RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2017, **7**, 27603

Rhodium-catalyzed malonation of 2-arylquinazolines with 2-diazomalonates: double C–H functionalization†

Zhipeng Zhang,[a] Xin Jiang,[a] Zhihong Deng,[a] Heng Wang,[a] Jian Huang[a] and Yiyuan Peng *[ab]

Received 25th January 2017
Accepted 8th May 2017

DOI: 10.1039/c7ra01131h

rsc.li/rsc-advances

Herein, rhodium-catalyzed malonation of 2-arylquinazolines with diazomalonates was described. A series of dimalonate-substituted 2-arylquinazolines were achieved through double C–H functionalization.

As privileged structural cores, quinazoline-based chemistry has been recognized as one of hot topics in the community of organic synthesis due to its ubiquity in many bioactive pharmaceuticals and agricultural chemistry molecules.[1] For example, Erlotinib and Gefitinib are well-known lung cancer drugs.[2] Trimetrexate has been used in the treatment of pneumocystis pneumonia[3] and Prazosin is used for curing high blood pressure[4] (Fig. 1).

To date, it is reasonable that a particular and intensive emphasis has been place on the development of synthetic methodologies and the further bioactivity evaluation of the quinazoline architectures. Classical protocols prefer the use of condensation reactions between carbonyl-containing compounds and amines.[5]

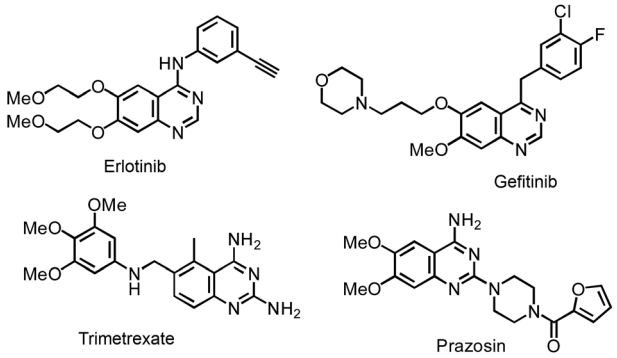


Fig. 1 Quinazolines as core structures in pharmaceuticals.

With the development of modern organic synthesis, transition metal-catalyzed transformations (especially, copper and palladium) have been accepted as an efficient alternative method for the synthesis of quinazolines.[6] Our group initiated studies on the development of this synthetic methodology since the year of 2009 and various 2,4-functionalized quinazolines were achieved *via* palladium-catalyzed C–O bond activation (Scheme 1a).[7]

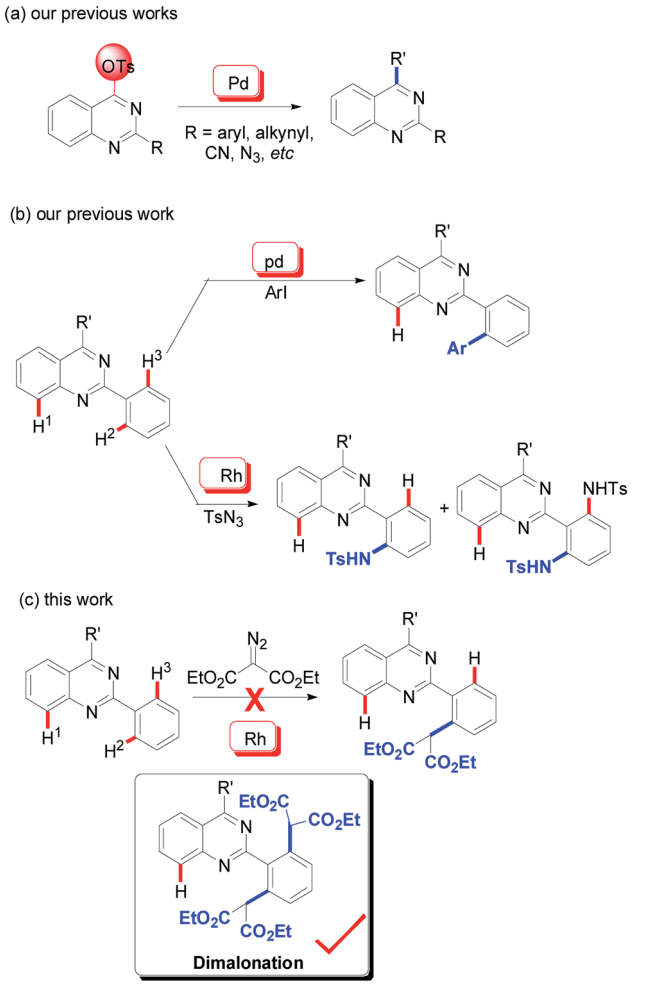
As an extension of our program, we were then pleased to discover that the quinazoline core is an efficient directing group in transition metal-catalyzed C–H functionalization (Scheme 1b). According to our findings, its directing properties are distinctive from that of pyridine and quinolines, and the regioselectivity observed in the palladium-catalyzed mono-iodination and mono-arylation of 2-phenylquinazolines specifically leads to the H^2-functionalized product (Scheme 1b).[8] Recently, amidation of 2-phenylquinazolines was also explored by our group using rhodium catalysis.[9] In the reactions, sulfonyl azide was used as a nitrogen source and diamidation was mainly observed. Similar with our previous results, this rhodium-catalyzed mono-amidation was also regioselective, predominately giving the H^2-functionalized products (Scheme 1b). The mono-amidation of the C–H^2 bonds can be regulated using 2-phenylquinazolines with steric hinderance at the 2-phenyl group as the substrate.

Acceptably, rhodium catalysis is one of versatile and powerful tools used in the formation of carbon–carbon bonds and carbon–heteroatom bonds.[10] In particular, rhodium catalysis plays a critical role in direct C–H functionalization, where the rhodium catalyst is readily inserted into C–H bonds due to its stronger electrophilicity.[11] Encouraged by that mentioned above and our continuous interest in quinazoline-based chemistry, we would like to develop more rhodium-catalyzed quinazoline-based transformations and then further evaluate the bioactivities of the resulting quinazoline derivatives. We therefore focused our attention on rhodium-catalyzed malonation using diazomalonates as the reaction partners, where a rhodium carbene was designed as the key intermediate (Scheme 1c).[12]

[a]*Key Laboratory of Functional Small Organic Molecule, Ministry of Education, College of Chemical and Engineering, Jiangxi Normal University, Nanchang 330013, China. E-mail: yypeng@jxnu.edu.cn*

[b]*CAS Key Laboratory of Molecular Recognition and Function, Institute of Chemistry, Chinese Academy of Sciences, 330022, PR China*

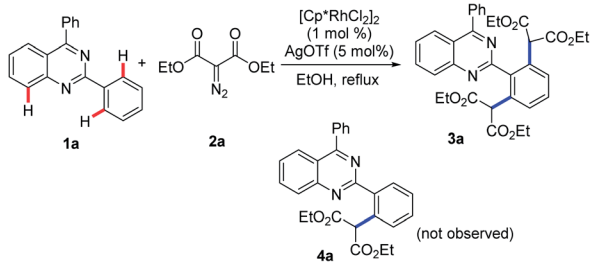
† Electronic supplementary information (ESI) available: Experimental procedure, characterization data, ^{1}H and ^{13}C NMR spectra of compounds **3** and **3a**. CCDC 1529457 and 1529463. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c7ra01131h



Scheme 1 The proposed route for the rhodium-catalyzed malonation reaction.

To verify this projected transformation, we selected the reaction of 2,4-diphenylquinazoline **1a** and ethyl diazomalonate **2a** as a model reaction. In our preliminary trials, a product was detected with high efficiency when the model reaction was carried out using 1 mol% of $[Cp^*RhCl_2]_2$, 5 mol% of AgOTf, and 3 equiv. of diazomalonate in ethanol at reflux (Table 1, entry 1). Structural identification of the product by NMR, HRMS and X-ray diffraction revealed that the double malonated quinazoline **3a** was observed and that dimalonation took place in the rhodium-catalyzed reaction of 2-phenylquinazoline **1a** and ethyl diazomalonate **2a**. The mono-malonation product **4a** was not detected at all. We thought the observation was probably attributed to the use of excess of diazomalonate **2a**. As a result, the reaction with 1.1 equiv. diazomalonate **2a** was conducted under the standard conditions. However, we were surprised to find the unique occurrence of dimalonation of 2-phenylquinazoline **1a** with high specificity, producing **3a** in 32% yield (Table 1, entry 2). Based on the information in hand, it was confirmed that the double malonations mentioned here were stepwise and the second malonation was faster than that of the first one. This double C–H functionalization was not observed in our previous 2-phenylquinazoline-based transformations.[8]

Table 1 The initial studies on the rhodium-catalyzed reaction of quinazolines **1a** with diazomalonate **2a**[a]



Entry	Conditions	Yield of **3a**[b] (%)
1	Standard conditions	83
2	1.1 equiv. diazomalonate was used	32
3	AgOTf was replaced by AgOAc	0
4	AgOTf was replaced by $AgBF_4$	25
5	The loading of AgOTf was increased to 10 mol%	82
6	The loading of the rhodium catalyst was increased to 5 mol%	72
7	$[Cp^*Rh(BF_4)_2]_2$ instead of $[Cp^*RhCl_2]_2$	0
8	The reaction temperature was reduced to 65 °C	64

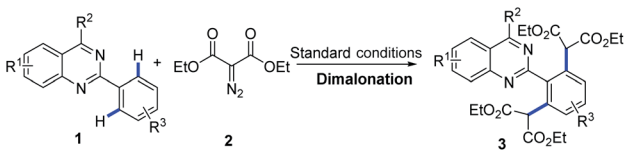
[a] Standard conditions: quinazoline **1a** (1.0 equiv.), diazomalonate **2a** (3 equiv.), rhodium catalyst $[Cp^*RhCl_2]_2$ (1 mol%), AgOTf (5 mol%), EtOH, reflux. [b] Isolated yield based on quinazoline **1a**.

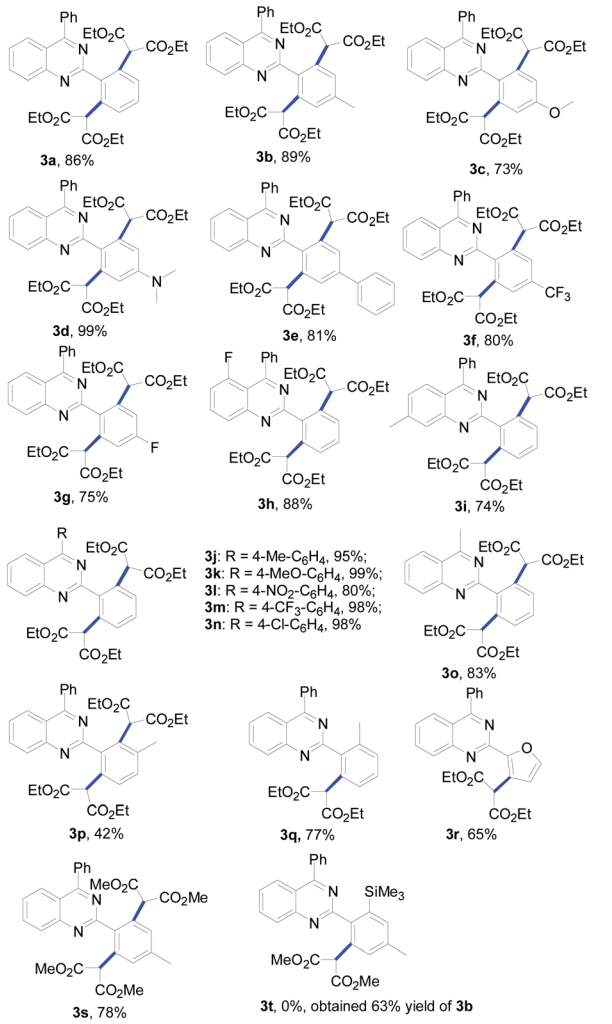
This result prompted us to optimize the reaction conditions (see ESI†). Changing silver triflate to other silver salts greatly affected the yield of the reaction. When silver acetate was used as the additive, the reaction completely failed (Table 1 entry 3). Additionally, silver tetrafluoroborate drastically retarded the reaction and a 25% yield of product was obtained (Table 1, entry 4). Increasing of loading of silver triflate had a slight impact on the outcome of the reaction (Table 1, entry 5). The reaction was unfavorable when the loading of the rhodium catalyst was increased to 5 mol% and an inferior yield was afforded (Table 1 entry 6). To our surprise, the use of another rhodium catalyst exerted a great impact on the reaction. When the rhodium catalyst was switched to $[Cp^*Rh(BF_4)_2]_2$, the reaction did not occur (Table 1, entry 7). Decreasing the reaction temperature was also unfavorable, resulting in product **3a** in 64% yield with no mono-malonation product **4a** isolated (Table 1, entry 8). A detailed evaluation of the solvent, rhodium catalyst, additive, temperature and the equivalent ratio of substrate is presented in the ESI.†

With the optimized conditions in hand (1 mol% of $[Cp^*RhCl_2]_2$, 5 mol% of AgOTf and 3 equiv. of diazomalonate in ethanol at reflux), we then examined the scope and generality of this rhodium-catalyzed dimalonation of 2-phenylquinazolines **1** and diazomalonates **2**. The results are illustrated in Table 2.

From the results in Table 2, a series of substituted dimalonated 2-phenylquinazoline **3** were achieved as expected. The electron-withdrawing/donating effects of the 2-phenyl group of

Table 2 Dimalonation *via* a rhodium-catalyzed double C–H functionalization of 2-phenylquinazolines with diazomalonates[a]



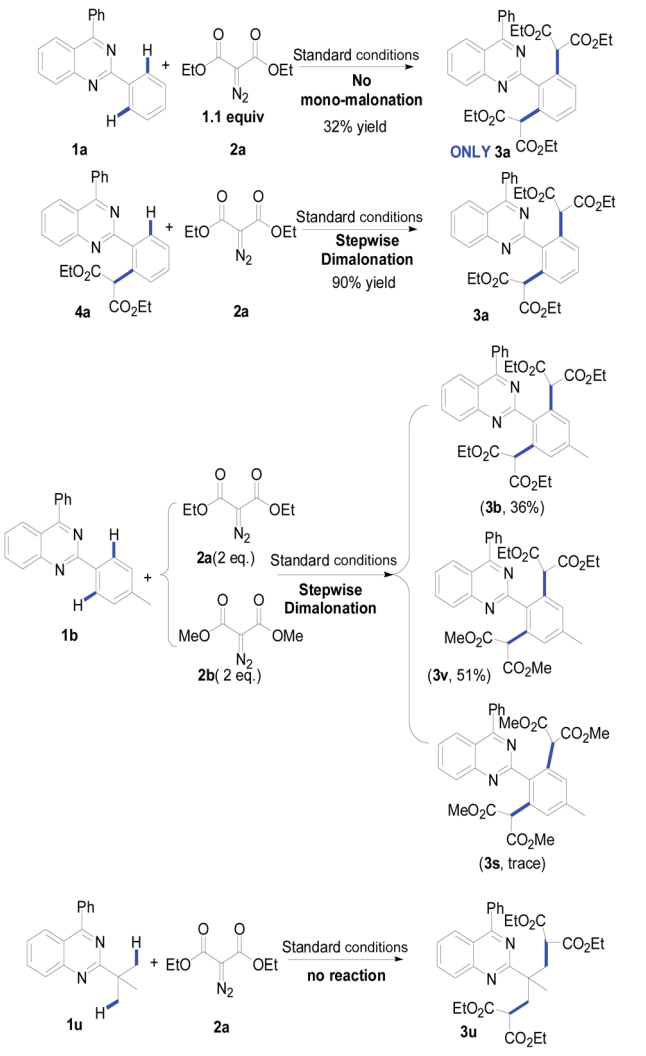


[a] Isolated yield based on quinazoline **1**.

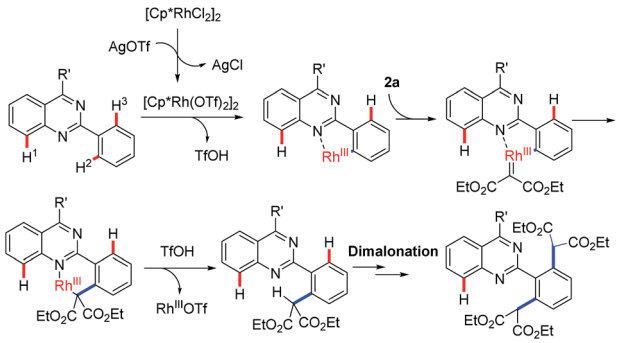
the quinazolines drastically affected the yields of the reactions. In the reactions, the substrates attached a 2-phenyl group bearing electron-rich groups were more efficient than that of electron-deficient groups. For examples, the reaction of 2-(4-*N*,*N*-dimethylaminophenyl)quinazoline **1d** with diazomalonate **2a** produced the corresponding product **3d** in 99% yield, while the reaction of 2-(4-trifluoromethylphenyl)quinazoline **1f** gave the product **3f** in 80% yield. The electron-withdrawing/donating effects of the R^2 substituent slightly influenced the results. The corresponding products **3j**–**3n** were delivered in excellent yields. To our delight, the R^2 substituent could be expanded to the methyl group, yielding the desired product **3o** in 83% yield. The steric hinderance of the substrate was also explored in the reaction. According to our previous findings, double C–H functionalization can be regulated by the use of sterically hindered 2-phenylquinazolines.[9] Interestingly, the reaction of 2-(3-methyl)phenylquinazoline **1p** still gave rise to the dimalonated product **3p** in moderate yield, although the reaction of 2-(2-methyl)phenylquinazolines provided the mono-malonated product **3q**. A heterocyclic unit at the 2-position of the quinazoline was also compatible in this reaction (entry **3r**).

The effect of the 2-diazomalonates was then explored. The corresponding 2-diazomalonate product **3s** was obtained in a yield of 78%, when 2-diazo-malonic acid dimethyl ester **2b** was reacted with **1b**. However the reactions of 2-diazo-malonic acid dipropyl **2c** and 5-diazo-2,2-dimethyl-[1,3]dioxane-4,6-dione **2d** gave only trace amounts of the desired products (not listed in Table 2). The reactions of 2-diazo-3-oxo-butyric acid ethyl ester **2e** and diazo-phenyl-acetic acid ethyl ester **2f** gave a complex mixture of products.

Table 3 Control experiment[a]



[a] Isolated yield based on quinazoline **1**.



Scheme 2 Possible mechanism.

In order to achieve selective mono-malonation, we tried to install a TMS group at one of the *ortho* positions of 2-phenylquinazoline, which could then be removed using TBAF in a subsequent step. Thus, 2-(4-methyl-2-trimethylsilanyl)phenyl-4-phenyl-quinazoline (**1t**) was synthesized in our laboratory. When **1t** was reacted with **1b**, the mono-malonated product **3t** was not obtained. However, the TMS group was removed and the reaction gave the double malonated product **3b** in a yield of 63%.

To understand the possible mechanism, several control experiments were carried out (Table 3). As mentioned above, when reducing the equivalent of diazomalonate **2a**, the dimalonated product **3a** was uniquely detected in 32% yield. The reaction of the as-prepared product **4a** with diazomalonate **2a** under the standard conditions provided the desired product **3a** in 90% yield. The reaction of **1b** with a mixture of **2a** and **2b** (1 : 1) gave a mixture of **3b** (36%) and **3v** (51%), and a trace amount of **3s**. This information indicates that the double malonation was stepwise and the second malonation was faster than that of the first one. The reaction using 2-*tert*-butylquinazolines **1u** did not produce the corresponding desired products. As illustrated in Scheme 2, the migration insertion of the rhodium carbene into the rhodium–carbon is the key step in the process.

In conclusion, we have developed a novel rhodium-catalyzed dimalonation of 2-phenylquinazolines with diazomalonates with high efficiency and a good tolerance of functional groups. In this reaction, only 1 mol% of the rhodium catalyst was required. This protocol represents the first rhodium-catalyzed examples using the quinazolines as the directing group in the dimalonation reaction *via* double C–H functionalization. The application of the quinazoline as a directing group in other C–H functionalization is currently underway in our laboratory.

Acknowledgements

Financial support from the National Natural Science Foundation of China (No. 21162012 and 21362014), the Science Foundation of Education Department of Jiangxi province (grant no. KJLD13020), the open project program of CAS Key Laboratory of Molecular Recognition and Function, Chinese Academy of Sciences (No. 2012LMRF004) and Key Laboratory of Functional Small Organic Molecule, Ministry of Education, Jiangxi Normal University (No. KLFS-KF-201408) is gratefully acknowledged.

Notes and references

1 For selected examples, see: (*a*) B. Baruah, K. Dasu, B. Vaitilingam, P. Mamnoor, P. P. Venkata, S. Rajagopal and K. R. Yeleswarapu, *Bioorg. Med. Chem.*, 2004, **12**, 1991–1994; (*b*) V. M. Sharma, P. Prasanna, K. V. A. Seshu, B. Renuka, C. V. L. Rao, G. S. Kumar, C. P. Narasimhulu, R. Rajagopalan, *et al.*, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 2303–2307.

2 R. Gundla, R. Kazemi, R. Sanam, R. Muttineni, J. A. R. P. Sarma, R. Dayam and N. Neamati, *J. Med. Chem.*, 2008, **51**, 3367–3377.

3 C. E. S. Short, Y. C. Gilleece, M. J. Fisher and D. R. Churchill, *AIDS*, 2009, **23**, 1287–1290.

4 S. F. Campbell, M. J. Davey, J. D. Hardstone, B. N. Lewis and M. J. Palmer, *J. Med. Chem.*, 1987, **30**, 49–57.

5 Reviews see: (*a*) D. J. Connolly, D. Cusack, T. P. O'Sullivan and P. J. Guiry, *Tetrahedron*, 2005, **61**, 10153–10202; (*b*) A. Witt and J. Bergman, *Curr. Org. Chem.*, 2003, **7**, 659–677; (*c*) S. B. Mhaske and N. P. Argade, *Tetrahedron*, 2006, **62**, 9787–9826; (*d*) A. Nefzi, J. M. Ostresh and R. A. Houghten, *Chem. Rev.*, 1997, **97**, 449–472.

6 X. Y. Wang and N. Jiao, *Org. Lett.*, 2016, **18**, 2150–2153.

7 (*a*) X. L. Ye, J. J. Yuan, Y. R. Zhou, Z. H. Deng, X. C. Mao and Y. Y. Peng, *Synthesis*, 2016, **48**, 3976–3984; (*b*) X. L. Ye, Z. H. Yuan, Y. R. Zhou, Q. Yang, Y. P. Xie, Z. H. Deng and Y. Y. Peng, *J. Heterocycl. Chem.*, 2016, **53**, 1956–1962; (*c*) X. Chen, Q. Yang, Y. R. Zhou, Z. H. Deng, X. C. Mao and Y. Y. Peng, *Synthesis*, 2015, **47**, 2055–2062; (*d*) X. Zhao, Y. R. Zhou, Q. Yang, Y. P. Xie, Q. P. Ding, Y. Y. Peng, *et al.*, *Synthesis*, 2013, **45**, 3245–3250; (*e*) Y. Y. Peng, P. Huang, Y. Wang, Y. R. Zhou, Q. Yang, X. Jiang, *et al.*, *Org. Biomol. Chem.*, 2014, **12**, 5922–5927; (*f*) G. Y. S. Qiu, P. Huang, Q. Yang, H. Lu, J. S. Xu, Z. H. Deng, M. Zhang and Y. Y. Peng, *Synthesis*, 2013, **45**, 3131–3136; (*g*) S. Wacharasindhu, S. Bardhan, Z.-K. Wan, K. Tabei and T. S. Mansour, *J. Am. Chem. Soc.*, 2009, **131**, 4174–4175.

8 Y. Y. Peng, M. J. Zeng, H. M. Wang, J. Zhu, Q. Yang, Z. H. Deng and C. Y. Yu, *Tetrahedron*, 2015, **71**, 9457–9462.

9 C. Y. Zhang, Y. R. Zhou, Z. H. Deng, X. Chen and Y. Y. Peng, *Eur. J. Org. Chem.*, 2015, 1735–1744.

10 Reviews see: (*a*) G. Y. Song, F. Wang and X. W. Li, *Chem. Soc. Rev.*, 2012, **41**, 3651–3678; (*b*) D. A. Colby, A. S. Tsai, R. G. Bergman and J. A. Ellman, *Acc. Chem. Res.*, 2012, **45**, 814–825Selected recent examples, see: (*c*) S. J. Yu, S. Liu, Y. Lan, B. S. Wan and X. W. Li, *J. Am. Chem. Soc.*, 2015, **137**, 1623–1631; (*d*) A. Geer, A. Serrano, B. Bruin, M. Ciriano and C. Tejel, *Angew. Chem., Int. Ed.*, 2015, **54**, 472–475; (*e*) K. Shibata and N. Chatani, *Org. Lett.*, 2014, **16**, 5148–5151; (*f*) J. Jeong, P. Patel, H. Hwang and S. Chang, *Org. Lett.*, 2014, **16**, 4598–4601; (*g*) R. Q. Ran, S. D. Xiu and C. Y. Li, *Org. Lett.*, 2014, **16**, 6394–6396.

11 (*a*) B. Parr and H. M. L. Davies, *Org. Lett.*, 2015, **17**, 794–797; (*b*) R. Azpiroz, L. Rubio-Perez, A. D. Giuseppe, V. Passarelli,

F. J. Lahoz, R. Castarlenas, J. J. Perez-Torrente and L. A. Oro, *ACS Catal.*, 2014, **4**, 4244–4253; (*c*) X. C. Ma, J. Jiang, S. Y. Lv, W. F. Yao, Y. Yang, S. Y. Liu, F. Xia and W. H. Hu, *Angew. Chem., Int. Ed.*, 2014, **53**, 13136–13139; (*d*) B. T. Parr and H. M. L. Davies, *Nat. Commun.*, 2014, **5**, 5455; (*e*) A. D. Giuseppe, R. Casrarlenas, J. J. Perez-Torrente, F. J. Lahoz and L. A. Oro, *Chem.–Eur. J.*, 2014, **20**, 8391–8403.

12 (*a*) Y. Xia, S. Feng, Z. Liu, Y. Zhang and J. B. Wang, *Angew. Chem., Int. Ed.*, 2015, **54**, 7891–7894; (*b*) X. Chen, X. W. Hu, S. Y. Bai, Y. F. Deng, H. F. Jiang and W. Zeng, *Org. Lett.*, 2016, **18**, 192–195; (*c*) C. Song, C. Yang, F. F. Zhang, J. H. Wang and J. Zhu, *Org. Lett.*, 2016, **18**, 4510–4513.