(ClO_4)_2 \cdot 6H_2O$ (4.6 mg, 0.0125 mmol) and (*S*)-^{t}Bu-BOX **1b** (4.5 mg, 0.015 mmol) in CH_3CN (2 mL) was stirred under air atmosphere at 15 °C for 1 h. The solution was cooled to 0 °C, and then $^i Pr_2NEt$ (9 μL, 0.05 mmol) and nitrone (0.25 mmol) were added. After 10 min, ethyl propiolate (50.6 μL, 0.5 mmol) was added. After the reaction was complete (monitored by TLC), the mixture was passed through a short silica gel column (neat CH_2Cl_2 as the eluent). The filtrate was concentrated, and the residue was purified by flash chromatography (PE/CH_2Cl_2) to afford the product. The diastereoselectivity was determined by ^1H NMR sepectroscopic analysis of the crude product. The determination of enantioselective excess of the trans-isomer was performed by chiral HPLC with a Daicel Chiralcel OD-H column (eluent: hexane/^{i}PrOH 85/15, flow rate: 0.9 mL/min).

(3*S*,4*S*)- 1,3,4-Triphenyl-2-azetidinone 6a. Procedure A: 56% yield (solid, 35 h); $[\alpha]^{20}_D$ −8.0 (*c* 1.62, $CHCl_3$; 82% ee); ^1H NMR (300 MHz, $CDCl_3$): δ 7.43−7.40 (m, 2H), 7.29−7.24 (m, 2H), 7.09−7.03 (m, 11H), 5.45 (d, J = 6.3 Hz, 1H), 5.00 (d, J = 6.6 Hz, 1H).

(3*S*,4*S*)-1-(4-Methylphenyl)-3,4-diphenyl-2-azetidinone 6b. Procedure A: 36% yield (solid, 56 h); $[\alpha]^{20}_D$ −10.5 (*c* 0.68, $CHCl_3$; 82% ee); ^1H NMR (300 MHz, $CDCl_3$): δ 7.32−7.26 (m, 2H), 7.11−7.03 (m, 12H), 5.44 (d, J = 6.0 Hz, 1H), 5.00 (d, J = 5.7 Hz, 1H), 2.29 (s, 3H).

(3*R*,4*S*)-Ethyl 2-Oxo-1,4-diphenylazetidine-3-carboxylate 6m. Procedure B: 67% yield (syrup, 1 h); $[\alpha]^{20}_D$ 34.9 (*c* 0.84, $CHCl_3$; 50% ee); ^1H NMR (300 MHz, $CDCl_3$): δ 7.41−7.23 (m, 9H), 7.09−7.07 (m, 1H), 5.35 (d, J = 3.0 Hz, 1H), 4.30 (q, J = 6.9 Hz, 2H), 3.99 (d, J = 2.7 Hz, 1H), 1.33 (t, J = 7.2 Hz, 8H).

(3*R*,4*S*)-Ethyl 1-(4-(Ethoxycarbonyl)phenyl)-2-oxo-4-phenylazetidine-3-carboxylate 6n. Procedure B: 80% yield (syrup, 1 h); $[\alpha]^{20}_D$ 17.4 (*c* 0.88, $CHCl_3$; 49% ee); ^1H NMR (300 MHz, $CDCl_3$): δ 7.96−7.93 (m, 2H), 7.40−7.27 (m, 7H), 5.38 (d, J = 2.4 Hz, 1H), 4.33 (q, J = 7.2 Hz, 2H), 4.30 (q, J = 7.2 Hz, 2H), 4.03 (d, J = 2.7 Hz, 1H), 1.35 (t, J = 7.2 Hz, 3H), 1.34 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.9, 165.8, 159.5, 140.5, 135.7, 130.8, 129.4, 129.2, 126.1, 126.0, 116.6, 36.7, 62.2, 60.9, 57.7, 14.2, 14.1; IR (KBr): 2982, 2938, 1768, 1723, 1606, 1514, 1456, 1365, 1173, 1114, 1013, 854, 769 cm^{-1}; EI (*m*/*z*): 367 (M^+), 131 (100); Anal. calcd for $C_{22}H_{16}F_3NO$: C, 68.31; H, 5.76; N, 3.81. Found: C, 68.31; H, 5.85; N, 3.46.

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Supporting Information Available: Characterization data for all compounds and experimental procedure. This material is available free of charge via the Internet at http://pubs.acs.org.

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