OL | Organic Letters

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

Asymmetric Synthesis of α-Alkylidene-β-Lactams through Copper Catalysis with a Prolinol-Phosphine Chiral Ligand

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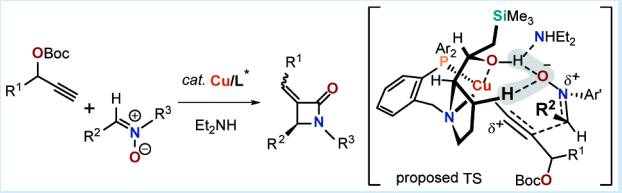
Supporting Information

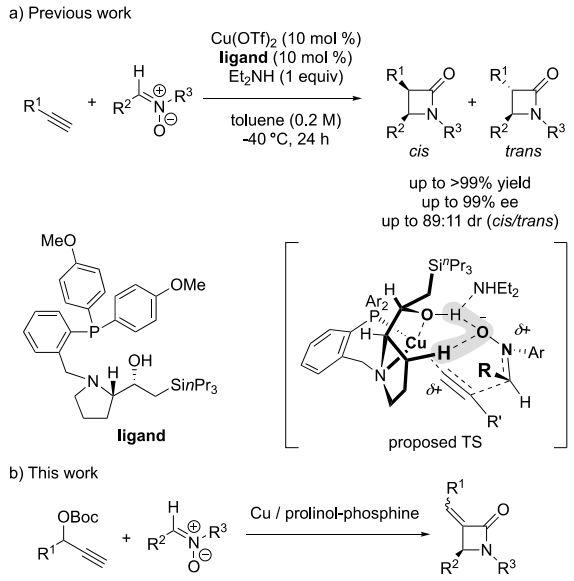
ABSTRACT: A copper/prolinol-phosphine chiral catalyst enabled the one-step synthesis of chiral α-alkylidene-β-lactams. Optimization of the chiral ligand for steric and electronic properties realized the highly enantioselective coupling of nitrones and propargyl alcohol derived alkynes. The resulting chiral α-alkylidene-β-lactams served as a platform for various β-lactams via well-established transformations of α,β-unsaturated carbonyl compounds.



Since the discovery of penicillin,[1] the first antibiotic in the world, chiral β-lactams have been recognized as a privileged structural motif in biologically active compounds.[2] The substituent at the α-position of the β-lactam is critically important for biological activity. Thus, synthetic approaches to install various α-substituents are in high demand. In this context, chiral α-alkylidene-β-lactams are attractive linchpin compounds since the C−C double bond serves as a platform for numerous transformations such as olefin metathesis, hydrogenation, Michael addition, etc. In addition, chiral α-alkylidene-β-lactams exhibit various biologic activities on their own.[3] Although several synthetic methods have been developed for chiral α-alkylidene-β-lactams,[4−6] most of them require multistep sequences or the use of stoichiometric amounts of chiral reagents. Thus, catalytic asymmetric reactions for the one-step synthesis of chiral α-alkylidene-β-lactams from readily available achiral starting materials remain unexplored.

The Kinugasa reaction, a coupling reaction between alkynes and nitrones,[7] serves as a straightforward method for the synthesis of β-lactams.[8] We previously developed a copper-catalyzed asymmetric Kinugasa reaction[9] with a prolinol-phosphine chiral ligand.[10] A hydrogen bonding network including a nonclassical hydrogen bond between a nonpolar C(sp^3)−H bond in the chiral ligand and the oxygen atom of the nitrone was proposed as an element critical to the catalytic activity and enantioselectivity (Scheme 1a). Next, we envisaged that the copper/prolinol-phosphine chiral ligand system may be utilized for the catalytic asymmetric Kinugasa reaction to afford chiral α-alkylidene-β-lactams by introducing a proper leaving group to the alkyne substrate (Scheme 1b). Basak reported a related reaction of a free propargyl alcohol promoted by a stoichiometric CuI/L-proline system to afford α-alkylidene-β-lactams with at most 15% ee.[6] More recently,

Scheme 1. Copper-Catalyzed Asymmetric Kinugasa Reaction with Prolinol-Phosphine Chiral Ligand



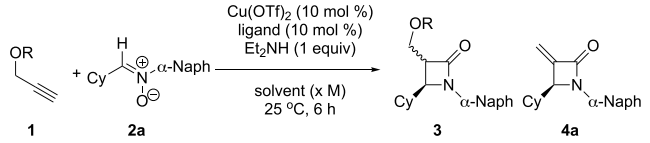
Grée extended the method to a catalytic reaction, though the reaction was only for a racemic system.[11] Herein, we report the first catalytic enantioselective Kinugasa reaction that provides chiral α-alkylidene-β-lactams in one step.

We initiated our investigation with a *C*-cyclohexyl-*N*-naphthylnitrone **2a** to explore the proper activating group for the propargyl alcohols using the copper/prolinol-phosphine chiral ligand (**L1**) catalyst (Table 1). When free propargyl

Received: January 22, 2019

DOI: 10.1021/acs.orglett.9b00276
Org. Lett. XXXX, XXX, XXX−XXX

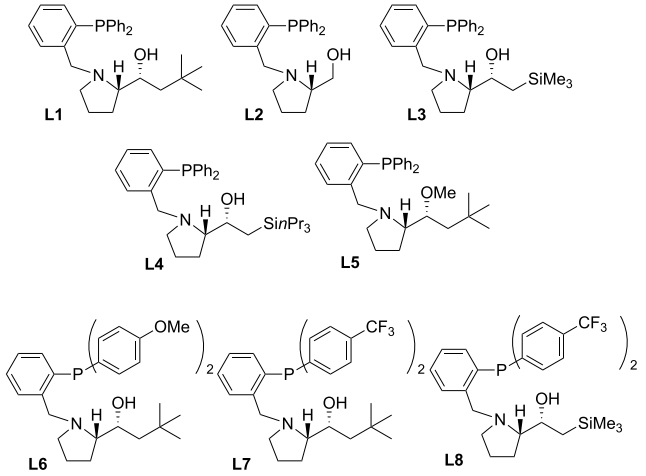
Table 1. Optimization of Reaction Conditions[a]



1 2a 3 4a

						4a	
entry	R	ligand	solvent	*x* (M)	**3** yield (%)	yield (%)	ee (%)
1	H (**1a**)	**L1**	toluene	0.2	77	22	80
2	MOM (**1b**)	**L1**	toluene	0.2	52	37	91
3	Boc (**1c**)	**L1**	toluene	0.2	0	85	67
4	Bz (**1d**)	**L1**	toluene	0.2	0	75	72
5	$P(O)(OEt)_2$ (**1e**)	**L1**	toluene	0.2	0	80	66
6	Boc (**1c**)	**L1**	toluene	0.05	0	88	80
7	Boc (**1c**)	**L1**	*t*BuOMe	0.05	0	quant	84
8	Boc (**1c**)	**L2**	*t*BuOMe	0.05	0	quant	83
9	Boc (**1c**)	**L3**	*t*BuOMe	0.05	0	94	87
10	Boc (**1c**)	**L4**	*t*BuOMe	0.05	0	quant	83
11	Boc (**1c**)	**L5**	*t*BuOMe	0.05	0	90	2
12	Boc (**1c**)	**L6**	*t*BuOMe	0.05	0	98	80
13	Boc (**1c**)	**L7**	*t*BuOMe	0.05	0	99	91
14	Boc (**1c**)	**L8**	*t*BuOMe	0.05	0	94	92

[a]**1** (0.2 mmol), **2a** (0.2 mmol), $Cu(OTf)_2$ (0.02 mmol), ligand (0.02 mmol), Et_2NH (0.2 mmol), 25 °C, 6 h. Yield was determined by ^1H NMR analysis using tetrabromoethane as an internal standard. Enantiomeric excess (ee) was determined by chiral HPLC analysis.



alcohol **1a** was the substrate (entry 1), a normal Kinugasa reaction product **3** was obtained as the major product (77% yield) and the desired α-methylene-β-lactam **4a** was obtained in 22% yield and 80% ee.[12] MOM-protected propargyl alcohol **1b** also gave **4a** (37% yield, 91% ee) in low yield with **3** (52% yield) as a major product (entry 2). On the other hand, substrates with better leaving groups, OBoc (**1c**), OBz (**1d**), and $OP(O)(OEt)_2$ (**1e**), provided **4a** in higher yields, albeit with moderate enantioselectivities (entries 3−5). The normal Kinugasa reaction product **3** was not obtained in these cases while the formation of a small amount of *N*,*N*-diethylacrylamide (<12% yield) was observed.[13] The most reactive **1c** was selected as the substrate for further reaction optimization. As a result, the yield and enantioselectivity were improved to quantitative yield and 84% ee by diluting the reaction and changing the solvent from toluene to *t*BuOMe (entry 7).

Next, we assessed the effect of each structural motif of the prolinol-phosphine chiral ligands. The effect of the alcohol structure was examined first. Sterically less demanding **L2** with a primary alcohol moiety provided **4a** with comparable results (quantitative yield, 83% ee, Table 1, entry 8). A slightly bulkier CH_2SiMe_3 substituent (**L3**) α to the hydroxy group marginally improved the enantioselectivity (94% yield, 87% ee), while a much bulkier CH_2SiPr_3 substituent (**L4**) did not (quantitative yield, 83% ee) (entries 9 and 10).[14] The enantioselectivity was nearly lost when the hydroxy group of the ligand was masked as a methoxy group (**L5**, entry 11, 90% yield, 2% ee), indicating that the hydrogen-bonding network was crucial in this catalytic system. Examination of the substituent effect of the phosphine moiety revealed that an electron-withdrawing CF_3 group at the *para* position of the *P*-phenyl group (**L7**) had a significant impact on increasing the enantioselectivity (99% yield, 91% ee, entry 13). Finally, the enantioselectivity was slightly improved to 92% ee by a ligand (**L8**) with a CH_2SiMe_3 group at the position α to the hydroxy group (entry 14).

Having the optimized conditions in hand, the substrate scope was examined (Scheme 2). Both alkyl and aryl *C*-substituents (R^2) of the nitrones were competent. The reaction smoothly proceeded in 1 mmol scale with comparable results (**4a**, 100% yield, 93% ee). An isopropyl substituent gave both a

DOI: 10.1021/acs.orglett.9b00276
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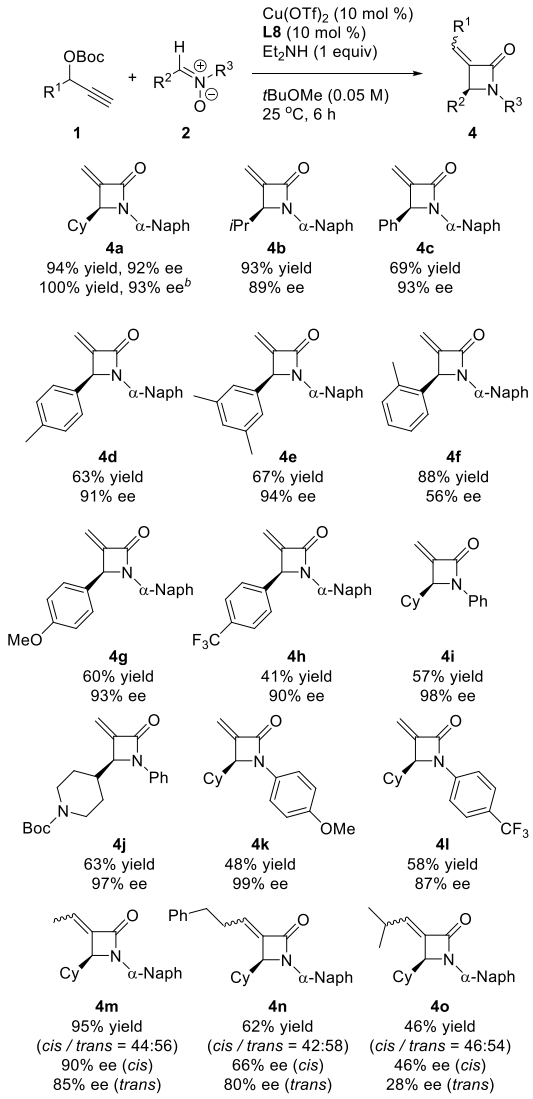
Scheme 2. Substrate Scope[a]



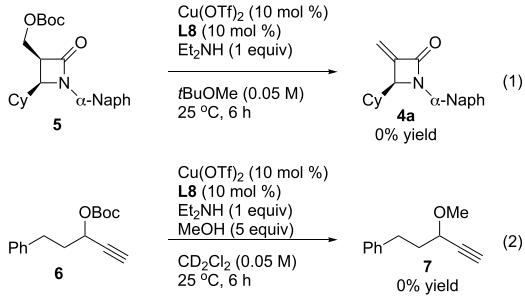
[a]**1** (0.2 mmol), **2** (0.2 mmol), $Cu(OTf)_2$ (0.02 mmol), **L8** (0.02 mmol), Et_2NH (0.2 mmol), 25 °C, 6 h. Isolated yields are shown. Enantiomeric excess (ee) was determined by chiral HPLC analysis. [b]The reaction was conducted in 1 mmol scale.

high yield and high enantioselectivity (**4b**, 93% yield, 89% ee). However, a nitrone with a bulkier substituent, a *tert*-butyl group, was unreactive. High enantioselectivity was retained with a phenyl substituent while the yield was moderate (**4c**, 69% yield, 93% ee). Substituents at the *para*- or *meta*-position on the aryl group provided the products in high enantioselectivities (**4d**, **4e**). On the other hand, *ortho* substituent diminished the enantioselectivity (**4f**, 88% yield, 56% ee). Both electron-donating (**4g**) and -withdrawing (**4h**) substituents were competent to afford high enantioselectivities.

Higher enantioselectivity was observed when the *N*-substituent of the nitrone (R^3) was changed to a phenyl group (**4i**, 57% yield, 98% ee). The *N*-phenyl-*C*-[*N*-(*tert*-butoxycarbonyl)piperazine-4-yl]nitrone was tolerated under the same conditions (**4j**, 63% yield, 97% ee). Introduction of a 4-MeO group to the *N*-phenyl moiety of the *C*-cyclohexyl-*N*-phenylnitrone resulted in even higher enantioselectivity (**4k**, 48% yield, 99% ee). On the other hand, the enantioselectivity was slightly decreased when a 4-CF_3 group was introduced to the *N*-phenyl moiety of the *C*-cyclohexyl-*N*-phenylnitrone (**4l**, 58% yield, 87% ee).

The secondary propargylic alcohol derivative with a methyl group at the propargylic position reacted smoothly to afford **4m** in 95% yield with high enantioselectivity (*cis*/*trans* 44:56, *cis*: 90% ee, *trans*: 85% ee). Although the influence of elongating the alkyl chain of the alkyne was marginal (**4n**, 62% yield, *cis*/*trans* 42:58, *cis*: 66% ee, *trans*: 80% ee), a branch at the homopropargylic position resulted in a significant decrease in the enantioselectivity (**4o**, 46% yield, *cis*/*trans* 46:54, *cis*: 46% ee, *trans*: 28% ee). An *O*-Boc-activated tertiary propargylic alcohol did not participate in the reaction.

To gain information on how the elimination of the Boc-activated hydroxy group occurs, we conducted the following two experiments (eqs 1 and 2). A β-lactam **5** containing the OBoc group at the position β to the carbonyl group was subjected to the conditions of the Kinugasa reaction. This resulted in no reaction with complete recovery of **5** (eq 1), strongly suggesting that the elimination of the OBoc group occurs prior to β-lactam formation. If the elimination occurs before the coupling of the alkyne and the nitrone, a copper–allenylidene complex is a probable intermediate. If this is the case, the copper complex should give the corresponding propargylic methyl ether **7** upon trapping with MeOH.[15] Having this in mind, alkyne **6** was treated with the copper/prolinol-phosphine catalyst in the presence of MeOH in CD_2Cl_2 and the reaction progress was monitored by ^1H NMR spectroscopy. The ^1H NMR spectra did not show any change during the reaction and no sign of propargyl methyl ether **7** was detected, ruling out the formation of the copper–allenylidene complex. These experimental results strongly suggest that the elimination of the OBoc group occurs during the coupling of the two compounds.



Based on the results shown above and the knowledge from our previous work,[9] we tentatively propose the following catalytic cycle (Figure 1). A copper–alkyne complex forms a hydrogen-bonding network via Et_2NH **A**, and deprotonation of the terminal proton of the alkyne produces a copper acetylide. Next, capturing the nitrone oxyanion by two-point-hydrogen-bonding, in which the copper-bound OH group and the C(sp^3)–H of the pyrrolidine moiety work as hydrogen bond donors, leads to assembly of the two reactants for the copper catalysis (**B**).[16] Since the oxyanion of the nitrone is hydrogen-bonded, subsequent C–C bond and C–O bond formations proceed in a stepwise fashion (**C** → **D** → **E**). The positive charge in the alkyne-derived moiety would hamper elimination of the $BocO^-$ leaving group from **C** or **D**. Rearrangement of **E** produces a copper enolate of the β-lactam (**F**), and elimination of $BocO^-$, which may be assisted by protonation with the hydrogen-bonded Et_2NH, affords a copper-coordinated β-lactam (**G**). Dissociation of the β-lactam (**4**) from **G** and recoordination of the alkyne (**1**) complete the catalytic cycle.

DOI: 10.1021/acs.orglett.9b00276
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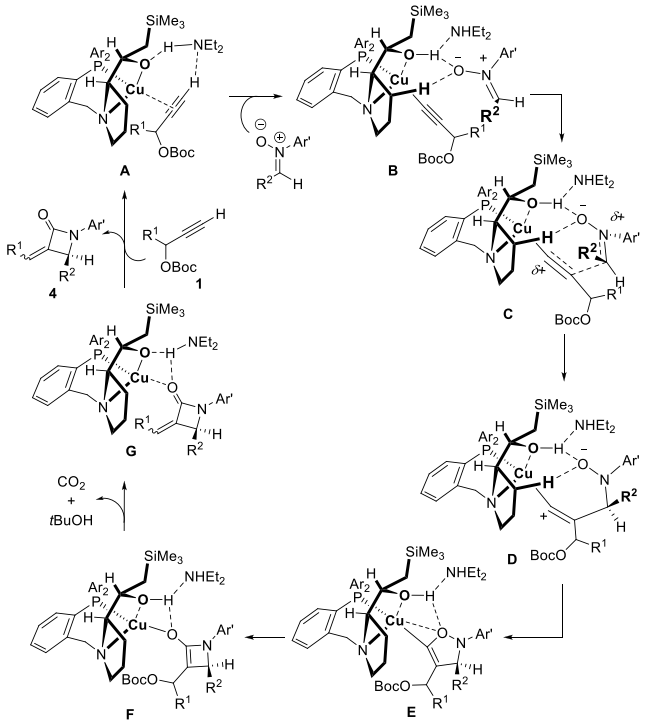
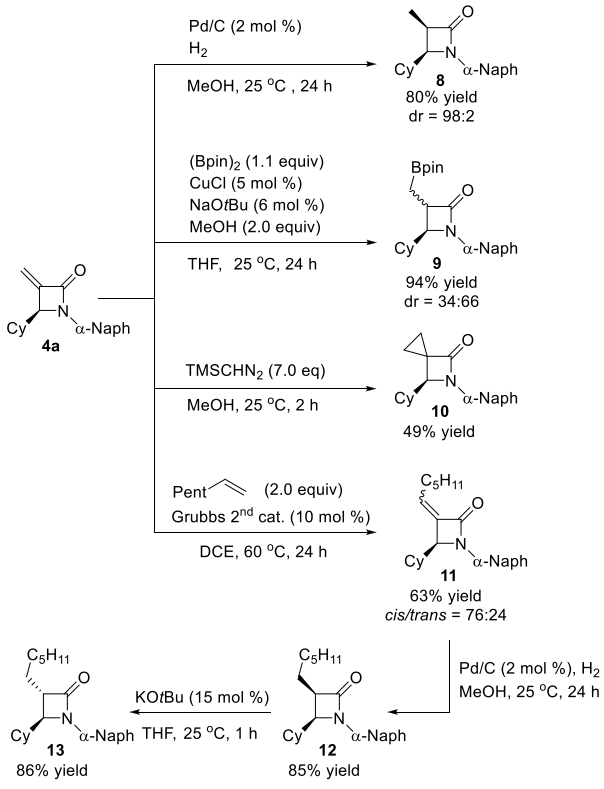


Figure 1. Proposed catalytic cycle.

Next, we assessed the potential of the α-methylene-β-lactam **4a** as a linchpin for various β-lactams (Scheme 3). Hydrogenation of the double bond occurred with high diastereoselectivity (dr 98:2) to give the 3,4-*cis*-dialkyl β-lactam **8**. Attempts at conjugate addition of alkyl groups with conventional Gilman reagents or higher-order cyanocuprates resulted in no reaction. On the other hand, β-(pinacolato)boryl derivative **9**, which has the potential for further derivatization, was obtained through copper-catalyzed boron conjugate addition.[17] An intriguing spiro compound (**10**) involving a three-membered ring was synthesized in 49% yield through cyclopropanation with trimethylsilyldiazomethane. Elongation of the carbon skeleton was possible by alkene cross-metathesis with heptene using the second generation Grubbs catalyst to afford **11** in 63% yield with moderate *cis*/*trans* selectivity.[18] Subsequent hydrogenation of the double bond produced 3,4-*cis*-dialkyl product **12** exclusively in 85% yield. Epimerization of **12** at the position α to the carbonyl group was feasible with 15 mol % of KO*t*Bu at room temperature to afford the 3,4-*trans*-dialkyl product selectively (**13**, 86% yield).

Scheme 3. Representative Transformations



In summary, the one-step asymmetric synthesis of chiral α-alkylidene-β-lactams has been achieved through the catalytic enantioselective Kinugasa reaction between *O*-Boc-activated propargylic alcohols and nitrones. Both *C*-aryl and *C*-alkyl nitrones are suitable substrates for the reaction with high enantioselectivity. Further studies on the transformative reactivities of the chiral α-alkylidene-β-lactams for the synthesis of various β-lactams and related compounds are underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00276.

Detailed experimental procedures, additional condition screening table, characterization data, HPLC charts, NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Institute for Chemical Reaction Design and Discovery (ICReDD) was established by World Premier International Research Initiative (WPI), MEXT, Japan. This work was supported by JST ACT-C Grant Number JPMJCR12YN and JSPS KAKENHI Grant Number JP18H03906 in Grant-in-Aid for Scientific Research (A) to M.S. Y.T. thanks JSPS for scholarship support.

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DOI: 10.1021/acs.orglett.9b00276
Org. Lett. XXXX, XXX, XXX−XXX