Asymmetric Catalysis

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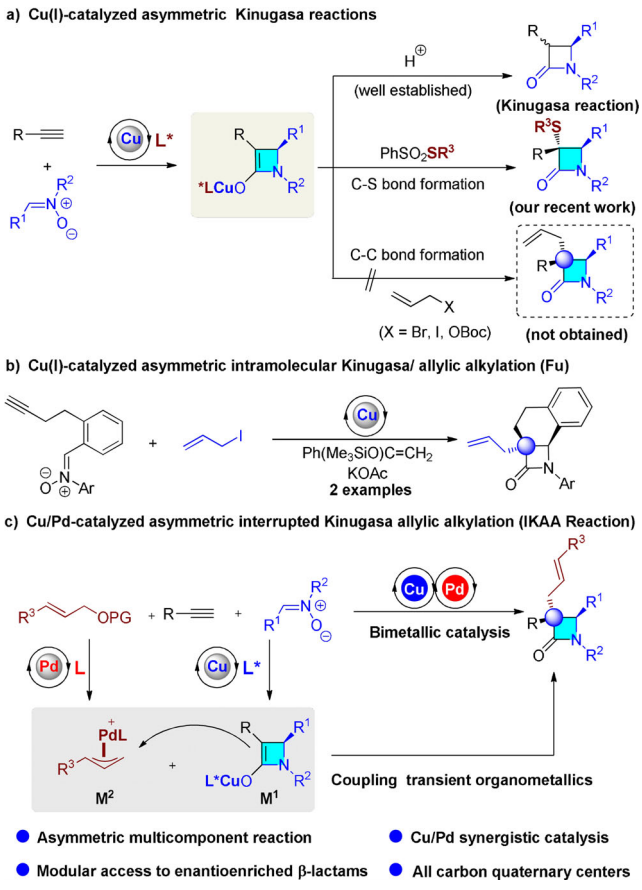
Modular Synthesis of α-Quaternary Chiral β-Lactams by a Synergistic Copper/Palladium-Catalyzed Multicomponent Reaction

*Jialin Qi, Fang Wei, Chen-Ho Tung, and Zhenghu Xu**

Abstract: *An asymmetric multicomponent, interrupted Kinugasa allylic alkylation (IKAA) reaction has been developed with a synergistic Cu-catalyzed Kinugasa system and a Pd-catalyzed allylic alkylation reaction. This unprecedented reaction provides in high yields and with high stereoselectivity a synthesis of α-quaternary chiral β-lactams, which cannot be produced with existing synthetic methods. Stereoselective coupling of two catalytic amounts of transient organometallic intermediates formed in situ is an important feature of this reaction.*

Multicomponent reactions (MCRs) can integrate three or more simple precursors into complex molecules in a single process.[1] They have the advantages of bond-formation efficiency, atom economy, product diversity and complexity, and avoid the lengthy purification procedures associated with traditional stepwise syntheses. Despite these advantages and the tremendous efforts that have been made to develop efficient MCRs, catalytic asymmetric MCRs to access enantioenriched complex molecules are not highly developed.[1c–h] Recently, by mimicking enzyme catalysis in biosystems, multicatalyst combination strategy, especially bimetallic catalysis has been developed as a promising strategy with which to produce asymmetric MCRs.[2–4] In such systems, various catalysts activate different reactants and complete the desired transformation in a highly stereoselective manner. Herein, we report the assembly of readily available alkynes, nitrones, and allylic carbonates into α-quaternary chiral β-lactams through a Cu/Pd-catalyzed IKAA reaction.

The β-lactam is the common core structure of clinically used drugs such as penicilin, cephalosporin, and also monocyclic antibiotics such as aztrenam.[5] Development of novel methods to access new β-lactams is important in further studies of this heterocyclic system, including structure–activity relationships and discovery of new antibiotics, and is thus important in global health problems. Although various syntheic methods have been developed to produce β-lactams,[6–9] synthesis of chiral β-lactams bearing an α-quaternary stereocenters is still very challenging.[10] The chiral Lewis base catalyzed asymmetric Staudinger reaction of disubstituted ketenes with imines can afford this type of structure, but the preparation and handling of highly reactive ketene intermediates limits their practical use.[7] The Kinugasa reaction, the copper(I)-catalyzed asymmetric coupling reaction of alkynes with nitrones, could produce α,β-disubstituted β-lactams efficiently, but couldn't access α-quaternary β-lactams.[8] In 2003, Fu et al. reported the only example using a two-component intramolecular Kinugasa and intermolecular allylation cascade with allyl iodide in the presence of mixed bases (Scheme 1 b).[8c] A complete three-component reaction however has not been realized to date. Very recently, we developed a copper(I)-catalyzed three-component, interrupted Kinugasa reaction to synthesize α-thiofunctional chiral β-lactams using a sulfur electrophile to intercept the key four-membered enolate copper(I) intermediate.[8g]



Scheme 1. Synthesis of α-quaternary chiral β-lactams with Kinugasa reaction.

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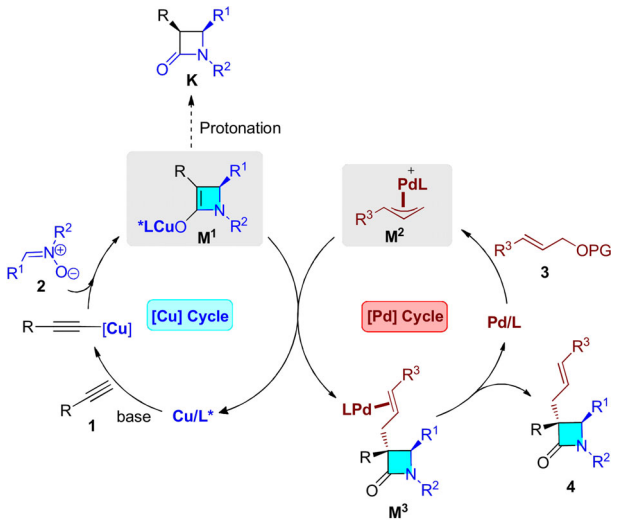
However, further application of this strategy in an attempt to trap this enolate intermediate with allyl electrophiles through C–C bond formation and building α,α-disubstituted chiral β-lactams with an all-carbon quaternary center failed (Scheme 1 a). Changing various allyl electrophiles or modification of reaction conditions failed to afford the desired products (for details, see the Supporting Information). This indicates that formation of this C–C bond is very challenging in this copper catalyzed cycle, probably due to the formation of the sterically hindered all-carbon quaternary center.

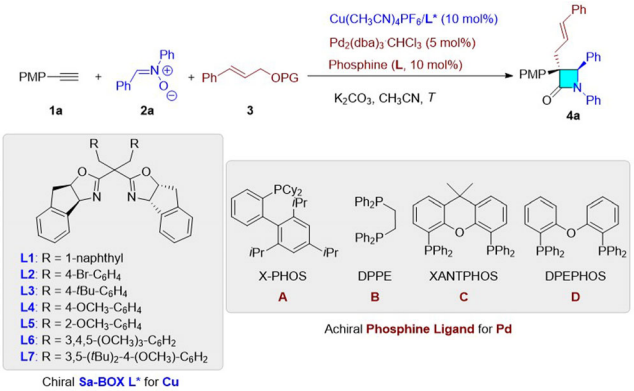
The allylic alkylation (AA) reaction, especially the palladium-catalyzed Tsuji–Trost reaction, is a fundamental C–C bond formation reaction and has been widely used in the synthesis of natural products and in medicinal chemistry.[11] The general AA is a base-promoted nucleophilic substitution on the allylic palladium intermediate. Recently such AA chemistry has been utilized in synergistic catalysis with a second transition metal to deliver unprecedented and challenging transformations.[12] Recently, Lee et al. reported a Rh^{II}-catalyzed intramoluecular C–H insertion reaction of α-diazo acetamides, followed by intermolecular AA, providing α-quaternary chiral β-lactams.[9e] In this context and with our continuing interests in bimetallic catalysis,[13] we speculated that a Cu/Pd-catalyzed, IKAA achieved by integrating the two name reactions together could resolve this C–C bond formation problem (Scheme 1 c). A plausible catalytic cycle is proposed in Scheme 2. The cycloaddition of copper(I) acetylide with nitrones generates the key chiral four-membered enolate copper(I) intermediate (**M¹**). In the meantime, palladium catalyst reacts with an allylic electrophile forming an allylic palladium intermediate (**M²**). Subsequent stereocontrolled allylic substitution between **M¹** and **M²** would produce the target α-quaternary chiral β-lactams, regenerating both the copper(I) and the palladium (0) catalysts. However, to realize this ideal synergistic cycle is difficult, because: (1) the copper(I)-catalyzed Kinugasa cycle and palladium-catalyzed AA cycle must be synchronized with each other to deliver the target products, otherwise side reactions such as protonation of **M¹** giving a two-component Kinugasa product (**K**) would dominate; (2) development of a chiral bimetallic system which could realize the precise control of chemo-, regio-, diastereo- and enantioselectivity is difficult. In addition, because two ligands and two metals are required in the system, the inevitable ligand exchange between two metals greatly enhances the complexity and difficulty of this target reaction.



Scheme 2. Proposed catalytic cycle of Cu/Pd-catalyzed IKAA.

Because no chiral center is formed on the alkyl side, we chose a chiral side arm bisoxazoline (SA-BOX) ligand coordinated with copper(I), and an achiral phosphine ligand coordinated with palladium to optimize the reaction conditions (for details, see the Supporting Information). The phosphine ligand plays an important role in the reaction. A generally used palladium catalyst such as $Pd(PPh_3)_4$ or $Pd_2(dba)_3$ together with phosphine ligands such as **A** or **B** formed only protonated Kinugasa product **K** and failed to produce any target products (entries 1 and 2, Table 1). When Xantphos **C** with a larger bite angle was applied with palladium, the desired product (**4a**) was isolated in 42% yield and 88:12 er (entry 3), and DPEphos (**D**) further increased the yield to 69% (entry 4). Application of a chiral phosphine ligand such as R- or S-BINAP led very low yields

Table 1: Optimization of reaction conditions.[a]



Entry	PG	L* for Cu	L for Pd	Yield [%][b]	er[c]
1	Boc	L1	A	n.d.	–
2	Boc	L1	B	n.d.	–
3	Boc	L1	C	42	88:12
4	Boc	L1	D	69	88:12
5	Boc	L1	R-BINAP	10	88:12
6	Boc	L1	S-BINAP	n.d.	–
7	COOMe	L1	D	36	88:12
8	Ac	L1	D	44	88:12
9	Boc	L2	D	60	87.5:12.5
10	Boc	L3	D	73	90:10
11	Boc	L4	D	65	90.5:9.5
12	Boc	L5	D	62	85.5:14.5
13	Boc	L6	D	77	94:6
14	Boc	L7	D	50	87:13
15[d]	**Boc**	**L6**	**D**	**75**	**96:4**
16[e]	Boc	L6	D	19	95:5

[a] Reaction conditions: a mixture of **1a** (0.2 mmol), **2a** (0.3 mmol), **3** (0.3 mmol), $Cu(CH_3CN)_4PF_6$ (10 mol%), ligand L* for Cu (11 mol%), $Pd_2dba_3{\cdot}CHCl_3$ (5 mol%), phosphine ligand for Pd (10 mol%), K_2CO_3 (0.3 mmol), CH_3CN (1 mL), RT, 30 h. [b] Isolated yields. [c] Determined by HPLC using a chiral stationary phase. [d] 0 °C. [e] −10 °C. PMP = 4-$MeOC_6H_4$; BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthalene.

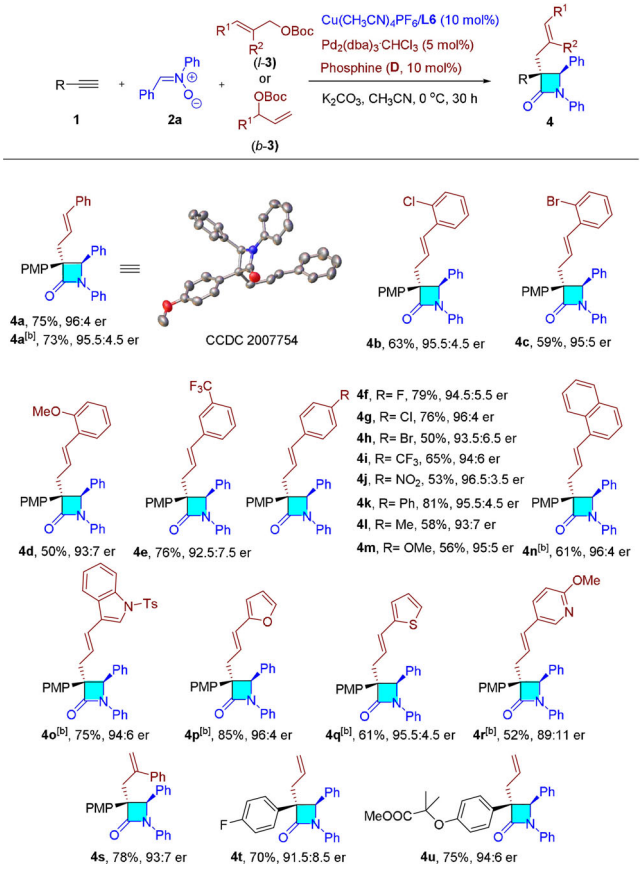
(entries 5 and 6), and varying the leaving group failed to give better results (entries 7 and 8). Next, the chiral SA-BOX ligands on a copper(I) catalyst were optimized (entries 9–14). Substituents with different steric and electronic effects were introduced into the two benzyl rings of chiral SA-BOX ligands, and the ligand (**L6**) with six methoxyl groups afforded the highest yield (77%) with an er of 94:6 (entry 13). Ligand **L7** bearing two t-butyl groups and one methoxy group gave a lower yield and enantioselectivity (entry 14). Lowering the reaction temperature to 0°C led to the highest er (96:4) and a 75% yield (entry 15) and these conditions were determined to be optimal. Further decreasing the reaction temperature to −10°C greatly inhibited the reaction (entry 16).

The side arm groups play an important role in improving the reactivity and selectivity in asymmetric catalysis.[14] To further understand the substituent effects in SA-BOX ligands, a single crystal of **L6**/$CuBr_2$ was obtained and analyzed by X-ray crystallography (for details, see the Supporting Information).[15] It has a C_2 symmetric structure in which the two pendant aromatic rings bend towards the metal center, affecting the shape of catalyst. The whole complex forms a chiral cage-like complex. The six methoxy groups on the two benzyl rings tune the electronic properties and extend the chiral space, thus giving the highest stereoselectivity. Such a strategy of introducing multiple methoxy groups onto chiral ligands could be utilized in further chiral catalyst design.

After establishing the optimal conditions for the asymmetric IKAA reaction, the scope of substrates was further investigated. First, the reactivities of various allylic electrophile precursors were examined (Table 2). Besides the linear cinnamic carbonates (l-**3a**), the branched carbonates (b-**3a**) were found to react equally efficiently with **1a** and **2a**, giving the same linear product (**4a**) in similar yield and with similar enantioselectivity, indicating formation of the same allylic palladium intermediate. Only one diastereoisomer with two cis aromatic rings was observed in all these reactions, and the absolute configuration of **4a** was established as (3S,4R) by X-ray crystallography (Table 2).[15] A series of substituted cinnamic carbonates bearing various electron-withdrawing or electron-donating functional groups at the ortho-, meta- or para-position of the phenyl ring reacted smoothly with **2a**, giving the corresponding α-quaternary β-lactams (**4b**–**4m**) in good yields with high enantioselectivity. Functional groups such as halogens, methoxy, trifluoromethyl and nitro are all well tolerated. It is noteworthy that branched allylic carbonates from various medicinally important heterocycles including indole (**4o**), furan (**4p**), and thiophene (**4q**), all react well in this dual catalytic system. Pyridine-functionalized allylic carbonate is amenable to this reaction, giving a β-lactam (**4r**) in 52% yield with 89:11 er. Simple allyl carbonates and 2-phenyl allylic carbonates give the corresponding products in good yields with good enantioselectivity (**4s**–**4u**). More challenging crotyl carbonates failed to react under these conditions.

The scope of terminal alkynes and nitrones was next examined (Table 3). All aromatic alkynes that were tested reacted smoothly, affording the corresponding β-lactams in good yields with high enantioselectivity (**4v**–**4ad**). An alkyne derived from clofibrate also reacted efficiently, providing the

Table 2: Substrate scope of allyl Boc carbonates.[a]



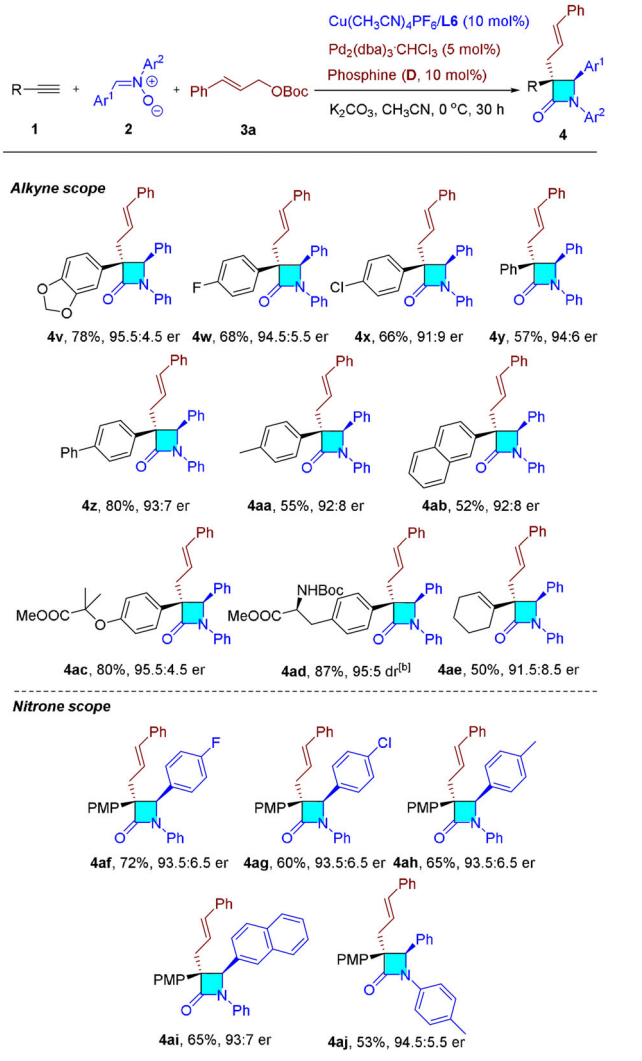
[a] Standard conditions were employed. Isolated yields are shown. [b] *b*-**3** was used.

desired product (**4ac**) in 80% yield. Reaction of a chiral tyrosine-functionalized alkyne under this dual catalytic system produced the corresponding lactam (**4ad**) in 87% yield with 95:5 dr. Cyclohexenyl alkyne reacted well with slightly decreased enantioselectivity, providing a lactam (**4ae**) which was isolated in 50% yield. Various nitrones with different electron-donating groups or electron-withdrawing groups on the aromatic ring are all amenable to this transformation, giving the corresponding products (**4af**–**4aj**) smoothly.

β-Lactams are very important synthetic building blocks in organic synthesis. To demonstrate the synthetic utility of this Cu/Pd-catalyzed IKAA reaction, the β-lactam (**4a**) was synthesized on a gram scale in 67% yield with 96:4 er, and several subsequent transformations were carried out. As shown in Scheme 3, reduction of **4a** with $LiAlH_4$ produced an amino alcohol (**5**), which has adjacent quaternary and tertiary chiral centers. Upon treatment of **4a** with Lewis acid ($AlCl_3$) and $LiAlH_4$ or $LiAlD_4$, a chiral azetidine (**7**) or the corresponding deuterated azetidine (**7-D**) were isolated in 91% yield without loss of enantiomeric purity. Wacker oxidation of the allyl group of lactam (**4u**) produced a chiral β-lactam with an attached acetone (**6**).

Further control experiments were conducted to understand the reaction mechanism [Eq. (1)]. The reaction of the

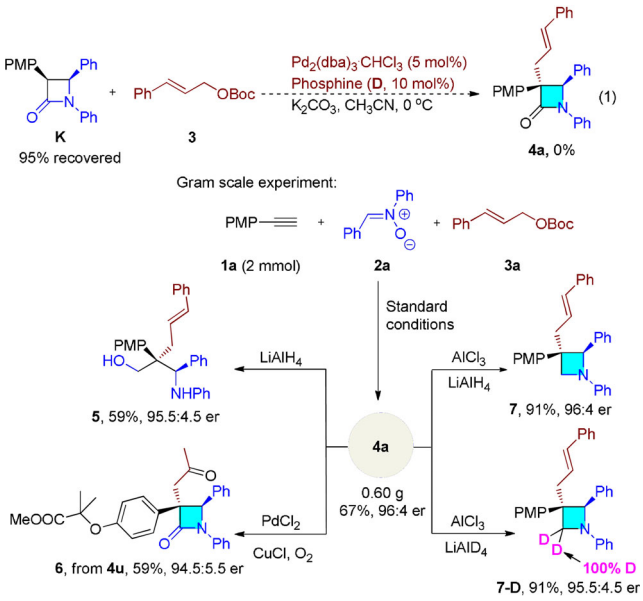
Table 3: Substrate scope with alkynes and nitrones.[a]



[a] Standard conditions were employed. Isolated yields are shown.
[b] Determined by ^{1}H NMR analysis of the products.

Kinugasa product (**K**) with **3** in a Pd^0-catalyzed diastereoselective intermolecular AA under standard condition failed to produce any products and 95% **K** was recovered. It indicates that **K** is not the reaction intermediate and thus interception of the enolate copper intermediate (**M^1**) is viable in this reaction.

In summary, by conducting a Cu-catalyzed Kinugasa reaction and a Pd-catalyzed AA in one pot, we have successfully developed a strategically novel IKAA reaction, which allows a step-economic and modular synthesis of enantioenriched α-quaternary β-lactams from three readily available precursors. This strategy is distinguished by a well-programmed reaction sequence, highly efficient formation of multiple bonds in asymmetric MCRs, construction of medically important α-quaternary chiral β-lactams, and a key stereoselective coupling of two in situ formed catalytic amounts of transient intermediates. We anticipate that this Cu/Pd-catalyzed IKAA strategy will be useful in medicinal chemistry and also provides new insights for further development of other challenging asymmetric transformations.



Scheme 3. Synthetic applications of chiral β-lactams.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: allylic alkylation · asymmetric multicomponent reaction · Kinugasa · synergistic reactions · β-lactam

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Communications

Asymmetric Catalysis

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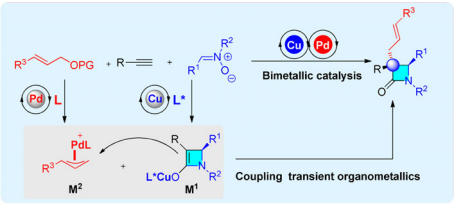
Modular Synthesis of α-Quaternary Chiral β-Lactams by a Synergistic Copper/Palladium-Catalyzed Multicomponent Reaction



An asymmetric multicomponent interrupted Kinugasa allylic alkylation (IKAA) reaction has been developed with a synergistic Cu-catalyzed Kinugasa and Pd-catalyzed allylic alkylation system. This strategy provides a high yield and highly selective synthesis of α-quaternary chiral β-lactams, which are not easily produced by other methods. Stereoselective coupling of two transient organometallic intermediates formed in situ is the most important feature of this reaction.