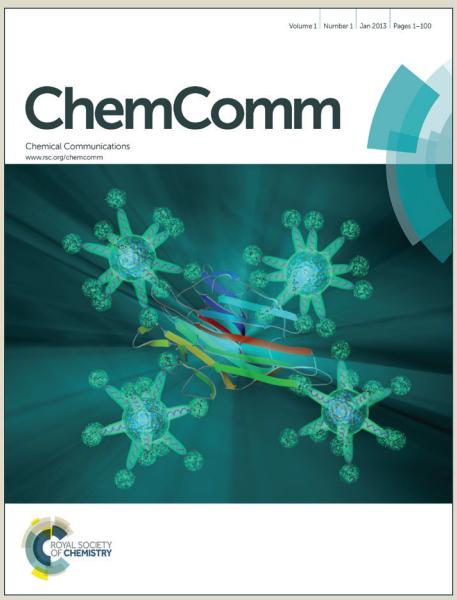
# ChemComm

Accepted Manuscript





ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

# Preparation of Highly Substituted (β-Acylamino)acrylates via Iron-catalyzed Alkoxycarbonylation of *N*-Vinylacetamides with Carbazates

**Ran Ding,[a] Qiu-Chi Zhang,[a] Yun-He Xu,[a]* and Teck-Peng Loh[a,b]***

***Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX***

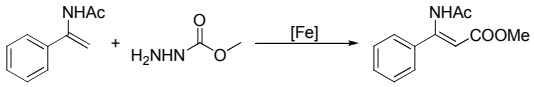
**DOI: 10.1039/b000000x**

**An efficient iron(II)-catalyzed alkoxycarbonylation reaction between *N*-vinylacetamides and carbazates is reported. The corresponding useful highly substituted (*β*-acylamino)acrylates could be obtained in reasonable to good yields and stereoselectivity under mild reaction conditions.**

(*β*-Acylamino)acrylate derivatives are useful building blocks in organic synthesis which have been used widely for the asymmetric synthesis of *β*-amino acids and chiral amines.[1] Accordingly, the synthesis of this class of compounds has attracted much attention.[2] Common methods to access this class of compounds include the condensation of *β*-ketoester with an amine source[3] and the Pd-catalyzed *α*-arylation of *β*-amido-acrylate[4]. However, these methods suffer from limited substrate scope and difficulties in controlling the *E*/*Z* selectivity of the product. Therefore, a more efficient and general method to access (*β*-acylamino)acrylate derivatives is highly desirable. We envisage that the direct C–H alkoxycarbonylation of *N*-vinylacetamides will provide one of the most direct entries to this class of compounds. However, the Pd-catalyzed C–H carbonylation of *N*-vinyl acetamides with carbon monoxide led to the formation of 1,3-oxazin-6-ones.[5] An attractive strategy is to use carbazate, a very useful source of ester group discovered by Taniguchi and coworkers, as the carbonylation reagent.[6] During the past few years, carbazates have been widely used by many groups including Tian,[7] Li,[8] Du,[9] Zhu,[10] etc. Inspired by these seminal works and due to our interest in developing direct C–H bond functionalization of *N*-vinylacetamides,[11] herein, we report a new and simple method to prepare highly substituted (*β*-acylamino)acrylates using *N*-vinylacetamides and carbazates catalyzed by cheap and low toxicity iron catalyst.

Initially, our attempt involved the search for an optimized reaction conditions by carrying out the reaction of *N*-vinylacetamide **1a** with carbazate **2a**. The observed results are shown in Table 1. With 20 mol% amount of [Fe(Pc)] (Iron(II) phthalocyanine) as catalyst, the desired product of (*Z*)-methyl 3-acetamido-3-phenylacrylate **3a** could be obtained only in low yields when PIDA (phenyliodine diacetate),

**Table 1.** Optimization of the reaction conditions of alkoxycarbonylation of acyclic *N*-vinylacetamide with carbazate **2a**.[a,b]




**1a** **2a** **3a**

| entry | catalyst (mol%) | oxidant[b] | T (°C) | base (equiv.) | solvent | t (h) | yield (%)[c] |
|---|---|---|---|---|---|---|---|
| 1 | [Fe(Pc)] (20) | PIDA | 80 | | $CH_3CN$ | 3 | 30% |
| 2 | [Fe(Pc)] (20) | BQ | 80 | | $CH_3CN$ | 3 | 37% |
| 3 | [Fe(Pc)] (20) | TBPB | 80 | | $CH_3CN$ | 3 | 35% |
| 4 | [Fe(Pc)] (20) | DTBP | 80 | | $CH_3CN$ | 3 | trace |
| 5 | [Fe(Pc)] (20) | DCP | 80 | | $CH_3CN$ | 3 | trace |
| 6 | [Fe(Pc)] (20) | TBHP | 80 | | $CH_3CN$ | 3 | 41% |
| 7 | [Fe(Pc)] (20) | TBHP | 80 | $Cs_2CO_3$ (2.0) | $CH_3CN$ | 3 | 68% |
| 8 | [Fe(Pc)] (20) | TBHP | 60 | $Cs_2CO_3$ (2.0) | $CH_3CN$ | 3 | 68% |
| 9 | [Fe(Pc)] (10) | TBHP | 60 | $Cs_2CO_3$ (2.0) | $CH_3CN$ | 3 | 68% |
| 10 | [Fe(Pc)] (5) | TBHP | 60 | $Cs_2CO_3$ (2.0) | $CH_3CN$ | 3 | 66% |
| 11 | [Fe(Pc)] (10) | TBHP | 60 | $Cs_2CO_3$ (1.0) | $CH_3CN$ | 3 | 68% |
| 12 | [Fe(Pc)] (10) | TBHP | 60 | $Na_2CO_3$ (1.0) | $CH_3CN$ | 3 | 47% |
| 13 | [Fe(Pc)] (10) | TBHP | 60 | $CH_3COOK$ (2.0) | $CH_3CN$ | 3 | 51% |
| 14 | [Fe(Pc)] (10) | TBHP | 60 | LiOH (2.0) | $CH_3CN$ | 3 | 62% |
| 15 | [Fe(Pc)] (10) | TBHP | 60 | $KHCO_3$ (2.0) | $CH_3CN$ | 3 | 58% |
| 16 | [Fe(Pc)] (10) | TBHP | 60 | $K_3PO_3$ (1.0) | $CH_3CN$ | 3 | 65% |
| 17 | $FeCl_3$ (20) | TBHP | 60 | $Cs_2CO_3$ (1.0) | $CH_3CN$ | 3 | trace |
| 18 | $FeCl_2$ (20) | TBHP | 60 | $Cs_2CO_3$ (1.0) | $CH_3CN$ | 3 | 22% |
| 19 | $FeBr_2$ (20) | TBHP | 60 | $Cs_2CO_3$ (1.0) | $CH_3CN$ | 3 | 26% |
| 20 | [Fe(Pc)] (10) | TBHP | 60 | $Cs_2CO_3$ (1.0) | THF | 3 | 47% |
| 21 | [Fe(Pc)] (10) | TBHP | 60 | $Cs_2CO_3$ (1.0) | Toluene | 3 | 47% |
| 22 | [Fe(Pc)] (10) | TBHP | 60 | $Cs_2CO_3$ (1.0) | $CH_2Cl_2$ | 3 | 56% |
| 23[d] | [Fe(Pc)] (10) | TBHP | 60 | $Cs_2CO_3$ (1.0) | $CH_3CN$ | 3 | 68% |
| 24[e] | [Fe(Pc)] (10) | TBHP | 60 | $Cs_2CO_3$ (1.0) | $CH_3CN$ | 3 | 68% |
| 25[e,f] | [Fe(Pc)] (10) | TBHP | 60 | $Cs_2CO_3$ (1.0) | $CH_3CN$ | 2 | 68% |
| 26 | | TBHP | 60 | $Cs_2CO_3$ (1.0) | $CH_3CN$ | 2 | trace |

[a] Reaction conditions: The mixture of **1a** (0.2 mmol), **2a** (0.8 mmol), oxidant (2.0 equiv.) and base in solvent (1.5 mL). [b] TBHP was used with 2.0~2.4 equiv. (5~6 M in decane) [c] Isolated yields. [d] Solvent (1.0 mL). [e] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), TBHP (2.0~2.4 equiv., 80 μL, 5~6 M in decane), solvent (1.0 mL). [f] A 94:6 Z/E ratio was determined from $^1$H NMR spectra of the crude product.

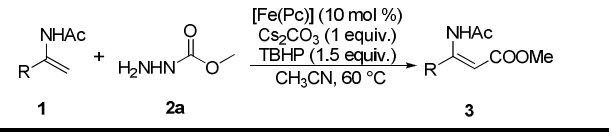
BQ (benzoquinone), TBPB (*tert*-butyl benzoperoxoate) DTBP (*di-tert*-butyl peroxide) or DCP (dicumyl peroxide) was used as oxidant in acetonitrile at 80 °C (Table 1, entries

[a]*Hefei National Laboratory for Physical Sciences at the Microscale and Department of Chemistry, University of Science and Technology of China, Hefei, 230026, China*

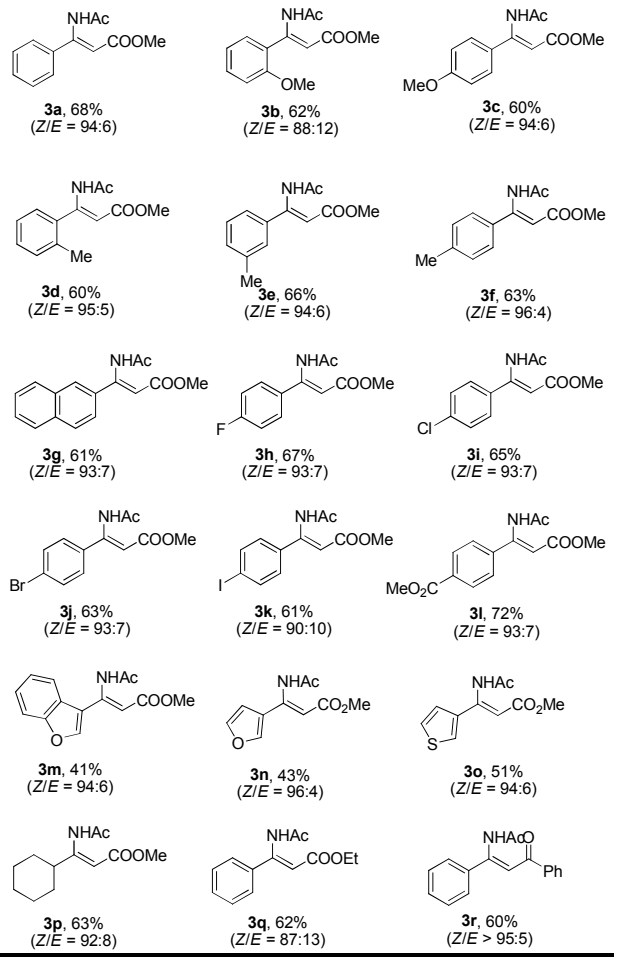
[b]*Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371*

1-5). To our delight, the desired product could be obtained in 68% yield when TBHP (*tert*-butyl hydroperoxide) was used as oxidant with $Cs_2CO_3$ as the additive. Furthermore, after reducing the catalyst's loading to 10 mol% and base's amount to one equivalent, the yield of desired product only decreased slightly at 60 °C (Table 1, entry 11). However, other tested bases (Table 1, entries 12-16), iron catalysts (Table 1, entries 17-19) or used solvents (Table 1, entries 20-22) did not favour the transformation to the desired product. It was found that increasing TBHP loading and increasing the reaction concentration could not improve the product yield significantly. Control experiments were also carried out and the iron catalyst was found to be necessary to afford the product (Table 1, entry 26). Finally, the optimized conditions were established to be: [Fe(Pc)] (10 mol %), $Cs_2CO_3$ (1 equiv.), TBHP (2 equiv.) at 60 °C in $CH_3CN$ for 2 hours.

**Table 2**. Iron-catalyzed direct alkoxycarbonylation of **1** with different carbazates.[a,b,c]




**1** **2a** **3**

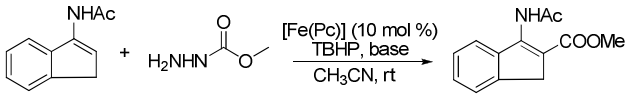



[a] Reaction conditions: The mixture of **1a** (0.3 mmol), **2a** (0.6 mmol), TBHP (2.0~2.4 equiv., 120 μL, 5~6 M in decane), $Cs_2CO_3$ (1.0 equiv.) and [Fe(Pc)] in 1.5 mL $CH_3CN$ was heated at 60 °C for 2 hours. [b] Isolated yields. [c] The ratios of *Z*/*E* shown in parentheses were determined from the crude $^1H$ NMR spectra of the corresponding reactions.

The optimized reaction conditions were then applied to various acyclic *N*-vinylacetamides (Table 2). It was found that the substitutents on the phenyl ring of the *N*-vinylacetamide did not affect the yields of the reaction **1** with **2a**. Different halide substituents were tolerated in the final products which permit them for further functionalization in subsequent steps. However, the substituents at the *ortho*-position could lead to a slightly decreased *Z*/*E* selectivity of the products. In addition, different heteroaryl such as benzofuran, furan and thiophene substituted *N*-vinylacetamides were also applied as substrates in this reaction, the corresponding products could be isolated in reasonable yields and with high stereoselectivities. Furthermore, the *N*-vinylacetamide **1p** with a cyclohexyl group also could be used well and afforded the desired product **3p** in 63% yield and in a 92/8 ratio of *Z*/*E* selectivity. Finally, ethyl hydrazinecarboxylate and benzohydrazide were carried out as carbonyl sources in current reaction,[12] products **3q** and **3r** were efficiently formed in 62% and 60% yields respectively. After establishing current simple and efficient method for preparation of highly substituted (*β*-acylamino)acrylates, a gram-scale experiment between **1a** and **2a** was tested. To our delight, the product **3a** also could be obtained in a steady 61% yield (Please see the details in SI).

When the optimized reaction conditions were employed for the alkoxycarbonylation reaction of the cyclic *N*-vinylacetamide **4a**, unfortunately, only very poor yield (<10%) of the product was obtained accompanied by decomposed starting material. After careful investigation (Table 3), we found that the choice of base was crucial for the product's yield. Following, different bases were further examined in the reaction and finally one equivalent of $K_2CO_3$ was found to be suitable for affording the product **5a** in an acceptable yield at room temperature. Other bases such as LiOH, KOH or $K_3PO_4$ were found to be less effective in affording the desired product.

**Table 3.** Optimization of the reaction conditions of alkoxycarbonylation of cyclic *N*-vinylacetamide with carbazate **2a**.[a,b]




**4a** **2a** **5a**

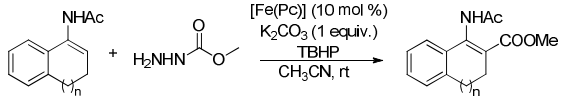
| entry | catalyst (mol%) | base (equiv.) | t (h) | yield (%) |
|---|---|---|---|---|
| 1 | [Fe(Pc)] (10) | LiOH (1) | 1 | 42 |
| 2 | [Fe(Pc)] (10) | $LiOH.H_2O$ (1) | 1 | 50 |
| 3 | [Fe(Pc)] (10) | $K_3PO_4$ (1) | 1 | 34 |
| 4 | [Fe(Pc)] (10) | KOH (1) | 1 | trace |
| 5 | [Fe(Pc)] (10) | $K_2CO_3$ (1) | 1 | 57 |
| 6 | [Fe(Pc)] (10) | $Cs_2CO_3$ (1) | 1 | trace |
| 7 | [Fe(Pc)] (10) | $K_2CO_3$ (1) | 0.5 | 54 |
| 8 | [Fe(Pc)] (20) | $K_2CO_3$ (1) | 0.5 | 60 |
| 9 | [Fe(Pc)] (20) | | 1 | 37 |

[a] Reaction conditions: The solution of **4a** (0.2 mmol), **2a** (0.4 mmol), TBHP (2.0~2.4 equiv., 80 μL, 5~6 M in decane), base (1.0 equiv.) and [Fe(Pc)] in 1.0 mL $CH_3CN$ was run at room temperature for 1 hour. [b] Isolated yields.

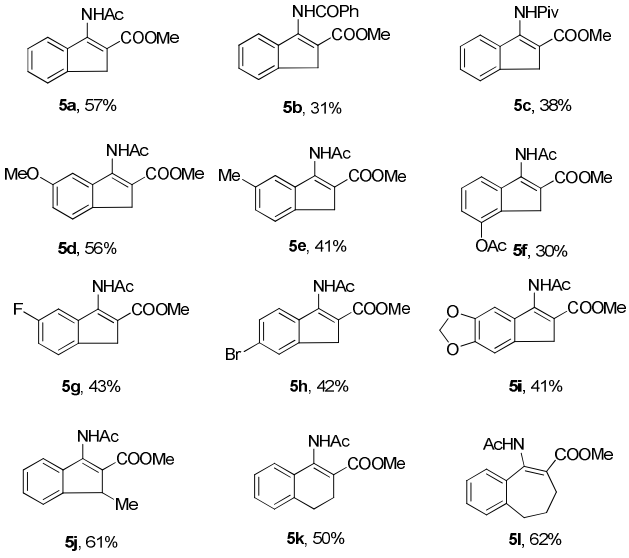
With the further optimized reaction conditions in hand, various cyclic *N*-vinylacetamides were tested for the preparation of tetra-substituted (*β*-acylamino)acrylate derivatives (Table 4). The selected protecting group on the nitrogen atom is important for the product's yield; as more bulky protecting group will decrease the yield. Moreover, it was noticed that the electronic effect from the substituents on the phenyl ring of the cyclic *N*-vinylacetamides forthe product's yields is quite different from that observed in acyclic *N*-vinylacetamides. For example, with the halide or ester substituent, only moderate yields of the products could be realized. It seems that the steric effect from the substituted methyl group at the 3-position is not sensitive for the generation the product, 61% yield of **5j** could be observed. Variation on the ring size was also studied; the substrates with a six- or seven-membered ring also could be smoothly transferred into the target products in 50% and 62% yields respectively (Table 4, entries **5k** and **5l**).

A plausible mechanism for the alkoxycarbonylation of *N*-vinylacetamides with carbazates could be proposed as shown in Scheme 1. After an addition of alkoxycarbonyl radical generated from carbazate with the aid of iron catalyst[6-10] to the double bond of the compound **1**, the more stable radical intermediate **7** could be further oxidized by Fe(III) or *tert*-butyloxide radical into the iminium ion **8**.[13] In the presence of base, deprotonation will lead to the formation of the desired product **3**.

**Table 4.** Iron-catalyzed direct alkoxycarbonylation of **4** with carbazate **2a**.[a,b]

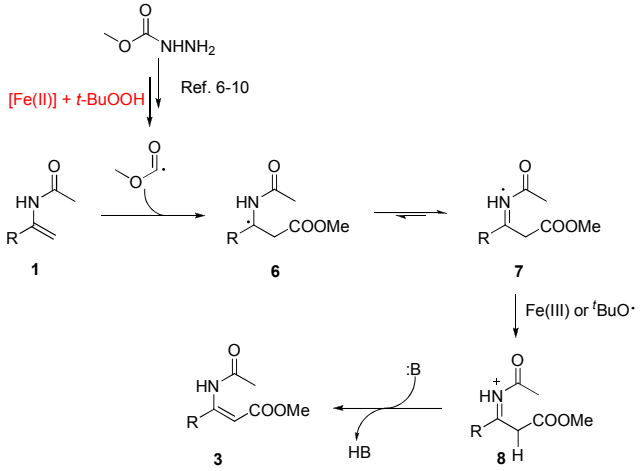



4 2a 5




[a] Reaction conditions: The solution of **4a** (0.3 mmol), **2a** (0.6 mmol), TBHP (2.0~2.4 equiv., 120 μL, 5~6 M in decane), $K_2CO_3$ (1.0 equiv.) and [Fe(Pc)] in 1.5 mL $CH_3CN$ was run at room temperature for 1 hour. [b] Isolated yields.

**Scheme 1.** Proposed possible mechanism for the alkoxycarbonylation of *N*-vinylacetamide with carbazate.




## Conclusions

In conclusion, we have developed an iron-catalyzed alkoxycarbonylation reaction of *N*-vinylacetamides with carbazates under simple and mild reaction conditions. Various acyclic and cyclic *N*-vinylacetamides as starting materials were found to be tolerated in the titled reaction. The observed good steroselectivities and reasonable yields of the products make this method a general tool for synthesis of highly substituted (*β*-acylamino)acrylate derivatives *via* direct functionalization of *N*-vinylacetamides.

## Acknowledgement

We gratefully acknowledge the funding support of National Science Foundation for Young Scientists of China (21202156), the National Natural Science Foundation of China (21372210), and the Fundamental Research Funds for the Central Universities (WK2060190023) and Natural Science Foundation of Anhui Province (1308085QB37). The authors also thank Nanyang Technology University for financial support of this research. The authors are grateful to Mr. Koh Peng Fei Jackson for his careful proofreading of the final manuscript.

## Notes and references

1 For selected reviews, see: (a) W.-J. Tang, X.-M. Zhang, *Chem. Rev*., 2003**, 103**, 3029; (b) W.-C. Zhang, Y.-X. C, X.-M. Zhang, *Acc. Chem. Res*., 2007**, 40,** 1278; (c) S.-H. Gellman, *Acc. Chem. Res*., 1998, **31**, 173; (d) Y. Wu, S.-B. Qi, F.-F. Wu, X.-C. Zhang, M. Li, J. Wu, A. S. C. Chan, *Org. Lett*., 2011, **13,** 1754; (e) P. Etayo, J. L. Núñez-Rico, A. Vidal-Ferran, *Organometallics*, 2011, **30**, 6718; (f) J. L. Núñez-Rico, P. Etayo, A. Vidal-Ferran, *Adv. Synth. Catal*., 2012, **354**, 3025; (g) W. Tang, A. G. Capacci, A. White，*Org. Lett*., 2010, **12**, 1104; (h) X. Wu, Y. Li, C. Wang, L. Zhou, X. Lu, J. Sun, *Chem. Eur. J*., 2011, **17**, 2846.

2 (a) W.-J. Tang, W.-M. Wang, Y.-X. Chi, X.-M, Zhang, *Angew. Chem*., *Int. Ed*., 2003, **42**, 3509; (b) S. Enthaler, G. Erre, K. Junge, M. Hapke, D. Redkin, M. Beller, *Eur. J. Org. Chem*., 2008, 3352; (c) S. Lee, Y. Zhang, *Org. Lett*., 2002, **4**, 2429.

3 (a) W. D. Lubell, M. Kitamura, R. Noyori, *Tetrahdron*: *Asymmetry* 1991, **2**, 543; (b) K. Achiwa, T. Soga, *Tetrahedon Lett*. 1978, 1119; (c) M. Furukawa, T. Okawara, Y. Noguchi, Y. Terawaki, *Chem. Pharm. Bull*. 1979, **27**, 2223. (d) A. P. Krapacho, J. Diamanti, C. Zayen, R. Binghan, *Org. Synth*. 1973, **5**, 198. (e) G.-X. Zhu, Z.-G. Chen, X.-M. Zhang, *J. Org. Chem*., 1999**, 64**, 6907; (f) N. D.

Ratnayake, U. Wanninayake, J. H. Geiger, K. D. Walker, *J. Am. Chem. Soc*., 2011, **133***,* 8531; (g) D. Peña , A. J. Minnaard, J. G. de Vries, B. L. Feringa, *J. Am. Chem. Soc*., 2002, **124**, 14552.

4 (a) Q. Gou, B. Deng, H. Zhang, J. Qin, *Org*. *Lett*., 2013, **15**, 4604; (b) Y. Liu, D. Li, C.-M. Park, *Angew*. *Chem*., *Int*. *Ed*., 2011, **50**, 7333.

5 M. Chen, Z.-H. Ren, Y.-Y. W, Z.-H. Guan, *Angew. Chem., Int. Ed*., 2013, **52**, 14196.

6 T. Taniguchi, Y. Sugiura, H. Zaimoku, H. Ishibashi, *Angew. Chem. Int. Ed*. 2010, **49**, 10154.

7 Y. Su, Z. Wu, S. Tian, *Chem. Commun*., 2013, **49**, 6528.

8 M.-W. Fang, P.-Z Hu, X.-Q. Li, X.-Y. Xu, *Adv*. *Synth*. *Catal*., 2014, **356**, 2103.

9 X.-S. X, Y.-C. T, G. Hong, M.-W. Fang, X.-Q. Li, X.-H. Du, *J. Org Chem*., 2014, **79**, 446.

10 C.-D. Pan, J. Hang, C.-J. Zhu, *J. Org. Chem*., 2014, **79**, 5374.

11 (a) H. Zhou, W.-J. Chung, Y.-H. Xu, T.-P. Loh, *Chem. Commun*., 2009, **45**, 3472; (b) H. Zhou, Y.-H. Xu, W.-J. Chang, T.-P. Loh, *Angew. Chem., Int. Ed.* 2009, **48**, 5355; (c) Y.-H. Xu, Y.-K. Chok, T.-P. Loh, *Chem. Sci.* 2011, **2**, 1822; (d) S. Pankajakshan, Y.-H. Xu, J.-K. Cheng, M.-T. Low, T.-P. Loh, *Angew. Chem., Int. Ed*., 2012, **51**, 5701; (e) C. Feng, T.-P. Loh, *Chem. Sci*., 2012, **3**, 3458; (f) Y.-H. Xu, T. He, Q.-C. Zhang, T.-P. Loh, *Chem. Commun*., 2014, **50**, 2784; (g) M.-K. Zhu, J.-F. Zhao, T.-P. Loh, *Org. Lett*., 2011, **13**, 6308; (h) Y.-H. Xu, Q.-C. Zhang, T. He, T.-P. Loh, *Adv. Synth. Catal*., 2014, **356**, 1539

12 (a) W.-M. Xu , S.-Z. Li, M. He, S. Yang , *Bioorg. Med. Chem. Lett*., 2013, **23***,* 5821; (b) A. E. Kümmerle, M. Schmitt, *J. Med. Chem*., 2012, **55**, 7525.

13 (a) W.-M. Xu, S.-Z. Li, M. He, S. Yang, *Org. Lett*., 2014, **16**, 2912; (b) J. Wang, C. Liu, J.-W. Yuan, A.-W. Lei, *Angew. Chem., Int. Ed*., 2013, **52**, 2256; (c) T. Xu, C.-W. Cheung, X.-L. Hu, *Angew. Chem., Int. Ed*., 2014, **53**, 4910.