

Copper-Catalyzed Intramolecular C(sp³)–H and C(sp²)–H Amidation by Oxidative Cyclization**

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Abstract: The first copper-catalyzed intramolecular C(sp³)–H and C(sp²)–H oxidative amidation has been developed. Using a Cu(OAc)₂ catalyst and an Ag₂CO₃ oxidant in dichloroethane solvent, C(sp³)–H amidation proceeded at a terminal methyl group, as well as at the internal benzylic position of an alkyl chain. This reaction has a broad substrate scope, and various β-lactams were obtained in excellent yield, even on gram scale. Use of CuCl₂ and Ag₂CO₃ under an O₂ atmosphere in dimethyl sulfoxide, however, leads to 2-indolinone selectively by C(sp²)–H amidation. Kinetic isotope effect (KIE) studies indicated that C–H bond activation is the rate-determining step. The 5-methoxyquinolyl directing group could be removed by oxidation.

Lactams (cyclic amides) and related compounds are important partial structures of natural products, such as penicillin and cephalosporin, and drugs such as ezetimibe^[1] and piperacillin^[2] (β-lactam antibiotics, Figure 1). The Beckmann rearrangement,^[3] Schmidt reaction,^[4] cyclization of amino acids,^[5] and iodolactamization^[6] are well-known synthetic

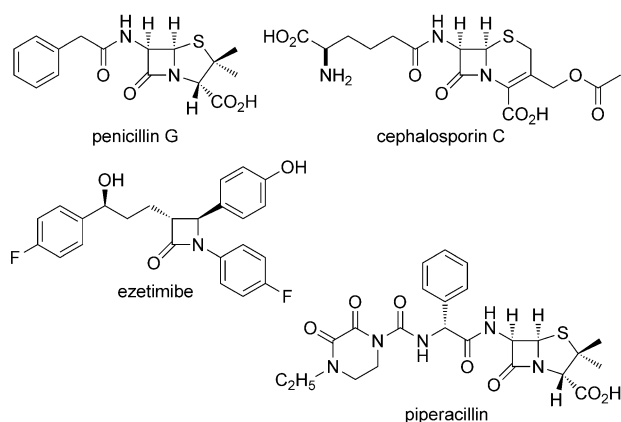


Figure 1. Examples of β-lactam antibiotics.

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methods for forming lactams. We selected a direct intramolecular C–H amidation as an alternative synthetic method. Although there are several reports of intramolecular C(sp²)–H amidation,^[7] examples of intramolecular C(sp³)–H amidation are still rare. The few examples include: a) rhodium-catalyzed C(sp³)–H amidation at internal positions of alkyl chains, such as benzylic and tertiary positions (Figure 2a);^[8] b) palladium-catalyzed allylic C(sp³)–H amidation (Figure 2b);^[9] and c) palladium-catalyzed C(sp³)–H amidation

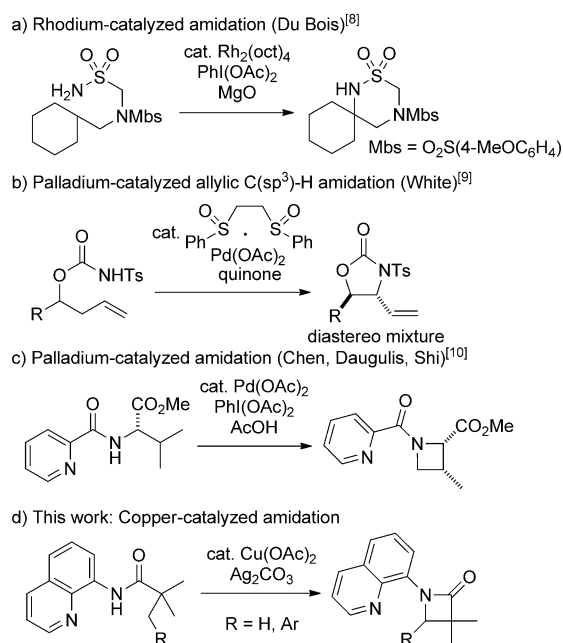


Figure 2. Examples of transition-metal-catalyzed intramolecular C(sp³)–H amidation. Mbs = (4-methoxyphenyl)sulfonyl, oct = octane, Ts = 4-toluenesulfonyl.

at terminal and internal positions (Figure 2c).^[7f,10] Intramolecular C(sp³)–H amidation using first-row transition-metal catalysts, however, has not been reported. We report herein the first copper-catalyzed intramolecular C(sp³)–H [and C(sp²)–H] amidation using a bidentate directing group.^[11] The amidation reaction proceeds at both terminal and internal C(sp³)–H bonds with broad substrate generality. Although substrate generality is slightly narrower than the palladium-catalyzed reaction originally developed by Chen and co-workers and Daugulis and co-workers,^[7f,10] it is noteworthy that the first-row transition-metal copper can promote the identical reaction.

Treatment of the amide **1a** with a catalytic amount of CuCl and Ag₂CO₃ as an oxidant in dimethyl sulfoxide at

Table 1: Investigation of several solvents and copper catalysts.

Entry	Solvent	Catalyst	Yield [%] ^[a]
1	DMSO	CuCl	17
2	acetonitrile	CuCl	trace
3	DMF	CuCl	19
4	benzonitrile	CuCl	41
5	1,2-dichloroethane	CuCl	47
6	chlorobenzene	CuCl	42
7	<i>tert</i> -butyl methyl ether	CuCl	trace
8	toluene	CuCl	31
9	1,4-dioxane	CuCl	40
10	octane	CuCl	33
11	1,2-dichloroethane	CuBr	50
12	1,2-dichloroethane	CuI	38
13	1,2-dichloroethane	CuCN	52
14	1,2-dichloroethane	CuSCN	93
15	1,2-dichloroethane	CuF ₂	43
16	1,2-dichloroethane	CuCl ₂	55
17	1,2-dichloroethane	CuBr ₂	45
18	1,2-dichloroethane	Cu(OAc) ₂	82
19	1,2-dichloroethane	Cu(OPiv) ₂	79

[a] Yield determined by ¹H NMR of the crude mixture using 1,1,2,2-tetrachloroethane as an internal standard. DMF = *N,N*-dimethylformamide, DMSO = dimethylsulfoxide, Piv = pivaloyl.

140 °C for 24 hours gave the β-lactam **2a** in only 17% yield (Table 1, entry 1). To improve the yield of **2a**, several solvents and catalysts were investigated (Table 1). The best solvent and catalyst were 1,2-dichloroethane and CuSCN (or Cu(OAc)₂), respectively (entries 14 and 18). In this reaction, β-lactam formation through C–H amidation at the terminal methyl group was predominant, and γ-lactam through internal methylene C–H amidation was not detected at all.

Although CuSCN was more reactive than Cu(OAc)₂ (Table 1), its applicability to other substrates was unsatisfactory. Therefore, we investigated the substrate scope using Cu(OAc)₂ as the catalyst (Table 2). For substrates **1b–g**, the amidation reaction proceeded selectively at a methyl group (entries 1–6). For the phenacyl amide substrate **1h**, the reaction proceeded at both C(sp³)–H and C(sp²)–H bonds, thus affording a mixture of the β-lactam **2h** and 2-indolinone **3h**, with **2h** as the preferred product (entry 7). The reaction also proceeded at an internal benzylic C(sp³)–H bond (entries 8–17). The selectivity between methyl C–H and benzyl C–H bonds was moderate (ca. 1:2, entries 8–15), but benzyl C–H amidation was the predominant pathway in entries 16 and 17. The reaction also proceeded using an amide with a cleavable 5-methoxyquinolyl directing group, thus producing the β-lactam **2s** in high yield (entry 18).

Considering the beneficial effects of acetate anions on reactivity (Table 1), we propose the following mechanism for the formation of β-lactams (Scheme 1): 1) oxidation of a copper salt Cu(OAc)₂ with Ag₂CO₃,^[12] 2) formation of the copper amide intermediate **A** by elimination of acetic acid,^[13] 3) formation of a the metalacyclic intermediate **B** through

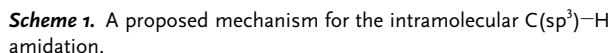
Table 2: Investigation of substrate scope.

Entry	2	Yield [%]
1	R ¹ = Me, R ² = Me	2b (86 %)
2	R ¹ = CF ₃ , R ² = Me	2c (89 %)
3	R ¹ = Ph(CH ₂) ₂ , R ² = Me	2d (86 %)
4	R ¹ = <i>t</i> Bu, R ² = Me	2e (93 %)
5	R ¹ = Ph(CH ₂) ₂ , R ² = Et	2f (90 %)
6	R ¹ = -(CH ₂) ₅ -, R ² = H	2g (77 %)
7	Mixture of 2h (65 %) and 3h (31 %)	
8	X = MeO, 2i (25 %), 2i' (52 %)	
9	X = Me, 2j (38 %), 2j' (51 %)	
10	X = H, 2k (25 %), 2k' (64 %)	
11	X = Br, 2l (24 %), 2l' (60 %)	
12	X = Cl, 2m (25 %), 2m' (62 %)	
13	X = F, 2n (30 %), 2n' (60 %)	
14	X = CF ₃ , 2o (21 %), 2o' (58 %)	
15	Mixture of 2p (30 %) and 2p' (60 %) ^[a]	
16	2q' (83 %), 2r' (75 %)	
17		
18	2s (71 %)	

Yields of product are given within parentheses. The yields are those of isolated products. [a] Diastereomeric ratio of 2.3:1.

a concerted metalation-deprotonation (CMD) pathway [C(sp³)–H bond activation];^[14] 4) reaction between **B** and acetic acid to give **C** by the elimination of CO₂ and H₂O; 5) reductive elimination to give a β-lactam and copper species CuOAc; and 6) oxidation of the CuOAc species with Ag₂CO₃ to regenerate Cu(OAc)(CO₃).^[12] After the first cycle, the reaction proceeds through steps 2–6.

Next, we performed a deuterium-labeling experiment to gain insight into the rate-determining step for the formation of β-lactams. Treatment of the amide **1d** or deuterated amide



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