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To be cited as: *Chem. Eur. J.* 10.1002/chem.201905777

Link to VoR: http://dx.doi.org/10.1002/chem.201905777

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Copper-Catalyzed Oxidative Benzylic C(sp^3)–H Cyclization for the Synthesis of β-Lactams

Kanako Nozawa-Kumada,* Satoshi Saga, Yuta Matsuzawa, Masahito Hayashi, Masanori Shigeno, and Yoshinori Kondo*

Abstract: β-Lactams are important structural motifs because of their ubiquity in natural products and pharmaceuticals. We report herein a Cu-catalyzed intramolecular oxidative C(sp^3)–H amidation for the synthesis of β-lactams using *t*BuOO*t*Bu. This method is based on Kharasch–Sosnovsky amidation and does not require prefunctionalization of C(sp^3)–H bonds or the installation of a directing group, thereby allowing for the straightforward synthesis of β-lactams. Our intramolecular functionalization protocol can be extended to diverse benzylic C(sp^3)–H bonds and shows excellent functional group tolerance.

The β-lactam motif is found in important natural and bioactive compounds[1] such as penicillin, ezetimibe,[2] and aztreonam[3] (Figure 1). Because of the structural significance of β-lactams, much effort has been devoted to their synthesis.[4] The classical methods for β-lactam synthesis include the Staudinger reaction,[5] Kinugasa reaction,[6] and cyclization of amino acids.[7] Recently, transition-metal-catalyzed C(sp^3)–H functionalization[8] has emerged as an attractive method in synthetic chemistry because it does not involve prefunctionalization, and thus features high atom economy and step economy. One of the conventional C(sp^3)–H functionalization reactions for β-lactam syntheses involves transition-metal (Pd,[9a,b,f,h] Ni,[9e,i] Cu,[9c,d] Co[9g])-catalyzed intramolecular oxidative coupling between N–H and C(β)–H bonds (Scheme 1a).[9] Although this approach avoids prefunctionalization of C(sp^3)–H bonds of the substrates, a pyridine- or quinoline-based directing group (DG) is typically used, thus necessitating addition and removal steps. Thus, DG-assisted synthesis offsets the synthetic efficiency provided by the direct C(sp^3)–H functionalization; for this reason, a DG-free route is also desirable.

In 1957, the Kharasch–Sosnovsky reaction[10] was introduced, namely the Cu-catalyzed transformation of an allylic C(sp^3)–H bond to an ester by using a peroxyester, which is proposed to be initiated by abstraction of an allylic hydrogen atom by an alkoxy radical derived from a copper-initiated decomposition of peroxyester. Following this, significant efforts have been invested to improve the efficiency of this methodology.[11] One of the most notable strategies in this regard is the construction of C(sp^3)–N bonds by using amines or amides with peroxides, as this strategy can be applied to not only allylic C(sp^3)–H bonds but also benzylic and aliphatic

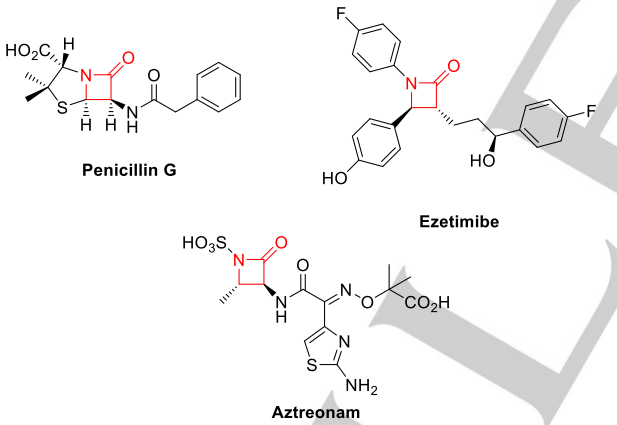
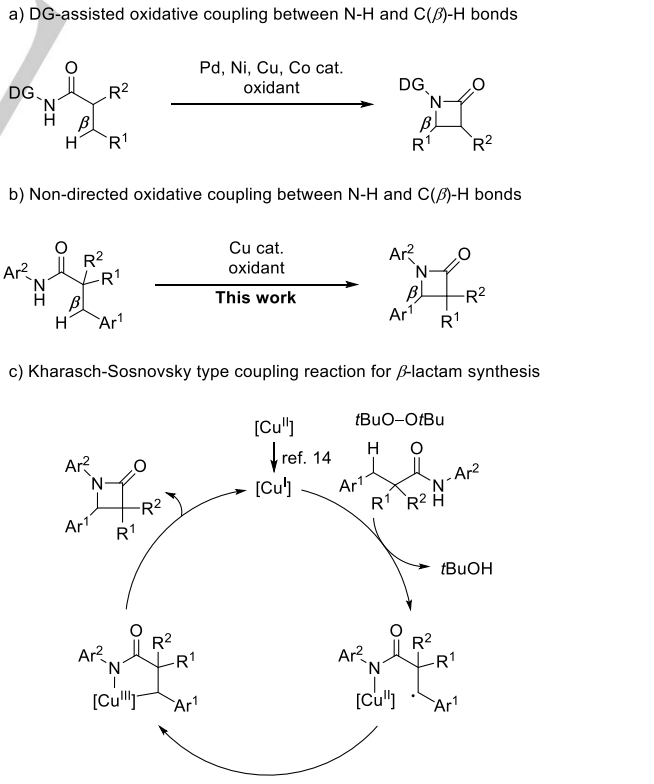


Figure 1. Natural and bioactive β-lactam derivatives.



Scheme 1. Transition-metal-catalyzed oxidative coupling between N–H and C(β)–H bonds for the synthesis of β-lactams.

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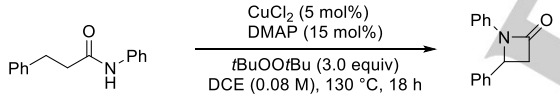
C(sp^3)–H bonds.[12] For example, Powell *et al.* have developed a copper-catalyzed intermolecular amidation of allylic and benzylic C−H bonds with sulfonamides using *t*BuOOAc.[12b] Compared to such intermolecular C(sp^3)–N bond formation, reports of intramolecular C(sp^3)–N bond formation to construct N-heterocyclic compounds have been limited. In our previous work, we have developed a copper-catalyzed oxidative isoindolinone synthesis using *t*BuOO*t*Bu *via* intramolecular benzylic C(sp^3)–H bond functionalization.[13a] However, there has been no report to build *β*-lactams by this strategy. Thus inspired, we attempted the Cu-catalyzed oxidative cyclization of linear alkanoic amides with a peroxide for the synthesis of *β*-lactams. This reaction proceeds *via* an intramolecular Kharasch–Sosnovsky-type C(sp^3)–H amidation in the presence of a first-row transition-metal, Cu catalyst, and no DG installation is needed (Scheme 1b). This reaction is assumed to be initiated by the abstraction of hydrogen at the benzylic position by the alkoxy radical, similar to the original Kharasch-Sosnovsky reaction. The radical species would be rapidly trapped by a copper(II) amide complex for efficient construction of the C(sp^3)–N bond (Scheme 1c).[14]

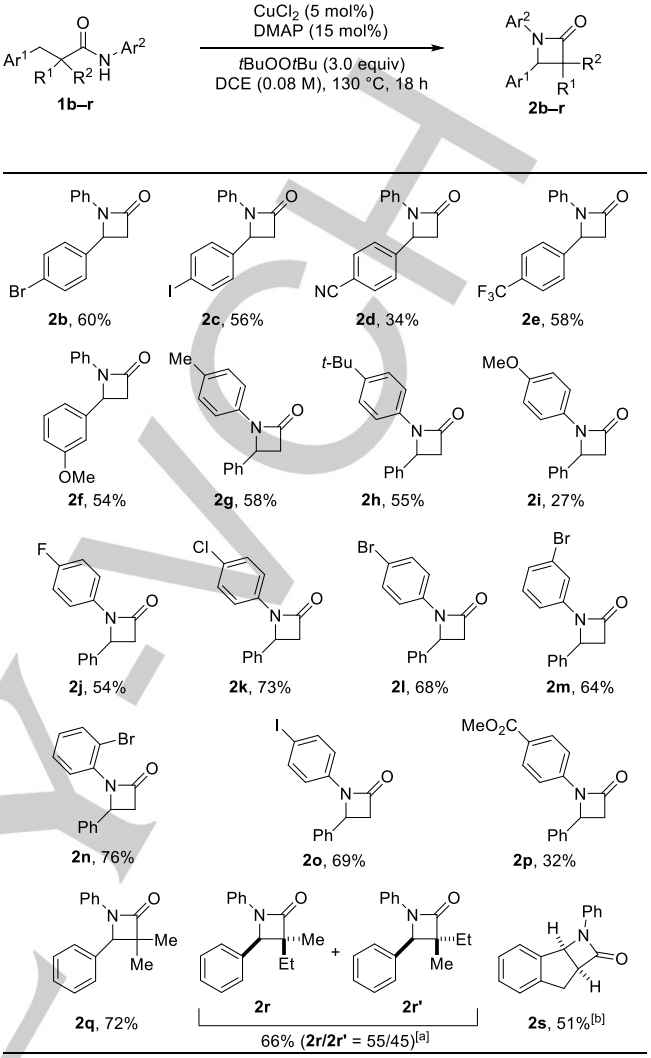
We began our investigation using *N*,3-diphenylpropanamide **1a** as the substrate to optimize the reaction conditions (Table 1). The use of $CuCl_2$/DMAP as the catalyst and *t*BuOO*t*Bu (peroxide) in 1,2-dichloroethane (DCE) at 130 °C was effective for the cyclization (entry 1). The desired reaction did not proceed in the absence of $CuCl_2$, DMAP, or *t*BuOO*t*Bu (entries 2–4). Using other copper sources instead of $CuCl_2$ decreased the yield (entry 5). The use of a phosphine ligand or bidentate nitrogen ligand Phen also led to lower yields (entry 6). Other oxidants such as *t*BuOOAc or *t*BuOOH did not work for the reaction (entry 7). Screening of a variety of solvents revealed that DCE was the best solvent (entry 8). A higher catalyst loading led to increased formation of a byproduct, thus reducing the yield slightly (entry 9).

Table 1. Effect of reaction parameters.



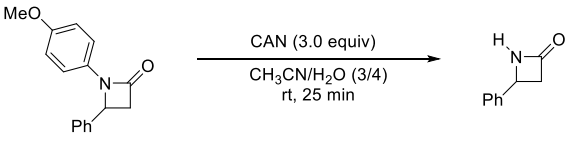
entry	variation from standard conditions	yield (%)[a]
1	none	72 (71)[b]
2	without $CuCl_2$	0
3	without DMAP	0
4	without *t*BuOO*t*Bu	0
5	CuCl, CuI, $[(MeCN)_4Cu]OTf$, $CuBr_2$, $Cu(OAc)_2$, or $Cu(OTf)_2$ instead of $CuCl_2$	34–66
6	PPh_3, Pyridine, or Phen, instead of DMAP	0–12
7	*t*BuOOAc or *t*BuOOH, instead of *t*BuOO*t*Bu	0
8	benzene, PhCl, or MeCN, instead of DCE	trace
9	10 mol% of $CuCl_2$ and 30 mol% of DMAP	61

[a] Determined by ^{1}H-NMR using 1,1,2-trichloroethane as an internal standard. [b] Isolated yield in parentheses.



Isolated yields. [a] The ratio was determined by ^{1}H-NMR. [b] 10 mol% of $CuCl_2$ and 30 mol% of DMAP were used.

Scheme 2. Scope and limitations of intramolecular C(sp^3)–H amidation for *β*-lactam synthesis.



Scheme 3. CAN-mediated removal of aryl group on nitrogen atom of **2i**.

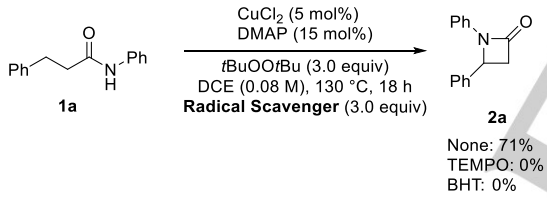
With the optimized reaction conditions in hand, we next investigated the substrate scope of C(sp^3)–H functionalization for the synthesis of *β*-lactams (Scheme 2). A wide range of functional groups, including halogens, were tolerated under the

reaction conditions. The reaction of substrates possessing halogen atoms or electron-withdrawing groups at *β*-position on the benzene ring gave the desired products in acceptable yields (**2b**–**f**). The substrate with the electron-donating methoxy group at the 4-position led to an undesired reaction, generating an olefin.[15] Next, we investigated the effect of aryl groups on the nitrogen atom. The reactions gave cyclized products **2g**–**p** in low to moderate yields, regardless of the electronic properties of the aryl groups. This method could be applied to synthesize the 3-substituted *β*-lactam **2q** in good yield. Furthermore, we investigated the reaction of **1r** with different substituents at α-position of the amide and found to give a mixture of diastereomers **2r** and **2r'** with almost the same ratio. Polycyclic fused *β*-lactams, which are widespread in pharmaceutical chemistry, could also be produced in an efficient manner (**2s**).

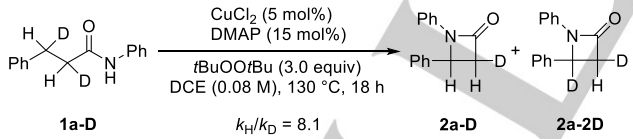
Subsequently, we treated *β*-lactam **2i** with ceric ammonium nitrate (CAN) under mild conditions and obtained an *N*-free *β*-lactam **3** (Scheme 3).[16] This result indicated that the synthesized *β*-lactams could be further transformed into useful compounds, thus demonstrating their structural diversity.

We next performed some experiments to gain insight into the reaction mechanism. Under the optimized conditions and in the presence of 3.0 equiv of a radical scavenger such as TEMPO or BHT (Scheme 4), the reaction was completely inhibited, indicating that the reaction proceeded *via* a radical process. Finally, we measured the kinetic isotope effect (KIE) of this *β*-lactam synthesis. First, the reaction was conducted using **1a-D** as a substrate under the optimized conditions and the intramolecular KIE value of 8.1 was observed (Scheme 5). Furthermore, based on the reaction with **1a** and **1a-2D** as the substrates under the standard conditions in a single vessel, the magnitude of the intermolecular KIE was determined to be 9.0 (Scheme 6). These results indicated that C(sp^3)–H abstraction may be the rate-determining step in this reaction.

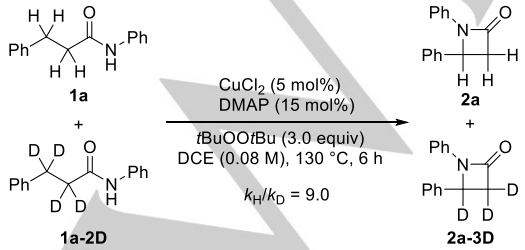
In conclusion, we have developed a Cu-catalyzed intramolecular oxidative C(sp^3)–H amidation for the synthesis of *β*-lactams, which are the core structures of many natural and bioactive compounds. Our protocol based on Kharasch–Sosnovsky amidation provides straightforward access to *β*-lactams, as prefunctionalization and DG installation are not required. Our intramolecular functionalization is applicable to a variety of benzylic C(sp^3)–H bonds. Further studies to expand the scope of the substrates and broaden the synthetic application of our method to other heterocycles are in progress, and the results will be reported in due course.



Scheme 4. Radical scavenger experiment.



Scheme 5. Intramolecular kinetic isotope effect.



Scheme 6. Intermolecular kinetic isotope effect.

Acknowledgements

This work was financially supported by the Japan Society for the Promotion of Science (JSPS) KAKENHI Grant no. 19K16309. This work was also supported by Grand for Basic Science Research Projects from The Sumitomo Foundation, the Platform Project for Supporting Drug Discovery and Life Science Research funded by Japan Agency for Medical Research and Development (AMED), Tohoku University Center for Gender Equality Promotion (TUMUG), and Morinomiyako Project for Empowering Women in Research.

Keywords: *β*-lactam • C(sp^3)–H functionalization • copper • oxidation • Kharasch–Sosnovsky reaction

[1] a) *The Organic Chemistry of β-Lactams* (Eds.: G. I. Georg), VCH, New York, **1993**; b) *Natural Lactones and Lactams: Synthesis, Occurrence and Biological Activity* (Eds.: T. Janecki), Wiley-VCH, Weinheim, **2014**; c) G. S. Singh, *Mini-Reviews Med. Chem.* **2004**, *4*, 93–109; d) E. Turos, C. Coates, J.-Y. Shim, Y. Wang, J. M. Leslie, T. E. Long, G. S. K. Reddy, A. Ortiz, M. Culbreath, S. Dickey, D. V. Lim, E. Alonso, J. Gonzalez, *Bioorganic Med. Chem.* **2005**, *13*, 6289–6308; e) A. MacGowan, *Curr. Opin. Pharmacol.* **2011**, *11*, 470–476; f) G. S. Singh, M. D'hooghe, N. De Kimpe, *Tetrahedron* **2011**, *67*, 1989–2012; g) L. Decuyper, K. Magdalenić, M. Verstraete, M. Jukič, I. Sosič, E. Sauvage, A. M. Amoroso, O. Verlaine, B. Joris, S. Gobec, M. D'hooghe, *Chem. Eur. J.* **2019**, *25*, 16128–16140.

[2] a) S. D. Turley, J. M. Dietschy, *Curr. Opin. Lipidol.* **2003**, *14*, 233–240; b) J. W. Clader, *J. Med. Chem.* **2004**, *47*, 1–9; c) M. A. Blazing, R. P. Giugliano, C. P. Cannon, T. A. Musliner, A. M. Tershakovec, J. A. White, C. Reist, A. McCagg, E. Braunwald, R. M. Califf, *Am. Heart J.* **2014**, *168*, 205–212; d) A. Tarui, A. Tanaka, M. Ueo, K. Sato, M. Omote, A. Ando, *New J. Chem.* **2015**, *39*, 9325–9329.

[3] a) R. N. Brogden, R. C. Heel, *Drugs* **1986**, *31*, 96–130; b) R. J. Duma, *Ann. Intern. Med.* **1987**, *106*, 766–767.

[4] a) S. France, A. Weatherwax, A. E. Taggi, T. Lectka, *Acc. Chem. Res.* **2004**, *37*, 592–600; b) B. Alcaide, P. Almendros, C. Aragoncillo, *Chem. Rev.* **2007**, *107*, 4437–4492; c) B. Alcaide, P. Almendros, C. Aragoncillo, *Curr. Opin. Drug Disc.* **2010**, *13*, 685–697; d) B. Alcaide, P.

Almendros, *Chem. Rec.* **2011**, *11*, 311–330; e) A. Kamath, I. Ojima, *Tetrahedron* **2012**, *68*, 10640–10664; f) T. Orbegozo, F. Burel, P. Jubault, X. Pannecoucke, *Tetrahedron* **2013**, *69*, 4015–4039; g) B. Alcaide, P. Almendros, A. Luna, *RSC Adv.* **2014**, *4*, 1689–1707; h) C. R. Pitts, T. Lectka, *Chem. Rev.* **2014**, *114*, 7930–7953; i) S. Hosseyni, A. Jarrahpour, *Org. Biomol. Chem.* **2018**, *16*, 6840–6852.

[5] a) H. Staudinger, *Liebigs Ann. Chem.* **1907**, *356*, 51–123; b) F. H. van der Steen, G. van Koten, *Tetrahedron* **1991**, *47*, 7503–7524; c) C. Palomo, J. M. Aizpurua, I. Ganboa, M. Oiarbide, *Eur. J. Org. Chem.* **1999**, 3223–3235; d) B. L. Hodous, G. C. Fu, *J. Am. Chem. Soc.* **2002**, *124*, 1578–1579; e) C. Palomo, J. M. Aizpurua, I. Ganboa, M. Oiarbide, *Curr. Med. Chem.* **2004**, *11*, 1837–1872; f) E. C. Lee, B. L. Hodous, E. Bergin, C. Shih, G. C. Fu, *J. Am. Chem. Soc.* **2005**, *127*, 11586–11587; g) Y.-R. Zhang, L. He, X. Wu, P.-L. Shao, S. Ye, *Org. Lett.* **2008**, *10*, 277–280.

[6] a) M. Kinugasa, S. Hashimoto, *J. Chem. Soc., Chem. Commun.* **1972**, 466–467; b) M. Miura, M. Enna, K. Okuro, M. Nomura, *J. Org. Chem.* **1995**, *60*, 4999–5004; c) A. Basak, S. C. Ghosh, T. Bhowmich, A. K. Das, V. Bertolasi, *Tetrahedron Lett.* **2002**, *43*, 5499–5501; d) M. M.-C. Lo, G. C. Fu, *J. Am. Chem. Soc.* **2002**, *124*, 4572–4573; e) R. Shintani, G. C. Fu, *Angew. Chem.* **2003**, *115*, 4216–4219; *Angew. Chem. Int. Ed.* **2003**, *42*, 4082–4085; f) J. Marco-Contelles, *Angew. Chem.*, **2004**, *16*, 2248–2250; *Angew. Chem. Int. Ed.* **2004**, *43*, 2198–2200; g) S. Stecko, B. Furman, M. Chmielewski, *Tetrahedron* **2014**, *70*, 7817–7844; h) M. Chigrinova, D. A. MacKenzie, A. R. Sherratt, L. L. W. Cheung, J. P. Pezacki, *Molecules* **2015**, *20*, 6959–6969; i) Y. Takayama, T. Ishii, H. Ohmiya, T. Iwai, M. C. Schwarzer, S. Mori, T. Taniguchi, K. Monde, M. Sawamura, *Chem. Eur. J.* **2017**, *23*, 8400–8404; j) T. Shu, L. Zhao, S. Li, X.-Y. Chen, C. von Essen, K. Rissanen, D. Enders, *Angew. Chem.* **2018**, *130*, 11151–11154; *Angew. Chem. Int. Ed.* **2018**, *57*, 10985–10988.

[7] a) T. Kunieda, T. Nagamatsu, T. Higuchi, M. Hirobe, *Tetrahedron Lett.* **1988**, *29*, 2203–2205; b) C. Palomo, J. M. Aizpurua, R. Urchegui, M. Iturburu, A. O. de Retana, C. Cuevas, *J. Org. Chem.* **1991**, *56*, 2244–2247; c) J. Escalante, M. A. González-Tototzin, J. Aviña, O. Muñoz-Muñiz, E. Juaristi, *Tetrahedron* **2001**, *57*, 1883–1890; d) M. A. Bonache, G. Gerona-Navarro, M. Martín-Martínez, M. T. García-López, P. López, C. Cativiela, R. González-Muñiz, *Synlett* **2003**, 1007–1011; e) S. Kanwar, S. D. Sharma, *Bull. Chem. Soc. Jpn.* **2006**, *79*, 1748–1752.

[8] For selected recent reviews, see: a) R. Jazzar, J. Hitce, A. Renaudat, J. Sofack-Kreutzer, O. Baudoin, *Chem. Eur. J.* **2010**, *16*, 2654–2672; b) O. Baudoin, *Chem. Soc. Rev.* **2011**, *40*, 4902–4911; c) C. Zhang, C. Tang, N. Jiao, *Chem. Soc. Rev.* **2012**, *41*, 3464–3484; d) G. Rouquet, N. Chatani, *Angew. Chem.* **2013**, *125*, 11942–11959; *Angew. Chem. Int. Ed.* **2013**, *52*, 11726–11743; e) S. A. Girard, T. Knauber, C.-J. Li, *Angew. Chem.* **2014**, *126*, 76–103; *Angew. Chem. Int. Ed.* **2014**, *53*, 74–100; f) C. Zheng, S.-L. You, *RSC Adv.* **2014**, *4*, 6173–6214; g) C. Liu, J. Yuan, M. Gao, S. Tang, W. Li, R. Shi, A. Lei, *Chem. Rev.* **2015**, *115*, 12138–12204; h) A. Batra, P. Singh, K. N. Singh, *Eur. J. Org. Chem.* **2016**, 4927–4947; i) S.-R. Guo, P. S. Kumar, M. Yang, *Adv. Synth. Catal.* **2017**, *359*, 2–25; j) M. K. Lakshman, P. K. Vuram, *Chem. Sci.* **2017**, *8*, 5845–5888; k) B. V. Varun, J. Dhineshkumar, K. R. Bettadapur, Y. Siddaraju, K. Alagiri, K. R. Prabhu, *Tetrahedron Lett.* **2017**, *58*, 803–824; l) H. Yi, G. Zhang, H. Wang, Z. Huang, J. Wang, A. K. Singh, A. Lei, *Chem. Rev.* **2017**, *117*, 9016–9085; m) H. Sterckx, B. Morel, B. U. W. Maes, *Angew. Chem.* **2019**, *131*, 8028–8055; *Angew. Chem. Int. Ed.* **2019**, *58*, 7946–7970; n) Q. Zhang, B.-F. Shi, *Chin. J. Chem.* **2019**, *37*, 647–656.

[9] a) M. Wasa, J.-Q. Yu, *J. Am. Chem. Soc.* **2008**, *130*, 14058–14059; b) Q. Zhang, K. Chen, W. Rao, Y. Zhang, F.-J. Chen, B.-F. Shi, *Angew. Chem.* **2013**, *125*, 13833–13837; *Angew. Chem. Int. Ed.* **2013**, *52*, 13588–13592; c) Z. Wang, J. Ni, Y. Kuninobu, M. Kanai, *Angew. Chem.* **2014**, *126*, 3564–3567; *Angew. Chem. Int. Ed.* **2014**, *53*, 3496–3499; d) X. Wu, Y. Zhao, G. Zhang, H. Ge, *Angew. Chem.* **2014**, *126*, 3780–3784; *Angew. Chem. Int. Ed.* **2014**, *53*, 3706–3710; e) X. Wu, Y. Zhao, H. Ge, *Chem. Eur. J.* **2014**, *20*, 9530–9533; f) W.-W. Sun, P. Cao, R.-Q. Mei, Y. Li, Y.-L. Ma, B. Wu, *Org. Lett.* **2014**, *16*, 480–483; g) X. Wu, K. Yang, Y. Zhao, H. Sun, G. Li, H. Ge, *Nat. Commun.* **2015**, *6*, 6462; h) S.-J. Zhang, W.-W. Sun, P. Cao, X.-P. Dong, J.-K. Liu, B. Wu, *J. Org. Chem.* **2016**, *81*, 956–968; i) Y. Aihara, N. Chatani, *ACS Catal.* **2016**, *6*, 4323–4329; j) T. Zhou, M.-X. Jiang, X. Yang, Q. Yue, Y.-Q. Han, Y. Ding, B.-F. Shi, *Chin. J. Chem.* **2020**, *38*, 242–246.
β-Lactam synthesis by other types of C(sp^3)–H functionalization, see: k) J. Pedroni, M. Boghi, T. Saget, N. Cramer, *Angew. Chem.* **2014**, *126*, 9210–9213; *Angew. Chem. Int. Ed.* **2014**, *53*, 9064–9067; l) A. McNally, B. Haffemayer, B. S. L. Collins, M. J. Gaunt, *Nature* **2014**, *510*, 129–133; m) D. Willcox, B. G. N. Chappell, K. F. Hogg, J. Calleja, A. P. Smalley, M. J. Gaunt, *Science* **2016**, *354*, 851–857; n) D. Dailler, R. Rocaboy, O. Baudoin, *Angew. Chem.* **2017**, *129*, 7324–7328; *Angew. Chem. Int. Ed.* **2017**, *56*, 7218–7222.

[10] M. S. Kharasch, G. Sosnovsky, *J. Am. Chem. Soc.* **1958**, *80*, 756.

[11] Kharasch−Sosnovsly type C(sp^3)–H functionalization (etherification or methylation, *etc.*), see: a) J. Eames, M. Watkinson, *Angew. Chem.* **2001**, *113*, 3679–3683; *Angew. Chem. Int. Ed.* **2001**, *40*, 3567–3571; b) M. B. Andrus, J. C. Lashley, *Tetrahedron* **2002**, *58*, 845–866; c) J. A. Mayoral, S. Rodríguez-Rodríguez, L. Salvatella, *Chem. Eur. J.* **2008**, *14*, 9274–9285; d) R. T. Gephart, C. L. Mcmullin, N. G. Sapiezynski, E. S. Jang, M. J. B. Aguila, T. R. Cundari, T. H. Warren, *J. Am. Chem. Soc.* **2012**, *134*, 17350–17353; e) S. K. Rout, S. Guin, K. K. Ghara, A. Banerjee, B. K. Patel, *Org. Lett.* **2012**, *14*, 3982–3985; f) Q. Xia, X. Liu, Y. Zhang, C. Chen, W. Chen, *Org. Lett.* **2013**, *15*, 3326–3329; g) J. Zhao, H. Fang, J. Han, Y. Pan, *Org. Lett.* **2014**, *16*, 2530–2533; h) S. K. Rout, S. Guin, W. Ali, A. Gogoi, B. K. Patel, *Org. Lett.* **2014**, *16*, 3086–3089; i) B. L. Tran, M. Driess, J. F. Hartwig, *J. Am. Chem. Soc.* **2014**, *136*, 17292–17301; j) C.-Y. Wang, R.-J. Song, W.-T. Wei, J.-H. Fan, J.-H. Li, *Chem. Commun.* **2015**, *51*, 2361–2363; k) T. K. Salvador, C. H. Arnett, S. Kundu, N. G. Sapiezynski, J. A. Bertke, M. R. Boroujeni, T. H. Warren, *J. Am. Chem. Soc.* **2016**, *138*, 16580–16583; l) W. Zhang, F. Wang, S. D. McCann, D. Wang, P. Chen, S. S. Stahl, G. Liu, *Science* **2016**, *353*, 1014–1018; m) B. Lu, F. Zhu, H.-M. Sun, Q. Shen, *Org. Lett.* **2017**, *19*, 1132–1135; n) H. F. T. Klare, A. F. G. Goldberg, D. C. Duquette, B. M. Stoltz, *Org. Lett.* **2017**, *19*, 988–991; o) A. Vasilopoulos, S. L. Zultanski, S. S. Stahl, *J. Am. Chem. Soc.* **2017**, *139*, 7705–7708.

[12] Kharasch−Sosnovsly type C(sp^3)–N bond formation, see: a) J. S. Clark, C. Roche, *Chem. Commun.* **2005**, 5175–5177; b) G. Pelletier, D. A. Powell, *Org. Lett.* **2006**, *8*, 6031–6034; c) S. Wiese, Y. M. Badiei, R. T. Gephart, S. Mossin, M. S. Varonka, M. M. Melzer, K. Meyer, T. R. Cundari, T. H. Warren, *Angew. Chem.* **2010**, *122*, 9034–9039; *Angew. Chem. Int. Ed.* **2010**, *49*, 8850–8855; d) D. A. Powell, H. Fan, *J. Org. Chem.* **2010**, *75*, 2726–2729; e) Q. Xia, W. Chen, H. Qiu, *J. Org. Chem.* **2011**, *76*, 7577–7582; f) S. Santoro, R.-Z. Liao, F. Himo, *J. Org. Chem.* **2011**, *76*, 9246–9252; g) Q. Xia, W. Chen, *J. Org. Chem.* **2012**, *77*, 9366–9373; h) R. T. Gephart, D. L. Huang, M. J. B. Aguila, G. Schmidt, A. Shahu, T. H. Warren, *Angew. Chem.* **2012**, *124*, 6594–6598; *Angew. Chem. Int. Ed.* **2012**, *51*, 6488–6492; i) B. L. Tran, B. Li, M. Driess, J. F. Hartwig, *J. Am. Chem. Soc.* **2014**, *136*, 2555–2563; j) P. K. Chikkade, Y. Kuninobu, M. Kanai, *Chem. Sci.* **2015**, *6*, 3195–3200; k) F. Teng, S. Sun, Y. Jiang, J.-T. Yu, J. Cheng, *Chem. Commun.* **2015**, *51*, 5902–5905; l) H.-T. Zeng, J.-M. Huang, *Org. Lett.* **2015**, *17*, 4276–4279; m) X. Qi, L. Zhu, R. Bai, Y. Lan, *Sci. Rep.* **2017**, *7*, 43579.

[13] a) K. Nozawa-Kumada, J. Kadokawa, T. Kameyama, Y. Kondo, *Org. Lett.* **2015**, *17*, 4479–4481. Also see: b) K. Nozawa-Kumada, S. Kurosu, M. Shigeno, Y. Kondo, *Asian J. Org. Chem.* **2019**, *8*, 1080–1083.

[14] In this reaction, the active Cu(I) species can be formed through the disproportionation of Cu(II), see: a) A. E. King, L. M. Huffman, A. Casitas, M. Costas, X. Ribas, S. S. Stahl, *J. Am. Chem. Soc.* **2010**, *132*, 12068–12073; b) B. Chen, X.-L. Hou, Y.-X. Li, Y.-D. Wu, *J. Am. Chem. Soc.* **2011**, *133*, 7668–7671; c) W.-J. Yoo, T. Tsukamoto, S. Kobayashi, *Angew. Chem. Int. Ed.* **2015**, *54*, 6587–6590; d) J. C. Vantourout, H. N. Miras, A. Isidro-Llobet, S. Sproules, A. J. B. Watson, *J. Am. Chem. Soc.* **2017**, *139*, 4769–4779.

[15] 29% of 3-(4-methoxyphenyl)-*N*-phenyl-2-propenamide was obtained.

[16] a) L. S. Hegedus, M. A. McGuire, L. M. Schultze, C. Yijun, O. P. Anderson, *J. Am. Chem. Soc.* **1984**, *106*, 2680–2687; b) B. Alcaide, M. F. Alyt, M. A. Sierra, *J. Org. Chem.* **1996**, *61*, 8819–8825; c) L. Banfi, G. Guanti, *Eur. J. Org. Chem.* **2002**, 3745–3755.

10.1002/chem.201905777

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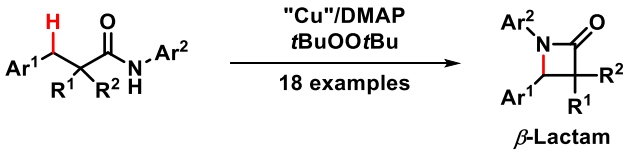

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Copper-Catalyzed Oxidative Benzylic C(sp^3)–H Cyclization for the Synthesis of *β*-Lactams

Straightforward *β*-lactam synthesis: Cu-catalyzed intramolecular oxidative C(sp^3)–H amidation for the synthesis of *β*-lactams has been developed. This reaction proceeds *via* an intramolecular Kharasch–Sosnovsky-type C(sp^3)–H amidation in the presence of a first-row transition-metal, Cu catalyst, and no DG installation is needed.