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Palladium-Catalyzed Carbonylation of Benzylic Ammonium Salts to Amides and Esters via C-N Bond Activation

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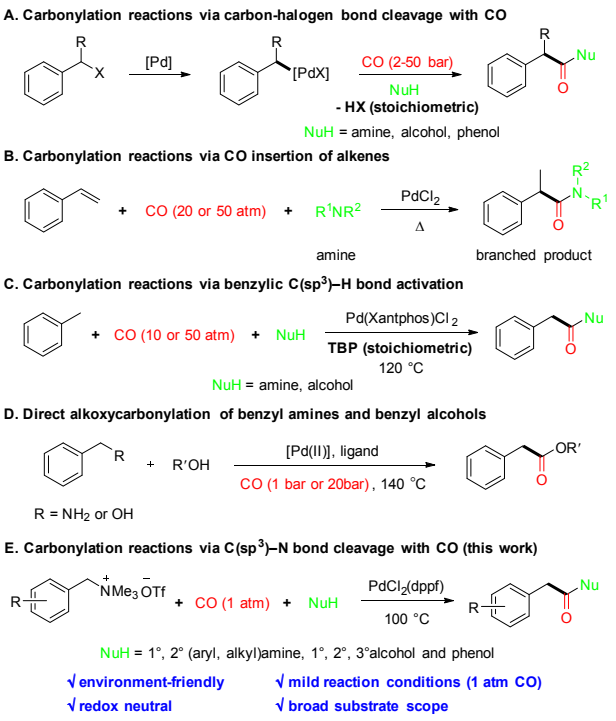
Weijie Yu[a], Shuwu Yang[a], Fei Xiong[a], Tianxiang Fan[a], Yan Feng[a], Yuanyuan Huang[a], Junkai Fu*[b], Tao Wang*[a]

An efficient palladium-catalyzed carbonylation reaction of readily available quaternary ammonium salts with CO is reported for the first time to afford arylacetamides and arylacetic acid esters via benzylic C-N bonds cleavage. This protocol is featured with mild reaction conditions under atmosphere pressure of CO, redox-neutral process without additional oxidant, and broad substrate scope for various kinds amines, alcohols and phenols.

Introduction

Since the seminal work by Heck and co-workers in 1974, the palladium-catalyzed carbonylation with CO as inexpensive and readily available C1 building block has attracted extensive attention in both scientific research and chemical industries.[1] A variety of carbonyl-containing products such as esters, amides, ketones, and aldehydes could be produced through carbonylation reactions in the presence of suitable nucleophiles.[2] In this case, arylacetamides and arylacetic acid esters, which are frequently encountered scaffold in nature products and pharmaceutical agents,[3] can be assembled through palladium-catalyzed carbonylation with inherent advantages over traditional amidation[4] and esterification[5] of benzyl carboxylic acids suffering from harsh reaction conditions or multistep operations. The most common method is to use benzylic halides as the palladium precursors (Scheme 1. A), which would result in the formation of stoichiometric amount of halides as the waste.[6] Another strategy is palladium-catalyzed aminocarbonylation of styrene involving alkene insertion into Pd–H species and subsequent migratory insertion of CO into the forming metal–alkyl bond (Scheme 1. B).[7] However, both linear and branched products can be obtained in most cases. Recently, the palladium-catalyzed oxidative carbonylation of benzylic C(sp3)−H bonds with stoichiometric amount of oxidants provides an atom-economic approach to arylacetamides and arylacetic acid esters (Scheme 1. C).[8] Additionally, most of the above methods require high pressures of CO gas, which are hazardous for large-scale preparation. In this context, searching for pratical and redox neutral method to promote carbonylation under mild reaction conditions is highly desirable.



[a] National Research Center for Carbohydrate Synthesis and Key Laboratory of Chemical Biology, Jiangxi Normal University, Nanchang 330022, Jiangxi, P. R. China. E-mail: wangtao@jxnu.edu.cn;
[a] Jilin Province Key Laboratory of Organic Functional Molecular Design & Synthesis, Department of Chemistry, Northeast Normal University, Changchun 130024, China.. E-mail: fujk109@nenu.edu.cn;
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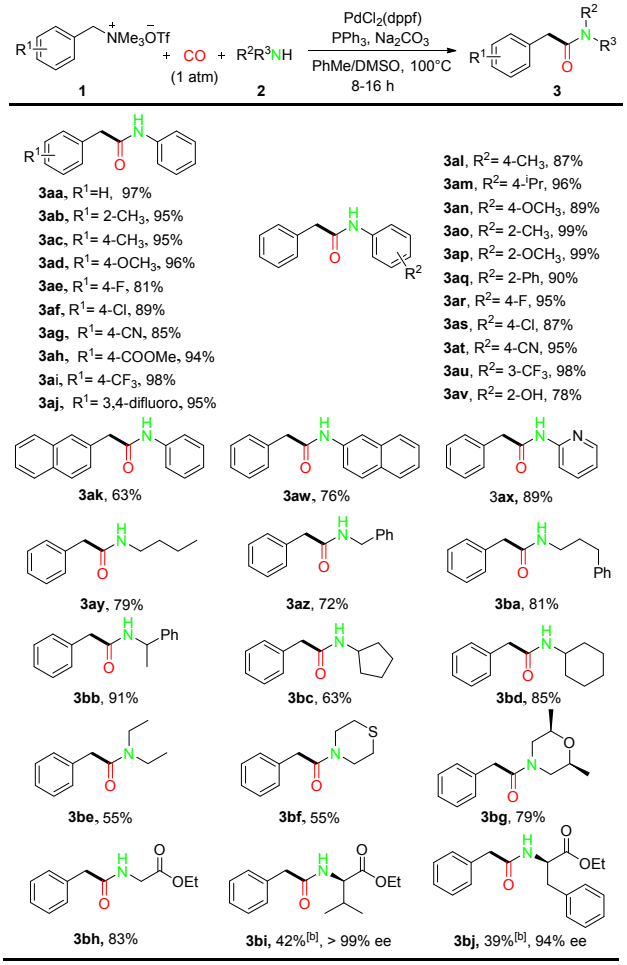
Scheme 1. Synthesis of arylacetamides and arylacetic acid esters via palladium-catalyzed carbonylation reactions

Quaternary ammonium salts have recently attracted much attention as C–N bond containing electrophiles with some remarkable features, such as nontoxic, thermally stable and easy to handle. Benefited from strong C–N bond polarity and release of electronically neutral amine companions, the ammonium salts show much higher C–N reactivity compared to the corresponding amine precursors. Since the pioneering work of Wenkert,[9] transition metal-catalyzed borylation,[10] Suzuki,[11] Negishi,[12] Kumada,[13] Stille[14] and some others cross coupling reactions[15] have been successfully developed based on quaternary ammonium salts. Watson[16] reported a nickel-catalyzed cross coupling of benzylic quaternary ammonium salts and boronic acids. Martin group[17] disclosed a user-friendly nickel-catalyzed reductive carboxylation of benzylic C-N bonds with CO_2. Very recently, the combination of quaternary ammonium salts and carbonylation reaction has got remarkable progress. Li utilized an in situ prepared $NaCo(CO)_4$ to promot carbonylation of quaternary ammonium salts to tertiary amides at 200 °C.[18] Huang reported a Ni-catalyzed carbonylation through an amine-I_2 charge-transfer complex.[19] During our preparation of this manuscript, Wu and co-workers[20] disclosed an elegant palladium-catalyzed direct alkoxycarbonylation of benzyl amines and benzyl alcohols (Scheme 1. D). In continuing with our interest in oxidative carbonylation of aryl hydrazines through C-N bond activation,[21] herein, we reported an efficient palladium-catalyzed carbonylation with CO to arylacetamides and arylacetic acid esters by utilizing benzylic ammonium salts as acylpalladium precursors under very mild conditions (Scheme 1. E).

We started our studies by using benzyl quaternary ammonium salt **1a** and aniline **2a** as the model substrates. After screening of the reaction conditions (see SI), the optimized conditions for the reaction were $PdCl_2$(dppf) (3 mol%) and PPh_3 (30 mol%) in a mixture solvent ($V_{toluene}$: V_{DMSO} = 5 : 1) under 1 atm CO at 100 °C in the presence of Na_2CO_3 (2 equivalent) as the base for 12 h, affording the desired product **3aa** in 97% yield. As can be seen in Table 1, the scope of the arylacetamides was firstly investigated. Various ammonium salts including benzylic ammonium salts with sterically hindered *ortho*-methyl group (**3ab**), electron-donating (**3ac**, **3ad**) or electron-withdrawing groups (**3ae-aj**) on the phenyl ring and 2-naphthyl ammonium salt (**3ak**) could afford the desired products in excellent yields. A variety of substituted anilines were then tested to react with benzylic ammonium salt to smoothly give corresponding amides **3al-au**, and the halogen atoms, such as F and Cl, did not affect the carbonylation reactions. When 2-aminophenol was employed as the nucleophile, **3av** was obtained in 78% yield without the detection of alkoxycarbonylation by-product. Other types of aryl amines, for instance, naphthalen-2-amine and pyridin-2-amine were successfully transformed into corresponding products **3aw** and **3ax** in good yields. Furthermore, alkylamines are suitable partners for this carbonylation reaction. Primary alkylamines could well undergo the reaction to afford amides **3ay-bd** in good yields, while secondary alkylamines just resulted in the formation of products **3be-bg** in moderate yields. Notably, α-amino-esters, which can be easily obtained from corresponding enantio-enriched natural amino acids, have proven to be compatible with the reaction conditions. Commercially available α-amino-esters derived from glycine, valine or phenylalanine could all be converted into the amide products **3bh-bj** in moderate yields with excellent *ee* value.

Table 1. Substrate Scope of Aminocarbonylation.[a]



[a]Reaction conditions: **1** (0.40 mmol), **2** (0.20 mmol), $PdCl_2$(dppf) (3 mol%), PPh_3 (30 mol%), Na_2CO_3 (0.40 mmol) in mixture solvent ($V_{toluene}$: V_{DMSO} = 5 : 1) under 1 atm CO at 100 °C for corresponding times. [b]30 mol% dppf was used to replace PPh_3.

The above encouraging results prompted us to extend the reaction to alkoxycarbonylation (Table 2).

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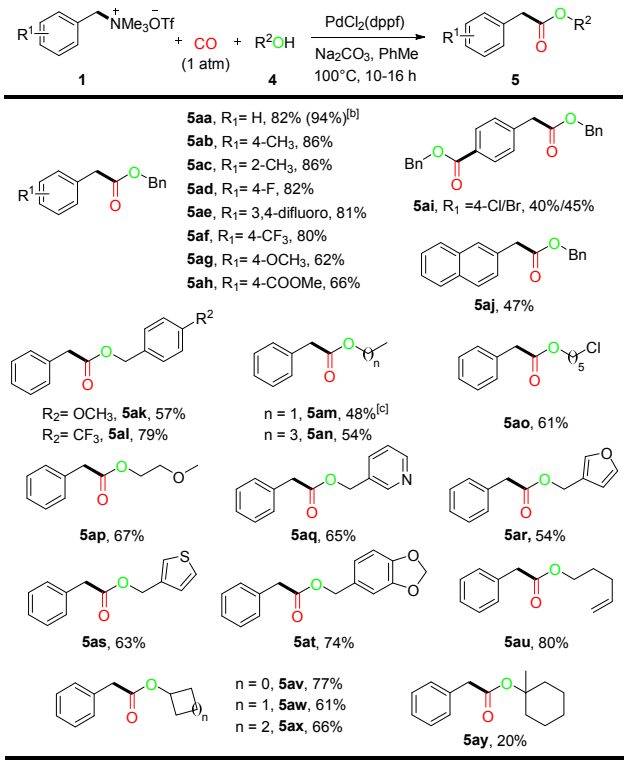
Substituents on the phenyl ring of benzylic quaternary ammonium salts were initially evaluated. The electronic effects of the substituents made little difference for the outcomes, and ester products 5aa-ah were obtained in good yields when using benzyl alcohol as the partner under modified reaction conditions (for details, see SI). It is worth noting that 4-chloro/bromo benzylic quaternary ammonium salts would undergo double alkoxycarbonylation reactions to afford 5ai in 40%/45% yields through simultaneous C-X (Cl, Br) bond cleavage and C-N bond activation. For ammonium salt containing naphthyl moiety, the alkoxycarbonylation reaction offered the corresponding ester **5aj** in 47% yield. Then different kinds of alcohols were tested. Benzylic alcohol with electron-withdrawing group at *para*-position of the phenyl ring (**5al**) gave a better yield of 79% compared to that with electron-donating group (**5ak**, 57%). Linear

Table 2. Substrate Scope of Alkoxycarbonylation with Alcohols.[a]

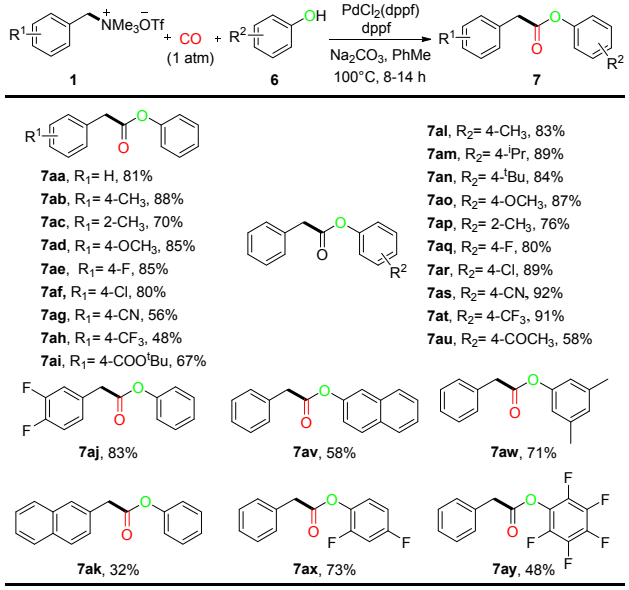


[a]Reaction conditions: **1** (0.20 mmol), **4** (1.0 mmol), $PdCl_2(dppf)$ (10 mol%), Na_2CO_3 (0.20 mmol) in PhMe (2.0 mL) under 1 atm CO at 100 °C for corresponding times. [b]Benzyl alcohol as solvent. [c]20 mol% dppf was used.

alcohols, such as ethanol and butanol, suffered from the reaction conditions to provide **5am** and **5an** in 48% and 54% yields, respectively. Other primary alcohols with diverse functionalities including chlorine atom (**5ao**), oxygen atom (**5ap**), pyridine moiety (**5aq**), furan moiety (**5ar**), thiophene (**5as**), functionalized phenyl ring (**5at**) and terminal alkene (**5au**) were all well-tolerated for the reaction. Later, the secondary alcohols were investigated. All of the four-membered, five-membered and six-membered secondary alcohols were suitable nucleophiles to give **5av-av** in moderate to good yields. However, cycloheptanol failed to give any desired products. The tertiary alcohol, for example, 1-methylcyclohexanol could also proceed smoothly to afford the ester **5ay**, albeit in a low yield of 20%.

Finally, the phenols were successfully employed in the alkoxycarbonylation reaction under slightly modified reaction conditions. As shown in Table 3, benzyl ammonium salts bearing electron-neutral (**7aa-ac**), electron-donating (**7ad**) or weak electron-withdrawing groups (**7ae**, **7af**, **7aj**) on the phenyl ring all generated the desired esters in good yields, while strong electron-withdrawing groups (**7ag-ai**) would slightly decrease the yields. The naphthalene-containing quaternary ammonium salt provided the product **7ak** in just 32% yield. Subsequently, a variety of phenols bearing different substituents with diverse electronic effects were tested, and gave the corresponding ester products **7al-at** in excellent yields except that the 4-acetylphenol resulted in a moderate yield (**7au**). Moreover, naphthalen-2-ol, disubstituted phenols and multifluoro-substituted phenols could all be transformed into the corresponding products **7av-ay** in acceptable yields.

Table 3. Substrate Scope of Alkoxycarbonylation with Phenols.[a]



[a]Reaction conditions: **1** (0.20 mmol), **6** (0.60 mmol), $PdCl_2(dppf)$ (10 mol%), dppp (20 mol%), Na_2CO_3 (0.20 mmol) in PhMe (2.0 mL) under 1 atm CO at 100 °C for corresponding times.

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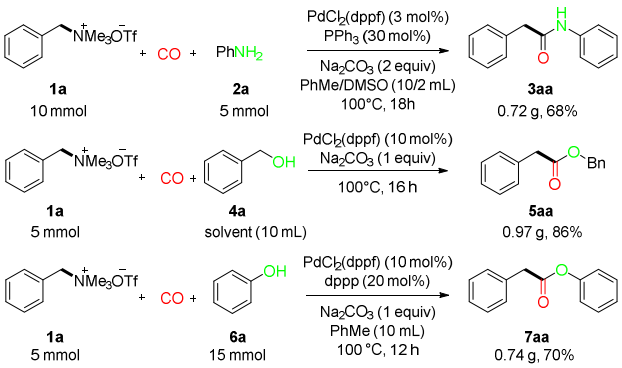
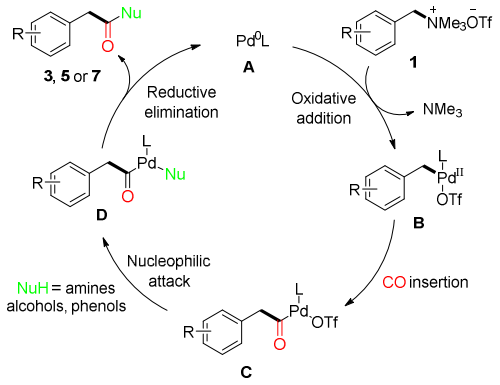
To prove the practicability of this methodology, the carbonylation reactions were carried out on gram-scale (Scheme 2). Delightedly, when aniline, benzyl alcohol and phenol were employed as the partners to react with benzylic quaternary ammonium salts on 5 mmol scale, the corresponding amide **3aa** and esters **5aa**, **7aa** were obtained in 68%, 86% and 70% yields, respectively.



Scheme 2. Proposed mechanism.

On the basis of our experimental results and known literatures,[2,22] a plausible reaction mechanism is depicted in Scheme 3. The Pd(0) species **A** reacts with benzyl quaternary ammonium salt **1** via oxidative addition to generate Pd(II) intermediate **B** and release electronically neutral NMe_3. Then CO insertion into the metal-alkyl bond of intermediate **B** would form acylpalladium **C**, which after nucleophilic attack by suitable nucleophiles (amines, alcohols or phenols) could deliver Pd(II) species **D**. Finally, reductive elimination of **D** provides the carbonyl product (**3**, **5** or **7**) and regenerate Pd(0) species.



Scheme 3. Proposed mechanism.

Conclusions

In conclusion, a high-efficient palladium-catalyzed aminocarbonylation and alkoxycarbonylation of readily available quaternary ammonium salts with CO via benzylic C-N bonds activation have been developed for the synthesis of arylacetamides and arylacetic acid esters. This redox-neutral protocol, with electronically neutral amine as waste, could be smoothly performed under atmosphere pressure of CO and compatible with a wide range of nucleophiles including aryl/alkyl amines, primary/secondary/ tertiary alcohols and various phenols. The successes for α-amino-esters and gram-scale synthesis show its potential applications in protein modifications and chemical industries.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

1 (a) A. Schoenberg, I. Bartoletti, R. F. Heck, *J. Org. Chem.* **1974**, *39*, 3318; (b) A. Schoenberg; R. F. Heck. *J. Org. Chem.* **1974**, *39*, 3327; (c) A. Schoenberg; R. F. Heck. *J. Am. Chem. Soc.* **1974**, *96*, 7761.

2 For select reviews on palladium-catalyzed carbonylation reactions with CO, see: (a) G. Kiss, *Chem. Rev.* **2001**, *101*, 3435; (b) R. Skoda-Földes, L. Kollár, *Curr. Org. Chem.* **2002**, *6*, 1097; (c) B. Gabriele, G. Salerno, M. Costa, *Top. Organomet. Chem.* **2006**, *18*, 239; (d) C. F. J. Barnard, *Organometallics* **2008,** *27,* 5402; (e) A. Brennfuhrer, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **2009**, *48*, 4114; (f) A. Brennführer, H. Neumann, M. Beller, *ChemCatChem* **2009**, *1*, 28; (g) R. Grigg, S. P. Mutton, *Tetrahedron* **2010**, *66*, 5515; (h) X. F. Wu, H. Neumann, M. Beller, *Chem. Soc. Rev.* **2011**, *40*, 4986; (i) X. F. Wu, H. Neumann, M. Beller, *Chem. Rev.* **2013**, *113*, 1; (j) L. Wu, X. Fang, Q. Liu, R. Jackstell, M. Beller, X.-F. Wu, *ACS Catal.* **2014**, *4*, 2977; (k) Y. Bai, D. C. Davis, M. Dai, *J. Org. Chem.* **2017**, *82*, 2319. For some other recent reviews on carbonylation, see: (l) Q. Liu, H. Zhang, A. Lei, *Angew. Chem. Int. Ed.* **2011**, *50*, 10788; (m) Z. Zhang, Y. Zhang, J. Wang, *ACS Catal.* **2011**, *1*, 1621; (n) K. Dong, X.-F. Wu, *Angew. Chem. Int. Ed.* **2017**, *56*, 5399; (o) J.-B. Peng, X.-F. Wu, *Angew. Chem. Int. Ed.* **2018**, *57*, 1152.

3 (a) B. Katzung, S. Masters, A. Trevor, *Basic and Clinical Pharmacology*, 12th ed.; Mcgraw-Hill: New York, **2011**. b) F. Bellina, R. Rossi, *Chem. Rev.* **2010**, *110*, 1082.

View Article Online
DOI: 10.1039/C8OB00488A

4 (a) Zdravkovski, Z. A. *Syn. Commun*. **1993**, *23*, 2761; (b) C. A. G. N. Montalbetti, V. Falque, *Tetrahedron* **2005**, *61*, 10827; (c) M. Bradley, *Chem. Soc. Rev*. *2009*, *38*, 606.

5 (a) H. N. Roy, A. H. A. Mamun, *Syn. Commun*. **2006**, *36*, 2975; (b) R. C. Larock, *Comprehensive Organic Transformations*, Wiley-VCH, New York, USA, 2nd edn, **1999**; (c) M. B. Smith, J. March, *Advanced Organic Chemistry*, Wiley, New York, USA, 5th edn, **2001**.

6 (a) L. Troisi, C. Granito, F. Rosato, V. Videtta, *Tetrahedron Lett*. **2010**, *51*, 371; (b) X.-F. Wu, J. Schranck, H. Neumann, M. Beller, *ChemCatChem.* **2012**, *4*, 69; (c) X.-F. Wu, L. Wu, R. Jackstell, H. Neumann, M. Beller, *Chem. - Eur. J.* **2013,** *19*, 12245.

7 (a) H. Liu, N. Yan, P. J. Dyson, *Chem. Commun*. **2014**, *50*, 7848; (b) J. Liu, H. Li, A. Spannenberg, R. Franke, R. Jackstell, M. Beller, *Angew. Chem. Int. Ed.* **2016**, *55*, 13544; (c) T. Xu, F. Sha, H. Alper, *J. Am. Chem. Soc*. **2016**, *138*, 6629; (d) Y. Hu, Z. Shen, H. Huang, *ACS Catal.* **2016**, *6*, 6785; (e) B. Gao, G. Zhang, X. Zhou, H. Huang, *Chem. Sci.* **2018**, *9*, 380.

8 (a) P. Xie, Y. Xie, B. Qian, H. Zhou, C. Xia, C, H. Huang, *J. Am. Chem. Soc*. **2012**, *134*, 9902; (b) P. Xie, C. Xia, H. Huang, *Org. Lett*. **2013**, *15*, 3370; (c) H. Liu, G. Laurenczy, N. Yan, P. J. Dyson, *Chem. Commun*. **2014**, *50*, 341.

9 E. Wenkert, A. L. Han, C. J. Jenny, *J. Chem. Soc. Chem. Commun*. **1988**, 975.

10 (a) H. Zhang, S. Hagihara, K. Itami, *Chem. - Eur. J.* **2015**, *21*, 16796; (b) J. Hu, H. Sun, W Cai, X Pu, Y. Zhang, Z. Shi, *J. Org. Chem*. **2016**, *81*, 14; (c) C. H. Basch, K. M. Cobb, M. P. Watson, *Org. Lett.* **2016**, *18*, 136.

11 (a) S. B. Blakey, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2003**, *125*, 6046; (b) G. de la Herran, A. G. Csákÿ, *Org. Lett.* **2007**, *9*, 961; (c) T. Wang, S. Yang, S. Xu, C. Han, G. Guo, J. Zhao, *RSC Adv*. **2017**, *7*, 15805.

12 (a) L.-G. Xie, Z.-X. Wang, *Angew. Chem. Int. Ed*. **2011**, *50*, 4901; (b) D. Wu, J.-L. Tao, Z.-X. Wang, *Org. Chem. Front.* **2015**, *2*, 265.

13 (a) J. T. Reeves, D. R. Fandrick, Z. Tan, J. J. Song, H. Lee, N. K. Yee, C. H. Senanayake, *Org. Lett*. **2010**, *12*, 4388; (b) W.-J. Guo, Z.-X. Wang, *Tetrahedron* **2013**, *69*, 9580.

14 (a) D. Y. Wang, M. Kawahata, Z. K. Yang, K. Miyamoto, S. Komagawa, K. Yamaguchi, C. Wang, M. Uchiyama, *Nat. Commun.* **2016**, *7*, 12937.

15 (a) Q. X, Z.-X. Wang, *Org. Biomol. Chem*. **2014**, *12*, 1448; (b) Z.-K. Yang, D.-Y. Wang, H. Minami, H. Ogawa, T. Ozaki, T. Saito, K. Miyamoto, C. Wang, M. Uchiyama, *Chem. - Eur. J.* **2016**, *22*, 15693; (c) H. J. Davis, M. T. Mihai, R. J. Phipps, *J. Am. Chem. Soc.* **2016**, *138*, 12759; (d) M. Guisán-Ceinos, V. Martín-Heras, M. Tortosa, *J. Am. Chem. Soc.* **2017**, *139*, 8448.

16 P. Maity, D. M. Shacklady-McAtee, G. P. A. Yap, E. R. Sirianni, M. P. Watson, *J. Am. Chem. Soc.* **2013**, *135*, 280.

17 T. Moragas, M. Gaydou, R. Martin, *Angew. Chem. Int. Ed*. **2016**, *55*, 5137.

18 Y. Lei, R. Zhang, Q. Wu, H. Mei, B. Xiao, G. Li, *J. Mol. Catal. A* **2014**, *381*, 120.

19 H. Yu, B. Gao, B. Hu, H. Huang, *Org. Lett.* **2017**, *19*, 3520.

20 (a) Y. Li, Z. Wang, X.-F. Wu, *ACS Catal.* **2018**, *8*, 738; (b) Y. Li, Z. Wang, X.-F. Wu, *Green Chem*. **2018**, *20*, 969.

21 Y. Tu, L. Yuan, T. Wang, C. Wang, J. Ke, J. Zhao, *J. Org. Chem.* **2017,** *82*, 4970.

22 (a) F. Zhu, J.-L. Tao, Z.-X. Wang, *Org Lett.* **2015**, *17*, 4926; (b) Q. Wang, Y. Su, L. Li, H. Huang, *Chem. Soc. Rev*. **2016**, *45*, 1257.