C–H Activation

DOI: 10.1002/anie.201311105

Copper-Catalyzed Intramolecular C(sp^3)–H and C(sp^2)–H Amidation by Oxidative Cyclization**

Zhen Wang, Jizhi Ni, Yoichiro Kuninobu, and Motomu Kanai**

Abstract: *The first copper-catalyzed intramolecular C(sp^3)–H and C(sp^2)–H oxidative amidation has been developed. Using a $Cu(OAc)_2$ catalyst and an Ag_2CO_3 oxidant in dichloroethane solvent, C(sp^3)–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 $CuCl_2$ and Ag_2CO_3 under an O_2 atmosphere in dimethyl sulfoxide, however, leads to 2-indolinone selectively by C(sp^2)–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 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(sp^2)–H amidation,[7] examples of intramolecular C(sp^3)–H amidation are still rare. The few examples include: a) rhodium-catalyzed C(sp^3)–H amidation at internal positions of alkyl chains, such as benzylic and tertiary positions (Figure 2a);[8] b) palladium-catalyzed allylic C(sp^3)–H amidation (Figure 2b);[9] and c) palladium-catalyzed C(sp^3)–H amidation

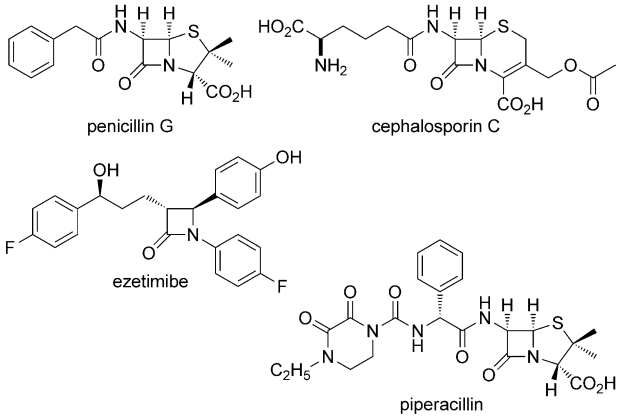

Figure 1. Examples of β-lactam antibiotics.

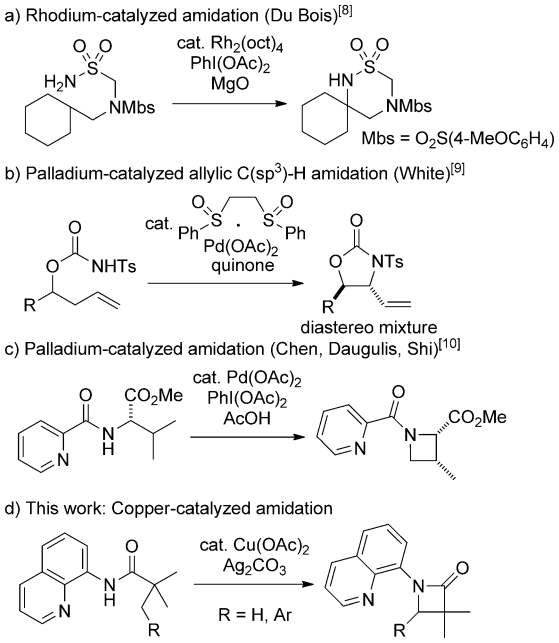

Figure 2. Examples of transition-metal-catalyzed intramolecular C(sp^3)–H amidation. Mbs = (4-methoxyphenyl)sulfonyl, oct = octane, Ts = 4-toluenesulfonyl.

at terminal and internal positions (Figure 2c).[7f,10] Intramolecular C(sp^3)–H amidation using first-row transition-metal catalysts, however, has not been reported. We report herein the first copper-catalyzed intramolecular C(sp^3)–H [and C(sp^2)–H] amidation using a bidentate directing group.[11] The amidation reaction proceeds at both terminal and internal C(sp^3)–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 Ag_2CO_3 as an oxidant in dimethyl sulfoxide at

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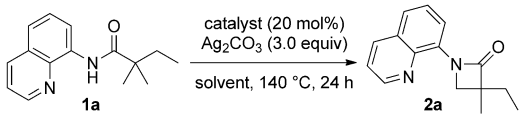
[**] This work was supported in part by ERATO from JST.
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201311105.

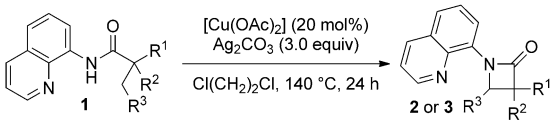
Table 1: Investigation of several solvents and copper catalysts.

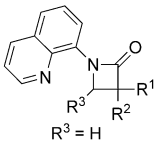
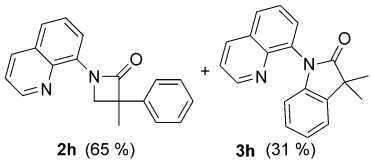
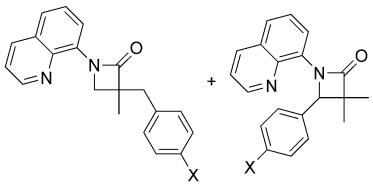
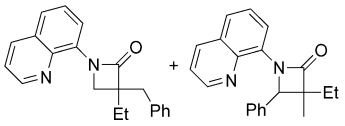
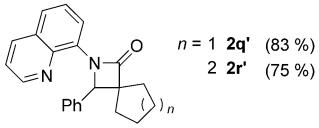
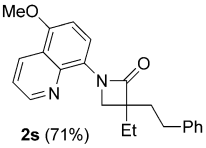


Entry	Solvent	Catalyst	Yield [%][a]
1	DMSO	CuCl	17
2	acetonitrile	CuCl	trace
3	DMF	CuCl	19
4	benzonitrile	CuCl	41
5	1,2-dichloroethane	CuCl	47
6	chlorobenzene	CuCl	42
7	*tert*-butyl methyl ether	CuCl	trace
8	toluene	CuCl	31
9	1,4-dioxane	CuCl	40
10	octane	CuCl	33
11	1,2-dichloroethane	CuBr	50
12	1,2-dichloroethane	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 ^{1}H NMR of the crude mixture using 1,1,2,2-tetrachloroethane as an internal standard. DMF = *N*,*N*,-dimethylformamide, DMSO = dimethylsulfoxide, Piv = pivaloyl.

Table 2: Investigation of substrate scope.



Entry	2			
		R^1	R^2	
1		Me	Me	**2b** (86 %)
2		CF_3	Me	**2c** (89 %)
3		$Ph(CH_2)_2$	Me	**2d** (86 %)
4		*t*Bu	Me	**2e** (93 %)
5		$Ph(CH_2)_2$	Et	**2f** (90 %)
6	R^3 = H	$-(CH_2)_5-$		**2g** (77 %)
7	 **2h** (65 %) **3h** (31 %)			
		X		
8		MeO	**2i** (25 %)	**2i'** (52 %)
9		Me	**2j** (38 %)	**2j'** (51 %)
10		H	**2k** (25 %)	**2k'** (64 %)
11		Br	**2l** (24 %)	**2l'** (60 %)
12		Cl	**2m** (25 %)	**2m'** (62 %)
13		F	**2n** (30 %)	**2n'** (60 %)
14		CF_3	**2o** (21 %)	**2o'** (58 %)
15	 **2p** (30 %) **2p'** (60 %)[a]			
16			n = 1	**2q'** (83 %)
17			2	**2r'** (75 %)
18	 **2s** (71%)			

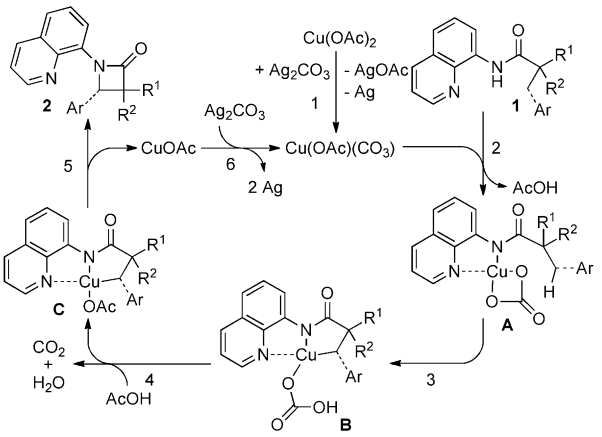
Yields of product are given within parentheses. The yields are those of isolated products. [a] Diastereomeric ratio of 2.3:1.

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 $C(sp^3)$–H and $C(sp^2)$–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 $C(sp^3)$–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).

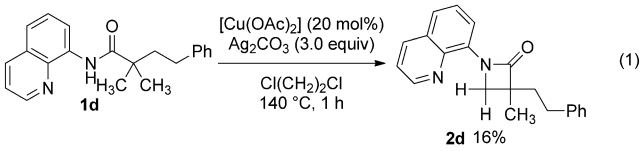
Considering the beneficial effects of acetate anions on reactivity (Table 1), we propose the following mechanism for the formation of β-lactams (Scheme 1): 1) oxidation of a copper salt $Cu(OAc)_2$ with Ag_2CO_3;[12] 2) formation of the copper amide intermediate **A** by elimination of acetic acid;[13] 3) formation of a the metalacyclic intermediate **B** through a concerted metalation-deprotonation (CMD) pathway [$C(sp^3)$–H bond activation];[14] 4) reaction between **B** and acetic acid to give **C** by the elimination of CO_2 and H_2O; 5) reductive elimination to give a β-lactam and copper species CuOAc; and 6) oxidation of the CuOAc species with Ag_2CO_3 to regenerate $Cu(OAc)(CO_3)$.[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

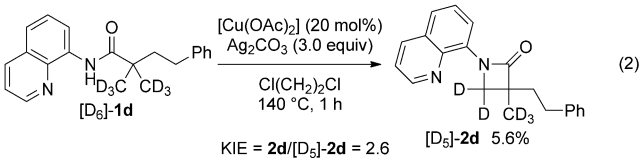


Scheme 1. A proposed mechanism for the intramolecular C(sp^3)–H amidation.

[D_6]-**1d** with a copper catalyst and oxidant gave the corresponding β-lactams **2d** and [D_5]-**2d** in 16% and 5.6% yields, respectively, after 1 hour [Eqs. (1) and (2)]. The kinetic



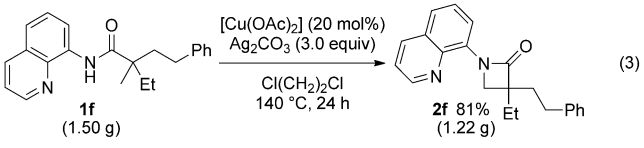
(1)



(2)

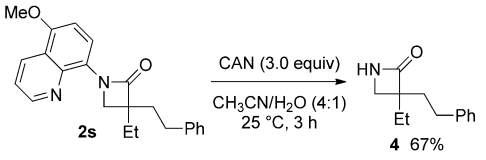
isotope effect value was 2.6, thus supporting our notion that C–H bond activation is the rate-determining step.[15]

The reaction could be performed on gram scale without significantly changing the efficiency [Eq. (3)]. Thus, treatment of 1.50 g of **1f** with $Cu(OAc)_2$ and $AgCO_3$ gave 1.22 g of **2f** in 81% yield, which is comparable to the yield shown in entry 5 of Table 2 (**1f**: 33.2 mg).



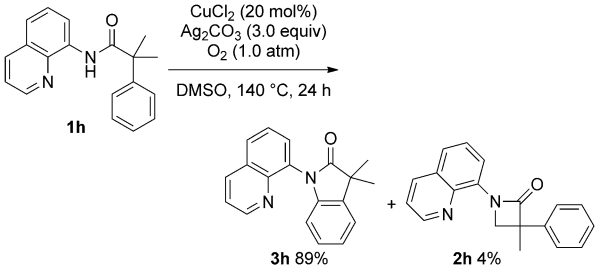
(3)

A residual directing group in the products decreases the practicality of the transformation. According to Chen's finding, the 5-methoxyquinolyl group can be cleaved under oxidative conditions [Eq. (4)].[10d] Treatment of the β-lactam **2s** with ceric ammonium nitrate (CAN) afforded the deprotected β-lactam **4** in 67% yield without opening the sensitive β-lactam scaffold [Eq. (4)].



(4)

Interestingly, the reaction of **1h** was C(sp^2)–H selective when the reaction conditions were slightly modified [Eq. (5)]. Thus, treatment of **1h** in the presence of the $CuCl_2$ catalyst and Ag_2CO_3 in dimethyl sulfoxide under an O_2 atmosphere at 140 °C for 24 hours produced the 2-indolinone **3h** and β-lactam **2h** in 89% and 4% yields, respectively. This result is in sharp contrast to the result shown in entry 7 of Table 2, where C(sp^3)–H amidation was the preferred reaction pathway.



(5)

In summary, we succeeded in intramolecular C(sp^3)–H and C(sp^2)–H amidation under copper catalysis. Although there are a few examples of palladium-catalyzed intramolecular C–H amidation, this is the first example of copper-catalyzed C(sp^3)–H amidation. The reaction proceeded at a terminal methyl group, as well as at the internal benzylic position of an alkyl chain. This reaction has broad substrate scope, and β-lactams were obtained in high yield even on gram scale. 2-Indolinone was also synthesized by C(sp^2)–H amidation by slightly modifying the optimized reaction conditions for C(sp^3)–H amidation. Because the 5-methoxyquinolyl directing group could be removed by oxidation, this reaction could become a useful method for the synthesis of β-lactams and 2-indolinones. Attempts to improve the position selectivity and catalyst activity are ongoing in our group.

Experimental Section

Gram-scale procedure for copper-catalyzed intramolecular C(sp^3)–H amidation: A mixture of 2-ethyl-2-methyl-4-phenyl-*N*-(8-quinolinyl)-butanamide (**1f**, 1.50 g, 4.65 mmol), $Cu(OAc)_2$ (169 mg, 0.930 mmol), Ag_2CO_3 (3.84 g, 13.9 mmol), and 1,2-dichloroethane (46.5 mL) was stirred at 140 °C for 24 h under argon atmosphere. Then, the reaction mixture was cooled to room temperature, and was subjected to column chromatography on silica gel (hexane/ethyl acetate = 8:1, ca. 2.0 L) without removing 1,2-dichloroethane to give 3-ethyl-3-phenethyl-1-(8-quinolinyl)-2-azetidinone (**2f**, 1.22 g, 81% yield).

Received: December 21, 2013
Published online: February 24, 2014

Keywords: C–H activation · copper · cyclization · heterocycles · lactams

[1] M. Garcia-Calvo, J. Lisnock, H. G. Bull, B. E. Hawes, D. A. Burnett, M. P. Braun, J. H. Crona, H. R. Davis Jr. , D. C. Dean, P. A. Detmers, M. P. Graziano, M. Hughes, D. E. Macintyre, A. Ogawa, K. A. O'neill, S. P. Iyer, D. E. Shevell, M. M. Smith, Y. S. Tang, A. M. Makarewicz, F. Ujjainwalla, S. W. Altmann, K. T. Chapman, N. A. Thornberry, *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 8132.

[2] W. K. Lau, D. Mercer, K. M. Itani, D. P. Nicolau, J. L. Kuti, D. Mansfield, A. Dana, *Antimicrob. Agents Chemother.* **2006**, *50*, 3556.

[3] For several examples, see: a) M. Hashimoto, Y. Obora, S. Sakaguchi, Y. Ishii, *J. Org. Chem.* **2008**, *73*, 2894; b) M. Hashimoto, Y. Obora, Y. Ishii, *Org. Process Res. Dev.* **2009**, *13*, 411.

[4] a) G. R. Krow, *Tetrahedron* **1981**, *37*, 1283; b) J. Aubé, G. L. Milligan, *J. Am. Chem. Soc.* **1991**, *113*, 8965; c) G. L. Milligan, C. J. Mossman, J. Aubé, *J. Am. Chem. Soc.* **1995**, *117*, 10449.

[5] For several examples, see: a) T. Kunieda, T. Nagamatsu, T. Higuchi, M. Hirobe, *Tetrahedron Lett.* **1988**, *29*, 2203; b) M. A. Bonache, G. Gerona-Navarro, M. Martín-Martínez, M. T. García-López, P. López, C. Cativiela, R. González-Muñiz, *Synlett* **2003**, 1007; c) S. Kanwar, S. D. Sharma, *Bull. Chem. Soc. Jpn.* **2006**, *79*, 1748.

[6] S. Knapp, F. S. Gibson, *Org. Synth.* **1992**, *70*, 101.

[7] a) W. C. P. Tsang, N. Zheng, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 14560; b) W. C. P. Tsang, R. H. Munday, G. Brasche, N. Zheng, S. L. Buchwald, *J. Org. Chem.* **2008**, *73*, 7603; c) J.-J. Li, T.-S. Mei, J.-Q. Yu, *Angew. Chem.* **2008**, *120*, 6552; *Angew. Chem. Int. Ed.* **2008**, *47*, 6452; d) M. Wasa, J.-Q. Yu, *J. Am. Chem. Soc.* **2008**, *130*, 14058; e) T.-S. Mei, X. Wang, J.-Q. Yu, *J. Am. Chem. Soc.* **2009**, *131*, 10806; f) E. T. Nadres, O. Daugulis, *J. Am. Chem. Soc.* **2012**, *134*, 7; g) G. He, C. Lu, Y. Zhao, W. A. Nack, G. Chen, *Org. Lett.* **2012**, *14*, 2944.

[8] a) C. G. Espino, J. Du Bois, *Angew. Chem.* **2001**, *113*, 618; *Angew. Chem. Int. Ed.* **2001**, *40*, 598; b) K. W. Fiori, J. Du Bois, *J. Am. Chem. Soc.* **2007**, *129*, 562; c) D. E. Olson, J. Du Bois, *J. Am. Chem. Soc.* **2008**, *130*, 11248; d) D. N. Zalatan, J. Du Bois, *J. Am. Chem. Soc.* **2009**, *131*, 7558.

[9] a) K. J. Fraunhoffer, M. C. White, *J. Am. Chem. Soc.* **2007**, *129*, 7274; b) S. A. Reed, M. C. White, *J. Am. Chem. Soc.* **2008**, *130*, 3316; c) S. A. Reed, A. R. Mazzotti, M. C. White, *J. Am. Chem. Soc.* **2009**, *131*, 11701; d) G. T. Rice, M. C. White, *J. Am. Chem. Soc.* **2009**, *131*, 11707; e) X. Qi, G. T. Rice, M. S. Lall, M. S. Plummer, M. C. White, *Tetrahedron* **2010**, *66*, 4816; f) S. M. Paradine, M. C. White, *J. Am. Chem. Soc.* **2012**, *134*, 2036.

[10] a) G. He, Y. Zhao, S. Zhang, C. Lu, G. Chen, *J. Am. Chem. Soc.* **2012**, *134*, 3; b) S.-Y. Zhang, G. He, Y. Zhao, K. Wright, W. A. Nack, G. Chen, *J. Am. Chem. Soc.* **2012**, *134*, 7313; c) X. Ye, Z. He, T. Ahmed, K. Weise, N. G. Akhmedov, J. L. Petersen, X. Shi, *Chem. Sci.* **2013**, *4*, 3712; d) G. He, S.-Y. Zhang, W. A. Nack, Q. Li, G. Chen, *Angew. Chem.* **2013**, *125*, 11330; *Angew. Chem. Int. Ed.* **2013**, *52*, 11124; e) Q. Zhang, K. Chen, W. Rao, Y. Zhang, F.-J. Chen, B.-F. Shi, *Angew. Chem.* **2013**, *125*, 13833; *Angew. Chem. Int. Ed.* **2013**, *52*, 13588.

[11] For a review of C–H bond transformations using a bidentate directing group, see: G. Rouquet, N. Chatani, *Angew. Chem.* **2013**, *125*, 11942; *Angew. Chem. Int. Ed.* **2013**, *52*, 11726.

[12] Silver mirror and/or silver black was observed after the reaction.

[13] M. Nishino, K. Hirano, T. Satoh, M. Miura, *Angew. Chem.* **2013**, *125*, 4553; *Angew. Chem. Int. Ed.* **2013**, *52*, 4457.

[14] For a report of $Cu(CO_3)$-species-mediated $C(sp^2)$–H bond activation and formation of Cu–C bond by a CMD pathway, see: A. M. Suess, M. Z. Ertem, C. J. Cramer, S. S. Stahl, *J. Am. Chem. Soc.* **2013**, *135*, 9797. For a report of $Pd(CO_3)$-species-mediated $C(sp^3)$–H bond activation and formation of Pd–C bond by a CMD pathway, see: S.-Y. Zhang, Q. Li, G. He, W. A. Nack, G. Chen, *J. Am. Chem. Soc.* **2013**, *135*, 12135.

[15] E. M. Simmons, J. F. Hartwig, *Angew. Chem.* **2012**, *124*, 3120; *Angew. Chem. Int. Ed.* **2012**, *51*, 3066.

