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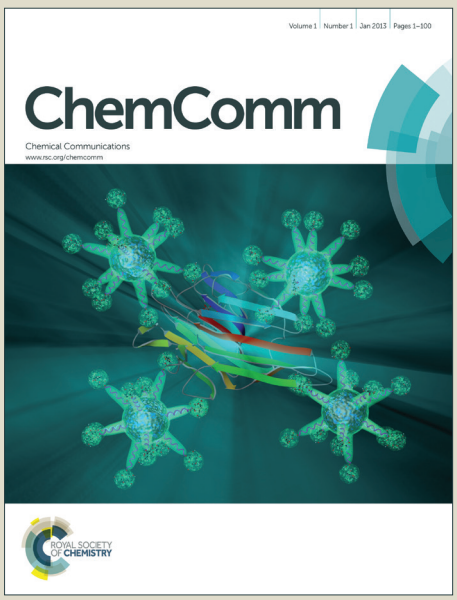

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ARTICLE TYPE

Palladium-Catalyzed C*sp*^{2}–H Carbonylation of Aromatic Oximes: Selective Access to Benzo[d][1,2]oxazin-1-ones and 3-Methyleneisoindolin-1-ones*

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A highly selective palladium-catalyzed carbonylation of C*sp*^{2}–H bonds with aromatic oximes for the synthesis of benzo[d][1,2]oxazin-1-ones and 3-methyleneisoindolin-1-ones has been developed. Interestingly, we found that the N-OH group of the oximes could be used as a directing group and/or an internal oxidant under different conditions. This transformation is supposed to undergo a hydroxyl-directed *ortho*-C*sp*^{2}–H carbonylation or an activation of vinyl C*sp*^{2}–H bond/*ortho*-C*sp*^{2}–H carbonylation process. The uses of readily available starting materials, atmospheric pressure of carbon monoxide, as well as operational simplicity make this practical and atom-economical method particularly attractive.

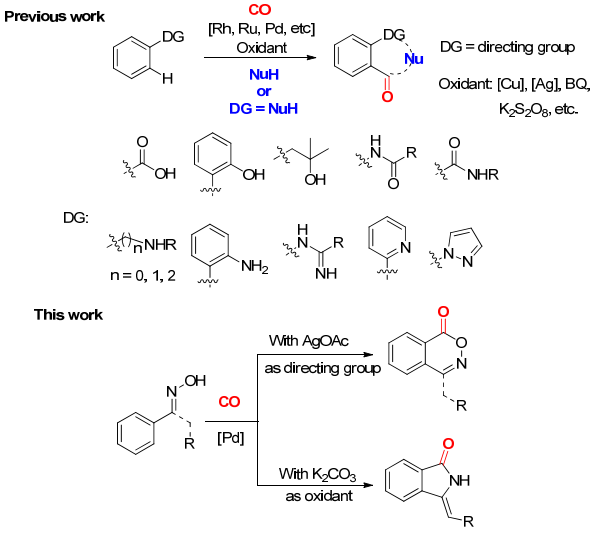
Introduction

Carbonylation reaction is an attractive synthetic method since it utilizes carbon monoxide (CO) as a carbon-atom source for the addition of a carbonyl group to organic molecules.[1] Particularly, palladium-catalyzed carbonylation for the construction of carbonyl compounds has received considerable attention.[2] There is no doubt that Pd(0)-catalyzed Heck carbonylation of aryl halides, triflates, and tosylates is an expedient access to carboxylic acid derivatives,[3] however, regioselective introduction of the halide group is not always straightforward, sometimes requiring several additional steps. Besides, the generation of environmentally unfriendly waste also makes the development of alternative approaches highly desirable. In order to achieve green and atom-economic synthesis, carbonylation of C–H bonds is undoubtedly an ideal strategy to introduce carbonyl functional units into molecules.

The Pd(II)-catalyzed C–H carbonylation of aromatic compounds, which was first discovered by Fujiwara and co-workers,[4] continues to attract considerable attention by virtue of its atom economy and high efficiency. However, the chemo- and regioselective activation of a specific C−H bond is still a big challenge, which should be due to the ubiquity and robustness of C−H bonds. Therefore, how to design reactions that are compatible with readily available starting materials where the inherent functionality of the molecule can be used to chelate with the metal and facilitate selective C−H activation is a great issue. A practical solution is to use a directing group which allows the selective C−H bond activation by the localized transition-metal catalyst. In recent years, a variety of functional groups including carboxylic acids,[5] hydroxyl groups,[6] amines,[7] amides,[8] amidines,[9] and *N*-containing heterocycles,[10] have been reported to direct C−H bond carbonylation (Scheme 1), and the choice of oxidant is also very important in these cases.

Oximes are easily prepared from aldehydes and ketones, and useful precursors for the synthesis of *N*-heterocycles.[11] Moreover, they also can be served as an internal oxidant and have been used as substrates for transition-metal catalyzed C−H activation.[12] To the best of our knowledge, there are no reported examples dedicated to oximes as substrates for the direct C−H bond carbonylation. Inspired by our previous research on palladium-catalyzed carbonylation reactions,[13] and oxime esters as substrates,[14] herein, we would like to disclose a palladium-catalyzed carbonylation of C*sp*^{2}–H bond with aromatic oximes for the selective synthesis of benzo[d][1,2]oxazin-1-ones and 3-methyleneisoindolin-1-ones (Scheme 1). In this reaction, we found that the N-OH group of the oximes could be used as a directing group or an internal oxidant under different conditions.

Scheme 1. **C(*sp*^{2})–H Carbonylation**



Results and Discussion

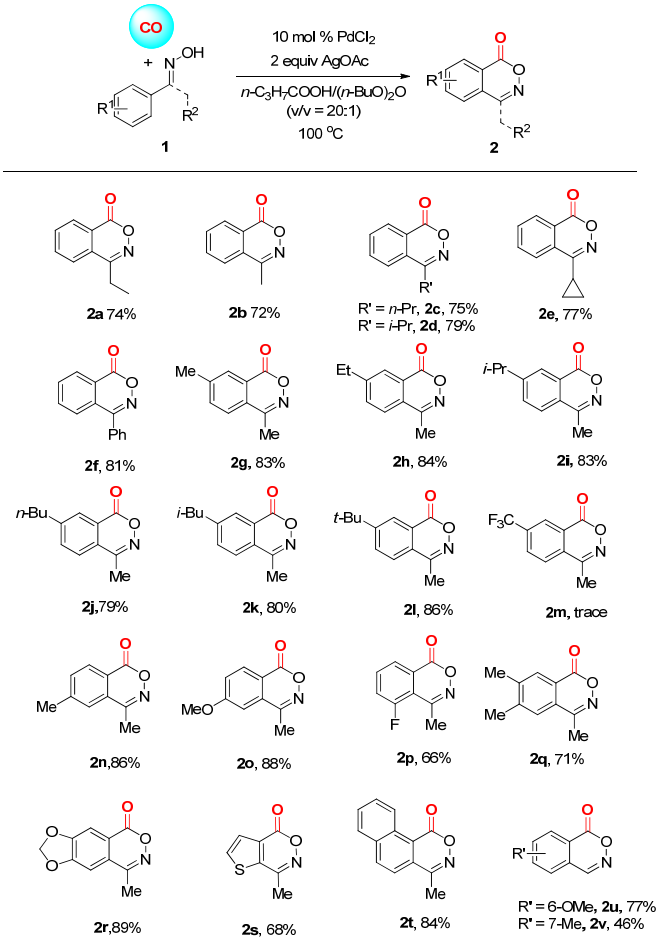
At first, propiophenone oxime (1a) was attached with CO balloon in the presence of 10 mol % $PdCl_2$ in 2 mL mixed solvent $C_3H_7COOH/(C_3H_7CO)_2O$ (*v*/*v* = 20: 1) at 100 °C, and the desired

product 4-ethyl-1*H*-benzo[d][1,2]oxazin-1-one (**2a**) was obtained in 74% yield (see the Supporting Information for details). It was reported that this skeleton is an important class of heterocycle exhibiting potential biological activities. For example, the tetrahydronaphthalene-benzoxazine glucocorticoid receptor (GR) partial agonists (I, II) were optimized to produce potent full agonists of GR, and compound ZK 21634832 has been also reported as GR agonists demonstrating dissociation between transrepression and transactivation activities.[15]

Considering the importance of this skeleton, we then studied the scope of the substrates, and the results are summarized in Table 1. Both phenyl alkyl ketone oximes and phenyl aryl ketone oximes were successfully subjected to this reaction system, and provided the corresponding benzoxazinone products **2b-2f** in good to excellent yields. The *para*-substituted acetophenone oximes with electron-donating groups could be converted into the corresponding 1*H*-benzo[d][1,2]oxazin-1-ones (**2g-2l**) in good to excellent yields. However, strong electron-withdrawing groups such as CF_3 on the aromatic ring did not show a positive effect to this transformation, and the desired product **2m** was just formed in very low GC yield. The acetophenone oxime substrates with substituents at the *meta* position reacted exclusively at the less sterically hindered position, leading to the formation of single regioisomers (**2n** and **2o**). Moreover, the *ortho*-substituted acetophenone oxime (R^1 = F) was also a suitable substrate for this transformation, and the reaction afforded **2p** in 66% yield. In addition, the substrates 3', 4'-dimethylacetophenone, 1-(benzo[d][1,3]dioxol-5-yl)-ethanone oximes also gave good yields of the desired products **2q** and **2r**. Heteroaromatic substrates such as thiophene oxime also participated well in this process and gave **2s** in 68% yield. More sterically hindered substrates such as 1-(naphthalen-2-yl)ethanone oxime, could be converted to the corresponding product **2t** in 84% yield. It should be noted that benzaldehyde oximes (3-methoxybenzaldehyde oxime and 4-methylbenzaldehyde oxime) were also good substrates for this transformation, and provided the desired products **2u** and **2v** in 77 and 46% yields, respectively.

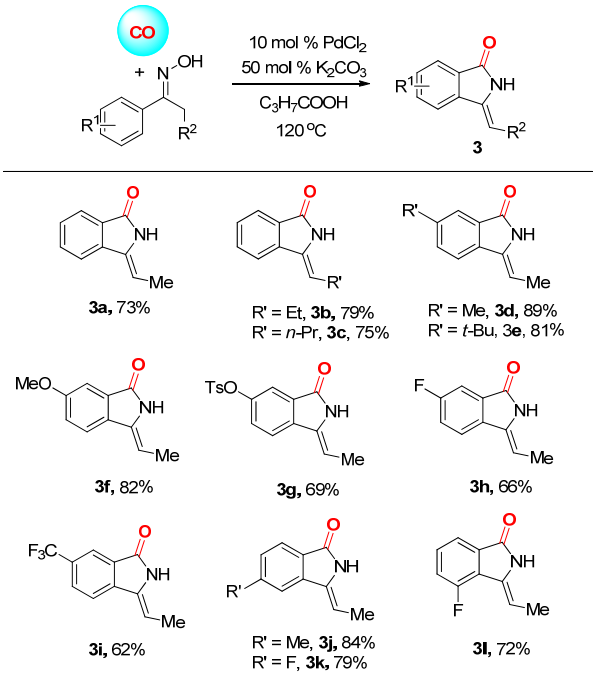
Pleasingly, another useful product **3a** was detected when the reaction mixture of propiophenone oxime (**1a**) and 10 mol % $PdCl_2$ in C_3H_7COOH with CO balloon, was carried out at 120 °C. We speculated that the formation of **3a** might firstly undergo the vinyl Csp^2–H bond activation followed by *ortho*-Csp^2–H carbonylation.[16] To our delight, a single crystal of product **3a**, obtained by slow crystallization from a mixture of petroleum ether and ethyl acetate, illustrated its structure was (*Z*)-3-ethylideneisoindolin-1-one,[17] which is an important structural

Table 1. Synthesis of benzoxazinones from a range of aromatic oximes[a]



[a] Reaction conditions: aromatic oximes **1** (0.5 mmol), $PdCl_2$ (0.05 mmol), AgOAc (1.0 mmol), CO (balloon), $C_3H_7COOH/(C_3H_7CO)_2O$ (2 mL, v/v = 20: 1), 100 °C. Yield is that of the isolated product.

Table 2. Synthesis of 3-methyleneisoindolin-1-ones from a variety of aromatic oximes[a]



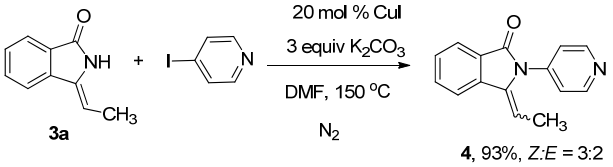
[a] Reaction conditions: **1** (0.5 mmol), $PdCl_2$ (0.05 mmol), K_2CO_3 (0.25 mmol), CO balloon, *n*-C_3H_7COOH (2 mL), 120 °C. Yield is that of the isolated product.

motif in a number of naturally compounds and designed pharmaceutical molecules.[18]. It is also an useful intermediate in the synthesis of alkaloids including lennoxamine, aristocularines and aristolactams.[19] In addition, numerous methods for their preparation have been developed,[20] however, these methods offen suffer from poor regioselectivity of the product, tedious and expensive substrate preparation or harsh reaction conditions.

Further optimization showed that the best conditions for the synthesis of **3a** included 10 mol % $PdCl_2$, 50 mol % K_2CO_3 in C_3H_7COOH with CO balloon at 120 °C (for details see the Supporting Information). With the optimal reaction conditions in hand, we next evaluated the substrate scope of this transformation and the results are shown in Table 2. The reactions of 1-phenylbutan-1-one and 1-phenylpentan-1-one oximes proceeded smoothly and gave the desired products **3b** and **3c** in 79 and 75% yields, respectively. Different *para*-substituted propiophenone oximes including some with electron-donating groups (R' = OMe, Me, *t*-Bu, OTs), and some with electron-withdrawing groups (R' = F, CF_3) could be converted into the corresponding products in good to excellent yields (**3d-3i**), and electron-donating groups showed a positive effect to this reaction. In the case of *meta*-substituted propiophenone oximes, excellent selectivity to the C−H bond with less steric hindrance was observed, regardless of the electronic character of the substituents in the *meta* position (**3j-3k**). Besides, the transformation of 1-(2-fluorophenyl)propan-1-one oxime could also proceed smoothly, and provided the desired product **3l** in 72% yield. These results indicated that this chemical process was tolerant towards the electronic and steric effects of the aromatic ring.

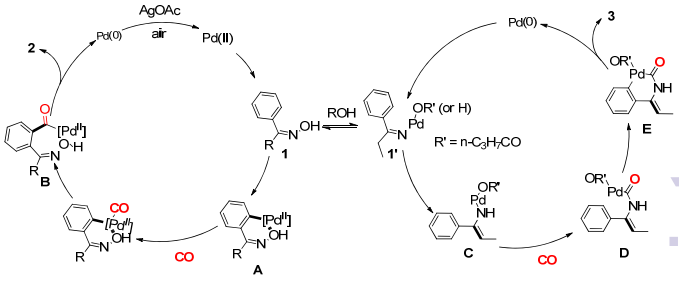
Moreover, the free NH group in the product of 3-methyleneisoindolin-1-ones makes it to be attractive and versatile synthetic building block in the chemical transformations. Thus, to further highlight the application of this strategy, we next found that compound **3a** could convert be to the desired product **4**, a good bioactivity indicator receptor antagonist, in 93% yield in the presence of 20 mol % CuI, 3 equiv K_2CO_3 in DMF at 150 °C under N_2 atmosphere (Scheme 2).

Scheme 2. **Synthesis of Bioactivity Indicator Receptor Antagonist 4.**



A tentative mechanism for the selectivity in Pd-catalyzed carbon monoxide insertion to oximes is proposed in Scheme 3. The left pathway[21] is an oxime hydroxyl directing *ortho*-C–H bond cleavage by Pd(II) to form the key six-membered palladacycle intermediate **A**. 1,1-Migratory insertion of CO into the Pd–C bond then occurred to forge the new C–C bond, generating a seven-membered cyclic intermediate **B**. Reductive elimination from the seven-membered palladocycle **B** led to the desired product **2** and concurrent formation of a Pd(0) species, which is oxidized to Pd(II) by AgOAc and air to fulfill the catalytic cycle.[6a] For the right pathway, oxidative addition of **1** afforded intermediate **1'**, which could undergo tautomerization to generate the enamine-derived amido-Pd^{II} species **C**. A molecule of CO then bound to **C** and led to the formation of complex **D**. And C–H bond cleavage would form palladacyclic complex **E**. Subsequent reductive elimination afforded the 3-methyleneisoindolin-1-one product **3** and regenerated the active Pd(0) catalyst.[11c, 22]

Scheme 3. **Plausible mechanism**



Conclusions

In summary, a new and convenient palladium-catalyzed carbonylation of Csp^2–H bond with aromatic oximes for the preparation of benzo[d][1,2]oxazin-1-ones and 3-methyleneisoindolin-1-ones has been developed. There are two pathways including a hydroxyl-directed *ortho*-Csp^2–H carbonylation and an activation of vinyl Csp^2–H bond/*ortho*-Csp^2–H carbonylation. The uses of readily available starting materials, atmospheric pressure of carbon monoxide, as well as operational simplicity make this practical and atom-economical method particularly attractive. Further investigations toward extending this transformation to the synthesis of biologically active compounds are currently ongoing in our laboratory.

Acknowledgments

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental section, characterization of all compounds, copies of ^1H and ^{13}C NMR spectra for selected compounds. See DOI: 10.1039/b000000x/

1. For selected examples, see a) R. Long, J. Huang, W. Shao, S. Liu, Y. Lan, J. Gong, Z. Yang, *Nat Commun.*, 2014, 5:5707 DOI: 10.1038/ncomms6707; b) S. Sumino, A. Fusano, T. Fukuyama, and I. Ryu, *Acc. Chem. Res.*, 2014, **47**, 1563; c) Z. Guan, Z. Ren, S. M.Spinella, S. Yu, Y. Liang, X. Zhang, *J. Am. Chem. Soc.*, 2009, **131**, 729; d) T. Asaumi, T. Matsuo, T. Fukuyama, Y. Ie, F. Kakiuchi, N. Chatani, *J. Org. Chem.*, 2004, **69**, 4433; e) N. Chatani, T. Asaumi, T. Ikeda, S. Yorimitsu, Y. Ishii, F. Kakiuchi, S. Murai,

J. Am. Chem. Soc., 2000, **122**, 12882; f) S. Inoue, H. Shiota, Y. Fukumoto, N. Chatani, *J. Am. Chem. Soc.,* 2009, **131**, 6898; g) N. Hasegawa, V. Charra, S. Inoue, Y. Fukumoto, N.Chatani, *J. Am. Chem. Soc.,* 2011, **133**, 8070.

2. a) L. Wu, X. Fang, Q. Liu, R. Jackstell, M. Beller, X. Wu, *ACS Catal.,* 2014, **4**, 2977; b) X. Wu, H. Neumann, M. Beller, *Chem. Rev.,* 2013, **113**, 1; c) C. E. Houlden, M. Hutchby, C. D. Bailey, J. G. Ford, S. N. G. Tyler, M. R. Gagné, G. C. Lloyd-Jones, K. I. Booker-Milburn, *Angew. Chem.Int. Ed.,* 2009, **48**, 1830; d) R. Giri, J. K. Lam, J. Yu, *J. Am. Chem. Soc.,* 2010, **132**, 686; e) N. Hasegawa, V. Charra, S. Inoue, Y. Fukumoto, N.Chatani, *J. Am. Chem. Soc.,* 2011, **133**, 8070.

3. a) A. Schoenberg, I. Bartoletti, R. F. Heck, *J. Org. Chem.,* 1974, **39**, 3318; b) R. H. Munday, J. R. Martinelli, S. L. Buchwald, *J. Am.Chem. Soc.,* 2008, **130**, 2754; c) A. Brennführer, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.,* 2009, **48**, 4114.

4. Y. Fujiwara, T. Kawauchi and H. Taniguchi, *J. Chem. Soc. Chem. Commun.,* 1980, 220.

5. R. Giri, J. Yu, *J. Am. Chem. Soc.,* 2008, **130**, 14082.

6. a) Y. Lu, D. Leow, X. Wang, K. E. Engle, J. Yu, *Chem. Sci.,* 2011, **2**, 967; b) S. Luo, F. Luo, X. Zhang, Z. Shi, *Angew. Chem. Int. Ed.,* 2013, **52**, 10598.

7. a) Z. Guan, M. Chen, Z. Ren, *J. Am. Chem. Soc.,* 2012, **134**, 17490; b) D. Liang, Z. Hu, J. Peng, J. Huang, Q. Zhu, *Chem. Commun.,* 2013, **49**, 173; c) B. López, A. Rodriguez, D. Santos, J. Albert, X. Ariza, J. Garcia, J. Granell, *Chem. Commun.,* 2011, **47**, 1054; d) B. Haffemayer, M. Gulias, M. J. Gaunt, *Chem. Sci.,* 2011, **2**, 312; e) K. Orito, A. Horibata, T. Nakamura, H. Ushito, H. Nagasaki, M. Yuguchi, S. Yamashita, M. Tokuda, *J. Am. Chem. Soc.,* 2004, **126**, 14342; f) H. Li, G. Cai, Z. Shi, *Dalton Trans.,* 2010, **39**, 10442.

8. a) C. E. Houlden, M. Hutchby, C. D. Bailey, J. G. Ford, S. N. G. Tyler, M. R. Gagné, G. C. Lloyd-Jones, K. I. Booker-Milburn, *Angew. Chem. Int. Ed.,* 2009, **48**, 1830; b) E. J. Yoo, M. Wasa, J. Yu, *J. Am. Chem. Soc.,* 2010, **132**, 17378; c) R. Giri, J. K. Lam, J. Yu, *J. Am. Chem. Soc.,* 2010, **132**, 686; d) N. Hasegawa, V. Charra, S. Inoue, Y. Fukumoto, N. Chatani, *J. Am. Chem. Soc.,* 2011, **133**, 8070; e) J. W. Wrigglesworth, B. Cox, G. C. Lloyd-Jones, K. I. Booker-Milburn, *Org. Lett.,* 2011, **13**, 5326.

9. B. Ma, Y. Wang, J. Peng, Q. Zhu, *J. Org. Chem.,* 2011, **76**, 6362.

10. D. Liang, Y. He, Q. Zhu, *Org. Lett.* 2014, **16**, 2748; b) T. Asaumi, N. Chatani, T. Matsuo, F. Kakiuchi, S. Murai, *J. Org. Chem.,* 2003, **68**, 7538; c) Y. Ie, N. Chatani, T. Ogo, D. R.Marshall, T. Fukuyama, F. Kakiuchi, S. Murai, *J. Org. Chem.,* 2000, **65**, 1475.

11. a) Y. Wei, N. Yoshikai, *J. Am. Chem. Soc.,* 2013, **135**, 3756; b) W. Du, M. Zhao, Z. Ren, Y. Wang, Z. Guan, *Chem. Commun.,* 2014, **50**, 7437; c) Y. Tan, J. F. Hartwig, *J. Am. Chem. Soc.,* 2010, **132**, 3676.

12. a) R. K. Chinnagolla, S. Pimparkar and M. Jeganmohan, *Chem. Commun.,* 2013, **49**, 3703; b) P. C. Too, Y. Wang, S. Chiba, *Org. Lett.,* 2010, **12**, 5688; c) R. K. Chinnagolla, S. Pimparkar and M. Jeganmohan, *Org. Lett.,* 2012, **14**, 3032; d) C. Kornhaaß, J. Li and L. Ackermann, *J. Org. Chem.,* 2012, **77**, 9190; e) Y. Yoshida, T. Kurahashi and S. Matsubara, *Chem. Lett.,* 2012, **41**, 1498; f) L. Zheng, J. Ju, Y. Bin, and R. Hua, *J. Org. Chem.,* 2012, **77**, 5794; g) J. Ju, C. Qi, L. Zheng, R. Hua, *Tetrahedron Lett.,* 2013, **54**, 5159.

13. a) F. Ji, X. Li, W. Wu, H. Jiang, *J. Org. Chem.,* 2014, **79**, 11246; b) J. Li, S. Yang, W. Wu, H. Jiang, *Chem. Commun.,* 2014, **50**, 1381; c) Y. Xu, J. Zhao, H. Chen, W. Wu, H. Jiang, *Chem. Commun.*, 2014, **50**, 2488; d) H. Chen, C. Cai, X. Liu, X. Li, H. Jiang, *Chem. Commun.,* 2011, **47**, 12224; e) L. Jia, H. Jiang, J. Li, *Green Chem.*, 1999, **4**, 91; f) J. Li, H. Jiang, M. Chen, *Green Chem.,* 2001, **3**, 137; g) J. Li, H. Jiang, A. Feng, L. Jia, *J. Org. Chem.,* 1999, **64**, 5984.

14. a) H. Huang, X. Ji, W. W, H. Jiang, *Chem. Soc. Rev.,* 2015**,** DOI: 10.1039/c4cs00288a; b) X. Tang, L. Huang, J. Yang, Y. Xu, W. Wu, H. Jiang, *Chem. Commun.,* 2014, **50**, 14793; c) X. Tang, L. Huang, C. Qi, W. Wu, H. Jiang, *Chem. Commun.,* 2013, **49**, 9597; d) H. Huang, X. Ji, X. Tang, M. Zhang, X. Li, H. Jiang, *Org. Lett.,* 2013, **15**, 6254; e) X. Tang, H. Gao, J. Yang, W. Wu, H. Jiang, *Org. Chem. Front.,* 2014, **1**, 1295.

15. a) M. Barker, M. Clackers, R. Copley, D. A. Demaine, D. Humphreys, G. G. A. Inglis, M. J. Johnston, H. T. Jones, M.V. Haase, D. House, R. Loiseau, L. Nisbet, F. Pacquet, P. A. Skone, S. E. Shanahan, D. Tape, V. M. Vinader, M. Washington, I. Uings, R. Upton, I. M. McLay, S. J. F. Macdonald, *J. Med. Chem.,* 2006, **49**, 4216; b) M. Barker, M. Clackers, D. A. Demaine, D. Humphreys, M. J. Johnston, H. T. Jones, F. Pacquet, J. M. Pritchard, M. Salter, S. E. Shanahan, P. A. Skone, V. M. Vinader, I. Uings, I. M. McLay, S. J. F. Macdonald, *J. Med. Chem.,* 2005, **48**, 4507; c) H. Schacke, A. Schottelius, W. D. Docke, P. Strehlke, S. Jaroch, N. Schmees, H. Rehwinkel, H. Hennekes, K. Asadullah, *Proc. Natl. Acad. Sci. U.S.A.*, 2004, **101**, 227.

16. X. Tang, L. Huang, Y. Xu, J. Yang, W. Wu, H. Jiang, *Angew. Chem. Int. Ed.,* 2014, **53**, 4205.

17. CCDC 1012731 (**3a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. A single crystal of product **3a** is in Supporting Information

18. a) E. Valencia, V. Fajardo, A. J. Freyer, M. Shamma, *Tetrahedron Lett.,* 1985, **26**, 993; b) G. Blasko, D. J. Gula, M. Shamma, *J. Nat. Prod.,* 1982, **45**, 105.

19. a) A. Couture, E. Deniau, P. Grandclaudon, C. Hoarau, *Tetrahedron,* 2000, **56**, 1491; b) S. Couty, B. Liegault, C. Meyer, J. Cossy, *Tetrahedron,* 2006, **62**, 3882; c) A. Moreau, A. Couture, E. Deniau, P. Grandclaudon, *J. Org. Chem.,* 2004, **69**, 4527; d) V. Rys, A. Couture, E. Deniau, S. Lebrun, P. Grandclaudon, *Tetrahedron,* 2005, **61**, 665; e) C. Hoarau, A. Couture, H. Cornet, E. Deniau, P. Grandclaudon, *J. Org. Chem.*, 2001, **66**, 8064.

20. For selected examples, see a) H. Cao, L. McNamee, H. Alper, *Org. Lett.,* 2008, **10**, 5281; b) B. Zhou, W. Hou, Y. Yang, and Y. Li, *Chem. Eur. J.,* 2013, **19**, 4701;c) S. Couty, B. Liegault, C. Meyer, J. Cossy, *Org. Lett.,* 2004, **6**, 2511; d) Y. Uozumi, N. Kawasaki, E. Mori, M. Mori, and M. Shibasaki, *J. Am. Chem. Soc.,* 1989, **111**, 3725; e) R. Mancuso, I. Ziccarelli, D. Armentano, N. Marino, S. V. Giofrè, and B. Gabriele, *J. Org. Chem.,* 2014, **79**, 3506.

21. The KIE for the synthesis of 1*H*-benzo[d][1,2]oxazin-1-ones is 3 (for details see support information).

22. W. P. Hong, A. V. Iosub, S. S. Stahl, *J. Am. Chem. Soc.,* 2013, **135**, 13664.

