CHEMISTRY
A EUROPEAN JOURNAL

FULL PAPER

DOI: 10.1002/chem.201204373

Asymmetric Synthesis of *trans*-β-Lactams by a Kinugasa Reaction on Water

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Abstract: The asymmetric Kinugasa reaction was performed on pure water for the first time without the need for any organic co-solvents. In contrast to most asymmetric Kinugasa reactions, *trans*-β-lactams were obtained as the major products in good yields, enantioselectivities, and diastereoselectivities (up to 90% yield, 98% *ee*, and >99:1 d.r.). This reaction is atom-economical, environmentally friendly, and affords synthetically useful but challenging products.

Keywords: asymmetric catalysis · β-lactams · diamine ligands · Kinugasa reaction · water chemistry

Introduction

Water is a "green" solvent that is used in biological chemistry in nature. It has the innate advantages of safety, low cost, and high relative abundance. The use of water as a reaction solvent or co-solvent has received much attention in synthetic organic chemistry.[1] In particular, the Sharpless group successfully pioneered "on water" reactions[2] for cases in which the insoluble reactants were stirred in aqueous emulsions or suspensions without the addition of any organic co-solvents. In such examples, considerable improvements in reactivity and selectivity are observed in the presence of water compared with reactions in organic solvents.[3] This "on water" approach also enables facile workup and product isolation. Therefore, the development of chiral Lewis acid catalyzed asymmetric carbon–carbon bond-forming reactions in aqueous media is of great interest and challenge. Thus far, only a limited number of catalytic asymmetric reactions have been performed effectively in aqueous suspensions.[4,5] For example, the asymmetric alkyne–imine coupling reaction catalyzed by aqueous copper(I)–bis(oxazolinyl)–pyridine complexes was developed by Wei and Li.[4e] It is imperative that the development of metal species that retain their Lewis activity in pure water and water-tolerant chiral ligands that have appropriate binding ability are pursued.

The 2-azetidinone (β-lactam) skeleton is widely recognized as one of the most significant heterocyclic structures in organic chemistry.[6] It is present in a variety of clinically relevant antibiotics, such as penicillin, cephalosporins, carbapenems, as well as inhibitors of HIV-1 protease.[7] Recently, there has been growing demand for new routes to *trans*-β-lactams, owing to their potential use as serine protease inhibitors and β-lactamase inhibitors.[8] The importance of β-lactam compounds has maintained a high level of interest in methods for their synthesis, both in academia and in industry. A number of notable strategies have been described,[9] of which the asymmetric catalytic Kinugasa reaction[10,11] provides easy access to optically pure β-lactams with different structures. The virtues of this reaction include the use of readily available starting materials, its high functional-group tolerance, and its high atom economy.

Since the pioneering studies by the groups of Miura,[12] Fu,[13] and Tang,[14] great endeavors have been devoted to the asymmetric Kinugasa reaction.[15] However, polar organic solvents, such as MeCN, DMF, and isopropyl acetate, are typically used for this reaction. Most of these methods have shown a preference for the formation of the *cis* diastereomer.[16] Although micelle-promoted, copper-catalyzed Kinugasa reactions in aqueous media have generated β-lactams in moderate to good yields,[17] an asymmetric version with water as the solvent has not yet been achieved. It has been shown in previous studies that a sterically hindered amine base is crucial for achieving high yields and selectivities in Kinugasa reactions. In addition, Tang's group demonstrated that a Cu^{II} catalytic system was also effective because catalytically active Cu^{I} species could be generated in situ upon the reaction of Cu^{II} with phenylacetylene. Based on these results, a new chiral diamine[18]–$Cu(OTf)_2$ complex was developed for the catalytic asymmetric Kinugasa reaction that allowed highly diastereoselective and enantioselective access to *trans*-β-lactams through an "on water" approach under mild reaction conditions.

Results and Discussion

Our studies began by investigating the reaction between alkyne **1a** and nitrone **2a** in the presence of a copper(II)/chiral secondary diamine[18j] complex that was generated in situ (Table 1). In a preliminary study, (*R*,*R*)-cyclohexane-

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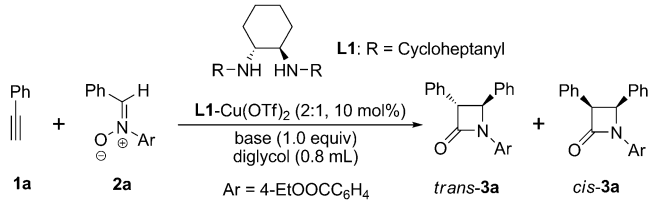
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201204373.

Table 1. Effect of the base on the asymmetric Kinugasa reaction between phenylacetylene (**1a**) and nitrone **2a**.[a]



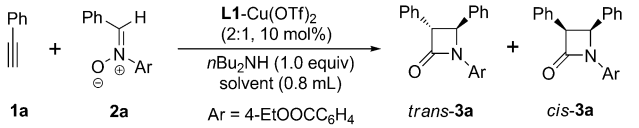
Entry[a]	Base	Yield [%][b]	*trans*/*cis*[c]	*ee* [%][c]
1	–	31	33:67	61
2	HCO_2Na	75	31:69	49
3	Et_3N	70	37:63	73
4	nBuNH$_2$	50	56:44	85
5	Et_2NH	56	97:3	92
6	iPr$_2$NH	77	86:14	88
7	iBu$_2$NH	77	55:45	84
8	nBu$_2$NH	71	97:3	93
9	Cy_2NH	74	91:9	84
10	nOct$_2$NH	93	49:51	83
11	pyrrolidine	58	96:4	85
12	TMP[d]	65	96:4	85
13	BnEtNH	65	31:69	76

[a] Reaction conditions: $Cu(OTf)_2$ (10 mol%), ligand **L1** (20 mol%), compound **1a** (0.2 mmol), compound **2a** (0.2 mmol), base (0.2 mmol), diglycol (0.8 mL), 20°C, 48 h. [b] Yield after flash chromatography on silica gel. [c] Determined by HPLC on a chiral stationary phase. [d] TMP = 2,2,6,6-tetramethylpiperidine.

1,2-diamine-derived ligand **L1** was the most-effective ligand among the chiral diamine derivatives that we examined. The reaction proceeded smoothly to afford the desired β-lactam (**3a**) with moderate geometric control, promoted by a **L1**–$Cu(OTf)_2$ complex in diglycol (31% yield, 33:67 *trans*/*cis*, 61% *ee* for the *trans* isomer and 64% *ee* for the *cis* isomer; Table 1, entry 1). Therefore, we turned to explore various achiral basic additives, which strongly influenced both the selectivity and the yield of the reaction. A survey of various bases showed great diversity, especially in terms of both diastereoselectivity and enantioselectivity, although primary, secondary, and tertiary amines, as well as inorganic bases, could all promote this reaction. These results suggested that achiral amines might coordinate to the copper center and modify the stereoenvironment of the chiral catalyst (Table 1, entries 3–13 versus entry 2). Higher yields and lower enantioselectivities were obtained with Et_3N related to with the primary nBuNH$_2$ (Table 1, entry 3 versus entry 4). For secondary aliphatic amines, with regarded to diastereoselectivity and enantioselectivity, the more sterically hindered the amine base, the lower the selectivity (Table 1, entries 5–10 and 13), with the exception of di-*n*-octylamine, which contained a long alkyl chain, and *N*-ethylbenzylamine (Table 1, entries 10 and 13). To our delight, most of the tested secondary amines afforded their corresponding *trans* isomers as the major products, whereas, in previous reports, *cis*-**3a** was given in >95:5 d.r. Dibutylamine was found to be the best base, thus giving 93% *ee*, 97:3 *trans*/*cis* and 71% yield (Table 1, entry 8). Pyrrolidine and TMP could accelerate the reaction to form the *trans*-β-lactam as the major product (Table 1, entries 11–12).

Encouraged by these initial results, various solvents were tested in the presence of nBu$_2$NH (Table 2). Both the dia-

Table 2. Effect of the solvent on the asymmetric Kinugasa reaction between phenylacetylene (**1a**) and nitrone **2a**.[a]



Entry[a]	Solvent	Yield [%][b]	*trans*/*cis*[c]	*ee* [%][c]
1	diglycol	71	97:3	93
2	MeCN	88	83:17	78
3	BuOAc	97	76:24	85
4	CH_3NO_2	66	42:58	78
5	EtOH	90	97:3	91
6	neat	86	94:6	91
7	water	83	99:1	90
8[d]	water	90	99:1	91

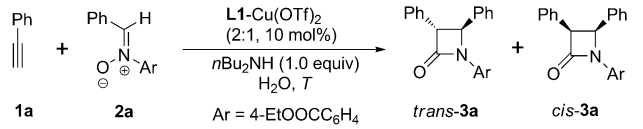
[a] Reaction conditions: $Cu(OTf)_2$ (10 mol%), **L1** (20 mol%), **1a** (0.2 mmol), **2a** (0.2 mmol), nBu$_2$NH (0.2 mmol), solvent (0.8 mL), 20°C, 48 h. [b] Yield after flash chromatography. [c] Determined by HPLC on a chiral stationary phase. [d] Water (0.4 mL).

stereoselectivity and enantioselectivity decreased when MeCN was used (Table 2, entry 2), which was surprising because MeCN has previously been found to be an excellent solvent for the Kinugasa reaction in most cases.[11–14,15a] A significant drop in both the diastereoselectivity and enantioselectivity was also found in many other solvents, such as BuOAc and CH_3NO_2 (Table 2, entries 3 and 4). In contrast, the reaction worked well in polar protic solvents, such as EtOH, thus affording lactam **3a** in improved yield and generally excellent diastereoselectivity (*trans*/*cis*, 97:3; Table 2, entry 5). Notably, when the reaction was performed under solvent-free conditions, a good yield and good enantioselectivity were achieved with a slightly loss of diastereoselectivity (*trans*/*cis*, 94:6; Table 2, entry 6). Interestingly, the reaction rate was accelerated by using water as the reaction medium, thus generating β-lactam **3a** in improved diastereoselectivity and yield (*trans*/*cis* 99:1, 83% yield, 90% ee; Table 2, entry 7). A comparison of Table 2, entries 7 and 8 revealed that we could enhance the enantioselectivity and the yield by lowering the amount of water (*trans*/*cis* 99:1, 90% yield, 91% *ee*). During the reaction process, the reactants were insoluble in pure water, which was the highlighted advantage of carrying out reactions of hydrophobic compounds "on water" by Sharpless and co-workers.[2a] The combination of $Cu(OTf)_2$, chiral diamine **L1**, and one equivalent of nBu$_2$NH in water generated a blue precipitate. Upon adding phenylacetylene, a yellow oil was generated that floated on top of the water, which indicated that copper(II) was reduced in situ into copper(I) by phenylacetylene to form a copper(I)–phenylacetylide species. The product was formed under the water layer, thus allowing it to be easily isolated by extraction. Perhaps the unique properties

of molecules at the macroscopic phase boundary between water and insoluble hydrophobic oil play a role[19] in affording the products in high yield and diastereoselectivity.

Subsequently, the reaction temperature was examined on water. As shown in Table 3, both the diastereoselectivity and enantioselectivity were dependent on the reaction temperature. When the temperature was increased from 20 to 35 °C, the enantioselectivity decreased, although the diastereoselectivity remained high (Table 3, entry 1). Decreasing the reaction temperature led to lower reactivity and a significant drop in diastereoselectivity, although the enantioselectivity remained comparable (Table 3, entry 3).

Table 3. Effect of temperature on the asymmetric Kinugasa reaction between phenylacetylene (**1a**) and nitrone **2a**.[a]



1a 2a trans-3a cis-3a

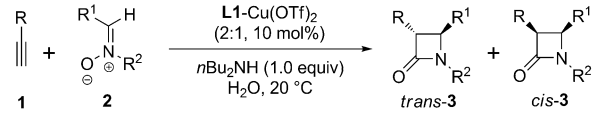
Entry[a]	*T* [°C]	Yield [%][b]	*trans*/*cis*[c]	*ee* [%][c]
1	35	84	96:4	75
2	20	90	99:1	91
3	0	83	42:58	95[d]

[a] Reaction conditions: $Cu(OTf)_2$ (10 mol%), ligand **L1** (20 mol%), compound **1a** (0.2 mmol), compound **2a** (0.2 mmol), nBu_2NH (0.2 mmol), water (0.4 mL), 48 h. [b] Yield after flash chromatography on silica gel. [c] Determined by HPLC on a chiral stationary phase. [d] Enantioselectivity of the *cis* product.

Under the established optimal reaction conditions, the substrate scope of the cycloaddition reaction between various alkynes and nitrones was examined next (Table 4). First, a series of nitrone derivatives that contained a substituted phenyl group at the C1 position was investigated. We found that the electronic character of the aromatic groups on the carbon atoms of the nitrones had almost no influence on the enantioselectivity of the reaction (Table 4, entries 1–4). Whether electron-deficient or electron-rich *C*-aryl nitrones were used, all of the reactions exclusively gave *trans*-β-lactams (**3a**–**3d**) in good yields and enantioselectivities (91–93% *ee*). A nitrone with a 2-naphthyl group furnished a good *ee* value, but slightly lower diastereoselectivity (Table 4, entry 5; 72% yield, 94:6 d.r., 92% *ee*). With respect to the alkyne component, nitrone **2a** reacted with aromatic alkynes to generate β-lactams with good diastereo- and enantioselectivities (Table 4, entries 6–10). Electron-rich phenylacetylenes showed higher reactivities than electron-deficient ones (Table 4, entries 6–8 versus entries 9 and 10). Alkenyl-substituted alkynes furnished good *ee* values but low diastereoselectivities (Table 4, entry 11). The electronic character of the *N*-bound aromatic group on the nitrone was also investigated. The generation of β-lactams proceeded with good enantioselectivities (Table 4, entries 15–20). With regard to the diastereoselectivity, electron-rich *N*-aryl nitrones gave β-lactams **3o** and **3p** in low diastereoselectivities (Table 4, entries 15–16), whereas electron-deficient *N*-aryl nitrones afforded *trans*-β-lactams **3q**–**3t** in high diastereoselectivities (Table 4, entries 1 and 17–20). Moderate to good results were also obtained with heterocyclic and aliphatic substrates (Table 4, entries 12–14).

To further evaluate the synthetic potential of this catalytic system, the gram-scale preparation of the Kinugasa adduct on water was investigated. The reaction of 4 mmol of the starting materials, under the optimized conditions, delivered their corresponding *trans*-β-lactams without any loss in reactivity and enantioselectivity (Scheme 1; 1.27 g, 78% yield, and 95% *ee* for *trans*-**3c**; 1.33 g, 74% yield, and 95% *ee* for *trans*-**3d**).

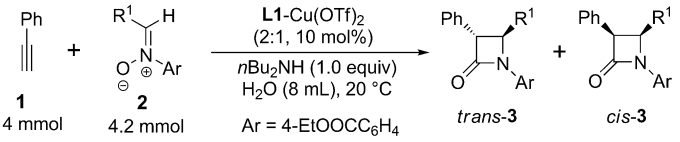
Table 4. Substrate scope of the asymmetric Kinugasa reaction between alkyne **1** and nitrone **2** on water.[a]



1 2 trans-3 cis-3

Entry[a]	R	R^1, R^2	Product	Yield [%][b]	*trans*/*cis*[c]	*ee* [%][d]
1	C_6H_5	C_6H_5, Ar	**3a**	90	99:1	91
2	C_6H_5	4-MeC_6H_4, Ar	**3b**	71	99:1	92
3	C_6H_5	4-ClC_6H_4, Ar	**3c**	75	>99:1	93
4	C_6H_5	4-BrC_6H_4, Ar	**3d**	70	>99:1	92
5	C_6H_5	2-naphthyl, Ar	**3e**	72	94:6	92
6	3-MeC_6H_4	C_6H_5, Ar	**3f**	85	99:1	92
7	4-MeC_6H_4	C_6H_5, Ar	**3g**	87	87:13	90
8	4-$MeOC_6H_4$,	C_6H_5, Ar	**3h**	81	90:10	91
9	4-FC_6H_4	C_6H_5, Ar	**3i**	73	>99:1	92
10	4-BrC_6H_4	C_6H_5, Ar	**3j**	67	87:13	88
11	1-cyclohexenyl	C_6H_5, Ar	**3k**	62	44:56	93[e]
12[f]	cyclohexyl	C_6H_5, Ar	**3l**	79 (50)	37:63 (25:75)	71[e] (79[e])
13[f]	C_6H_5	cyclohexyl, C_6H_5	**3m**	73 (55)	46:54 (48:52)	90, 92[e] (98, 98[e])
14[f]	C_6H_5	2-furyl, C_6H_5	**3n**	57 (52)	71:29 (74:26)	84, 93[e] (90, 88[e])
15	C_6H_5	C_6H_5, C_6H_5	**3o**	59	43:57	95[e]
16	C_6H_5	C_6H_5, 4-MeC_6H_4	**3p**	63	63:37	90
17	C_6H_5	C_6H_5, 4-ClC_6H_4	**3q**	58	83:17	90
18	C_6H_5	C_6H_5, 3-ClC_6H_4	**3r**	56	90:10	92
19	C_6H_5	C_6H_5, 2-ClC_6H_4	**3s**	60	91:9	88
20	C_6H_5	C_6H_5, 4-$MeOOCC_6H_4$	**3t**	89	98:2	91

[a] Reaction conditions: $Cu(OTf)_2$ (10 mol%), ligand **L1** (20 mol%), compound **1** (0.2 mmol), compound **2** (0.21 mmol), nBu_2NH (0.2 mmol), water (0.4 mL), 20 °C. Ar = 4-$EtOOCC_6H_4$. [b] Yield after flash chromatography on silica gel. [c] d.r. (*trans*/*cis*) and *ee* values were determined by HPLC on a chiral stationary phase. [d] Enantioselectivity of the *trans* product. [e] Enantioselectivity of the *cis* product. [f] The data given in parentheses were obtained in diglycol as the solvent and Et_2NH as the base at 0 °C.



2c: R^1 = 4-ClC_6H_4 *trans*-**3c**: 1.27 g, 78% yield, >19:1 d.r., 95% *ee*

2d: R^1 = 4-BrC_6H_4 *trans*-**3d**: 1.33 g, 74% yield, >19:1 d.r., 95% *ee*

Scheme 1. Gram-scale synthesis of *trans*-β-lactams **3c** and **3d**.

Examination of the X-ray data revealed that the absolute configuration of *trans*-**3c** and *trans*-**3s** was (3*R*,4*S*) (Figure 1).[20] The absolute configuration of the stereogenic

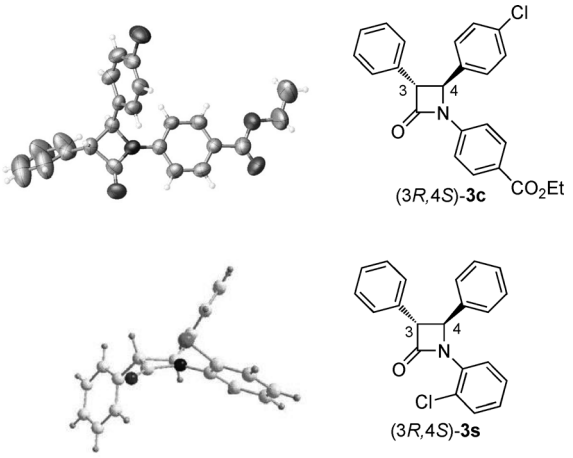
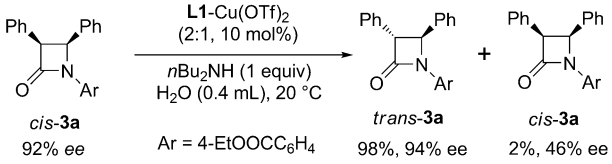


Figure 1. Crystal structures of compounds **3c** and **3s**, as determined by X-ray analysis.

centers in other products was substantiated by comparison of the CD spectra of *trans*-**3c**. In the case of β-lactams **3n**–**3r**, the decisive CD band was observed at about 240 nm, whereas, in compounds **3a**–**3j** and **3t**, its position was shifted to 240–300 nm, as a result of the presence of ester substituents (see the Supporting Information). The azetidinone shows coplanarity for the latter products. Application of the established β-lactam octant rule, sector rules, and helicity rules for the stereochemical assignment of these β-lactam products[21] indicates unanimous agreement between the observed and predicted CE (Cotton effect) signs. Accordingly, the major *trans* products **3a**–**3j**, **3n**–**3r**, and **3t**, which have a decisive negative CD sign, have the (3*R*,4*S*) configuration, whereas the corresponding *cis* products that were obtained in this catalyst system, with a similar negative band, have the (3*S*,4*S*) configuration. Interestingly, CD measurements of (3*R*,4*S*)-**3s** led to a change in sign. In this case, the nonplanarity of the azetidinone, as evident from Figure 1, might explain such an unexpected result.

To elucidate the diastereoselection process, some control experiments were performed. The extent of the formation of *trans*-β-lactam **3a** seemed to be related to the ease of C3-isomerization of *cis*-**3a** under the catalytic conditions (Scheme 2), which was an advantage over the high-temperature conditions that are needed to effect the epimerization of an amide.[12] The epimerization process was substrate de-

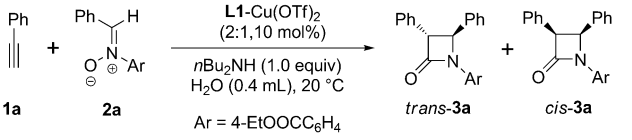


Scheme 2. Transformation of the two diastereomers.

pendent. The transformation of *cis*-**3o** into *trans*-**3o** did not happen under the same conditions. Based on these results, an electron-withdrawing substituents on the *N*-aryl nitrone was assumed to stabilize a negative charge at the C3 position. These results were consistent with the observed variation in d.r. value (Table 4).

To gain further insight into the reaction pathway, tracking experiments were performed on the catalytic system and the results are summarized in Table 5. The reaction was very

Table 5. Effect of reaction time on the catalytic reaction for a mechanistic study.[a]

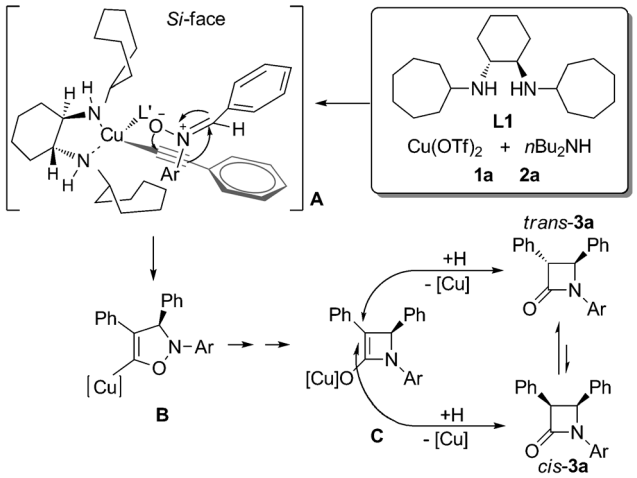


Entry[a]	*t*	Yield [%][b]	*trans*/*cis*[c]
1	5 min	83	38:62
2	10 min	84	42:58
3	1 h	84	41:59
4	4 h	90	56:44
5	8 h	91	76:24
6	24 h	91	>95:5

[a] Reaction conditions: $Cu(OTf)_2$ (10 mol%), ligand **L1** (20 mol%), compound **1a** (0.2 mmol), compound **2a** (0.21 mmol), nBu_2NH (0.2 mmol), water (0.4 mL), 20 °C. Ar = 4-$EtOOCC_6H_4$. [b] Yield after flash chromatography on silica gel. [c] d.r. (*trans*/*cis*) was determined by ^1H NMR spectroscopy.

fast and the product (**3a**) was obtained in 83% yield within 5 min (Table 5, entry 1; *trans*/*cis*, 38:62). Over the next few hours, the *trans*/*cis* ratio gradually increased such that, after 24 h, the *trans* product became the predominant isomer (>95:5 d.r.; Table 5, entry 6). This scenario indicated that the product had epimerized under the effect of the basic catalyst, thus converting the original product from *cis* into *trans* during the course of the reaction. The high enantioselectivity for *trans*-**3a** implied the same 4*S* arrangement in the dominant enantiomer of both *trans*-**3a** and *cis*-**3a** in the initial state, in accordance with the observed CE signs. The facial selection for the interactions of the reactants was efficient.

According to the generally accepted mechanism[10b] of the Kinugasa reaction, we postulated a possible intermediate that could rationalize the observed sense of geometric induction. In the aforementioned Kinugasa reactions by Tang's group, copper(II) was reduced in situ into copper(I) by phenylacetylene.[14b] As shown in Scheme 3, owing to the



Scheme 3. Proposed catalytic model.

steric hindrance of one cycloheptyl subunit on the diamine ligand and the amine additive, the [3+2] cycloaddition proceeded with attack of the copper(I) phenylacetylide on the *Si* face of nitrone **2a**. Isoxazoline intermediate **B** was then transformed into enolate **C**, which was intercepted with a proton to generate a mixture of *cis*- and *trans*-β-lactam **3a**. The extent of formation of the *trans* isomer was a result of isomerization at the C3 position under the basic conditions of the catalyst that were used. Such a method is attractive as a facile route to the highly diastereoselective and enantioselective synthesis of *trans*-lactams.

Conclusion

We have successfully developed a highly enantioselective Kinugasa reaction by using water as the solvent for the first time. This mild and operationally simple method provides a one-step route to optically active *trans*-β-lactams in good yields, enantioselectivities, and diastereoselectivities (up to 90% yield, >99:1 d.r., and 98% *ee*). This procedure tolerates a relatively wide range of substrates and excellent results can be obtained for gram-scale reactions "on water", which opens up a new pathway to various biologically important, non-racemic β-lactam derivatives in one pot. This promising result should enhance the use of water as a reaction medium in enantioselective catalysis.

Experimental Section

Preparation of chiral secondary diamine ligand L1: To a solution of (1*R*,2*R*)-(+)-1,2-diaminocyclohexane (19.0 mmol, 2.166 g) in MeOH (30 mL) was added cycloheptanone (38 mmol, 4.5 mL, 2.0 equiv) at 25 °C and the mixture was stirred for 30 min. To this mixture was added MeOH (10 mL) and $NaBH_4$ (41.8 mmol, 1.581 g, 2.2 equiv) and the reaction was monitored by TLC. The residue was diluted with EtOAc (15 mL) and wished with water (3×20 mL). The product was isolated by flash column chromatography on silica gel (EtOAc/MeOH, 8:1 to 4/1) to give compound **L1** (5.248 g, 17.0 mmol, 89% yield) as an oil.

Typical experimental procedure for the Kinugasa reaction of nitrone 2a with phenylacetylene (1a; Table 2, entry 8): Ligand **L1** (12.2 mg, 0.04 mmol) and $Cu(OTf)_2$ (7.2 mg, 0.02 mmol) were stirred together in water (0.4 mL) at 35 °C for 30 min. Then, the solution was cooled to 20 °C and nBu_2NH (34 μL, 0.2 mmol) was added. After 10 min, phenylacetylene (**1a**, 22 μL, 0.2 mmol) was added and, when the color of the resulting mixture had turned light yellow, nitrone **2a** (56.6 mg, 0.21 mmol) was added to the solution and the mixture was stirred for 2 days. The crude product was directly purified by flash chromatography on silica gel (petroleum ether/EtOAc, 30:1 to 9:1) to afford compound **3a** (90% yield, *trans*/*cis* 99:1, 91% *ee*) as a white solid. Further purification by column chromatography afforded compound *trans*-**3a**. M.p. 144 °C; $[\alpha]_D^{22}=+9.96$ ($CHCl_3$, $c=0.552$, 91% *ee*); ^1H NMR (400 MHz, $CDCl_3$): $\delta=7.96$ (d, $J=8.7$ Hz, 2H), 7.55–7.27 (m, 12H), 5.01 (d, $J=2.6$ Hz, 1H), 4.18–4.44 (m, 3H), 1.35 ppm (t, $J=7.1$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=165.98$, 165.92, 140.98, 137.02, 134.33, 130.89, 129.45, 129.13, 128.93, 128.09, 127.42, 125.87, 116.71, 65.40, 63.88, 60.89, 14.33 ppm; HRMS (ESI): *m*/*z* calcd for $C_{24}H_{21}NO_3+Na^+$: 394.1419 $[M+Na]^+$; found: 394.1416; the *ee* and d.r. were determined by comparison with authentic racemates, chiral HPLC (Daicel Chiralcel IA column; *n*-hexane/2-propanol, 90:10; flow rate: 1.0 mL min^{-1}; $\lambda=254$ nm): $t=23.0$ min (*trans*, major), 21.4 min (*trans*, minor).

Experimental procedure for the scale-up reaction: Ligand **L1** (244.0 mg, 0.8 mmol) and $Cu(OTf)_2$ (144.0 mg, 0.4 mmol) were stirred together in water (8 mL) in a round-bottomed flask (25 mL) under a N_2 atmosphere at 35 °C for 30 min. Then, the solution was cooled to 20 °C and nBu_2NH (680 μL, 4 mmol) was added. After 10 min, alkyne **1a** (440 μL, 4.0 mmol) was added and, when the color of the resulting mixture had turned light yellow, nitrone **2c** (1.272 g, 4.2 mmol) was added to and the mixture was stirred for 4 days. The resulting mixture was quenched with an aqueous solution of NaCl and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and evaporated in vacuo. The crude product was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 30:1 to 9:1) to give compound *trans*-**3c** (1.269 g, 3.1 mmol) as a white solid (78% yield, >19:1 d.r., 95% *ee*).

Procedure for the transformation of *cis*-3a into *trans*-3a: Ligand **L1** (6.2 mg, 0.02 mmol), $Cu(OTf)_2$ (3.6 mg, 0.01 mmol), and *cis*-**3a** (37.1 mg, 0.1 mmol) were mixed with water (0.2 mL) and stirred in a test tube under a N_2 atmosphere at 20 °C. Then, nBu_2NH (17 μL, 0.1 mmol) was added and the mixture was stirred for 2 days. The reaction mixture was purified by flash column chromatography on silica gel (petroleum ether/EtOAc, 30:1 to 9:1) to give compound **3a** (33.7 mg, 0.091 mmol) as a white solid (91% yield, 98:2 d.r., 94% *ee*). The d.r. was determined by ^1H NMR spectroscopy and the *ee* value was determined by HPLC analysis (Chiral IA column; *n*-hexane/2-propanol, 90:10; flow rate: 1.0 mL min^{-1}; $\lambda=254$ nm): $t=23.0$ min (*trans*, major), 21.4 min (*trans*, minor).

Acknowledgements

We appreciate the National Natural Science Foundation of China (21021001 and 20902060), the Ministry of Education of China (20110181130014), and the Major State Basic Research and Development Program (973 Program, 2011CB808600) for financial support.

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Received: December 8, 2012

Please note: Minor changes have been made to this manuscript since its publication in *Chemistry—A European Journal* Early View. The Editor.

Published online: April 9, 2013

