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Asymmetric Synthesis of Spirocyclic β-Lactams *via* Copper-Catalyzed Kinugasa/Michael Domino Reactions

Tao Shu, Long Zhao, Sun Li, Xiang-Yu Chen, Carolina von Essen, Kari Rissanen and Dieter Enders*

Abstract: The first copper-catalyzed highly chemo-, regio-, diastereo-, and enantioselective Kinugasa/Michael domino reaction for the desymmetrization of prochiral cyclohexadienones is described. In the presence of a chiral copper catalyst, alkyne-tethered cyclohexadienones couple with nitrones to generate the chiral spirocyclic lactams with excellent stereoselectivities (up to 97% *ee*, >20:1 dr). The new protocol provides a direct access to versatile highly functionalized spirocyclic β-lactams possessing four contiguous stereocenters including one quaternary and one tetra-substituted stereocenter.

Desymmetrization processes are powerful strategies for the transformation of prochiral molecules into functionalized enantioenriched molecules. Chiral cyclohexenones are versatile building blocks which have been widely used in the synthesis of natural products and bioactive compounds. Various methodologies have been developed to construct enantioenriched cyclohexenone derivatives, one of them being the catalytic enantioselective desymmetrization, which is one of the most efficient and pratical protocols.[1] In the past decades, the differentiation of two enantiotopic enones of cyclohexadienones for the construction of complex molecule frameworks has been applied extensively in a wide range of transformations utilizing both transition metal catalysts and organocatalysts.[2-9]

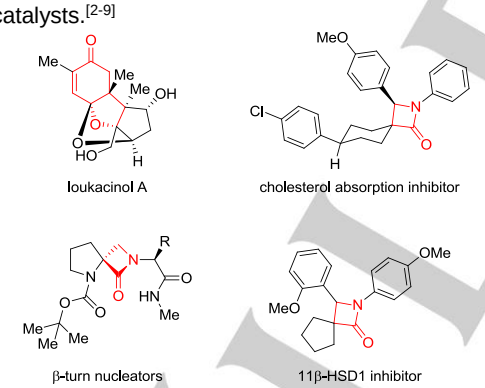

Figure 1. Typical bioactive compounds containing cyclohexenones and spiro β -lactams.

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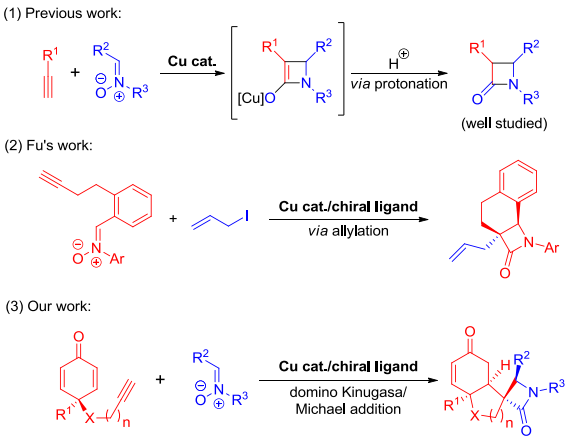
β-Lactams are privileged scaffolds which widely exist as core structures in many bioactive compounds and natural products, such as penicillins, showing antibacterial, antifungal, and anti-inflammatory activities.[10a, b] In particular, spirocyclic β-lactams or azetidines, a unique class of four-membered heterocycles with enhanced three dimensionality, are of growing interest to medicinal chemistry owing to the more desirable physicochemical and biological activities, such as cholesterol absorption inhibitors and 11β-HSD1 inhibitor activities (Figure 1).[10c, d] Owing to the biological importance of the chiral cyclohexenones and β-lactams, developing an efficient method to merge them into a single molecule *via* a catalytic domino reaction is highly desirable.

Among numerous approaches towards four-membered lactam moieties, the Kinugasa reaction was the most straightforward one to rapidly assemble highly densely-functionalized β-lactams in a domino fashion using readily available terminal alkynes and nitrones as starting materials.[11a-e] The first catalytic asymmetric Kinugasa reaction was developed by Miura in 1995. Since then significant advance has been made,[12a-l] nevertheless the domino sequences have rarely been investigated. The only example reported by Fu shows that the copper enolate was intercepted by allyl iodide.[12c] To the best of our knowledge, there is no report that the copper enolate in the Kinugasa reaction was intercepted by a subsequent Michael acceptor, so we speculated that the enone motif of the cyclohexadienones could serve as the desired Michael acceptor, thus affording important spirocyclic β-lactams incorporating both cyclohexenones and β-lactams (Scheme 1).



Scheme 1. Previous work and our present work.

However, there are several challenges involving chemo-, regio-, diastereo-, and enantioselectivity that need to be addressed. 1) Chemoselectivity, the enone functional group of the cyclohexadienones could undergo a [3+2]-cycloaddition with the nitrones, hence there should be enough difference in reactivity to selectively take place at the alkyne group rather than at the enone motif. 2) Regioselectivity, the dipolar [3+2]-cycloaddition could

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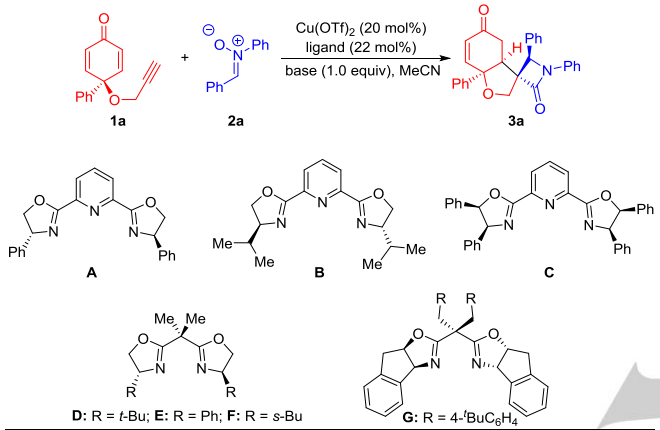
lead to regioisomeric isoxazolines, as the Kinugasa intermediate could lead to spirocyclic β-lactams *via* the Kinugasa/Michael domino reaction, while the Baldwin intermediate could lead to spirocyclic aziridines *via* the Baldwin/Michael domino reaction.[13] 3) The reaction of alkylacetylenes, an unfavorable substrate in previous reports, always affords moderate enantioselectivity, hence the identification of a suitable catalyst system for the alkylalkyne-tethered cyclohexadienones is also challenging.[14]

As part of our ongoing interest,[15] we herein report our study of a copper-catalyzed Kinugasa/Michael domino sequence of alkyne-tethered cyclohexadienones and nitrones to stereoselectively afford spirocyclic β-lactams.

Table 1. Optimization of the reaction conditions. [a]

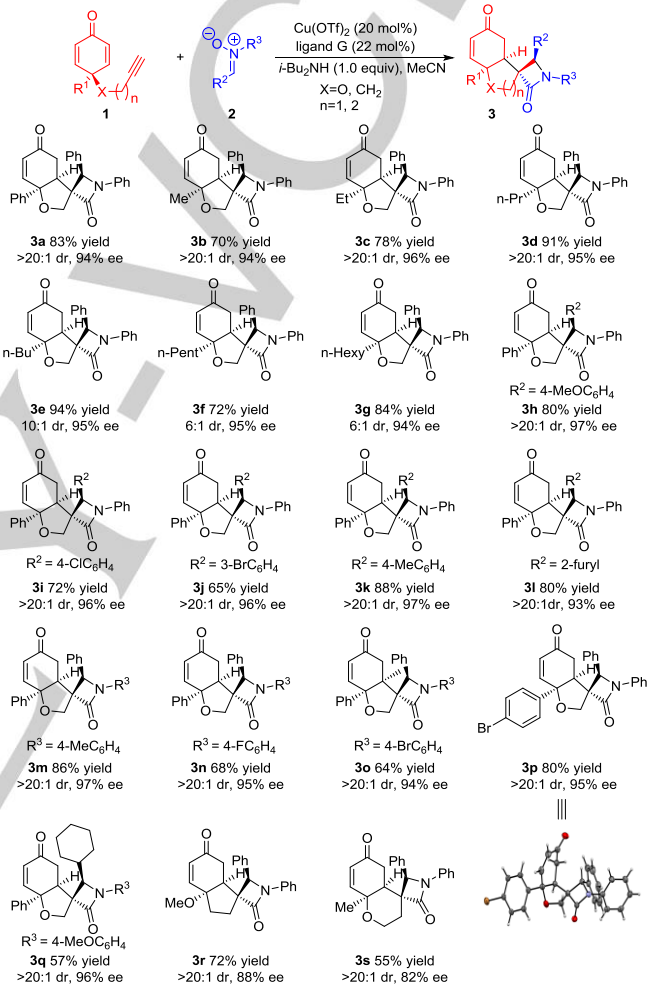


Entry	Ligand	Base	Yield (%)[b]	ee (%)[c]
1	A	DIPEA	36	9
2	B	DIPEA	50	20
3	C	DIPEA	29	33
4	D	DIPEA	52	0
5	E	DIPEA	40	7
6	F	DIPEA	26	17
7[d,e]	G	DIPEA	50	66
8[e]	G	*c*-Hex$_2$NH	50	93
9[e]	G	*n*-Bu$_2$NH	81	92
10[e]	**G**	***i*-Bu$_2$NH**	**83**	**94**

[a] Reaction conditions unless otherwise specified: **1a** (0.1 mmol), **2a** (0.1 mmol), $Cu(OTf)_2$ (20 mol%), ligand (22 mol%), base (0.1 mmol), CH_3CN (1 mL) under Ar at RT. [b] Yield of isolated products. [c] ee was determined by chiral-phase HPLC analysis. [d] $CuBr_2$ was used as copper source. [e] 0 °C, 48 h.

We initiated our investigation by examining the alkyne-tethered cyclohexadienone **1a**, which is easily accessible from oxidative dearomatization of 4-phenylphenol and nitrone **2a** as model substrates using 20 mol% $Cu(OTf)_2$ as copper source, 22 mol% BOX ligands **A-F**, and 1.0 equivalent DIPEA as base in acetonitrile. Gratifyingly, all reactions proceeded smoothly to deliver the desired product **3a** as a single diastereomer in 1 hour, however, low enantioselectivities were observed with these screened BOX ligands **A-F** (entry 1-6). Then we tested the Evans' condition[16] using $CuBr_2$ as the copper source, indane-BOX **G** as the ligand at 0 °C, and albeit moderate enantioselectivity was obtained (66% ee, entry 7), the ligand **G** provided the promising ee for further optimization. We then focused on the highly sterically demanding ligand **G** using $Cu(OTf)_2$ as copper source and several bases were screened. To our delight, the bases showed strong impact on both the yield and the enantioselectivity and the ee increased significantly to 93% (*c*-Hex$_2$NH, entry 8), 92% (*n*-Bu$_2$NH, entry 9) and 94% (*i*-Bu$_2$NH, entry 10), respectively.[17] We finally identified $Cu(OTf)_2$ (20 mol%), ligand **G** (22 mol%), *i*-Bu$_2$NH (1.0 equivalent) in acetonitrile at 0 °C as the optimized conditions.

Table 2. Substrate scope[a]



[a] The reactions were performed with the alkyne-tethered cyclohexadienones **1** (0.2 mmol), nitrones **2** (0.2 mmol), $Cu(OTf)_2$ (20 mol%), **G** (22 mol%), *i*-Bu$_2$NH (0.2 mmol) in MeCN (2.0 mL) at 0 °C for 48 h. Yields of isolated products **3** after chromatography. The dr was determined by ^{1}H NMR analysis and the ee by HPLC analysis of the purified product on a chiral stationary phase.

With the optimized reaction conditions in hand, we next evaluated the reaction scope with different substituted alkyne-tethered cyclohexadienones and nitrones. As summarized in Table 2, the reaction exhibits a high functional group tolerance, a broad substrate scope with various substituents on the cyclohexadienones and nitrones. With R^1= Me, Et, *n*-Pr, the reaction proceeded smoothly, providing the desired products in good yields, excellent diastereoselectivities (>20:1) and enantioselectivities (**3b**, 94% ee; **3c**, 96% ee; **3d**, 95% ee, respectively). With the longer alkyl chains R^1= *n*-Bu, *n*-Pentyl and

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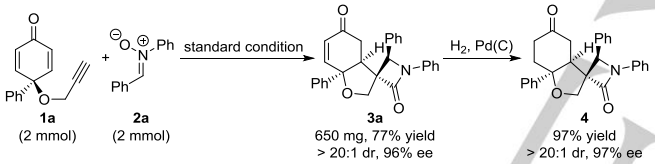
n-Hexyl group, the reaction also worked well in good yields and excellent enantioselectivities (**3e**, 95% ee; **3f**, 95% ee; **3g**, 94% ee respectively), albeit the diastereoselectivities were inferior (**3e**, 10:1 dr; **3f**, 6:1 dr; **3g**, 6:1 dr, respectively). Different substituents R^2 and R^3 on the nitrones have been investigated. The change of R^3 of the nitrones worked well and substituents as halogens and the methyl group proceeded well to deliver the desired product (**3m-o**) in good yields and excellent enantioselectivities. The heterocyclic 2-furyl-substituted nitrone also worked well, providing the desired spiro β-lactam **3l** in 80% yield, >20:1 dr, 93% ee. With the alkyl group R^2 = cyclohexyl the desired product was also obtained smoothly (**3q**). To further show the generality of this protocol, we also investigated different cyclohexadienone substrates (X = CH_2, n = 1; X = O, n = 2) under the optimal conditions and the desired cyclopentane and tetrahydropyran spirocyclic products were obtained in good yields and stereoselectivities (**3r** and **3s**). To our surprise, when we changed the linker from oxygen to a NTs group, no desired product was detected. The absolute configuration of **3p** was unambiguously determined by single-crystal X-ray diffraction analysis.[18] **3a-3s** were assigned according to the analogy with **3p**.

To demonstrate the scalability of the novel domino protocol, a 10-fold (2 mmol scale) of the model reaction was performed and it was found to maintain its effectiveness (77% yield, 96% ee, >20:1 dr). The remaining enone motif in the chiral spirocyclic lactams could readily be hydrogenated by treatment of H_2/Pd(C) to afford the saturated cyclohexanone derivative **4** (Scheme 2).



Scheme 2. Scale up reaction and hydrogenation of **3a** to form **4**.

The proposed mechanism is illustrated in Figure 2. Cu(II) is reduced *in situ* into a catalytically active Cu(I) species to afford a copper acetylide intermediate **I**, which undergoes a [3+2] dipolar cycloaddition with nitrones to form the copper-bound isoxazoline intermediate **II**. A rearrangement leads to a tethered four-membered copper enolate intermediate **III**, allowing a subsequent desymmetric Michael addition to afford the spirocyclic β-lactams and returns the copper catalyst.

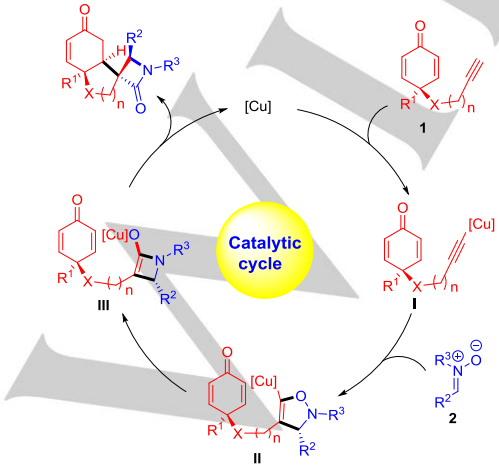


Figure 2. Proposed catalytic cycle (X = O, n = 1, 2; X = CH_2, n = 1).

In conclusion, we have developed a copper-catalyzed highly chemo-, regio-, diastereo-, and enantioselective Kinugasa/ Michael domino reaction in good yields and excellent stereoselectivities. The new protocol provides an efficient access to unprecedented spirocyclic β-lactams bearing a fused bicyclic and spiro-fused bicyclic framework with four contiguous stereocenters with an excellent level of step- and atom-economy. The reaction conditions are mild and the procedure can be easily scaled up while maintaining its effectiveness.

Acknowledgements

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Keywords: copper catalysis• β-lactam • desymmetrization •cyclohexadienone • asymmetric synthesis

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[18] CCDC 1831622 contains the supplementary crystallographic data of compound **3p**. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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Layout 2:

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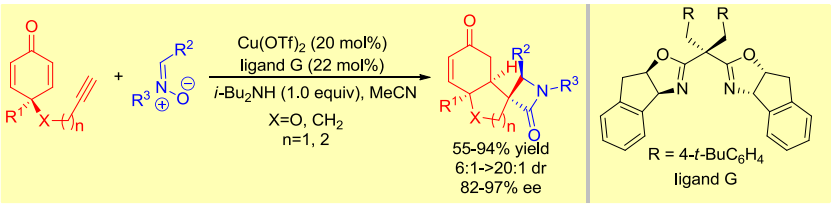

Spirocyclic β-Lactams via Domino [3+2]/1,4: Copper-catalyzed asymmetric Kinugasa/Michael domino reactions of alkyne-tethered cyclohexadienones and nitrones provide a direct stereoselective approach to spirocyclic β-lactams.

*Tao Shu, Long Zhao, Sun Li, Xiang-Yu Chen, Carolina von Essen, Kari Rissanen and Dieter Enders**

Asymmetric Synthesis of Spirocyclic β-Lactams via Copper-Catalyzed Kinugasa/Michael Domino Reactions