Organic LETTERS

Letter

Cite This: Org. Lett. XXXX, XXX, XXX-XXX

pubs.acs.org/OrgLett

Copper-Catalyzed Aerobic Oxidative [2 + 3] Cyclization/Aromatization Cascade Reaction: Atom-Economical Access to Tetrasubstituted 4,5-Biscarbonyl Imidazoles

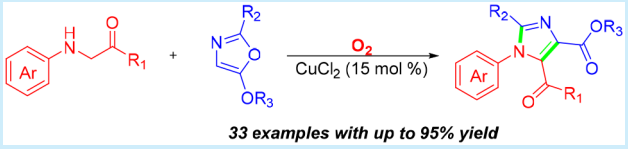
Jialin Xie,[†] Yuanqiong Huang,[†] Hongjian Song,*[,†] Yuxiu Liu,[†] and Qingmin Wang*[,†,‡]

[†]State Key Laboratory of Elemento-Organic Chemistry, Research Institute of Elemento-Organic Chemistry, College of Chemistry, Nankai University, Tianjin 300071, People's Republic of China

[‡]Collaborative Innovation Center of Chemical Science and Engineering (Tianjin), Tianjin 300071, People's Republic of China

Supporting Information

ABSTRACT: An atom-economical method for accessing tetrasubstituted 4,5-biscarbonylimidazoles by reaction between glycine derivatives and 5-alkoxyoxazoles is reported. The method, which involves a copper-catalyzed aerobic oxidative [2 + 3] cyclization/aromatization cascade process, starts from readily available and inexpensive materials, uses molecular oxygen as a co-oxidant, and has a broad substrate scope.



Tetrasubstituted imidazole moieties are widespread in natural products,[1] pharmaceuticals,[2] pesticides,[3] and functional materials,[4] and they are commonly used as ligands.[5] The fully substituted 4,5-biscarbonyl imidazole moiety is important because it constitutes the core of some bioactive compounds[6] (Figure 1), and the carbonyl group can serve as a versatile handle

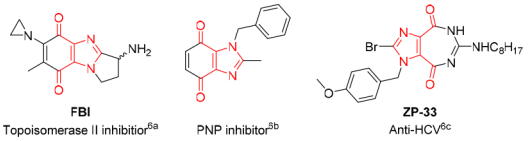


Figure 1. Bioactive compounds with a fully substituted 4,5-biscarbonylimidazole moiety.

for the preparation of different imidazole derivatives. Various approaches to the synthesis of fully substituted imidazoles have recently been developed.[7] The most common approach involves multicomponent reactions,[7c−i] usually condensation reactions of diketones and aldehydes with amines or ammonia. Another approach involves transition-metal-catalyzed direct C−H or N−H functionalization reactions of less substituted imidazoles.[8] However, most of the existing methods show poor regioselectivity and give only 4,5-bisarylimidazoles, and few of these methods can be used to synthesize fully substituted 4,5-biscarbonyl imidazoles in one step.[9] Thus, the development of a new type of approach to these compounds remains highly desirable.

During the past decade, various effective methods for activating C−H bonds for direct transformation into useful functional groups have been developed.[10] Among such methods, the oxidative cross-dehydrogenative coupling (CDC)[11] of glycine derivatives has attracted widespread attention since it was first reported.[12] The reactions of this type reported to date can be classified into three main categories (Figure 2). Path a involves direct oxidative CDC between glycine derivatives and

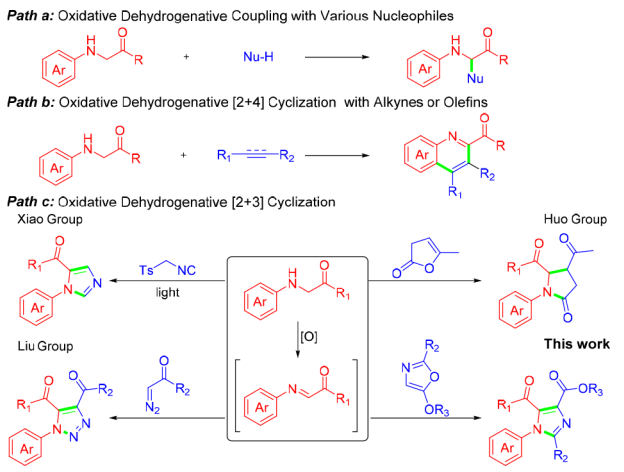


Figure 2. Oxidative cross-dehydrogenative coupling reactions of glycine derivatives.

nucleophiles to construct α-substituted glycine derivatives.[13] Path b involves direct oxidative cross-dehydrogenative [4 + 2] cyclization reactions between glycine derivatives and alkynes or olefins to form substituted quinolines.[14] Path c, which is the least common of the reported methods, involves direct oxidative cross-dehydrogenative [2 + 3] cyclization of glycine derivatives.[15] In 2014, Xiao et al. reported the synthesis of substituted imidazoles by means of a visible-light-induced iridium-catalyzed aerobic oxidation/[2 + 3] cycloaddition/aromatization cascade

Received: September 5, 2017

DOI: 10.1021/acs.orglett.7b02767
Org. Lett. XXXX, XXX, XXX−XXX

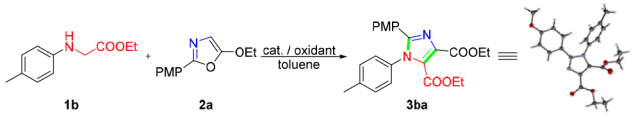
reaction between glycine derivatives and isocyanides to construct substituted imidazoles.[15a] However, the substrate scope of the reaction is limited, and a Ts group is removed in the final step, which reduces the atom economy of the process. In 2015, Liu et al. reported the formation of 1,2,3-triazoles by means of a copper-catalyzed aerobic oxidation/[2 + 3] cycloaddition/aromatization cascade reaction between glycine derivatives and ethyl diazoacetate.[15b] In the same year, Huo et al. used a similar strategy to construct polysubstituted pyrrolidones by reaction between glycine esters and α-angelicalactone.[15c] Herein, we report a novel copper-catalyzed aerobic oxidation [2 + 3] cycloaddition/aromatization cascade reaction between glycine derivatives and 5-alkoxyoxazoles[16] for the synthesis of highly substituted 4,5-biscarbonylimidazoles via a cross-dehydrogenative coupling process. Molecular oxygen[13a−e,14a−c,15] is used as a co-oxidant in place of an organic oxidant[13f−l,14d,e] such as DDQ, TBHP, DTBP (di-*tert*-butylperoxide), or TEMPO oxoammonium salt. Water is the only side product.

We began by investigating the reaction of *N*-4-methylphenylglycine ester **1b** and 5-ethoxyoxazole **2a** as model substrates (Table 1). When we used 15 mol % of $CuCl_2$ as the catalyst, toluene as the solvent, and O_2 as the oxidant, the [2 + 3] cycloaddition reaction afforded expected product **3ba** in 87% yield after 24 h at 75 °C (entry 1; also see Table S1). The structure of **3ba** was confirmed by single-crystal X-ray analysis (see Table S2).[17] Encouraged by this result, we optimized the reaction conditions for these two substrates. Other solvents (e.g., DCE and CH_3CN) also gave the desired product but in lower yields; however, none of the desired product was obtained in THF (Table S1). Increasing the reaction temperature to 90 °C increased the yield to 95% (entry 2). We investigated various other copper salts (e.g., CuCl, Cu_2O, CuBr, $CuBr_2$, $Cu(OTf)_2$, and $Cu(OAc)_2$) and $FeCl_3$ (entries 3−10), but the yield was highest with $CuCl_2$. Changing the oxidant to TBHP, DTBP, $K_2S_2O_8$, or DDQ did not improve the results (Table S1). Unsurprisingly, when air was used as the oxidant instead of O_2, the yield of the desired product decreased (entry 11). None of the desired product was obtained in the absence of $CuCl_2$ (entry 12). Decreasing the $CuCl_2$ load to 10 mol % decreased the yield of **3ba** slightly (entry 13).

We then used the optimal conditions to investigate the substrate scope of the copper-catalyzed oxidative [2 + 3] cycloaddition reaction (Scheme 1). Satisfyingly, a host of glycine derivatives **1** could be transformed into the desired products. First, we evaluated the effect of the electronic properties of the substituents on the benzene ring of **1**. Substrates with an electron-donating or electron-withdrawing substituent at the *para*- or *meta*-position were compatible with the reaction conditions, affording the corresponding products (**3aa**−**3ka**) in good yields. An *ortho*-substituted substrate also underwent the desired transformation to **3la**, but a longer reaction time was required and a lower yield was obtained (41%), probably because of steric hindrance. Next, we examined the effects of variations in the carbonyl fragment of **1**. The reactions of methyl, isopropyl, *tert*-butyl, and benzyl esters (**1m**−**1p**, respectively) proceeded smoothly. In addition to the glycine esters, α-amino amides **1q**−**1s** and α-amino ketone **1t** afforded corresponding products **3qa**−**3ta** in good yields.

We also evaluated the scope of the reaction with respect to 5-alkoxyoxazole substrates **2** (Scheme 2). Substrates with one or more alkyl or methoxyl groups on the benzene ring afforded the corresponding products (**3bd**−**3bj**) in good yields, indicating that neither the position nor the number of substituents on the benzene ring influenced reaction outcome. Note in particular that 2-(2-methoxyphenyl) oxazole (**2g**) reacted smoothly under the optimal conditions to afford **3bg** in 78% yield, which suggests that the steric bulk of the phenyl group of **2** had a negligible effect on the reaction. The electronic properties of the substituent on the benzene ring of **2** appeared to play a more important role, as indicated by the fact that **2c**, which bears an electron-withdrawing chlorine atom, was less reactive; to obtain an acceptable yield of **3bc**, we had to use 3 equiv of glycine ester **1b** and extend the reaction time. The R^2 group of **2** was not restricted to ethyl, other alkyl substrates afforded high yields of the corresponding products, such as methyl product **3bk** and isopropyl product **3bl**. Finally, we evaluated substrates **2** with other aromatic groups at the 2-position. 2-Naphthyl- and 2-

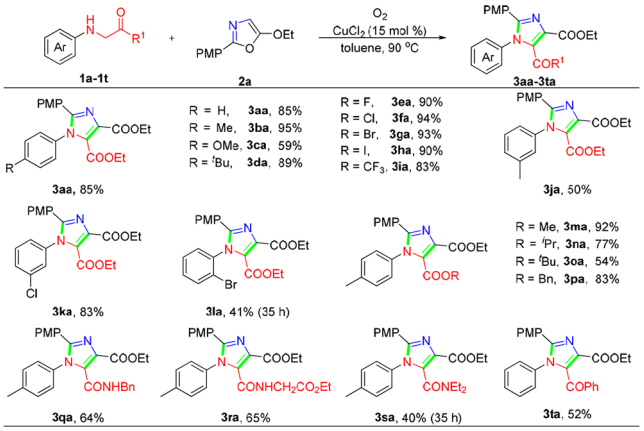
Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	oxidant	*t* (°C)	yield[b] (%)
1	$CuCl_2$	O_2	75	87
2	$CuCl_2$	O_2	90	95
3	CuCl	O_2	90	37
4	Cu_2O	O_2	90	NP
5	CuI	O_2	90	NP
6	CuBr	O_2	90	15
7	$CuBr_2$	O_2	90	58
8	$Cu(OTf)_2$	O_2	90	64
9	$Cu(OAc)_2$	O_2	90	NP
10	$FeCl_3$	O_2	90	40
11	$CuCl_2$	air	90	88
12		O_2	90	NP
13[c]	$CuCl_2$	O_2	90	87

[a]Reaction conditions, unless otherwise noted: **1b** (0.3 mmol), **2a** (0.2 mmol), catalyst (15 mol %), toluene (2.5 mL), O_2 (1 atm) or other oxidant (2.5 equiv), 24 h. PMP = 4-$CH_3OC_6H_4$. [b]Isolated yield. NP: no product. [c]$CuCl_2$ (10 mol %).

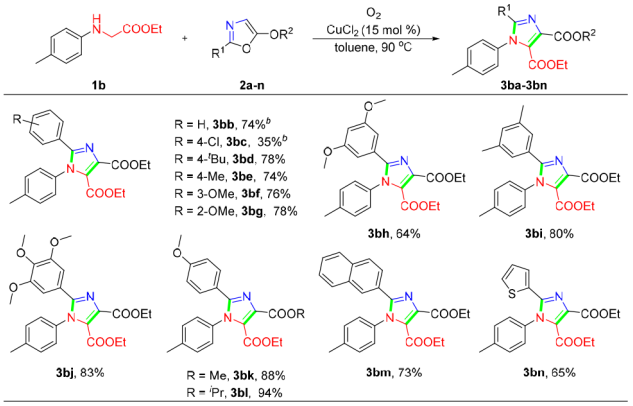
Scheme 1. Reactions of Other α-Amino Carbonyl Compounds[a]



[a]Reaction conditions, unless otherwise noted: **1** (0.45 mmol), **2** (0.3 mmol), $CuCl_2$ (15 mol %), toluene (4 mL), 1 atm O_2, 90 °C, 24 h. Isolated yields are given. PMP = 4-$CH_3OC_6H_4$.

DOI: 10.1021/acs.orglett.7b02767
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 2. Reactions of Various 5-Alkoxyoxazoles[a]

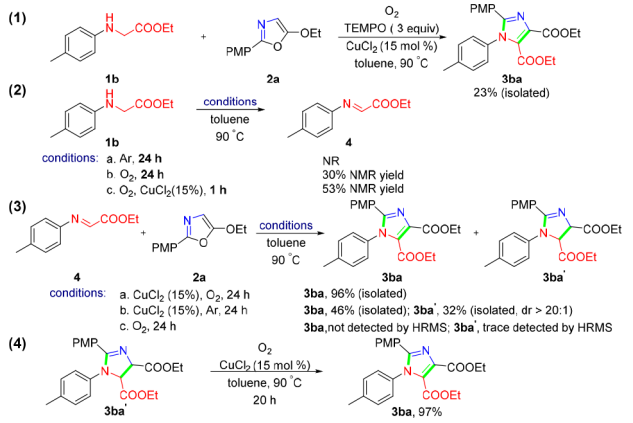


[a]Reaction conditions, unless otherwise noted: 1 (0.45 mmol), **2** (0.3 mmol), $CuCl_2$ (15 mol %), toluene (4 mL), 1 atm O_2, 90 °C, 24 h. Isolated yields are given. [b]Reaction conditions: **1** (0.9 mmol), **2** (0.3 mmol), $CuCl_2$ (15 mol %), toluene (4 mL), 1 atm O_2, 90 °C, 30 h. Isolated yields are given.

thienyl-substituted oxazoles **2m** and **2n** afforded **3bm** and **3bn** in 73% and 65% yields, respectively.

To investigate the mechanism of this cascade reaction, we conducted several control experiments (Scheme 3). When

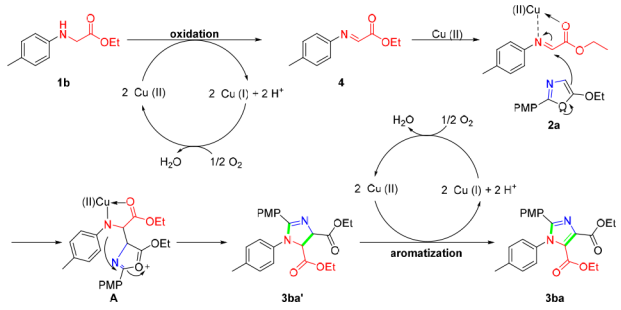
Scheme 3. Control Experiments



TEMPO (3 equiv) was included in the reaction mixture containing **1b** and **2a**, the yield of **3ba** sharply decreased to 23% (eq 1), which suggests that a single-electron-transfer pathway was involved in the reaction. Exposure of a toluene solution of **1b** to O_2 for 24 h in the absence of **2a** afforded imine **4** in 30% yield (by NMR),[13b] but when $CuCl_2$ was present in the reaction mixture, **4** was generated within an hour (53% yield by NMR, eq 2). These results indicate that imine **4** may be a reaction intermediate and that the copper salt may accelerate its formation. To assess this possibility, we isolated **4** and studied its reaction with **2a** (eq 3). As expected, under the optimal reaction conditions, **3ba** was obtained in a yield similar to that for the reaction of **2a** with amine **1b** (conditions a), whereas **3ba** did not form in the absence of the copper salt (conditions c). This experiment confirmed the intermediacy of **4** and suggested that $CuCl_2$ was necessary for the cycloaddition reaction. When the reaction of **4** and **2a** was carried out under Ar (conditions b), imidazoline product **3ba'** was obtained along with **3ba**, which suggests that the formation of **3ba** involved a second oxidative dehydrogenation procedure. To verify this possibility, we isolated **3ba'** and subjected it to the standard conditions; we found that **3ba'** was smoothly converted to **3ba** in an excellent yield (eq 4).

On the basis of the results of the control experiments, as well as previously reported results,[13d,j,15] we propose the plausible mechanism outlined in Scheme 4. First, glycine derivative **1b** is

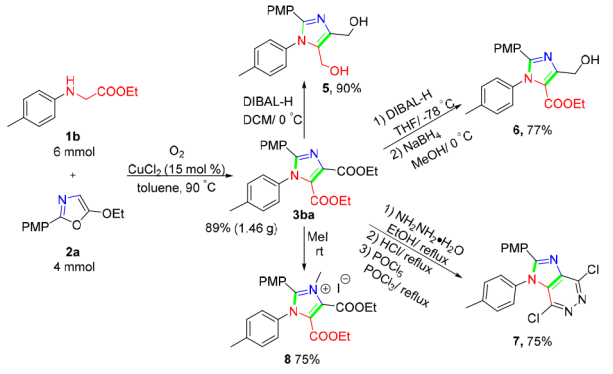
Scheme 4. Plausible Reaction Mechanism



oxidized to imine **4** under the combined effects of the copper salt and O_2. Then the electron-rich carbon nucleophile at the 4-position of **2a**[16] attacks imine **4**, which is activated by the copper salt, to afford oxocarbenium intermediate **A**. Subsequent cyclization and oxazole ring opening afford imidazoline intermediate **3ba'**.[18] Finally, **3ba'** undergoes a second oxidative dehydrogenation to form **3ba**.

To demonstrate the utility of this method, we synthesized imidazole **3ba** on a gram scale (Scheme 5). In addition, we

Scheme 5. Gram-Scale Synthesis of 3ba and Subsequent Functional Group Transformations



subjected **3ba** to a series of functional group transformations. Specifically, selective reduction of the ester groups under two different sets of conditions afforded diol **5** and monohydric alcohol **6** in acceptable yields.[19] Treatment of **3ba** with excess hydrazine, subsequent annelation in acidic media, and treatment with a mixture of $POCl_3$ and PCl_5 afforded 4,7-dichloro-imidazo[4,5-*d*]pyridazine derivative **7** in 75% yield.[20] Finally, *N*-methylation of **3ba** smoothly afforded imidazolium iodide **8** in 75% yield.

In summary, we have developed an atom-economical method for accessing tetrasubstituted 4,5-biscarbonyl imidazoles via copper-catalyzed aerobic oxidative [2 + 3] cyclization/aromatization cascade reaction between glycine derivatives and 5-alkoxyoxazoles. This method starts from readily available and inexpensive materials, uses O_2 as a co-oxidant, and has a broad substrate scope. An imidazole product was synthesized on a gram

DOI: 10.1021/acs.orglett.7b02767
Org. Lett. XXXX, XXX, XXX−XXX

scale in high yield and then subjected to various functional group transformations to afford a series of different imidazole derivatives, thus demonstrating the synthetic utility of the reaction products. Further studies on the applications of this cascade method for construction of nitrogen heterocycles are in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02767.

Experimental procedures, characterization data and ^{1}H and ^{13}C NMR of all compounds (PDF)
Crystallographic data for **3ba** (CIF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: songhongjian@nankai.edu.cn.
*E-mail: wangqm@nankai.edu.cn.

ORCID

Qingmin Wang: 0000-0002-6062-3766

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to the National Natural Science Foundation of China (21732002, 21372131, 21672117, 21602117) and the Tianjin Natural Science Foundation (16JCZDJC32400) for generous financial support for our programs.

■ REFERENCES

(1) (a) Lewis, J. R. *Nat. Prod. Rep.* **2001**, *18*, 95. (b) Weinreb, S. M. *Nat. Prod. Rep.* **2007**, *24*, 931.

(2) (a) Laufer, S.; Wagner, G.; Kotschenreuther, D. *Angew. Chem., Int. Ed.* **2002**, *41*, 2290. (b) Xiao, M.; Ahn, S.; Wang, J.; Chen, J.-J.; Miller, D. D.; Dalton, J. T.; Li, W. *J. Med. Chem.* **2013**, *56*, 3318.

(3) Li, W.-J.; Li, Q.; Liu, D.-L.; Ding, M.-W. *J. Agric. Food Chem.* **2013**, *61*, 1419.

(4) (a) Lin, W.-Y.; Long, L.-L.; Yuan, L.; Cao, Z.-M.; Chen, B.-B.; Tan, W. *Org. Lett.* **2008**, *10*, 5577. (b) Kwon, J. E.; Park, S.; Park, S. Y. *J. Am. Chem. Soc.* **2013**, *135*, 11239.

(5) (a) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290. (b) Poyatos, M.; Mata, J. A.; Peris, E. *Chem. Rev.* **2009**, *109*, 3677.

(6) (a) Ghodousi, A.; Huang, X.-F.; Cheng, Z.; Skibo, E. B. *J. Med. Chem.* **2004**, *47*, 90. (b) Alvarez, F.; Ghérardi, A.; Nebois, P.; Sarciron, M. E.; Pétavy, A. F.; Walchshofer, N. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 977. (c) Zhang, P.; Zhang, N.; Korba, B. E.; Hosmane, R. S. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2225.

(7) For selected examples, see: (a) Xu, W.; Wang, G.-N.; Sun, N.; Liu, Y.-H. *Org. Lett.* **2017**, *19*, 3307. (b) Yu, H.-H.; Xiao, L.; Yang, X.-C.; Shao, L.-M. *Chem. Commun.* **2017**, *53*, 9745. (c) Siamaki, A. R.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2006**, *128*, 6050. (d) Giles, R. L.; Sullivan, J. D.; Steiner, A. M.; Looper, R. E. *Angew. Chem., Int. Ed.* **2009**, *48*, 3116. (e) Shen, H.; Xie, Z.-W. *J. Am. Chem. Soc.* **2010**, *132*, 11473. (f) Kumar, D.; Kommi, D. N.; Bollineni, N.; Patel, A. R.; Chakraborti, A. K. *Green Chem.* **2012**, *14*, 2038. (g) Rajaguru, K.; Suresh, R.; Mariappan, A.; Muthusubramanian, S.; Bhuvanesh, N. *Org. Lett.* **2014**, *16*, 744. (h) Samanta, S.; Roy, D.; Khamarui, S.; Maiti, D. K. *Chem. Commun.* **2014**, *50*, 2477. (i) Tjutrins, J.; Arndtsen, B. A. *Chem. Sci.* **2017**, *8*, 1002.

(8) (a) Samann, C.; Coya, E.; Knochel, P. *Angew. Chem., Int. Ed.* **2014**, *53*, 1430. (b) Albertshofer, K.; Mani, N. S. *J. Org. Chem.* **2016**, *81*, 1269.

(9) (a) O'Donovan, l.; Carty, M. P.; Aldabbagh, F. *Chem. Commun.* **2008**, *43*, 5592. (b) Kamal, A.; Reddy, C. N.; Satyaveni, M.; Chandrasekhar, D.; Nanubolu, J. B.; Singarapu, K. K.; Maurya, R. A. *Chem. Commun.* **2015**, *51*, 10475.

(10) For selected reviews of C−H functionalization, see: (a) Bandini, M.; Eichholzer, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9608. (b) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (c) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev.* **2011**, *111*, 1293. (d) Le Bras, J.; Muzart, J. *Chem. Rev.* **2011**, *111*, 1170.

(11) For selected reviews of CDC reactions, see: (a) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068. (b) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (c) Matcha, K.; Antonchick, A. P. *Angew. Chem., Int. Ed.* **2013**, *52*, 2082. (d) Louillat, M.-L.; Patureau, F. W. *Chem. Soc. Rev.* **2014**, *43*, 901. (e) Girard, S. A.; Knauber, T.; Li, C.-J. *Angew. Chem., Int. Ed.* **2014**, *53*, 74.

(12) Zhao, L.; Li, C.-J. *Angew. Chem., Int. Ed.* **2008**, *47*, 7075.

(13) For very recent progress, see: (a) Zhu, S.-Q.; Rueping, M. *Chem. Commun.* **2012**, *48*, 11960. (b) Huo, C.-D.; Yuan, Y.; Wu, M.-X.; Jia, X.-D.; Wang, X.-C.; Chen, F.-J.; Tang, J. *Angew. Chem., Int. Ed.* **2014**, *53*, 13544. (c) Tan, Y.-Q.; Yuan, W.; Gong, L.; Meggers, E. *Angew. Chem., Int. Ed.* **2015**, *54*, 13045. (d) Xie, Z.-Y.; Liu, X.-G.; Liu, L. *Org. Lett.* **2016**, *18*, 2982. (e) Liu, X.-X.; Wu, Z.-Y.; He, Y.-Q.; Zhou, X.-Q.; Hu, T.; Ma, C.-W.; Huang, G.-S. *Adv. Synth. Catal.* **2016**, *358*, 2385. (f) Zhang, G.; Zhang, Y.-H.; Wang, R. *Angew. Chem., Int. Ed.* **2011**, *50*, 10429. (g) Qiu, L.; Guo, X.; Qian, Y.; Jing, C.-C.; Ma, C.-Q.; Liu, S.-Y.; Hu, W.-H. *Chem. Commun.* **2016**, *52*, 11831. (h) Xie, J.; Huang, Z.-Z. *Angew. Chem., Int. Ed.* **2010**, *49*, 10181. (i) Wu, J.-C.; Song, R.-J.; Wang, Z.-Q.; Huang, X.-C.; Xie, Y.-X.; Li, J.-H. *Angew. Chem., Int. Ed.* **2012**, *51*, 3453. (j) Yang, B.; Yang, T.-T.; Li, X.-A.; Wang, J.-J.; Yang, S.-D. *Org. Lett.* **2013**, *15*, 5024. (k) Zhi, H.-Z.; Ung, S. P.-M.; Liu, Y.; Zhao, L.; Li, C.-J. *Adv. Synth. Catal.* **2016**, *358*, 2553. (l) Li, K.-Z.; Tan, G.-Y.; Huang, J.-S.; Song, F.-J.; You, J.-S. *Angew. Chem., Int. Ed.* **2013**, *52*, 12942. (m) Gao, X.-W.; Meng, Q.-Y.; Li, J.-X.; Zhong, J.-J.; Lei, T.; Li, X.-B.; Tung, C.-H.; Wu, L.-Z. *ACS Catal.* **2015**, *5*, 2391.

(14) (a) Liu, J.; Liu, F.; Zhu, Y.-Z.; Ma, X.-G.; Jia, X.-D. *Org. Lett.* **2015**, *17*, 1409. (b) Xie, Z.-Y.; Jia, J.; Liu, X.-G.; Liu, L. *Adv. Synth. Catal.* **2016**, *358*, 919. (c) Ni, M.-J.; Zhang, Y.; Gong, T.-T.; Feng, B.-N. *Adv. Synth. Catal.* **2017**, *359*, 824. (d) Huo, C.-D.; Chen, F.-J.; Yuan, Y.; Xie, H.-S.; Wang, T.-J. *Org. Lett.* **2015**, *17*, 5028. (e) Richter, H.; Mancheno, O. G. *Org. Lett.* **2011**, *13*, 6066.

(15) (a) Deng, Q.-H.; Zou, Y.-Q.; Lu, L.-Q.; Tang, Z.-L.; Chen, J.-R.; Xiao, W.-J. *Chem. - Asian J.* **2014**, *9*, 2432. (b) Li, Y.-J.; Li, X.; Zhang, S.-X.; Zhao, Y.-L.; Liu, Q. *Chem. Commun.* **2015**, *51*, 11564. (c) Huo, C.-D.; Yuan, Y.; Chen, F.-J.; Tang, J.; Wang, Y.-J. *Org. Lett.* **2015**, *17*, 4208.

(16) (a) Evans, D. A.; Janey, J. M.; Magomedov, N.; Tedrow, J. S. *Angew. Chem., Int. Ed.* **2001**, *40*, 1884. (b) Mitchell, J. M.; Shaw, J. T. *Angew. Chem., Int. Ed.* **2006**, *45*, 1722. (c) Badillo, J. J.; Ribeiro, C. J. A.; Olmstead, M. M.; Franz, A. K. *Org. Lett.* **2014**, *16*, 6270. (d) Ma, B.-W.; Luo, W.-W.; Lin, L.-L.; Liu, X.-H.; Feng, X.-M. *Chem. Commun.* **2017**, *53*, 4077.

(17) CCDC 1580191 contains the supplementary crystallographic data for **3ba**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif..

(18) An alternative plausible mechanism involving a stereoselective 1,3-dipolar cycloaddition of imine **4** and the nitrile ylide which generated from oxazole **2a** through a Cornforth rearrangement process.

(19) Eckhardt, M.; Hauel, N.; Langkopf, E.; Himmelsbach, F. *Tetrahedron Lett.* **2008**, *49*, 1931.

(20) Belaroussi, R.; El Hakmaoui, A.; Percina, N.; Chartier, A.; Marchivie, M.; Massip, S.; Jarry, C.; Akssira, M.; Guillaumet, G.; Routier, S. *Eur. J. Org. Chem.* **2015**, *2015*, 4006.

DOI: 10.1021/acs.orglett.7b02767
Org. Lett. XXXX, XXX, XXX−XXX