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Aerobic Oxidative Coupling

Cu-Catalyzed Synthesis of C-3 Dicarbonyl Indoles via Aerobic Oxidative Coupling of Acetophenones with Indoles

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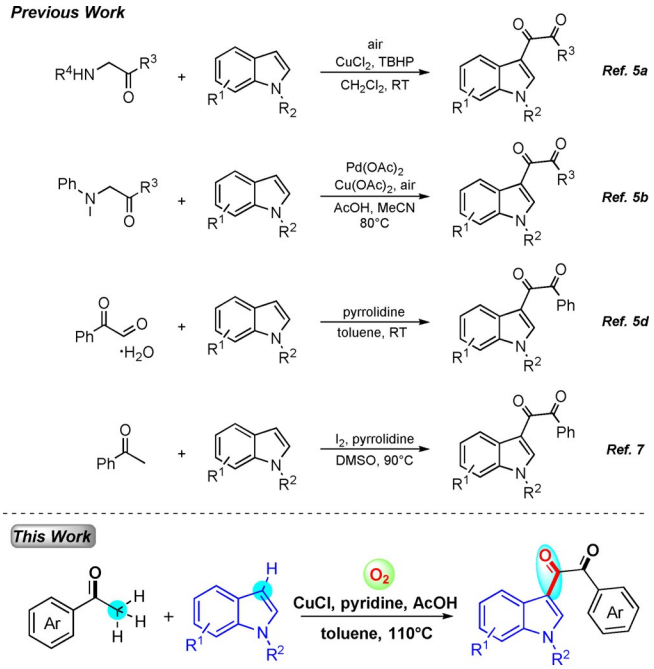
Abstract: A Cu-catalyzed aerobic oxidative coupling of acetophenones with indoles has been developed, and is an efficient and practical C–H (sp^3) functionalization approach to C-3 dicarbonyl indoles, using O_2 as the green oxidant. Moreover, a series of dicarbonyl indoles have been obtained smoothly and the plausible mechanism is proposed based on control experiments.

Indoles, a class of key structural elements with biological and pharmacological activities, are prevalent in plenty of natural products, and bioactive synthetic and functional materials.[1] Moreover, they also play an important role in drug development.[2] Consequently, the research of further functional modifications of indoles is a hot topic in organic synthesis, which has attracted interest from chemists all over the world.[3] Particularly, C-3 dicarbonyl indoles containing both indole and dicarbonyl structural units are powerful precursors for a variety of functional group transformations.[4]

Owing to the significance of C-3 dicarbonyl indoles, strategies for the synthesis of these useful units have been developed in the past few years.[5] Significantly, Li and co-workers reported two methods: (1) Cu-catalyzed C–H oxidation/cross-coupling of α-amino carbonyl compounds with indoles;[5a] (2) Pd-catalyzed synthesis of 3-acylated indoles involving oxidative cross-coupling of indoles with α-amino carbonyl compounds.[5b] In addition, Ahmed and co-workers developed an aminocatalytic cross-coupling approach via iminium ions to dicarbonyl indoles from 2-oxoaldehydes with indoles.[5d] Nevertheless, the advances mentioned above suffered from some drawbacks: (1) the relatively low atom efficiency; (2) starting materials were not easily available, which might limit their applications. Therefore, it is highly desirable to develop a feasible and highly efficient method to C-3 dicarbonyl indoles using practical starting materials. In this regard, acetophenones as simple and versatile building blocks are a great choice as reagents in oxidative coupling transformations.[6] Very recently, Wu and co-workers reported a route to C-3 dicarbonylation of indoles by direct regioselective oxidative cross-coupling of indoles with acetophenones under metal-free conditions.[7] However, O_2 has been regarded as an ideal oxidant and oxygen source in organic synthesis because of it is natural, abundant and environmentally friendly.[8] Herein, we presented a novel Cu-catalyzed oxidative coupling of acetophenones with indoles to C-3 dicarbonyl indoles, which is a practical method that uses O_2 as the green oxidant (Scheme 1). This methodology based on C–H (sp^3) cleavage is highly efficient and has a broad substrate scope.

To initiate our study, the reaction of acetophenone (**1 a**) with 1-methylindole (**2 a**) was selected as the model reaction to op-



Scheme 1. Cu-catalyzed aerobic oxidative coupling of acetophenones with indoles to C-3 dicarbonyl indoles.

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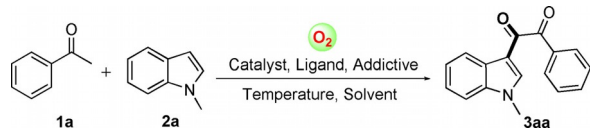
timize reaction conditions by examining a series of reaction parameters. All reactions were performed under an O_2 environment and the results were summarized in Table 1 and in the Supporting Information. First, the model reactions were carried out in the presence of pyridine and TFA at 100 °C in toluene to screen a variety of copper catalysts (Table 1, entry 1–5). Among these copper salts, CuCl exhibited the best catalytic effect, affording the desired dicarbonyl product **3 aa** in 52% yield (Table 1, entry 3). With the view of further enhancing its catalytic ability, ligands and additives were examined (Table 1, entry 6–13). To our delight, CuCl combined with pyridine and AcOH effectively catalyzed this aerobic oxidative coupling reaction and the yield of **3 aa** increased to 73% (Table 1, entry 10). In order to further optimize the reaction conditions, reaction temperatures of 80–120 °C were also examined (Table 1, entry 14–17). When the temperature was increased to 110 °C, the highest yield (85%) was obtained (Table 1, entry 16). Then, some other solvents were examined, such as PhCl, MeCN, DMF and 1,4-dioxane, which showed that toluene was the ideal solvent in this reaction (Table 1, entry 18–21). For the reason that atomic economy of chemical reactions is one of the important contents of green chemistry, we tried to reduce the amounts of 1-methylindoles in this reaction. However, 3 equiv of 1-methylindoles were required for the highest yield of product **3 aa** (see the Supporting Information). Finally, 5 and 20% CuCl were also tested (Table 1, entry 22, 23); however, their yields were lower than when using 10% CuCl. Based on the screening experiments above, the optimized reaction conditions of this Cu-catalyzed aerobic oxidative coupling of acetophenones with indoles were: 0.5 mmol acetophenone **1 a**, 1.5 mmol 1-methylindole **2 a**, 10% CuCl, 0.5 equiv pyridine and AcOH dissolved in 3 mL toluene and stirred at 110 °C for 16 h in a sealed tube under an O_2 environment.

Table 1. Reaction optimizations.[a]

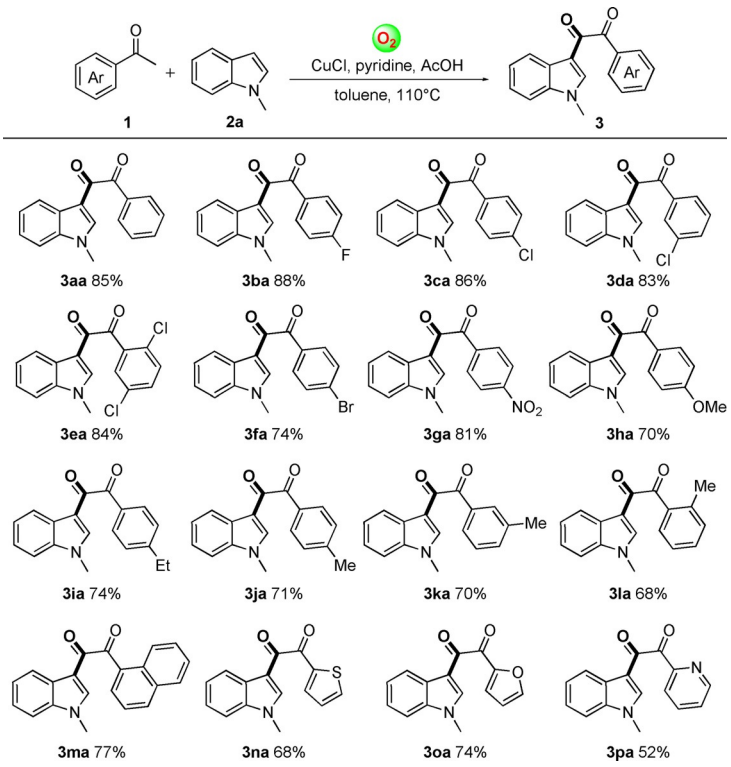


Entry	Catalyst	Ligand	Additive	T [°C]	Yield[b] [%]
1	$Cu(OAc)_2$	pyridine	TFA	100	<10%
2	$Cu(TFA)_2$	pyridine	TFA	100	22%
3	CuCl	pyridine	TFA	100	52%
4	CuBr	pyridine	TFA	100	36%
5	CuI	pyridine	TFA	100	Trace
6	CuCl	2,4-DMP	TFA	100	48%
7	CuCl	DMAP	TFA	100	44%
8	CuCl	2,2′-Bpy	TFA	100	35%
9	CuCl	pyridine	PivOH	100	33%
10	CuCl	pyridine	AcOH	100	73%
11	CuCl	pyridine	$PhCO_2H$	100	46%
12	CuCl	pyridine	HCl	100	Trace
13	CuCl	pyridine	H_2O	100	Nr[c]
14	CuCl	pyridine	AcOH	80	Trace
15	CuCl	pyridine	AcOH	90	65%
16	CuCl	pyridine	AcOH	110	85%
17	CuCl	pyridine	AcOH	120	81%
18[d]	CuCl	pyridine	AcOH	110	72%
19[e]	CuCl	pyridine	AcOH	110	37%
20[f]	CuCl	pyridine	AcOH	110	76%
21[g]	CuCl	pyridine	AcOH	110	54%
22	CuCl[h]	pyridine	AcOH	110	79%
23	CuCl[i]	pyridine	AcOH	110	83%

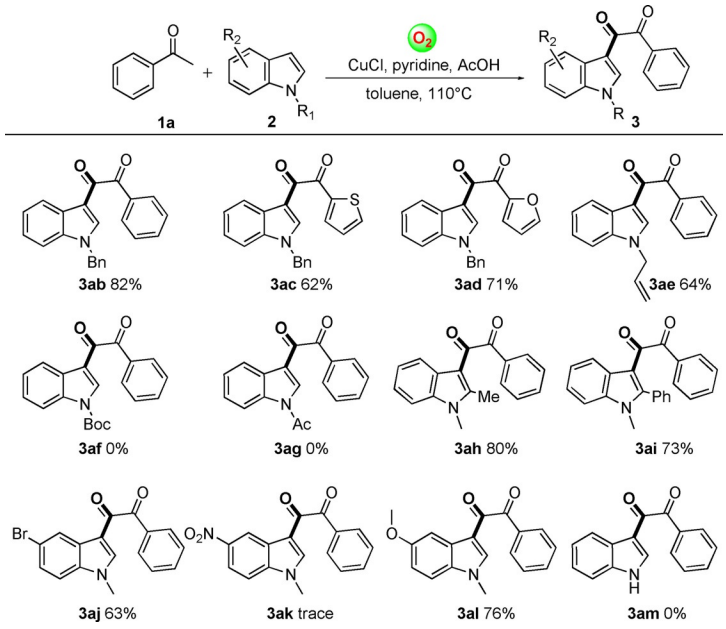
[a] Reaction conditions: 0.5 mmol **1 a**, 1.5 mmol indoles **2**, 10% CuCl, 0.25 mmol pyridine and AcOH solved in 3 mL toluene stirred at 100 °C for 16 h in a sealed tube equipped with an O_2 balloon, unless otherwise noted; [b] Isolated yields; [c] No reaction; [d] PhCl used as solvent; [e] MeCN used as solvent; [f] DMF used as solvent; [g] 1,4-Dioxane used as solvent; [h] CuCl (5%); [i] CuCl (20%). TFA = trifluoroacetic acid; 2,4-DMP = 2,4-dimethylpyridine; DMAP = 4-dimethylaminopyridine.

With the optimized reaction conditions in hand, a series of experiments were carried out to investigate the universality of this method with regard to both acetophenones **1** and indoles **2**. As shown in Scheme 2, acetophenones bearing different electron-donating and electron-withdrawing substituents reacted smoothly with 1-methylindole (**2 a**), affording the corresponding products in moderate to good yields (Scheme 2, **3 aa**–**3 la**). Moreover, the results indicated that electron-withdrawing groups (-F, -Cl, -Br, $-NO_2$) performed slightly better than electron-donating groups (-OMe, -Et, -Me), but the position (*ortho, meta,* or *para*) of the substituents had no obvious influence on the efficiency of this reaction. Then, ketones with polycyclic aromatic and heterocyclic substituents were also subjected to the optimized conditions. To our delight, 1-acetylnaphthalene could also undergo reaction with **2 a**, affording the desired product **3 ma** in 77% yield. In addition, 2-acetylthiophene, 2-acetylfuran and 2-acetylpyridine were all compatible reaction partners for this transformation (52–74% yield, Scheme 2, **3 na**–**3 pa**). Besides, we also examined some other aliphatic ketones, such as cyclohexanone, acetone and 2-butanone under our optimized reaction conditions. However, no corresponding target products were detected, implying that aliphatic ketones were not suitable for our recommended reaction conditions with indoles.

Next, a wide range of indoles **2** were subjected to the optimized reaction conditions. As shown in Scheme 3, indoles with different *N*-protective groups (-R_1) could be transformed smoothly with acetophenone (**1 a**) to corresponding dicarbonyl products in good yields (Scheme 3, **3 ab**–**3 ae**). However, electron-withdrawing substituents, such as *N*-Boc-, *N*-acetyl- and 5-nitroindole failed to produce corresponding products likely owing to their decreasing electron density on the indole ring (Scheme 3, **3 af**, **3 ag** and **3 ak**, respectively), showing that this reaction is sensitive to electronic characteristics of substituents groups on the indole rings. We were delighted to find that dicarbonyl products containing an *N*-benzyl indole structural unit (Scheme 3, **3 ab**–**3 ad**) have been disclosed to act as either positive or negative modulators of the human A_{2B} adenosine receptor (A_{2B}AR) and C-3 diketoindole scaffolds have the potential to design new analogs, which could be generated in moderate to excellent yields by using our method.[9] Moreover, some 2-substitued and 5-substitued indoles were also subjected to the oxidative cross-coupling reaction with **1 a**, affording 63–80% yields of the corresponding products (Scheme 3, **3 ah**, **3 ai**, **3 aj** and **3 al**). However, when the reaction was carried out



Scheme 2. Substrate scope of acetophenones. Reaction conditions: 0.5 mmol acetophenones **1**, 1.5 mmol 1-methylindole **2a**, 10% CuCl, 0.25 mmol pyridine and AcOH solved in 3 mL toluene stirred at 110 °C for 16 h in a sealed tube equipped with an O_2 balloon; yields are given for isolated products after chromatography.



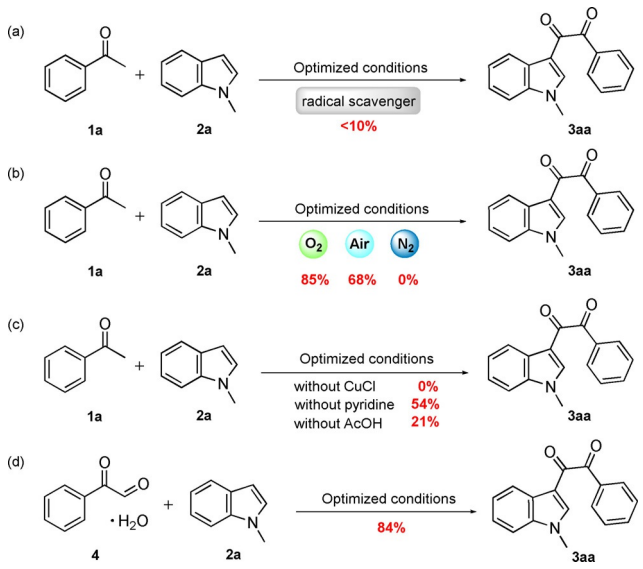
Scheme 3. Substrate scope of indoles. Reaction conditions: 0.5 mmol acetophenone **1**, 1.5 mmol indoles **2a**, 10% CuCl, 0.25 mmol pyridine and AcOH solved in 3 mL toluene stirred at 110 °C for 16 h in a sealed tube under an O_2 environment; yields are given for isolated products after chromatography.

between N–H indole **3m** (R_1 = H) with **1a** under the optimized reaction conditions, no desired product was obtained.

In order to understand the mechanism of dicarbonyl indole formation, several control experiments were conducted (Scheme 4). When the radical scavenger BHT (2 equiv) was added to the optimized reaction conditions, the reaction was strongly hindered and the BHT-captured intermediate was detechted by ESI-MS analysis (see the Supporting Information), suggesting that the oxidation process undergoes through a radical pathway (Scheme 4a]. In the second experiment, reactions under different gaseous environments were examined. The results showed that reactions under O_2 or air could proceed smoothly while the reaction under N_2 atmosphere failed to produce desired product **3aa**, which indicated that O_2 was the essential oxidant in this reaction. Next, we found that no desired product was detected if CuCl was removed from the optimized reaction conditions. Compound **3aa** was isolated in only 54 and 21% yield under modified conditions without pyridine or AcOH [Scheme 4c]. Furthermore, phenylglyoxal (**4**) was also subjected to the optimized reaction conditions with 1-methylindole (**2a**) and the desired product could be obtained in good yield (Scheme 4d), which confirms our conjecture that that compound **4** serves as the important intermediate in the reaction process.

On the basis of previous reports[10] and the experimental results above, a mechanism for the Cu-catalyzed aerobic oxidative coupling of acetophenones with indoles was proposed (Scheme 5). Initially, acetophenone **1a** is enolized to the intermediate **B** in the presence of a more active Cu^{II} salt, which is generated from the oxidation of CuCl by O_2.[10i] Meanwhile, pyridine may serve as a base to promote the release of HCl in this step. Next, a single electron transformation occurs to the intermediate **B** to generate the radical intermediates **C**/**C′**,[10j] which react with O_2 to form a four-membered intermediate **F** though the free radical reaction. Homolytic cleavage of intermediate **D** produces the key intermediate **4**, releasing the hydroxyl radical which could be simultaneously reduced to ^{-}OH in the presence of CuCl and AcOH. Then, the Friedel–Crafts type reaction between phenylglyoxal **4** and indole **2a** is occurred, affording the benzoin intermediate **5**. Finally, copper-catalyzed aerobic oxidation of intermediate **5** gives the desired dicarbonyl product **3aa**.

In conclusion, a novel Cu-catalyzed aerobic oxidative cross-coupling of acetophenones with indoles has been developed, and provides an efficient approach to synthesize a series of dicarbonyl compounds containing indole structural moieties. Moreover, readily available starting materials, the broad substrate scope, and the use of a green oxidant, make it very practical and environmental friendly. A reaction mechanism was proposed based on a series of control experiments. Further investigations on the



Scheme 4. Control experiments.

synthetic application of this strategy are underway in our laboratory.

Experimental Section

Acetophenones **1** (0.5 mmol), indoles **2** (1.5 mmol), CuCl (0.005 g, 10%), pyridine (0.02 g, 0.25 mmol) and AcOH (0.015 g, 0.25 mmol) were dissolved in 3 mL toluene and stirred at 110 °C for 16 h in a sealed tube equipped with an O_2 balloon. To determine the status of the reaction, it was monitored by TLC. After its completion, the reaction mixture was cooled to room temperature, then quenched with saturated NH_4Cl solution and extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. Removal of the organic solvent in vacuo followed by flash column chromatography on silica gel (hexane/ethyl acetate 60:1) afforded the desired products **3** in good yields (51–88%).

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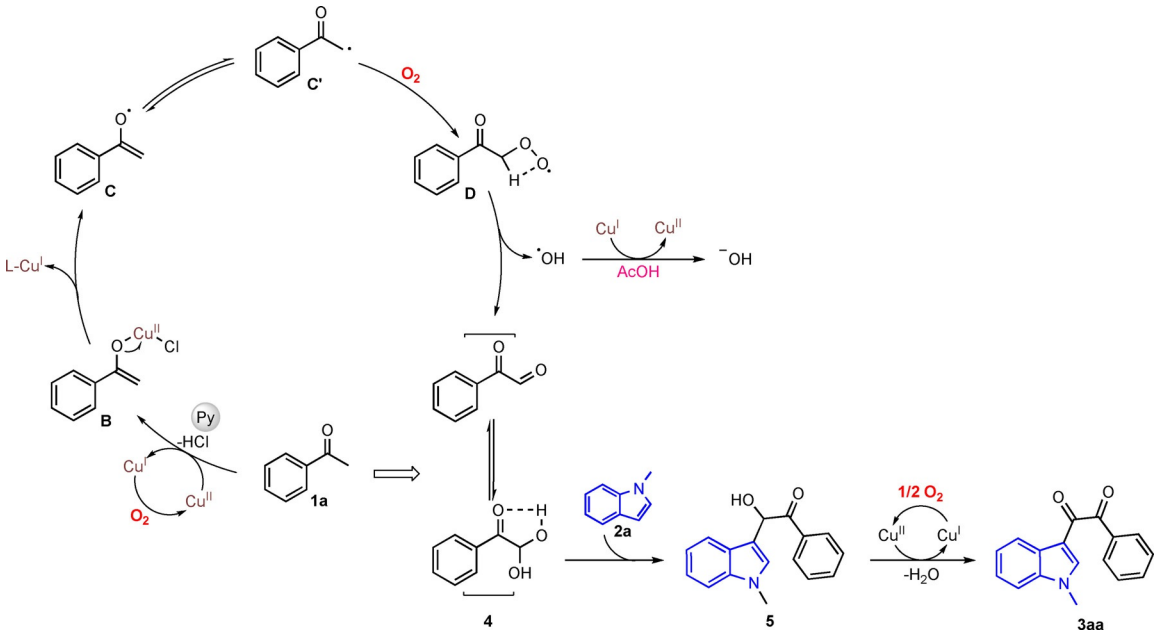
Conflict of interest

The authors declare no conflict of interest.

Keywords: acetophenones · aerobic oxidative coupling · copper · dicarbonyl indoles · synthetic methods

[1] a) A. D. Lebsack, J. T. Link, L. E. Overman, B. A. Stearns, *J. Am. Chem. Soc.* **2002**, *124*, 9008–9009; b) S. Cacchi, G. Fabrizi, *Chem. Rev.* **2005**, *105*, 2873–2920; c) M. Somei, F. Yamada, *Nat. Prod. Rep.* **2005**, *22*, 73–103; d) M. Movassaghi, M. A. Schmidt, *Angew. Chem. Int. Ed.* **2007**, *46*, 3725–3728; *Angew. Chem.* **2007**, *119*, 3799–3802.
[2] a) H. Takayama, S. Tsutsumi, M. Kitajima, D. Santiarworn, B. Liawruangrath, N. Aimi, *Chem. Pharm. Bull.* **2003**, *51*, 232–233; b) G. R. Humphrey, J. T. Kuethe, *Chem. Rev.* **2006**, *106*, 2875–2911; c) A. Brancale, R. Silvestri, *Med. Res. Rev.* **2007**, *27*, 209–238.
[3] a) I. V. Seregin, V. Gevorgyan, *Chem. Soc. Rev.* **2007**, *36*, 1173–1193; b) M. Bandini, A. Eichholzer, *Angew. Chem. Int. Ed.* **2009**, *48*, 9608–9644; *Angew. Chem.* **2009**, *121*, 9786–9824; c) C. J. Ball, M. C. Willis, *Eur. J. Org. Chem.* **2013**, 425–441.



Scheme 5. Proposed mechanism.

[4] a) T. Bark, T. Weyhermuller, F. Heirtzler, *Chem. Commun.* **1998**, 1475 – 1476; b) A. J. Collis, M. L. Foster, F. Halley, C. Maslen, I. M. McLay, K. M. Page, E. J. Redford, J. E. Souness, N. E. Wilsher, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 693 – 696; c) Z. X. Zhang, Z. Yang, H. Wong, J. L. Zhu, N. A. Meanwell, J. F. Kadow, T. Wang, *J. Org. Chem.* **2002**, *67*, 6226 – 6227; d) E. Merkul, J. Dohe, C. Gers, F. Rominger, T. J. J. Mueller, *Angew. Chem. Int. Ed.* **2011**, *50*, 2966 – 2969; *Angew. Chem.* **2011**, *123*, 3023 – 3026; e) Q. Xing, L. Shi, R. Lang, C. Xia, F. Li, *Chem. Commun.* **2012**, *48*, 11023 – 11025; f) M. Ishikura, T. Abe, T. Choshi, S. Hibino, *Nat. Prod. Rep.* **2015**, *32*, 1389 – 1471.

[5] a) J. C. Wu, R. J. Song, Z. Q. Wang, X. C. Huang, Y. X. Xie, J. H. Li, *Angew. Chem. Int. Ed.* **2012**, *51*, 3453 – 3457; *Angew. Chem.* **2012**, *124*, 3509 – 3513; b) R. Y. Tang, X. K. Guo, J. N. Xiang, J. H. Li, *J. Org. Chem.* **2013**, *78*, 11163 – 11171; c) C. F. Gers, J. Nordmann, C. Kumru, W. Frank, T. J. J. Mueller, *J. Org. Chem.* **2014**, *79*, 3296 – 3310; d) N. Mupparapu, N. Battini, S. Battula, S. Khan, R. A. Vishwakarma, Q. N. Ahmed, *Chem. Eur. J.* **2015**, *21*, 2954 – 2960; e) J. M. Yang, Z. J. Cai, Q. D. Wang, D. Fang, S. J. Ji, *Tetrahedron* **2015**, *71*, 7010 – 7015; f) Z. Zhang, Z. Dai, X. Jiang, *Asian J. Org. Chem.* **2015**, *4*, 1370 – 1374; g) C. Wu, F. Zhao, S. Shu, J. Wang, H. Liu, *RSC Adv.* **2015**, *5*, 90396 – 90399; h) J. Yan, G. He, F. Yan, J. Zhang, G. Zhang, *RSC Adv.* **2016**, *6*, 44029 – 44033.

[6] a) F. T. Du, J. X. Ji, *Chem. Sci.* **2012**, *3*, 460 – 465; b) W. Wei, Y. Shao, H. Hu, F. Zhang, C. Zhang, Y. Xu, X. Wan, *J. Org. Chem.* **2012**, *77*, 7157 – 7165; c) X. Xu, W. Ding, Y. Lin, Q. Song, *Org. Lett.* **2015**, *17*, 516 – 519.

[7] Q. Gao, J. Zhang, X. Wu, S. Liu, A. Wu, *Org. Lett.* **2015**, *17*, 134 – 137.

[8] a) S. S. Stahl, *Angew. Chem. Int. Ed.* **2004**, *43*, 3400 – 3420; *Angew. Chem.* **2004**, *116*, 3480 – 3501; b) T. Punniyamurthy, S. Velusamy, J. Iqbal, *Chem. Rev.* **2005**, *105*, 2329 – 2363; c) K. M. Gligorich, M. S. Sigman, *Chem. Commun.* **2009**, 3854 – 3867; d) J. Guilleme, D. Gonzalez-Rodriguez, T. Torres, *Angew. Chem. Int. Ed.* **2011**, *50*, 3506 – 3509; *Angew. Chem.* **2011**, *123*, 3568 – 3571.

[9] S. Taliani, M. L. Trincavelli, B. Cosimelli, S. Laneri, E. Severi, E. Barresi, I. Pugliesi, S. Daniele, C. Giacomelli, G. Greco, E. Novellino, C. Martini, F. Da Settimo, *Eur. J. Med. Chem.* **2013**, *69*, 331 – 337.

[10] a) C. Zhang, Z. Xu, L. Zhang, N. Jiao, *Angew. Chem. Int. Ed.* **2011**, *50*, 11088 – 11092; *Angew. Chem.* **2011**, *123*, 11284 – 11288; b) C. Zhang, X. Zong, L. Zhang, N. Jiao, *Org. Lett.* **2012**, *14*, 3280 – 3283; c) Z. Xie, J. Jia, X. Liu, L. Liu, *Adv. Synth. Catal.* **2016**, *358*, 919 – 925; d) Z. Xie, X. Liu, L. Liu, *Org. Lett.* **2016**, *18*, 2982 – 2985; e) W. B. Tolman, *Acc. Chem. Res.* **1997**, *30*, 227 – 237; f) S. Itoh, M. Taki, H. Nakao, P. L. Holland, W. B. Tolman, L. Que, S. Fukuzumi, *Angew. Chem. Int. Ed.* **2000**, *39*, 398 – 400; *Angew. Chem.* **2000**, *112*, 409 – 411; g) M. Taki, S. Teramae, S. Nagatomo, Y. Tachi, T. Kitagawa, S. Itoh, S. Fukuzumi, *J. Am. Chem. Soc.* **2002**, *124*, 6367 – 6377; h) C. X. Zhang, H. C. Liang, E. I. Kim, J. Shearer, M. E. Helton, E. Kim, S. Kaderli, C. D. Incarvito, A. D. Zuberbuhler, A. L. Rheingold, K. D. Karlin, *J. Am. Chem. Soc.* **2003**, *125*, 634 – 635; i) Z. Huang, L. Jin, Y. Feng, P. Peng, H. Yi, A. Lei, *Angew. Chem. Int. Ed.* **2013**, *52*, 7151 – 7155; *Angew. Chem.* **2013**, *125*, 7292 – 7296; j) M. P. DeMartino, K. Chen, P. S. Baran, *J. Am. Chem. Soc.* **2008**, *130*, 11546 – 11560; k) T. Chen, Y. F. Li, Y. An, F. M. Zhang, *Org. Lett.* **2016**, *18*, 4754 – 4757.

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