# Asymmetric Synthesis of β-Lactams through Copper-Catalyzed Alkyne–Nitrone Coupling with Prolinol-Phosphine Chiral Ligand

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**Abstract:** Prolinol-phosphine chiral ligands enabled highly enantioselective copper-catalyzed intermolecular alkyne–nitrone coupling (Kinugasa reaction) to produce 1,3,4-trisubstituted chiral β-lactams. A high level of enantiocontrol was achieved not only with aryl- or alkenylacetylenes but also with alkylacetylenes, which were important but unfavorable substrates in the previously reported protocols. Two-point hydrogen-bonding between the chiral ligand and the nitrone oxyanion consisting of O–H···O and C($sp^3$)–H···O hydrogen bonds is proposed.

Chiral β-lactams constitute an important heterocycle family due to their biological activity and utility as building blocks in organic synthesis.[1,2] Among various approaches to β-lactams, copper-catalyzed coupling between terminal alkynes and nitrones (Kinugasa reaction) is the most straightforward.[3] The first catalytic asymmetric version was reported by Miura in 1995.[4] The reaction between phenylacetylene and *C*,*N*-diphenylnitrone with a copper(I)/bisoxazoline chiral catalyst afforded a cis/trans mixture of 1,3,4-triphenyl-β-lactam with moderate diastereo- and enantioselectivities. Since this work, significant progress in enantioselectivity of the asymmetric Kinugasa reaction of aryl- or alkenylacetylenes has been made owing to the development of new chiral ligands on copper.[5–7] However, the substrate scope is still limited. In particular, the intermolecular asymmetric Kinugasa reaction of alkylacetylenes producing chiral β-lactams having an alkyl side chain at the carbonyl α-position (C3) remains underdeveloped[6d–f]. This is an important issue because most β-lactam drug molecules have an alkyl pendant at this position (Figure 1).[8,9] Enabling to install alkyl groups at this position would also be important in using the β-lactams as chiral building blocks for asymmetric synthesis of acyclic compounds.[2]

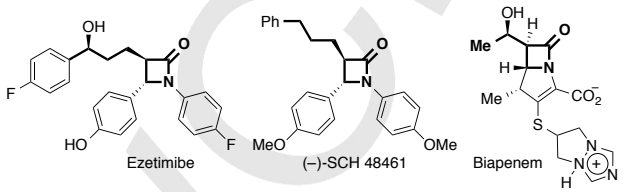


**Figure 1.** β-Lactam drug molecules.

Previously, we reported the copper-catalyzed asymmetric direct alkynylation of aldehydes with terminal alkynes with prolinol-phosphine chiral ligands (represented by **L1**) (Figure 2).[10] DFT calculations indicated directional catalyst–substrate two-point hydrogen-bonding involving a non-classical C($sp^3$)–H···O hydrogen bond in the enantioselectivity-determining transition state.[11] In the present work, we examined the prolinol-phosphine-copper system for its ability to solve problems in the asymmetric Kinugasa reaction, expecting that similar two-point hydrogen-bonding may also occur with the oxyanion of the nitrone instead of the carbonyl oxygen of the aldehyde.

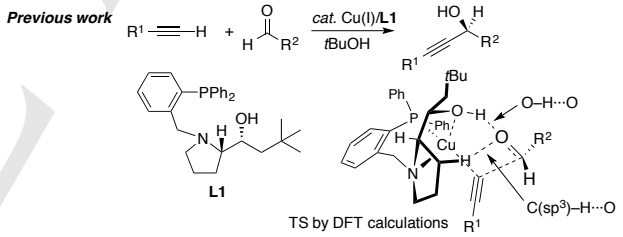


**Figure 2.** Copper-catalyzed asymmetric direct alkynylation of aldehydes with terminal alkynes with prolinol-phosphine chiral ligand **L1**.

Preliminary screening of reaction conditions was conducted using **L1** with a well-studied substrate combination of phenylacetylene (**1a**) and *C*-cyclohexyl-*N*-phenylnitrone (**2a**). Product yield, cis/trans selectivity, and enantioselectivity were sensitive to reaction parameters such as copper sources, bases (typically used in a stoichiometric amount), solvents, and reaction temperature (see Supporting Information for details). To our delight, the reaction occurred under significant enantiocontrol in some cases, and the most efficient reaction (**1a**/**2a** 1:1, 0.2 mmol) occurred in the presence of $Cu(OTf)_2$/**L1** (1:1 10 mol%) and $Et_2NH$ (1 equiv) in toluene (1 mL) at –40 °C over 24 h, giving the β-lactam **3aa** in 81% yield with a moderate diastereoselectivity (87:13) in favor of the cis isomer (Table 1, entry 1). The cis isomer was enantioenriched at 84% ee for (3*R*,4*S*)-**3aa**, while the trans isomer was enriched for (3*S*,4*S*)-**3aa** with 20% ee. The reaction also occurred even in the absence of a ligand under otherwise identical conditions to afford racemic **3aa** in 56% yield with a low cis/trans selectivity (Table 1, entry 2).

Among the other observations in the condition screening, it should be noted that alcohol solvents gave nearly racemic

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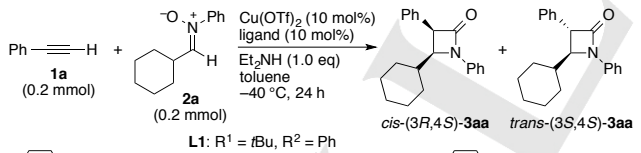
products. This is in sharp contrast to the mandatory use of an alcohol solvent in the asymmetric copper-catalyzed aldehyde alkynylation with **L1**. Another important observation is that bases had a strong impact on the enantioselectivity. This suggests participation of the base in an enantioselectivity-determining step.

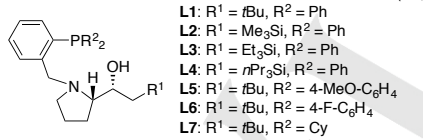
Effects of ligand modification are listed in Table 1, entries 3–10. Overall, cis/trans ratios were low or moderate, and higher yields obtained using better ligands were accompanied by better cis/trans selectivities and enantioselectivities. Changing the hydroxy group of **L1** into a methoxy group (**L1-OMe**) resulted in almost total loss of enantioselectivity (entry 3). The yield was lower than that in the no-ligand reaction. These results support our assumption that the hydroxy group of **L1** works as a hydrogen-bonding donor site toward the oxyanion of the nitrone for enantioface discrimination.

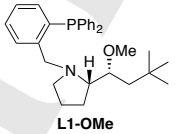
Next, effects of the substituent ($R^1$) at the position $\alpha$ to the hydroxyl group were investigated. By replacing the neopentyl group of **L1** with a $Me_3SiCH_2$ group (**L2**), significant improvements in yield (95%) and enantioselectivities for both diastereomers (*cis*-**3aa**, 87% ee; *trans*-**3aa**, 31% ee) were achieved (Table 1, entry 4). Elongation of alkyl chains in the $R_3Si$ group into ethyl (**L3**) or *n*-propyl (**L4**) groups caused a slight increase in enantioselectivity (entries 5 and 6).

Next, *P*-substituents ($R^2$) were explored. Introduction of electron-donating MeO groups at the *para* position of the *P*-aromatic rings of the neopentyl-armed ligand (**L5**) induced slight increases in yield (84%), cis/trans ratio (90:10), and enantiomeric excess of *cis*-**3aa** (86% ee) (Table 1, entry 7). On the other hand, an F atom at the same position (**L6**) was unfavorable (entry 8). The reactions with **L7**[10] bearing a dicyclohexylphosphino group gave low yield and stereoselectivities, while the higher enantiomeric excess of *trans*-**3aa** over that of the cis isomer was noticeable (entry 9). Next, we tried to find the best mix. In fact, the ligand **L8** having a $nPr_3SiCH_2$ group at the alcohol moiety and the 4-MeO-$C_6H_4$ *P*-substituent produced the most efficient catalyst system, affording **3aa** in 97% yield with 90% cis/trans selectivity and 92% ee for *cis*-(3*R*,4*S*)-**3aa** (entry 10).

**Table 1.** Ligand effects in the reaction between **1a** and **2a**[a]




| entry | ligand | | | yield | cis/trans[c] | ee (%)[d] | |
|---|---|---|---|---|---|---|---|
| | | $R^1$ | $R^2$ | (%)[b] | | cis | trans |
| 1 | **L1** | *t*Bu | Ph | 81 | 87:13 | 84 | 20 |
| 2 | no ligand | n.a. | n.a. | 56 | 56:44 | n.a. | n.a. |
| 3 | **L1-OMe** | *t*Bu | Ph | 27 | 69:31 | 6 | 10 |
| 4 | **L2** | $SiMe_3$ | Ph | 95 | 86:14 | 87 | 31 |
| 5 | **L3** | $SiEt_3$ | Ph | 90 | 87:13 | 89 | 47 |
| 6 | **L4** | $SinPr_3$ | Ph | 89 | 88:12 | 89 | 49 |
| 7 | **L5** | *t*Bu | 4-MeO-$C_6H_4$ | 84 | 90:10 | 86 | 8 |
| 8 | **L6** | *t*Bu | 4-F-$C_6H_4$ | 67 | 86:14 | 71 | 31 |
| 9 | **L7** | *t*Bu | Cy | 43 | 69:31 | 29 | 52 |
| 10 | **L8** | $SinPr_3$ | 4-MeO-$C_6H_4$ | 97 | 90:10 | 92 | 51 |

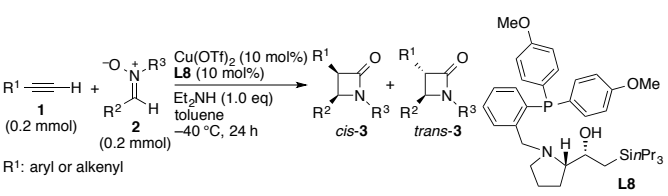
[a] Conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), $Cu(OTf)_2$/ligand (10 mol%), $Et_2NH$ (0.2 mmol), toluene (1.0 mL) at –40 °C for 24 h. [b] Yield of isolated product as isomeric mixture. [c] Determined by $^1H$ NMR spectroscopy. [d] The ee values were determined by HPLC analysis. Absolute configurations of *cis*- and *trans*-**3aa** were separately determined by their optical rotations (*c.f.* ref. 6c).

The scope of the Kinugasa reaction of aryl- or alkenylacetylenes was explored under the optimized conditions [**1a-g**/**2a-h** (0.2 mmol), $Cu(OTf)_2$/**L8** (10 mol%), $Et_2NH$ (1 equiv), toluene, –40 °C, 24 h] (Table 2). Yields of β-lactams (**3**) and cis selectivities were moderate or good in most cases. As another general trend, the cis isomers had higher enantiomeric purities than the trans isomers. As listed in Table 2, entries 1–4, various *N*-substituents ($R^3$) were compatible. Thus, the nitrones with electron-donating (**2b**: *p*-MeO) or -withdrawing (**2c**: *p*-$CF_3$) substituents underwent the reaction with **1a** under a high level of enantiocontrol (entries 1 and 2). More sterically demanding *N*-substituents such as *o*-tolyl (**2d**) and 1-naphthyl (**2e**) groups were compatible (entries 3–4). Remarkably, the reaction of the *C*-cyclohexyl-*N*-naphthylnitrone (**2e**) occurred with high yield (91%) with almost complete enantioselectivity (99% ee) for the cis isomer, and the trans isomer also had a high enantiomeric purity (90% ee).

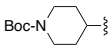
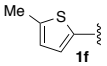
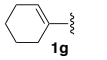
Next, effects of *C*-substituents of the nitrone were investigated with the *N*-substituent fixed to Ph (Table 2, entries 5–7). Nitrones with α-branched *C*-alkyl groups such as isopropyl (**2f**) or *N*-Boc-4-piperidyl (**2g**) groups underwent the reaction with **1a** to give the corresponding *cis*-β-lactams (**3af** and **3ag**) with 91% ee and 92% ee, respectively (entries 5 and 6). The reaction between **1a** and the nitrone **2h** with an unbranched *C*-alkyl group gave *cis*-**3ah** with 82% ee (entry 7). Thus, various alkyl groups were tolerated as the *C*-substituent of the nitrone. Unfortunately, however, nitrones with aryl *C*-substituents were not suitable for the reaction with phenylacetylene (**1a**). Under the reaction conditions, decomposition of the *C*-arylnitrones was dominant, resulting in the formation of deoxygenated imines and other unidentified compounds accompanied by oxidative coupling between **1a** and $Et_2NH$ to form *N*,*N*-diethylphenylacetamide.[12] Even when β-lactams were obtained in low yield, enantioselectivities (≤73% ee) were lower than those in the reaction of the *C*-alkylnitrones.

Phenylacetylene derivatives (**1b**, **1c**, **1d**, and **1e**) with MeO, F, Br, or $CO_2Me$ *para*-substituents also participated in the reaction with *C*-cyclohexyl-*N*-phenylnitrone (**2a**) (Table 2, entries 8–11). The reaction between thiophene-substituted acetylene **1f** and **2a** occurred under a very high level of enantiocontrol for both cis and trans isomers (**3fa**, 99 and 98% ees) (entry 12). As shown in entry 13, conjugated enyne **1g** was also a suitable substrate; the reaction with **2a** gave a 3-alkenylated *cis*-β-lactam (**3ga**) with 98% ee (entry 13).

**Table 2.** Asymmetric Kinugasa reaction of aryl- and alkenylacetylenes.[a]




| entry | alkyne | nitrone | | yield | cis/trans[c] | ee (%)[d] | |
|---|---|---|---|---|---|---|---|
| | $R^1$ | $R^2$ | $R^3$ | (%)[b] | | cis | trans |
| 1 | Ph (**1a**) | Cy | 4-MeO-$C_6H_4$ (**2b**) | 54 (**3ab**) | 87:13 | 80 | 37 |
| 2 | Ph (**1a**) | Cy | 4-F-$C_6H_4$ (**2c**) | 61 | 80:20 | 90 | 54 |

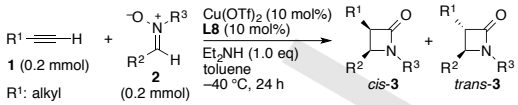
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | (**3ac**) | | | |
| 3 | Ph (**1a**) | Cy | 2-Me-$C_6H_4$ (**2d**) | 31 (**3ad**) | 92:8 | 92 | 80 |
| 4 | Ph (**1a**) | Cy | 1-naphthyl (**2e**) | 91 (**3ae**) | 90:10 | 99 | 90 |
| 5 | Ph (**1a**) | *i*Pr | Ph (**2f**) | 79 (**3af**) | 89:11 | 91 | 54 |
| 6 | Ph (**1a**) |  | Ph (**2g**) | 71 (**3ag**) | 75:25 | 92 | 46 |
| 7 | Ph (**1a**) | *n*Pent | Ph (**2h**) | 72 (**3ah**) | 77:23 | 82 | 7 |
| 8 | 4-MeO-$C_6H_4$ (**1b**) | Cy | Ph (**2a**) | 95 (**3ba**) | 96:4 | 92 | 36 |
| 9 | 4-F-$C_6H_4$ (**1c**) | Cy | Ph (**2a**) | 55 (**3ca**) | 88:12 | 91 | 44 |
| 10 | 4-Br-$C_6H_4$ (**1d**) | Cy | Ph (**2a**) | 67 (**3da**) | 83:17 | 92 | 41 |
| 11 | 4-$MeO_2C$-$C_6H_4$ (**1e**) | Cy | Ph (**2a**) | 82 (**3ea**) | 62:38 | 83 | 78 |
| 12 |  **1f** | Cy | Ph (**2a**) | 71 (**3fa**) | 83:17 | 99 | 98 |
| 13 |  **1g** | Cy | Ph (**2a**) | 73 (**3ga**) | 78:22 | 98 | 73 |

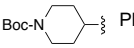
[a] Conditions: **1** (0.2 mmol), **2** (0.2 mmol), $Cu(OTf)_2$/**L8** (10 mol%), $Et_2NH$ (0.2 mmol), toluene (1.0 mL) at –40 ˚C for 24 h. [b] Yield of isolated product as isomeric mixture. [c] Determined by $^1H$ NMR spectroscopy. [d] The ee values were determined by HPLC analysis. See Supporting Information for determination of absolute configurations.

As mentioned above, enantiocontrolled installation of an alkyl chain at the C3 position of β-lactams is an important task in the development of the asymmetric Kinugasa reaction. As shown in Table 3, alkylacetylenes were suitable substrates for the present asymmetric Kinugasa reaction protocol with **L8**. Although yields and cis selectivities were moderate in most cases, both cis and trans isomers of β-lactams had high enantiomeric purities (91–99% ees).[13] The absolute configurations of the cis and trans isomers were identical at the C4 position and inverted at the C3 position (*vide infra* for C3-epimerization). Simple unbranched alkylacetylene 1-hexyne (**1h**) underwent a highly enantioselective reaction with various *C*-cyclohexylnitrones (**2a**–**e**) with different *N*-aryl groups (entries 1–5). The alkyne **1h** also reacted with *C*-isopropyl- or -*n*-pentyl-*N*-phenylnitrones (**2f**,**h**) with high enantioselectivities (entries 6 and 7).

The protocol was effective for the reactions of terminal alkynes with varied steric effects such as 5-phenyl-1-pentyne (**1i**), isobutylacetylene (**1j**), or cyclohexylacetylene (**1k**) (Table 3, entries 8–10). Functionalized alkylacetylenes with a pivalate ester (**1l**), silyl ether (**1m**), acetal (**1n**), or alkyl chloride (**1o**) at the chain terminus participated in the reaction with **2a** (entries 11–17). Among these functionalized alkynes, 6-chlorohexyne (**1o**) was also used for the reactions with *C*-cyclohexyl-*N*-1-naphthylnitrone (**2e**), *C*-(*N*-Boc-4-piperidyl)-*N*-phenylnitrone (**2g**), and *C*-phenyl-*N*-4-ethoxycarbonylphenylnitrone (**2i**) (entries 15–17). It should be noted that even the *C*-arylnitrone **2i**, which was not suitable for the reaction with phenylacetylene (**1a**), reacted with an acceptable yield under efficient enantiocontrol (entry 17). Propargyl *N*,*N*-dibenzylamine (**1p**) and methoxymethyl propargyl ether (**1q**) were also suitable substrates (entries 18 and 19). Interestingly, non-protected propargyl alcohol (**1r**) reacted with **2a** in good yield to furnish 3-hydroxymethyl-substituted β-lactam **3ra** (entry 20).

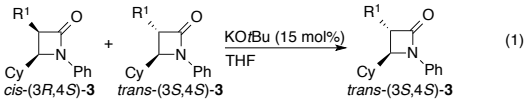
**Table 3.** Asymmetric Kinugasa reaction of alkylacetylenes.[a]




| entry | alkyne $R^1$ | nitrone $R^2$ | nitrone $R^3$ | yield (%)[b] | cis/trans[c] | ee (%)[d] cis | ee (%)[d] trans |
|---|---|---|---|---|---|---|---|
| 1 | *n*Bu (**1h**) | Cy | Ph (**2a**) | 55 (**3ha**) | 80:20 | 98 | 97 |
| 2 | *n*Bu (**1h**) | Cy | 4-MeO-$C_6H_4$(**2b**) | 44 (**3hb**) | 88:12 | >99 | 99 |
| 3 | *n*Bu (**1h**) | Cy | 4-F-$C_6H_4$ (**2c**) | 30 (**3hc**) | 79:21 | 98 | 97 |
| 4 | *n*Bu (**1h**) | Cy | 2-Me-$C_6H_4$ (**2d**) | 92 (**3hd**) | 71:29 | >99 | 98 |
| 5 | *n*Bu (**1h**) | Cy | 1-naphthyl (**2e**) | >99 (**3he**) | 68:32 | 99 | 98 |
| 6 | *n*Bu (**1h**) | *i*Pr | Ph (**2f**) | 38 (**3hf**) | 79:21 | 99 | 98 |
| 7 | *n*Bu (**1h**) | *n*Pent | Ph (**2h**) | 50 (**3hh**) | 72:28 | 98 | 96 |
| 8 |  **1i** | Cy | Ph (**2a**) | 50 (**3ia**) | 78:22 | 97 | 91 |
| 9 | *i*Bu (**1j**) | Cy | Ph (**2a**) | 52 (**3ja**) | 67:33 | 99 | 98 |
| 10 | Cy (**1k**) | Cy | Ph (**2a**) | 48 (**3ka**) | 78:22 | 97 | 92 |
| 11 |  **1l** | Cy | Ph (**2a**) | 48 (**3la**) | 71:29 | 99 | 99 |
| 12 |  **1m** | Cy | Ph (**2a**) | 53 (**3ma**) | 84:16 | 98 | 97 |
| 13 |  **1n** | Cy | Ph (**2a**) | 66 (**3na**) | 80:20 | 97 | 94 |
| 14 |  **1o** | Cy | Ph (**2a**) | 49 (**3oa**) | 82:18 | 98 | 95 |
| 15 |  **1o** | Cy | 1-naphthyl (**2e**) | >99 (**3oe**) | 75:25 | 99 | 98 |
| 16 |  **1o** |  | Ph (**2g**) | 58 (**3og**) | 88:12 | 99 | 98 |
| 17 |  **1o** | Ph | 4-$EtO_2C$-$C_6H_4$ (**2i**) | 41 (**3oi**) | 89:11 | 94 | 78 |
| 18 |  **1p** | Cy | Ph (**2a**) | 42 (**3pa**) | 68:32 | 99 | 97 |
| 19 |  **1q** | Cy | Ph (**2a**) | 69 (**3qa**) | 54:46 | 96 | 97 |
| 20 |  **1r** | Cy | Ph (**2a**) | 76 (**3ra**) | 87:13 | 98 | 95 |

[a] Conditions: **1** (0.2 mmol), **2** (0.2 mmol), $Cu(OTf)_2$/**L8** (10 mol%), $Et_2NH$ (0.2 mmol), toluene (1.0 mL) at –40 ˚C for 24 h. [b] Yield of isolated product as isomeric mixture. [c] Determined by $^1H$ NMR spectroscopy. [d] The ee values were determined by HPLC analysis. See Supporting Information for determination of absolute configurations.

Feasibility of epimerization[4,6f] at the alkylated C3 position to allow cis-to-trans isomerization was examined with KO*t*Bu as a base for representative 3-alkyl-β-lactams in a cis/trans mixture (eq 1). These reactions gave diastereomerically pure *trans*-β-lactams with high enantiomeric purities, confirming the stereochemical course leading to the trans isomers (Tables S5–7).




(1)

**3ha**: $R^1$ = *n*Bu, 93% yield, 97% ee (r.t., 1 h)
**3ka**: $R^1$ = Cy; 96% yield, 96% ee (50 °C, 6 h)
**3na**: $R^1$ = 2-(1,3-dioxane-2-yl)ethyl, 93% yield, 97% ee (r.t., 1 h)

Our scenario for the catalytic asymmetric Kinugasa reaction is illustrated in Figure 3. We propose that $Cu(OTf)_2$ is first reduced to a Cu(I) species in the reaction mixture containing potential reducing agents such as the terminal alkyne and $Et_2NH$. A P,N,O-bound copper(I)–alkyne complex forms a hydrogen-bonded complex (**A**) with $Et_2NH$. Proton relay through $Et_2NH$ in **A** leads to C(sp)–H activation of terminal alkyne **1** to form copper acetylide **B** with a Cu-bound OH group. Nitrone **2** is captured by **B** through O–H···O/C($sp^3$)–H···O two-point-hydrogen-bonding to form complex **C**.[10,11] Subsequent C–C bond formation may occur in a stepwise manner rather than a [3+2] cycloaddition manner because the oxyanion is hydrogen-bonded.[14, 15] In the transition state [**TS** (C-D)] for bond formation between the alkyne carbon β to Cu and the nitrone imino carbon, the steric repulsion between the substituent of the alkyne (R) and the *N*-aryl group (Ar') should be minimized. We propose this stereochemical model based on the observation that more sterically demanding *N*-substituents such as *o*-tolyl and 1-naphthyl groups gave better enantioselectivities (Table 2, entries 3 and 4; Table 3, entries 4 and 5). Next, C–C-bonded product **D** undergoes a second bond formation between the oxyanion and the acetylide carbon α to Cu to give a five-membered *N*,*O*-heterocyclic organocopper intermediate (**E**). Rearrangement of **E** accompanied by diastereoselective protodemetalation and re-coordination of the alkyne **1** produces β-lactam **3** and **A**. The major diastereomer with the cis-configuration should result from protonation from the less hindered diastereotopic face. This rearrangement/protodemetalation may demand an additional $Et_2NH$ molecule.

The significant difference in enantiomeric purities between the *cis*- and *trans*-β-lactams observed in the reactions of aryl- or alkenylacetylenes (Tables 1 and 2) is curious. This suggests reversibility of the C–C bond formation step or the existence of different reaction pathways.

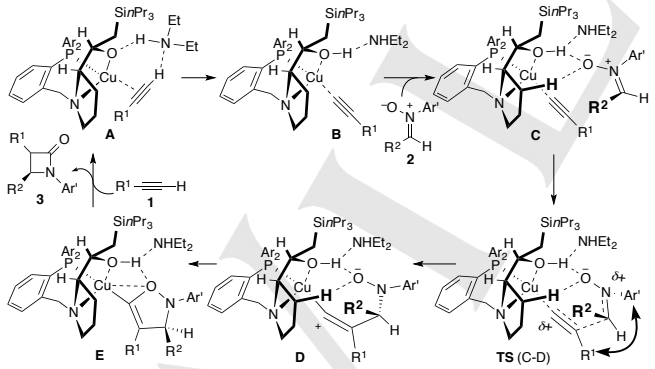



**Figure 3.** A scenario for the catalytic enantiocontrolled Kinugasa reaction.

In summary, prolinol-phosphine chiral ligands served as efficient catalysts for the asymmetric Kinugasa reaction. While limited applicability toward *C*-arylnitrones remains an issue, high enantioselectivities were attained in the reaction of *C*-alkylnitrones not only with aryl- or alkenylacetylenes but also with alkylacetylenes. This new protocol for the Kinugasa reaction with alkylacetylenes enabled straightforward asymmetric synthesis of a variety of 3-alkyl-β-lactams. Further elaboration of the chiral catalyst system is underway in our laboratory.

## Acknowledgements

This work was supported by CREST and ACT-C (JPMJCR12YN), JST to M.S. Y.T. thanks JSPS for scholarship support.

**Keywords:** asymmetric catalysis · cooperative catalysis · copper · nitrone · β-lactam

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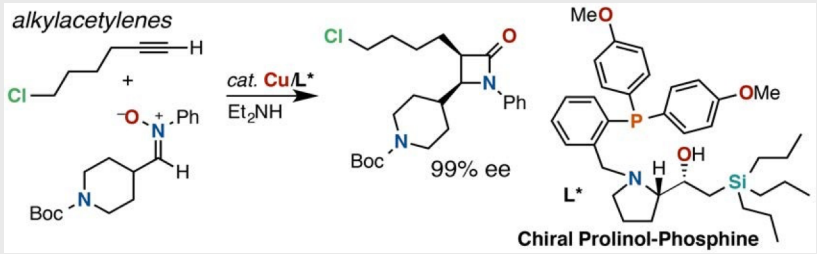
## COMMUNICATION

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**Asymmetric Synthesis of β-Lactams through Copper-Catalyzed Alkyne–Nitrone Coupling with Prolinol-Phosphine Chiral Ligand**