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Enantioselective synthesis of β-lactams via the IndaBox–Cu(II)-catalyzed Kinugasa reaction

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ABSTRACT

The enantioselective Kinugasa reaction of nitrones with terminal alkynes in the presence of 20 mol % of IndaBox–Cu(OTf)$_2$ and di-*sec*-butylamine (1.5 equiv) produced β-lactams with the highest level of enantiomeric excesses among the catalytic enantioselective Kinugasa reactions reported so far.

β-Lactams[1] are an important class of compounds because of their utility as antibiotics such as penicillins, cephalosporins, monobactams, and carbapenems. In addition, chiral β-lactams also serve as versatile building blocks for stereocontrollable synthesis of complex organic compounds. Among a number of synthetic approaches to chiral β-lactams,[1,2] the chiral ligand–Cu(I or II)-catalyzed cycloaddition of nitrones with terminal alkynes (known as the enantioselective Kinugasa reaction) has recently received much attention.[3]

In 1972, Kinugasa and Hashimoto first reported the reaction between copper(I) phenylacetylide and nitrones in dry pyridine to produce β-lactams.[4] In 1995, Miura et al. described the first catalytic version of the Kinugasa reaction using bis-diphenylphosphinoalkane catalysts, and they also pioneered the enantioselective Kinugasa reaction using 10–100 mol % of CuI–bis(oxazoline) **1a–c** catalysts in the reaction of phenylacetylene (**7a**) with diphenylnitrone **8a** to give *cis*-β-lactam (*cis*-**9a**) with 40–68% enantiomeric excesses (ees) and 30% diastereomeric excess (de) (Fig. 1).[5] Fu and coauthors reported the C_2-symmetric bis(azaferrocene) **2**–CuCl-catalyzed Kinugasa reaction, in which they succeeded in achieving excellent cis:trans diastereoselectivity (71:29 to >95:5 drs) and enantioselectivity (67–93% ees).[6] Tang and co-workers demonstrated the pseudo C_3-symmetric tris(oxazoline) **3**–Cu(II)-catalyzed highly enantioselective (45–85% ees) and diastereoselective (cis:trans = 97:3–67:33, 20:80–11:89) Kinugasa reaction.[7] They stated that the Cu(II) catalytic system is effective even under air atmosphere and without rigorously dry reaction conditions. Shintani and Fu described the first examples of an intramolecular enantioselective Kinugasa reaction using a P,N-mixed ligand **4**–CuBr complex to attain 85–91% ees.[8] Guiry et al. also employed HETPHOX **5**–Cu(I) as a P,N-mixed ligand complex in the Kinugasa reaction; however, the enantioselectivities of the predominant *cis*-β-lactams were only 4–48% ees with cis-selectivity (up to 88% de).[9] L-Proline-mediated Kinugasa reaction for synthesis of exomethylene β-lactams with up to 15% ee was reported by Basak et al.[10] Thus, only a very limited number of the enantioselective Kinugasa reactions have appeared so far,[11] and development of catalytic highly enantioselective Kinugasa reactions is still a challenging task.

It is of value to find a potential ability of a simple and readily available chiral ligand–metal complex inducing high enantioselectivity in the Kinugasa reaction. In this context, IndaBox **6** would be a candidate ligand for the chiral Lews acid-catalyzed Kinugasa reaction.[12] IndaBox **6** has received increasing attention among C_2-symmetric chiral bis(oxazoline) ligands.[13] We have previously found that the IndaBox **6a**–Cu(II) complex catalyst effectively induces high enantioselectivities in a hetero-Diels–Alder reaction of 1-thiabutadienes[14] and 1,3-dipolar cycloaddition of nitrones with 3-alkenoyl-2-oxazolidinones.[15] These findings suggested to us that the IndaBox **6**–Cu(II)-catalytic system would be applicable to a Kinugasa reaction that must be carried out under Lewis base conditions.[12] We report here the catalytic, highly enantioselective Kinugasa reaction using IndaBox **6** as the homochiral ligand.

In initial studies, we selected the reaction of phenylacetylene (**7a**) with *C,N*-diphenylnitrone **8a** as the model reaction using

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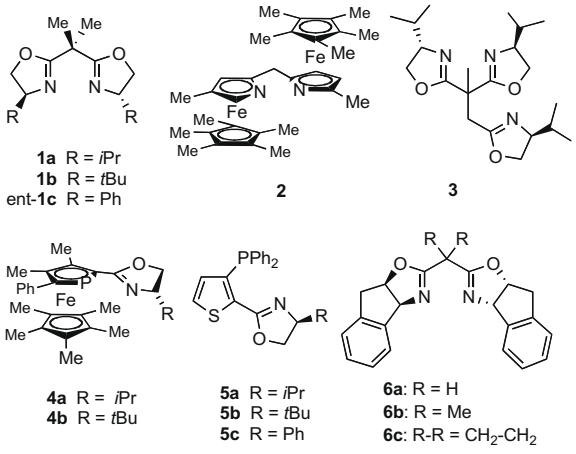
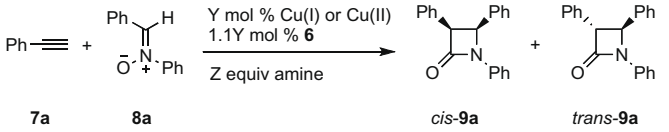


Figure 1. Chiral ligands used in the Kinugasa reaction.



Scheme 1.

Table 2
Catalytic enantioselective Kinugasa reaction: variation of the nitrone *N*-aryl substituent R

Entry	8	R	Time (h)	Adduct	Yield[a] (%)	Cis:trans[b]	Cis ee[c] (%)
1	**8a**	H	38	**9a**	47	85:15	90
2	**8b**	Me	136	**9b**	41	81:19	89
3	**8c**	MeO	135	**9c**	40	79:21	93
4	**8d**	Cl	106	**9d**	49	86:14	79
5	**8e**	EtO_2C	138	**9e**	72	83:17	81

[a] Total yield of cis- and trans-isomers.
[b] Determined by ^1H NMR.
[c] Determined by chiral HPLC.

6–Cu(I or II) chiral catalyst (*Y* mol %) and an amine (*Z* equiv) under the conditions (solvent, temperature, and time) listed in Table 1 (Scheme 1). First, in order to evaluate the IndaBox ligands **6a**–**c**, the model reaction between **7a** and **8a** was carried out in the presence of 20 mol % **6a**–**c**–$Cu(ClO_4)_2{\cdot}6H_2O$ and 1.0 equiv dicyclohexylamine (Cy_2NH) in dichloromethane at room temperature (20 °C) (entries 1–3).[7] β-Lactam **9a** was obtained (42%, 49%, and 51% yields) in cis:trans ratios of 85:15–86:14 with 78%, 67%, and 69% ees of the cis-isomer, respectively. Thus, IndaBox **6a** gave the best enantioselectivity. We next examined **6a**–Cu(I) salt complexes in the Kinugasa reaction (entries 4–7) because Fu et al. achieved high enantioselectivity (77% ee for **9a**) using the CuCl–**2** complex.[6] Copper(I) halides gave high cis-selectivities (95:5–86:14) but moderate enantioselectivities (53–23% ees) (entries 4–6), with no β-lactam (**9a**) being formed with CuOTf (entry 7). The $Cu(OTf)_2$–**6a** catalyst was found to be the best choice among the copper salts examined, giving 84:16 cis:trans selectivity and 82% ee (entry 8).

Next, screening of amines as a base was performed. Primary amines RNH_2 (R = *n*-Pr, Cy), secondary amines R_2NH (R = Et, *i*-Pr, *n*-Bu, *n*-Oct, piperidine, and morpholine), and triethylamine showed low to moderate enantioselectivities (15–71% ees) and cis:trans selectivities (86–61:14–39). Gratifyingly, di-*sec*-butylamine (*s*-Bu_2NH) gave high enantio- and diastereoselectivities (82% ee and cis:trans 84:16, entry 9), which are comparable with the results (Cy_2NH) in entry 8. When the reaction using 1.5 equiv amounts of *s*-Bu_2NH was carried out, a high level of enantioselectivity (85% ee) and diastereoselectivity (cis:trans 84:16) was obtained (entry 10), but the use of an excess amount (2.0 equiv) of the amine resulted in reduction of both yield and enantioselectivity (21%, 69% ee).

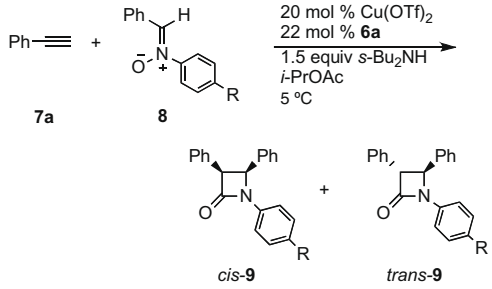
Optimization of the solvents (entries 10–14) led us to find somewhat higher enantioselectivity (87% ee) with good diastereoselectivity (cis:trans 84:16) when using isopropyl acetate (entry 14). The reaction at a higher temperature (40 °C) shortened the reaction time (to 1 h) with slight reduction of both the stereoselectivities (83% ee, cis:trans 83:17) (entry 15). Finally, when the reaction at 5 °C in *i*-PrOAc was performed using a 20 mol % $Cu(OTf)_2$–**6a** catalyst and 1.5 equiv *s*-Bu_2NH, the highest enantioselectivity (90% ee) of cis-isomer **9a** was attained in a cis:trans ratio of 85:15 (entry 16). The amounts of the catalyst could be reduced to 15 mol % or 10 mol % while maintaining a good enantiomeric excess of 88% ee (entry 17) or 85% ee (entry 18), respectively.

Under the optimized reaction conditions (Table 1, entry 16), the reaction of phenylacetylene (**7a**) with nitrones **8** with variation of

Table 1
Screening of the copper catalysts and amines and optimization of the reaction conditions

Entry	Ligand	Cu(I) or Cu(II)	*Y* (mol %)	Amine	*Z* (Equiv)	Solvent	Temp (°C)	Time (h)	Yield[a] (%)	Cis:trans[b]	Cis ee[c] (%)
1	**6a**	$Cu(ClO_4)_2{\cdot}6H_2O$	20	Cy_2NH	1.0	CH_2Cl_2	20	14	42	85:15	78
2	**6b**	$Cu(ClO_4)_2{\cdot}6H_2O$	20	Cy_2NH	1.0	CH_2Cl_2	20	21	49	85:15	67
3	**6c**	$Cu(ClO_4)_2{\cdot}6H_2O$	20	Cy_2NH	1.0	CH_2Cl_2	20	22	51	86:14	69
4	**6a**	CuCl	20	Cy_2NH	1.0	CH_2Cl_2	20	17	58	95:5	53
5	**6a**	CuBr	20	Cy_2NH	1.0	CH_2Cl_2	20	6	55	92:8	35
6	**6a**	CuI	20	Cy_2NH	1.0	CH_2Cl_2	20	8	50	86:14	23
7	**6a**	CuOTf	20	Cy_2NH	1.0	CH_2Cl_2	20	8	0	—	—
8	**6a**	$Cu(OTf)_2$	20	Cy_2NH	1.0	CH_2Cl_2	20	15	32	84:16	82
9	**6a**	$Cu(OTf)_2$	20	*s*-Bu_2NH	1.0	CH_2Cl_2	20	21	40	84:16	82
10	**6a**	$Cu(OTf)_2$	20	*s*-Bu_2NH	1.5	CH_2Cl_2	20	14	32	84:16	85
11	**6a**	$Cu(OTf)_2$	20	*s*-Bu_2NH	1.5	PhMe	20	28	40	77:23	68
12	**6a**	$Cu(OTf)_2$	20	*s*-Bu_2NH	1.5	THF	20	16	60	78:22	75
13	**6a**	$Cu(OTf)_2$	20	*s*-Bu_2NH	1.5	MeCN	20	5	61	91:9	18
14	**6a**	$Cu(OTf)_2$	20	*s*-Bu_2NH	1.5	*i*PrOAc	20	14	39	84:16	87
15	**6a**	$Cu(OTf)_2$	20	*s*-Bu_2NH	1.5	*i*-PrOAc	40	1	30	83:17	83
16	**6a**	$Cu(OTf)_2$	20	*s*-Bu_2NH	1.5	*i*-PrOAc	5	38	47	85:15	90
17	**6a**	$Cu(OTf)_2$	15	*s*-Bu_2NH	1.5	*i*-PrOAc	5	46	47	82:18	88
18	**6a**	$Cu(OTf)_2$	10	*s*-Bu_2NH	1.5	*i*-PrOAc	5	65	41	84:16	85

[a] Total yield of cis- and trans-isomers.
[b] Determined by ^1H NMR.
[c] Determined by chiral HPLC.

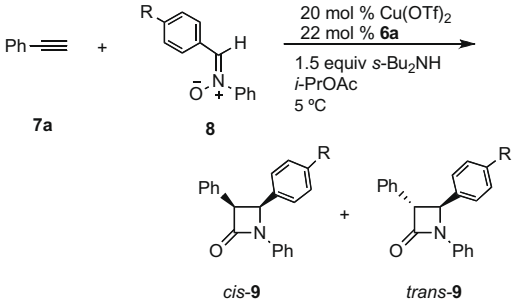


Scheme 2.

Table 3
Catalytic enantioselective Kinugasa reaction: variation of the nitrone *C*-aryl substituent R

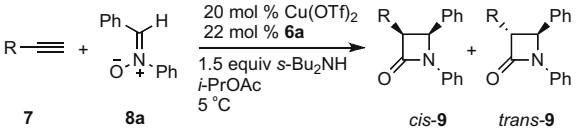
Entry	8	R	Time (h)	Adduct	Yield[a] (%)	Cis:trans[b]	Cis ee[c] (%)
1	**8a**	H	38	**9a**	47	85:15	90
2	**8f**	Me	48	**9f**	50	80:20	92
3	**8g**	MeO	40	**9g**	64	84:16	87
4	**8h**	Br	48	**9h**	45	87:13	81
5	**8i**	CF_3	48	**9i**	41	84:16	92
6	**8j**	NO_2	37	**9j**	47	84:16	94

[a] Total yield of cis- and trans-isomers.
[b] Determined by ^{1}H NMR.
[c] Determined by chiral HPLC.



Scheme 3.

N-aryl substituents R was examined (Scheme 2). The results are shown in Table 2. The electron-withdrawing *N*-aryl substituent (R = Cl, EtO_2C) lowered the enantioselectivity to 79% and 81% ee (entries 4 and 5) compared with the phenyl and *p*-tolyl groups (R = H, Me entry 1 and 2, 90% and 89% ees), whereas the electron-donating *p*-$MeOC_6H_4$ substituent showed the highest 93% ee (entry 3). Because the reaction of **7a** with nitrones **8** bearing an alkyl substituent such as methyl or benzyl group failed, an *N*-aryl substituent seems to be necessary for the reaction, which is compatible with Fu's and Tang's results.[6,7]



Scheme 4.

The nitrone *C*-aryl substituent effects were also examined (Scheme 3, Table 3). In these cases, the strongly electron-withdrawing substituents (R = CF_3, NO_2) showed the highest level of enantioselectivity (entries 5 and 6, 92% ee and 94% ee), in contrast to slight lowering by the *p*-MeO group (87% ee, entry 3). The *p*-bromo group was as low as 81% ee.

Finally, the scope with respect to the alkyne component **7** was probed (Scheme 4, Table 4). The electron-donating *p*-tolyl and *p*-$MeOC_6H_4$ substituents showed the highest level of enantioselectivity (93% and 94% ees, entries 2 and 3). Although, in the case of the *p*-BrC_6H_4 and *p*-$CF_3C_6H_4$ substituents, the cis-isomer was the major product (76:24 and 72:28, entries 4 and 5), the much more electron-withdrawing substituent (R = *p*-$NO_2C_6H_4$) clearly affects the cis:trans diastereoselectivity (18:82, entry 6). In contrast, trans-isomer was formed as the major β-lactam while maintaining a high level of enantioselectivity. Because of the fact that separated *cis*-**9o** with 86% ee was completely transformed into *trans*-**9o** maintaining 86% ee after addition of an amine (*s*-Bu_2NH) or left under the same reaction conditions, it is likely that the initially formed cis-isomer bearing an electron-withdrawing substituent (R) epimerizes highly selectively at the acidic 3-CH, α to the lactam carbonyl group, to the thermodynamically more stable trans-isomer while maintaining high enantioselectivity.[5,16] Similarly, the reaction of ethyl propiolate (**7g**) produced trans-isomer **9p** only (54%) but, in this case, with low enantioselectivity (32% ee, entry 7). The reaction of aliphatic acetylene, 1-cyclohexenylacetylene (**7h**), gave **9q** (31%) in a cis:trans ratio of 83:17 with high enantioselectivity (83% ee, entry 8).

Although in the present reaction chemical yields and diastereoselectivities were not improved, the highest level of enantioselectivities were attained using the $Cu(OTf)_2$ complex with the simple and readily available C_2-symmetric IndaBox ligand (**6a**) (commercially and cheaply available) and the optimal amine under the optimized reaction conditions.

Table 4
Catalytic enantioselective Kinugasa reaction: variation of the alkyne substituent R

Entry	7	R	Time (h)	Adduct	Yield[a] (%)	Cis:trans[b]	Cis ee[c] (%)
1	**7a**	Ph	38	**9a**	47	85:15	90
2	**7b**	*p*-MeC_6H_4	21	**9k**	38	63:37	93
3	**7c**	*p*-$MeOC_6H_4$	90	**9l**	40	83:17	94
4	**7d**	*p*-BrC_6H_4	336	**9m**	38	76:24	88
5	**7e**	*p*-$CF_3C_6H_4$	25	**9n**	55	72:28	91
6	**7f**	*p*-$NO_2C_6H_4$	64	**9o**	51	18:82	86[d]
7	**7g**	EtO_2C	0.1	**9p**	54	Trans only	32[d]
8	**7h**	1-Cyclohexenyl	36	**9q**	31	83:17	83

[a] Total yield of cis- and trans-isomers.
[b] Determined by ^{1}H NMR.
[c] Determined by chiral HPLC.
[d] ee for trans-isomer.

Supplementary data

Supplementary data (experimental procedure, full entries data of Table 1, ^{1}H and ^{13}C NMR spectral data, compounds characterization data, and chiral HLPC copies of compounds **9**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.06.050.

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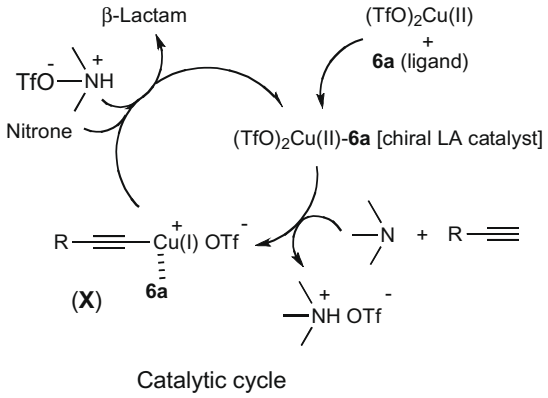
12. A referee pointed out that the reaction would proceed through Cu(I) acetylides as a key intermediate, rather than a Lewis acid-catalyzed reaction in the presence of a Lewis base. However, we believe that the following catalytic cycle is involved in this Kinugasa reaction. Cu(II) triflate and chiral ligand **6a** produce $(TfO)_2Cu(II)$–**6a** complex. This complex actually works as the *chiral Lewis acid* in the catalytic cycle to give the copper acetylide–**6a**-complex (**X**) by the reaction with acetylide formed by the action of an amine (base) as shown in the scheme. The complex **X** is indeed the key species as the *chiral dipolarophile* reacting with a nitrone to finally give a β-lactam together with the reformed chiral Lewis acid catalyst after stereo-controlled protonation.



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