Organic LETTERS

Letter

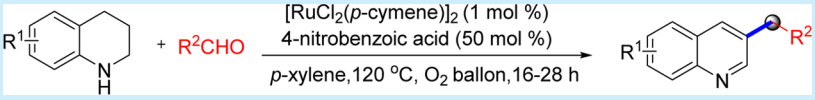
pubs.acs.org/OrgLett

Ruthenium-Catalyzed Dehydrogenative β-Benzylation of 1,2,3,4-Tetrahydroquinolines with Aryl Aldehydes: Access to Functionalized Quinolines

Zhenda Tan, Huanfeng Jiang, and Min Zhang*

School of Chemistry & Chemical Engineering, South China University of Technology, Wushan Road - 381, Guangzhou 510641, People's Republic of China

Supporting Information



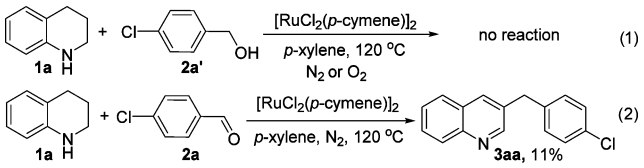
ABSTRACT: A new benzylation protocol, enabling straightforward access to β-benzylated quinolines, has been demonstrated. By employing readily available $[RuCl_2(p\text{-cymene})]_2$ as a catalyst and O_2 as a sole green oxidant, various 1,2,3,4-tetrahydroquinolines were efficiently converted in combination with aryl aldehydes into desired products in a step- and atom-economic fashion together with the advantages of excellent functional group tolerance and chemoselectivity, offering an important basis for the transformation of saturated *N*-heterocycles into functionalized *N*-heteroaromatics via a dehydrogenative cross-coupling strategy. Mechanistic investigations support that the reaction undergoes a monodehydrogenation-triggered β-benzylation mode.

Due to the extensive applications of alkylated *N*-heteroaromatics in many fields including medicinal and material science, the development of efficient alkylation methods to access such compounds has emerged as one of the most attractive topics in organic chemistry. Pioneered by the Friedel−Crafts reaction,[1] much attention has been focused on discovering alternative protocols to realize the related end in recent years. Representative examples mainly involve the cross-coupling reactions with alkyl halides via directing group-assisted C−H bond activation,[2] hydroheteroarylation of alkenes,[3] ring-opening alkylation,[4] radical alkylation[5] including Minisci-type reactions,[6] carbene insertion,[7] and Catellani-Lauten-type coupling reactions.[8] Despite these important advances, many of the existed methods require the use of prefunctionalized or less environmentally benign halogenated reagents, which could easily result in preparation difficulties and a detrimental influence on environment. Hence, the search for green alkylation shortcuts still remains a challenge.

In recent years, the direct dehydrogenation of saturated *N*-heterocycles to *N*-heteroaromatics has been elegantly achieved by employing improved catalyst systems.[9,10] However, the strategy that combines dehydrogenation of saturated *N*-heterocycles and coupling processes in one operation, leading to functionalized *N*-heteroaromatics, has been scarcely explored. To realize such a goal, at least two challenging issues have to be addressed: (i) The *in situ* formed metal hydride species should not reduce the coupling reagents. (ii) There should be a compatible catalyst system to ensure that the coupling process is much faster than the second dehydroaromatization step, thus suppressing the formation of non-coupling *N*-heteroaromatics.

The above-described idea and our continuous efforts in the transformation of alcohols[11] and CO_2[12] into value-added products prompted us to test the reaction of 1,2,3,4-tetrahydroquinoline **1a** with 4-chlorobenzylic alcohol **2a′** using $[RuCl_2(p\text{-cymene})]_2$ as a catalyst. However, it failed to yield any product (Scheme 1, eq 1) under a N_2 or an O_2

Scheme 1. New Observation on Dehydrogenative β-Benzylation Reaction



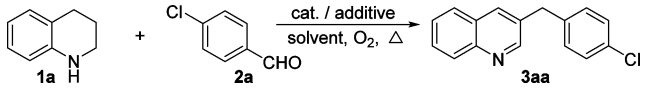
atmosphere, whereas replacing alcohol **2a′** with 4-chlorobenzaldehyde **2a** under N_2 protection produced a β-benzylated quinoline **3a** in 11% yield (Scheme 1, eq 2). Upon thorough investigation of this new observation, we wish herein to report a ruthenium-catalyzed dehydrogenative β-benzylation of 1,2,3,4-tetrahydroquinolines with aryl aldehydes, leading to β-functionalized quinolines in a step- and atom-economic fashion.

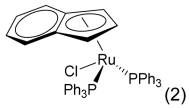
Initially, we tried to formulate an effective reaction system. The coupling of **1a** and **2a** was chosen as a model reaction to evaluate different parameters. First, the reaction was performed in *p*-xylene at 120 °C for 16 h under an O_2 atmosphere. Gratifyingly, the product (**3aa**) yield increased to 36% (Table 1, entry 1), and the addition of benzoic acid significantly

Received: May 12, 2016

DOI: 10.1021/acs.orglett.6b01390
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Optimization of Reaction Conditions[a]



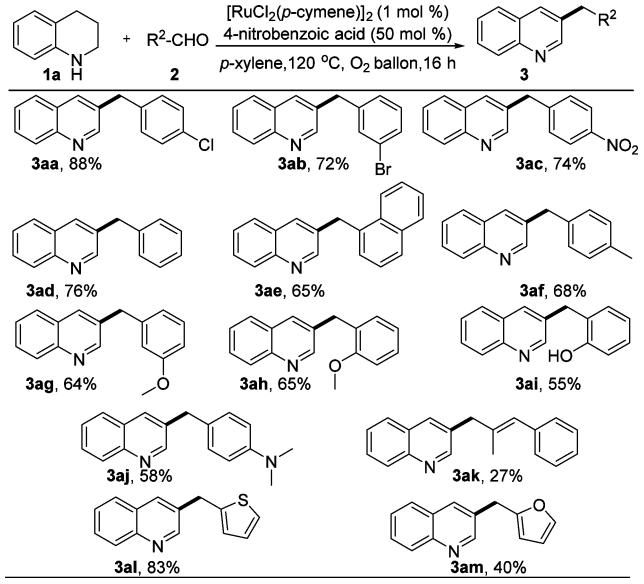
entry	catalyst (mol %)	additive	yields of **3aa**[d]
1	$[RuCl_2(p\text{-cymene})]_2$ (1)	-	36
2	$[RuCl_2(p\text{-cymene})]_2$ (1)	benzoic acid	75
3	-	benzoic acid	-
4	$[RuCl_2(p\text{-cymene})]_2$ (1)	4-nitrobenzoic acid	90
5	$[RuCl_2(p\text{-cymene})]_2$ (1)	CH_3COOH	19
6	$[RuCl_2(p\text{-cymene})]_2$ (1)	CF_3COOH	24
7	$[RuCl_2(p\text{-cymene})]_2$ (1)	NH_2SO_3H	10
8	$[RuCl_2(p\text{-cymene})]_2$ (1)	$FeCl_3$ or K_2CO_3	-
9	$[RuCl_2(p\text{-cymene})]_2$ (1)	4-nitrobenzoic acid	(33, 30, 46)[b]
10	$[RuCl_2(COD)]_n$ (2)	4-nitrobenzoic acid	63
11	$Ru_3(CO)_{12}$ (0.67)	4-nitrobenzoic acid	30
12	$[Cp^*RuCl_2]_n$ (2)	4-nitrobenzoic acid	23
13	$RuCl(PPh_3)_3$ (2)	4-nitrobenzoic acid	58
14	 (2)	4-nitrobenzoic acid	86
15	$[RuCl_2(p\text{-cymene})]_2$ (1)	4-nitrobenzoic acid	(75, 88)[c]

[a]Unless otherwise stated, the reaction was performed with **1a** (1.5 mmol), **2a** (0.5 mmol), cat. (1 mol %), additive (50 mol %), in *p*-xylene (1.5 mL) at 120 °C for 16 h using O_2 balloon. [b]Yields are with respect to DMF, DMSO, and chlorobenzene used as the solvents, respectively. [c]Yields are with respect to at 110 and 130 °C, respectively. [d]GC yields (%).

improved the reaction efficiency to afford a 75% yield (entry 2). However, the absence of a ruthenium complex failed to give any product (entry 3), indicating that the ruthenium catalyst is essential in affording the product. Next, we tested several other organic acids (entries 4−7); 4-nitrobenzoic acid was proven to be the best choice (90% yield). Lewis acid $FeCl_3$ and base K_2CO_3 were totally ineffective for the transformation (entry 8). Several polar and less-polar solvents were less effective than *p*-xylene (entry 9). Further, another five ruthenium catalyst precursors were examined, but the results indicated that they were inferior to $[RuCl_2(p\text{-cymene})]_2$ (entries 10−14). Finally, a decrease or an increase of reaction temperature led to a diminished product yield (entry 15). Thus, the optimized reaction conditions are as described in entry 4 of Table 1.

With the optimal reaction conditions in hand, we then examined the generality and the limitation of the synthetic protocol. First, **1a** in combination with various benzaldehydes **2** were tested. As shown in Scheme 2, all the reactions proceeded smoothly and furnished the desired products in good to excellent yields upon isolation (see **3aa**−**3aj**). The results indicated that the electronic property of substituents on the aryl ring of benzaldehydes slightly affected the product yields. Generally, electron-deficient substituents afforded the products (**3aa**−**3ac**) in relatively higher yields than those of electron-rich

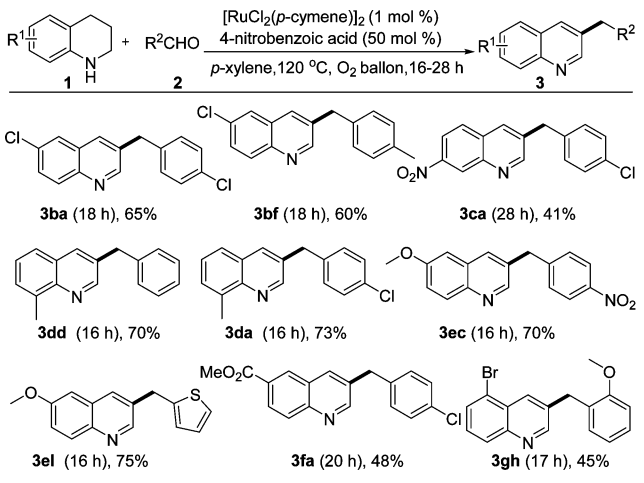
Scheme 2. Variation of Aldehydes



ones (**3af**−**3aj**), presumably because benzaldehydes possessing an electron-withdrawing group could enhance the electrophilicity of the carbonyl group, thus favoring the coupling process. Gratifyingly, (*E*)-2-methyl-3-phenylacrylaldehyde could undergo a smooth dehydrogenative cross-coupling reaction to give product **3ak** bearing an allylic group, albeit the yield was somewhat low. Heteroaryl aldehydes (**2l**, **2m**) were also proven to be effective coupling partners, affording the corresponding products **3al** and **3am** in 83% and 40% yields, respectively.

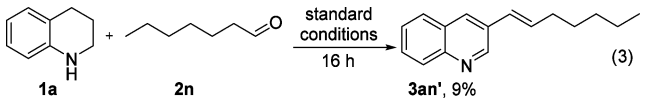
Next, we turned our attention to the variation of 1,2,3,4-tetrahydroquinolines **1**. Thus, various combinations of **1** with aldehydes **2** were tested. Similar to the results described in Scheme 2, all the reactions afforded the desired products in moderate to excellent isolated yields (Scheme 3). In comparison with aryl aldehydes, the electronic property of substituents of **1** significantly affected the product formation. Specifically, an electron-donating group containing 1,2,3,4-tetrahydroquinolines **1** afforded the products in much higher yields (see **3dd**, **3da**, **3ec**, and **3el**) than those of electron-deficient ones (see **3ca** and **3fa**), which is ascribed to electron-

Scheme 3. Variation of 1,2,3,4-Tetrahydroquinolines



DOI: 10.1021/acs.orglett.6b01390
Org. Lett. XXXX, XXX, XXX−XXX

rich 1,2,3,4-tetrahydroquinolines enabling enhancement of the nucleophilicity of the *in situ* formed intermediates, which is in favor of the cross-coupling process with aldehydes. Finally, we tested the dehydrogenative cross-coupling reaction of 1,2,3,4-tetrahydroquinoline **1a** with heptanal **2n**. Interestingly, a *β*-alkenylated product **3an′** was obtained in 9% yield (eq 3).



It is worth mentioning that various function groups (i.e., −OH, −Cl, −Br, $-NO_2$, and ester group) are well tolerated in the synthetic protocol (Schemes 1 and 2), which offers the potential for elaboration of complex molecules via further chemical transformations. Moreover, the N-alkylation, which is generally believed to be a favorable reaction, was not observed in all tested reactions. More importantly, all the dehydrogenative cross-coupling products did not undergo further benzylic oxidation to form the ketones, whereas such a oxidation occurred efficiently in Bert's catalyst system.[14] The excellent chemoselectivity demonstrated in our synthetic protocol affords the potential for further preparation of functional products.

To gain insight into the reaction mechanism, a time−concentration profile of the dehydrogenative *β*-benzylation of 1,2,3,4-tetrahydroquinoline **1a** with aldehyde **2a** under the optimized conditions was performed. As shown in Figure 1, **1a**

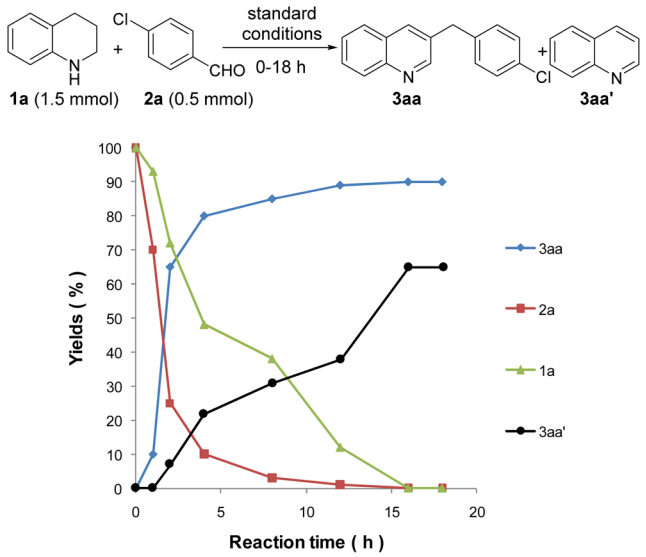
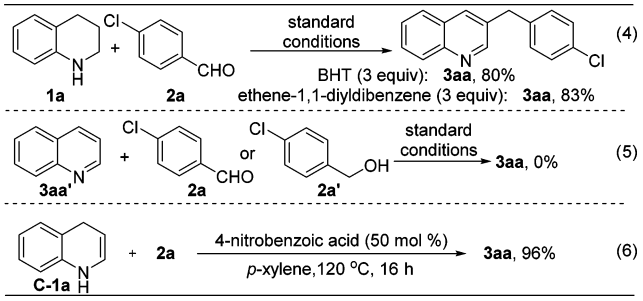


Figure 1. Representative time course of the model reaction.

with aldehyde **2a** was converted into **3aa** in a maximum yield (90%) within 16 h. The growth rate of **3aa** and the descending speed of **2a** were very fast within the first 8 h and then became slow. Because **1a** was excessive, the reaction inevitably gave quinoline **3aa′**, and it reached the highest concentration (65% in terms of the original **1a**) within 16 h. **3aa′** was not observed in the first 1 h, whereas **3aa** was detected in 10% yield, which indicates, after the first dehydrogeantion of **1a**, the subsequent coupling step with aldehyde **2a** is much faster than the second dehydrogenation to form quinoline **3aa′**.

To gain more product-forming information, several verification experiments were performed. First, addition of excess radical scanvengers such as 2,6-di-*tert*-butyl-4-methylphenol (BHT) and ethene-1,1-diyldibenzene to the model reaction had little influence on product yields (Scheme 4, eq 4), showing

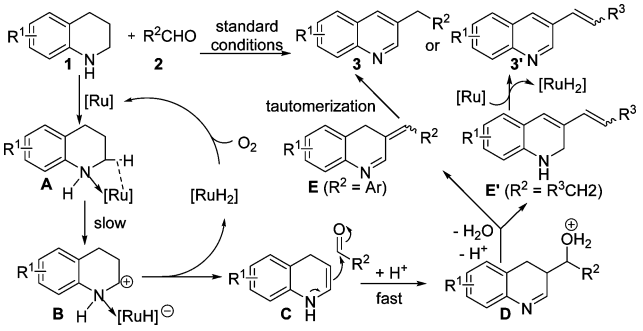
Scheme 4. Verification Experiments



that the reaction undergoing a radical pathway is less likely. Then, the reaction of **3aa′** with aldehyde **2a** or alcohol **2a′** was not able to afford **3aa** (eq 5), indicating that quinoline **3aa′** serving as a reaction intermediate can be ruled out. Finally, enamine **C-1a** could efficiently couple with aldehyde **2a** to yield product **3aa** in almost quantative yield in the presence of of 4-nitrobenzoic acid, showing **2a** is a key reaction intermediate (eq 6), and the cross−coupling step occurs prior to the second dehydrogenation of **1a** to **3aa′**.

Based on the above-observed findings, a monodehydrogenation-triggered benzylation mode was proposed in Scheme 5.

Scheme 5. Possible Reaction Pathway



The reaction initiates with the activation of 1,2,3,4-tetrahydroquinoline **1** via N atom coordination to ruthenium, which results in an *ortho*-C−H bond activation.[15] Then, a slow *α*-hydride disassociation (**B**) followed by a deprotonation process gives a cyclic enamine **C** and [RuH_2], and the catalytic species is regenerated in the presence of O_2. Further, a fast trap of **C** by aryl aldehyde, via successive nucleophilic addition and dehydration steps assisted by 4-nitrobenzoic acid, generates an alkenyl imine **E**. Finally, the tautomerization of **E** yields the *β*-benzylated product **3**. Differentially, the dehydration of **D** occurs on the outside alkyl chain while employing an alkyl aldehyde, and a diene **E′** is afforded via a tautomerization step, which would result in the *β*-alkenylated product **3′** via further dehydroaromatization.

In summary, by employing readily available [$RuCl_2$(*p*-cymene)]$_2$ as the catalyst and molecular O_2 as the sole green oxidant, we have demonstrated a new benzylation approach, enabling straightforward access to various *β*-benzylated quinolines. A variety of 1,2,3,4-tetrahydroquinolines were efficiently converted in combination with aryl aldehydes into desired products in a step- and atom-economic fashion together with

DOI: 10.1021/acs.orglett.6b01390
Org. Lett. XXXX, XXX, XXX−XXX

the advantages of excellent functional group tolerance and chemoselectivity, offering an important basis for the transformation of saturated *N*-heterocycles into functionalized *N*-heteroaromatics. Mechanistic studies support the reaction proceeding in a monodehydrogenation-triggered benzylation mode. Further investigations applying the dehydrogenative cross-coupling strategy in creation of other functionalized heterocycles are ongoing 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.6b01390.

Experimental procedures and spectral data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*minzhang@scut.edu.cn

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the "1000 Youth Talents Plan", Science Foundation for Distinguished Young Scholars of Guangdong Province (2014A030306018), the National Natural Science Foundation of China (21472052), and the Fundamental Research Funds for the Central Universities (2015PT018) for financial support.

■ REFERENCES

(1) Selected examples, see: (a) Hu, Y. B.; Li, Y.; Zhang, N. S.; Li, C.; Li, L. J.; Zha, Z.-G.; Wang, Z.-Y. *Org. Lett.* **2015**, *17*, 4018−4021. (b) Iovel, I.; Mertins, K.; Kischel, J.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3913−3917.

(2) Selected examples: (a) Wang, H.; Yu, S. J.; Li, X. W. *Org. Lett.* **2015**, *17*, 2812−2815. (b) Fruchey, E. R.; Monks, B. M.; Cook, S. P. *J. Am. Chem. Soc.* **2014**, *136*, 13130−13133. (c) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879−5918.

(3) Selected examples: (a) Wu, K. K.; Wu, P.; Chen, J. P.; Sun, C. L.; Yu, Z. K. *Adv. Synth. Catal.* **2015**, *357*, 3353−3358. (b) Jin, H. M.; Zhu, Z.-B.; Jin, N.; Xie, J.; Cheng, Y.-X.; Zhu, C. J. *Org. Chem. Front.* **2015**, *2*, 378−382. (c) Deng, H.; Li, H. J.; Wang, L. *Org. Lett.* **2015**, *17*, 2450−2453. (d) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624−655.

(4) Selected examples: (a) Cheng, G. L.; Li, T. J.; Yu, J. Q. *J. Am. Chem. Soc.* **2015**, *137*, 10950−10953. (b) Gao, K.; Paira, R.; Yoshikai, N. *Adv. Synth. Catal.* **2014**, *356*, 1486−1490.

(5) Selected examples: (a) Wu, X. J.; See, J. W. T.; Hirao, K.; Xu, H.; Roger, J.; Hierso, J. C.; Zhou, J. R. *Angew. Chem., Int. Ed.* **2014**, *53*, 13573−13577. (b) Kandukuri, S. R.; Bahamonde, A.; Chatterjee, I.; Jurberg, I. D.; Escudero-Adan, E. C.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2015**, *54*, 1485−1489. (c) Arora, A.; Teegardin, K. A.; Weaver, J. D. *Org. Lett.* **2015**, *17*, 3722−3725.

(6) Selected examples: (a) Bowman, W. R.; Storey, J. M. D. *Chem. Soc. Rev.* **2007**, *36*, 1803−1822. (b) O'Hara, F.; Blackmond, D. G.; Baran, P. S. *J. Am. Chem. Soc.* **2013**, *135*, 12122−12134. (c) Fujiwara, Y.; Dixon, J. A.; O'Hara, F.; Funder, E. D.; Dixon, D. D.; Rodriguez, R. A.; Baxter, R. D.; Herle, B.; Sach, N.; Collins, M. R.; Ishihara, Y.; Baran, P. S. *Nature* **2012**, *492*, 95.

(7) Selected examples: (a) Cui, X.; Xu, X.; Jin, L. M.; Wojtas, L.; Zhang, X. P. *Chem. Sci.* **2015**, *6*, 1219−1224. (b) Mishra, N. K.; Choi, M.; Jo, H.; Oh, Y.; Sharma, S.; Han, S. H.; Jeong, T.; Han, S.; Lee, S. Y.; Kim, I. S. *Chem. Commun.* **2015**, *51*, 17229−17232.

(8) Selected examples: (a) Shen, P. X.; Wang, X. C.; Wang, P.; Zhu, R. Y.; Yu, J. Q. *J. Am. Chem. Soc.* **2015**, *137*, 11574−11577. (b) Lei, C. H.; Jin, X. J.; Zhou, J. S. *Angew. Chem., Int. Ed.* **2015**, *54*, 13397−13400.

(9) Selected examples on homogeneous catalysis: (a) Chowdhury, A. D.; Weding, N.; Julis, J.; Franke, R.; Jackstell, R.; Beller, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 6477−6481. (b) Xu, R. B.; Chakraborty, S.; Yuan, H. M.; Jones, W. D. *ACS Catal.* **2015**, *5*, 6350−6354. (c) Chakraborty, S.; Brennessel, W. W.; Jones, W. D. *J. Am. Chem. Soc.* **2014**, *136*, 8564−8567.

(10) Selected example on heterogeneous catalysis: Cui, X. J.; Li, Y. H.; Bachmann, S.; Scalone, M.; Surkus, A.-E.; Junge, K.; Topf, C.; Beller, M. *J. Am. Chem. Soc.* **2015**, *137*, 10652−10658.

(11) (a) Xiong, B.; Zhang, S. D.; Jiang, H. F.; Zhang, M. *Org. Lett.* **2016**, *18*, 724−727. (b) Xiong, B.; Li, Y.; Lv, W.; Tan, Z. D.; Jiang, H. F.; Zhang, M. *Org. Lett.* **2015**, *17*, 4054−4057. (c) Xie, F.; Zhang, M.; Jiang, H. F.; Chen, M. M.; Lv, W.; Zheng, A. B.; Jian, X. J. *Green Chem.* **2015**, *17*, 279−284. (d) Xie, F.; Zhang, M.; Chen, M. M.; Lv, W.; Jiang, H. F. *ChemCatChem* **2015**, *7*, 349−353. (e) Chen, M. M.; Zhang, M.; Xiong, B.; Tan, Z. D.; Lv, W.; Jiang, H. F. *Org. Lett.* **2014**, *16*, 6028−6031. (f) Chen, M. M.; Zhang, M.; Xie, F.; Wang, X. T.; Jiang, H. F. *ChemCatChem* **2014**, *6*, 2993−2997. (g) Xie, F.; Chen, M. M.; Wang, X. T.; Jiang, H. F.; Zhang, M. *Org. Biomol. Chem.* **2014**, *12*, 2761−2768.

(12) (a) Xiong, W. F.; Qi, C. R.; He, H. T.; Ouyang, L.; Zhang, M.; Jiang, H. F. *Angew. Chem., Int. Ed.* **2015**, *54*, 3084−3087. (b) Xiong, W. F.; Qi, C. R.; Peng, Y. B.; Guo, T. Z.; Zhang, M.; Jiang, H. F. *Chem. - Eur. J.* **2015**, *21*, 14314−14318.

(13) (a) Girard, S. A.; Knauber, T.; Li, C.-J. *Angew. Chem., Int. Ed.* **2014**, *53*, 74−100. (b) Simon, M.-O.; Girard, S. A.; Li, C.-J. *Angew. Chem., Int. Ed.* **2012**, *51*, 7537−7540. (c) Wang, P.; Rao, H.-H.; Hua, R.-M.; Li, C.-J *Org. Lett.* **2012**, *14*, 902−905. (d) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335−344. (e) Li, Z.-P.; Cao, L.; Li, C.-J *Angew. Chem., Int. Ed.* **2007**, *46*, 6505−6507.

(14) (a) De Houwer, J. De; Tehrani, K. A.; Maes, B. U. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 2745−2748. (b) Sterckx, H.; De Houwer, J.; Mensch, C.; Herrebout, W.; Tehrani, K. A.; Maes, B. U. W.; Beilstein. *Beilstein J. Org. Chem.* **2016**, *12*, 144−153.

(15) (a) Sahli, Z.; Sundararaju, B.; Achard, M.; Bruneau, C. *Green Chem.* **2013**, *15*, 775−779. (b) Yuan, K.; Jiang, F.; Sahli, Z.; Roisnel, T.; Bruneau, C. *Angew. Chem., Int. Ed.* **2012**, *51*, 8876−8880. (c) Boudiar, T.; Sahli, Z.; Sundararaju, B.; Achard, M.; Kabouche, Z.; Doucet, H.; Bruneau, C. *J. Org. Chem.* **2012**, *77*, 3674−3678. (d) Sundararaju, B.; Achard, M.; Sharma, G. V. M; Bruneau, C. *J. Am. Chem. Soc.* **2011**, *133*, 10340−10343. (e) Sundararaju, B.; Tang, Z.; Achard, M.; Sharma, G. V. M; Toupet, L.; Bruneau, C. *Adv. Synth. Catal.* **2010**, *352*, 3141−3146. (f) Jiang, F.; Achard, M.; Bruneau, C. *Chem. - Eur. J.* **2015**, *21*, 14319−14323.

DOI: 10.1021/acs.orglett.6b01390
Org. Lett. XXXX, XXX, XXX−XXX