ChemInform Abstract: Rhodium(III)-Catalyzed C2-Selective Carbenoid Functionalization and Subsequent C7-Alkenylation of Indoles.

ARTICLE *in* CHEMICAL COMMUNICATIONS · MAY 2014

Impact Factor: 6.83 · DOI: 10.1039/c4cc01593b · Source: PubMed

5 AUTHORS, INCLUDING:

Jingjing Shi
Chinese Academy of Sciences
17 PUBLICATIONS **216** CITATIONS
SEE PROFILE

Eric Xu
Van Andel Research Institute
140 PUBLICATIONS **6,015** CITATIONS
SEE PROFILE

Wei Yi
Chinese Academy of Sciences
54 PUBLICATIONS **787** CITATIONS
SEE PROFILE

ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Rhodium(III)-catalyzed C2-selective carbenoid functionalization and subsequent C7-alkenylation of indoles†

Cite this: *Chem. Commun.*, 2014, **50**, 6483

Received 3rd March 2014,
Accepted 30th March 2014

DOI: 10.1039/c4cc01593b

www.rsc.org/chemcomm

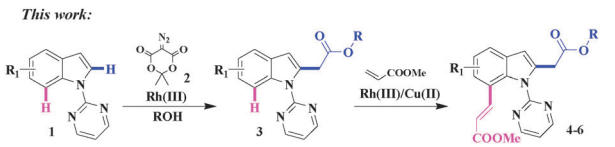
Jingjing Shi,[a] Yunnan Yan,[ab] Qiu Li,[a] H. Eric Xu*[ac] and Wei Yi*[a]

Here a new, mild and versatile method for efficient synthesis of a diverse range of 2-acetate substituted indoles *via* Rh(III)-catalyzed and alcohol-mediated C2-selective carbenoid insertion functionalization of indoles by α-diazotized Meldrum's acid has been developed. Furthermore, for the first time, a Rh(III)/Cu(II)-catalyzed direct C7-alkenylation of such functionalized products has also been demonstrated.

Indoles are commonly occurring structural motifs found in numerous natural products, pharmaceuticals, and biologically active compounds, which are very attractive synthetic targets for synthetic medicinal chemists.[1] Driven by their potential biological application, developing mild and highly efficient methods for the synthesis of functionalized indoles has attracted considerable attention in modern organic chemistry.[2] Among these, transition-metal-catalyzed C–H functionalization has in recent years emerged as one of the most powerful tools for preparing organic building blocks in a step- and atom-economical fashion.[3] Since the pioneering work by the research groups of Lewis,[4a] Murai[4b] and Fujiwara,[4c] significant progress has been made in this hot area of research. Nevertheless, compared with C3–H functionalization,[5] the methods that allow for C2–H functionalization of indole are still limited due to the weak reactivity of the C–H bond at the C-2 position of indole.[6] A particular challenge is the direct regioselective C2-alkylation for the synthesis of 2-acetate substituted indoles despite the potential utility of such products, for which very few metal-catalyzed protocols have been reported.[7] For example, Baciocchi,[7a] Ricciardi[7b] and Heaney[7c] have independently reported the C2-alkylation for building 2-acetate substituted indoles. However, these approaches require pre-functionalized acetates as substrates, which result in formation of stoichiometric amounts of salt waste as byproducts. Moreover, the lower yield and/or poor regioselectivity were also found in their catalysis. In 2010, Kerr and co-workers also developed the Cu(II)-catalyzed direct C2-functionalization of indoles for synthesizing this type of molecule. However, this catalysis needed an additional substituent at the C3-position of indoles for blocking this position.[7d] Therefore, the development of new strategies for efficient construction of valuable 2-acetate substituted indoles is still highly desirable.

In recent years, the acceptor–acceptor substituted diazo compounds, in particular those derived from malonates or β-ketoesters, have been widely used as powerful cross-coupling partners for direct C–H functionalization in transition-metal-catalyzed reactions,[8] of which Rh complexes have occupied a prevalent position. However, the Rh(III)-catalyzed insertion of carbenoids into C(sp^2)–H bonds of heterocycles, especially for the C2–H bonds of indole cores, is still underexplored, and thus, such a useful coupling is worth further development.

Motivated by this and our continuing interest in developing Rh(III)-catalyzed C–H bond functionalizations,[6e,g,9] in this communication, we report for the first time a Rh(III)-catalyzed and alcohol-mediated C2-selective carbenoid insertion functionalization of indoles by α-diazotized Meldrum's acid and subsequent decarboxylation to give access to 2-acetate substituted indoles (eqn (1)). Additionally, we also demonstrated the first example of direct C7-alkenylation of such functionalized indole products in this classical Rh(III)/Cu(II) catalysis.[6g,9]



(1)

At the outset, we examined this Rh(III)-catalyzed carbenoid insertion reaction in EtOH at 80 °C for 15 h employing $[Cp^*Rh(MeCN)_3](SbF_6)_2$ as the catalyst and using indole **1a** bearing a

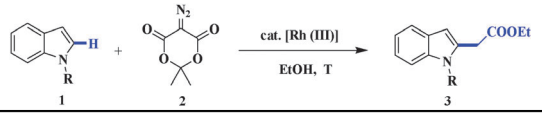
[a] *VARI/SIMM Center, Center for Structure and Function of Drug Targets, CAS-Key Laboratory of Receptor Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, P.R. China. E-mail: yiwei.simm@simm.ac.cn, eric.xu@simm.ac.cn; Fax: +86-21-20231000-1715; Tel: +86-21-20231000-1715*

[b] *College of Pharmaceutical Sciences, Gannan Medical University, Ganzhou, Jiangxi 341000, P.R. China*

[c] *Laboratory of Structural Sciences, Program on Structural Biology and Drug Discovery, Van Andel Research Institute, Grand Rapids, Michigan 49503, USA*

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c4cc01593b

Table 1 Selected optimization of reaction conditions[a]



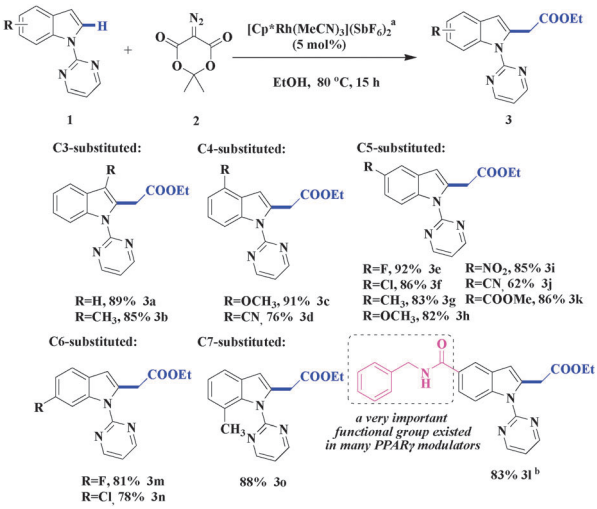
1 2 3

Entry	R	Catalyst system (mol%)	T (°C)	Yield[b] (%)
1	**2-Pyrimidyl**	**$[Cp^*Rh(MeCN)_3](SbF_6)_2$ (5)**	**80**	**89**
2	$(CH_3)_2NCO$	$[Cp^*Rh(MeCN)_3](SbF_6)_2$ (5)	80	0
3	H	$[Cp^*Rh(MeCN)_3](SbF_6)_2$ (5)	80	0
4	2-Pyrimidyl	$[Cp^*RhCl_2]_2$ (5) + $AgSbF_6$ (40)	80	52
5	2-Pyrimidyl	—	80	0
6	2-Pyrimidyl	$[Cp^*Rh(MeCN)_3](SbF_6)_2$ (5)	R.T.	0
7	2-Pyrimidyl	$[Cp^*Rh(MeCN)_3](SbF_6)_2$ (2)	80	56
8[c]	2-Pyrimidyl	$[Cp^*Rh(MeCN)_3](SbF_6)_2$ (5)	80	87
9[d]	2-Pyrimidyl	$[Cp^*Rh(MeCN)_3](SbF_6)_2$ (5)	80	85

[a] Reaction conditions: **1** (0.12 mmol, 1.2 eq.), **2** (0.1 mmol, 1.0 eq.), Rh catalyst (X mol%), EtOH (0.5 mL), 15 h, under air. [b] Isolated yields. [c] H_2O (0.2 mmol, 2.0 eq.) was added. [d] Performed on a 5.0 mmol scale.

readily removable *N*-2-pyrimidyl group as the model substrate, which had been a success story in our recent studies.[6e,g] To our delight, the anticipated product **3a** was cleanly obtained as the sole coupling product in 89% isolated yield with excellent regioselectivity (Table 1, entry 1). The brief directing group (DG) screening showed that the *N*-2-pyrimidyl moiety is an ideal metal-directing group (Table 1, entries 1–3), which is in good agreement with the previous investigations.[2c,6d,10] Changing the catalyst $[Cp^*Rh(MeCN)_3](SbF_6)_2$ to another well known catalyst $[Cp^*RhCl_2]_2$ obviously inhibited the process (Table 1, entry 4). No desired product was formed in the absence of catalyst (Table 1, entry 5) or at room temperature (Table 1, entry 6). It is notable that the amount of the catalyst was critical to the catalytic activity, as the reduction of the amount of catalyst led to a significant decrease in the product yield (Table 1, entry 7). In summary, the optimal conditions in EtOH were $[Cp^*Rh(MeCN)_3](SbF_6)_2$ (5.0 mol%) at 80 °C for 15 h under air. Finally, we were pleased to find that the reaction was compatible with water (Table 1, entry 8) and could also be performed on a 5.0 mmol scale under the optimized conditions without significant decrease in the product yield (Table 1, entry 9).

With this efficient catalytic system in hand, we sought to study the scope of indoles and generality of this reaction (Scheme 1). As shown in Scheme 1, substrate **2** efficiently coupled with a variety of substituted indoles in EtOH to give the corresponding C2-ethyl acetate substituted indoles in good to excellent yields (62–92%) with exclusive region and site selectivities. Substitutions at the C3- (**3b**), C4- (**3c–d**), C5- (**3e–l**), C6- (**3m–n**), or C7- (**3o**) positions were all well tolerated. More importantly, the reaction showed good compatibility with many valuable functional groups such as methoxy (**3c** and **3h**), cyano (**3d** and **3j**), fluoro (**3e** and **3m**), chloro (**3f** and **3n**), nitro (**3i**), and ester (**3k**) substituents. Tolerance to the fluoro, chloro, cyano, and ester functional groups is especially noteworthy since they are useful intermediates for further transformation through standard cross-coupling reactions. Furthermore, we were pleased to find that indole **1l**, bearing a bulkier BnNHCO-substituent (a very important functional group found in many PPARγ modulators[11]), also smoothly reacted with **2** on 1.0 mmol scale to deliver the desired product **3l** in 83% yield, which could



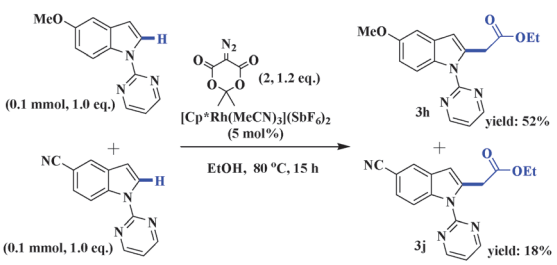
Scheme 1 Scope of indoles. [a] The reaction was carried out using **1a–o** (0.12 mmol), **2** (0.10 mmol), Rh(III) catalyst (5.0 mol%), and EtOH (0.5 mL) under air at 80 °C for 15 h. Isolated yields. [b] Performed on a 1.0 mmol scale.

provide an attractive strategy for rapidly building new potential PPARγ modulators for the treatment of diabetes mellitus (DM).

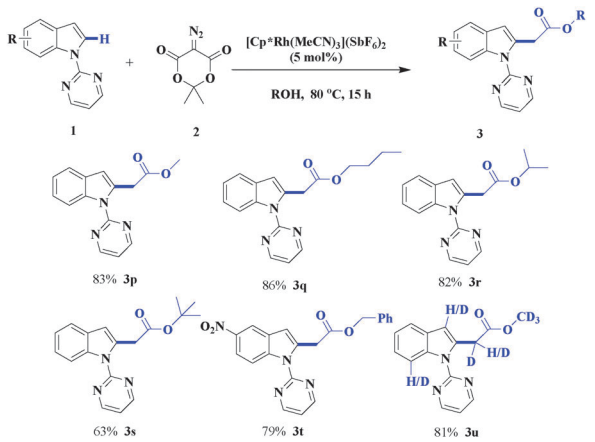
Considering the remarkably broad substrate scope displayed by the Rh(III) catalyst in ethanol, we performed mechanistic studies to delineate its mode of action. To this end, a competition experiment between differently substituted indoles was carried out. As shown in Scheme 2, the result indicated that electron-rich indoles were preferentially converted, suggesting that they were better substrates than electron-deficient indoles.

Since ethanol was employed not only as the solvent but also as the reagent in the above C–H activation reaction, subsequently, several alkyl alcohols were tested in the current catalyst system. As illustrated in Scheme 3, the reaction in all the selected alcohols proceeded successfully to afford the desired products **3p–t** in synthetically useful yields (63–86%). Notably, the reaction also worked well in CD_3OD to afford the methyl-deuterated product **3u** in good yield, along with additional deuterium incorporation at the C2-α-, C3- and C7-positions of the indole (for detail, see ESI†). This result implied that these synthesized C2-alkylated indole products can serve as useful platforms for further synthetic manipulations.

Indeed, it is well known that the α-position in esters and the C3-position of indole cores are the inherently reactive sites for Claisen-type condensation[12] and Friedel–Crafts-type chemistry,[5]



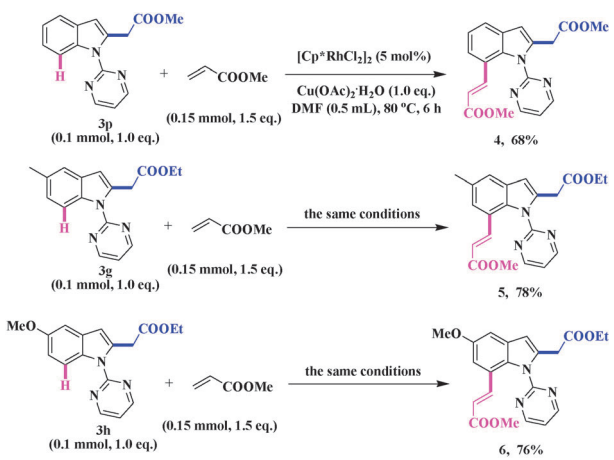
Scheme 2 Intermolecular competition experiment.



Scheme 3 Scope of alcohols. The reaction was carried out using **1a** or **1i** (0.12 mmol), **2** (0.10 mmol), Rh(III) catalyst (5.0 mol%), and the corresponding alcohol (0.5 mL) under air at 80 °C for 15 h. Isolated yields.

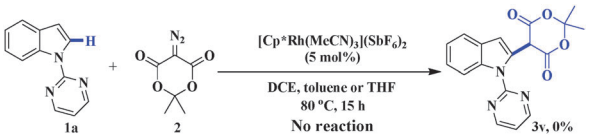
respectively. However, so far the transformation for direct functionalization of the C7-position is still unexplored in the literature. Inspired by this, we have been interested to probe the C7–H functionalization of 2-acetate substituted indoles with methyl acrylate by employing the recently popular transition-metal-catalyzed C–H activation strategy. Therefore, the reactions of **3g**, **3h** and **3p**, respectively, with methyl acrylate were examined in the most representative and classical Rh(III)/Cu(II) catalysis (Scheme 4). As expected, these couplings occurred at 80 °C in DMF within 6 h to give the corresponding C7-alkenylated products in good isolated yields (68–78%). To the best of our knowledge, this is the first report of Rh(III)-catalyzed direct C7–H functionalization of indoles.

To further probe the role of alcohols in this coupling process, an experiment using either DCE, toluene or THF to replace alcohol was performed under otherwise identical conditions. Notably, the reaction of **1a** and **2** did not proceed at all (eqn (2)). The result showed that the introduction of alcohols was crucial for starting this reaction, and suggested that the Rh(III)-catalyzed carbene insertion coupling process might not



Scheme 4 C7–H functionalization of 2-acetate substituted indoles.

be involved in the formation step of **3v**, even though such a pathway has been deduced in a recent work.[8g]

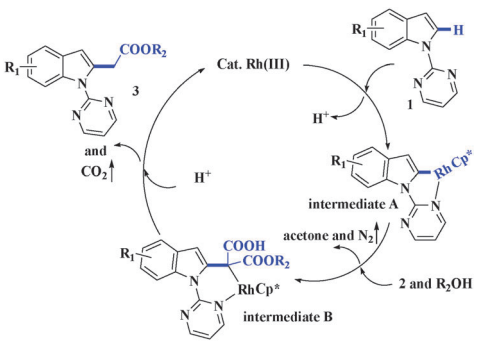


(2)

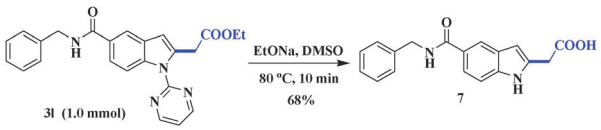
Based on these observations and literature precedents, we proposed a possible mechanism as illustrated in Scheme 5. First, the coordination of substrate **1** to a [Cp*Rh(III)] species is the key step for the regioselective C2–H bond cleavage to form a five-membered rhodacyclic intermediate **A**. Subsequently, the region-selective transfer of alcohol-mediated carbenoid insertion forms six-membered rhodacycle intermediate **B** with the emission of N_2 and acetone. Finally, protonolysis and decarboxylation of **B** generate the desired C2-functionalized product **3** and the active Rh catalyst.

Due to the importance of free-NH indoles for further synthetic transformations, we finally attempted to deprotect the pyrimidyl group of the indoles. As shown in Scheme 6, the deprotection of the pyrimidyl group of product **3l** was conveniently achieved by treatment with EtONa in dry DMSO at 80 °C to provide free-NH indole derivative **7** as the final product in good yield,[13] in which the C5-amido moiety of the indole was untouched. This could provide an efficient and versatile route for the synthesis of new potential PPARγ modulators for antidiabetic drug discovery.

In conclusion, we have developed the first example of a Rh(III)-catalyzed and alcohol-mediated direct carbenoid insertion C2-alkylation of indoles by using the pyrimidyl group as a readily installable and removable directing group. The remarkable features of this reaction include mild reaction conditions, high product yields, broad functional group tolerance, and exclusive region and site selectivities, thus rendering it a highly versatile alternative to the existing methods for synthesizing the important 2-acetate substituted indole unit. Moreover, we



Scheme 5 Proposed mechanism.



Scheme 6 Deprotection of the pyrimidyl group.

also reported for the first time a Rh(III)/Cu(II)-catalyzed direct C7-alkenylation of such C2-alkylated products, which would provide a new perspective for how to open up the C7–H functionalization of indole cores. Further applications of this strategy to the total synthesis of biologically active compounds (*e.g.*, PPARγ modulators and alkaloids[12]) and more detailed pathway investigations are currently underway.

We thank the Jay and Betty Van Andel Foundation, Amway (China) and the Chinese Postdoctoral Science Foundation (2012M511158 and 2013T60477) for financial support on this study.

Notes and references

1 For recent reviews, see: (*a*) T. B. Poulsen and K. A. Jørgensen, *Chem. Rev.*, 2008, **108**, 2903; (*b*) L. Joucla and L. Djakovitch, *Adv. Synth. Catal.*, 2009, **351**, 673; (*c*) S. Cacchi and G. Fabrizi, *Chem. Rev.*, 2011, **111**, 215.

2 (*a*) M. Bandini and A. Eichholzer, *Angew. Chem., Int. Ed.*, 2009, **48**, 9608; (*b*) A. García-Rubia, B. Urones, R. Gómez Arrayás and J. C. Carretero, *Chem. – Eur. J.*, 2010, **16**, 9676; (*c*) L. Ackermann and A. V. Lygin, *Org. Lett.*, 2011, **13**, 3332; (*d*) Y. Huang, Z. Lin and R. Cao, *Chem. – Eur. J.*, 2011, **17**, 12706; (*e*) W. Song and L. Ackermann, *Angew. Chem., Int. Ed.*, 2012, **51**, 8251; (*f*) X.-B. Xu, J. Liu, J.-J. Zhang, Y.-W. Wang and Y. Peng, *Org. Lett.*, 2013, **15**, 550; (*g*) L. Yu, P. Li and L. Wang, *Chem. Commun.*, 2013, **49**, 2368.

3 Recent reviews on transition-metal-catalyzed C–H functionalization: (*a*) J. Wencel-Delord, T. Dröge, F. Liu and F. Glorius, *Chem. Soc. Rev.*, 2011, **40**, 4740; (*b*) F. W. Patureau, J. Wencel-Delord and F. Glorius, *Aldrichimica Acta*, 2012, **45**, 31; (*c*) L. Ackermann, *Acc. Chem. Res.*, 2014, **47**, 281; (*d*) V. S. Thirunavukkarasu, S. I. Kozhushkov and L. Ackermann, *Chem. Commun.*, 2014, **50**, 29.

4 (*a*) L. N. Lewis and J. F. Smith, *J. Am. Chem. Soc.*, 1986, **108**, 2728; (*b*) S. Murai, F. Kakiuchi, S. Sekine, Y. Tanaka, A. Kamatani, M. Sonoda and N. Chatani, *Nature*, 1993, **366**, 529; (*c*) C. Jia, D. Piao, J. Oyamada, W. Lu, T. Kitamura and Y. Fujiwara, *Science*, 2000, **287**, 1992.

5 The C3-position of indoles is the inherently reactive site for Friedel–Crafts-type chemistry: G. A. Olah, R. Khrishnamurti and G. K. S. Prakash, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon, Oxford, 1st edn, 1991, vol. 3, pp. 293–335. For the latest examples on C3–H functionalization of indoles, see: F. Shibahara, T. Kanai, E. Yamaguchi, A. Kamei, T. Yamauchi and T. Murai, *Chem. – Asian J.*, 2014, **9**, 237.

6 For representative examples on C2–H functionalization of indoles, see: (*a*) A. García-Rubia, R. Gómez Arrayás and J. C. Carretero, *Angew. Chem., Int. Ed.*, 2009, **48**, 6511; (*b*) D. J. Schipper, M. Hutchinson and K. Fagnou, *J. Am. Chem. Soc.*, 2010, **132**, 6910; (*c*) L. Jiao, E. Herdtweck and T. Bach, *J. Am. Chem. Soc.*, 2012, **134**, 14563; (*d*) Z. Ding and N. Yoshikai, *Angew. Chem., Int. Ed.*, 2012, **51**, 4698; (*e*) J.-J. Shi, B. Zhou, Y.-X. Yang and Y.-C. Li, *Org. Biomol. Chem.*, 2012, **10**, 8953; (*f*) V. Lanke and K. R. Prabhu, *Org. Lett.*, 2013, **15**, 2818; (*g*) B.-W. Gong, J.-J. Shi, X.-W. Wang, Y.-N. Yan, Q. Li, Y.-Q. Meng, H. E. Xu and W. Yi, *Adv. Synth. Catal.*, 2014, **356**, 137.

7 (*a*) E. Baciocchi, E. Muraglia and G. Sleiter, *J. Org. Chem.*, 1992, **57**, 6817; (*b*) M. Nuth, H. Guan, N. Zhukovskaya, Y. L. Saw and R. P. Ricciardi, *J. Med. Chem.*, 2013, **56**, 3235; (*c*) M. J. Earle, R. A. Fairhurst and H. Heaney, *Tetrahedron Lett.*, 1991, **32**, 6171; (*d*) M. B. Johansen and M. A. Kerr, *Org. Lett.*, 2010, **12**, 4956; (*e*) W.-W. Chan, S. H. Yeung, Z.-Y. Zhou, A. S. C. Chan and W.-Y. Yu, *Org. Lett.*, 2010, **12**, 604.

8 For reviews, see: (*a*) J. Barluenga and C. Valdés, *Angew. Chem., Int. Ed.*, 2011, **50**, 7486; (*b*) Z.-H. Shao and H.-B. Zhang, *Chem. Soc. Rev.*, 2012, **41**, 560; (*c*) Q. Xiao, Y. Zhang and J.-B. Wang, *Acc. Chem. Res.*, 2013, **46**, 236; (*d*) Z.-X. Liu and J.-B. Wang, *J. Org. Chem.*, 2013, **78**, 10024; (*e*) Y. Xia, Y. Zhang and J.-B. Wang, *ACS Catal.*, 2013, **3**, 2586. For recent examples, see: (*f*) W.-W. Chan, S.-F. Lo, Z. Zhou and W.-Y. Yu, *J. Am. Chem. Soc.*, 2012, **134**, 13565; (*g*) X.-Z. Yu, S.-J. Yu, J. Xiao, B.-S. Wan and X.-W. Li, *J. Org. Chem.*, 2013, **78**, 5444; (*h*) Q. Xiao, B.-L. Wang, L.-M. Tian, Y. Yang, J. Ma, Y. Zhang, S.-F. Chen and J.-B. Wang, *Angew. Chem., Int. Ed.*, 2013, **52**, 9305; (*i*) Z. Shi, D. C. Koester, M. Boultadakis-Arapinis and F. Glorius, *J. Am. Chem. Soc.*, 2013, **135**, 12204; (*j*) T. K. Hyster, K. E. Ruhl and T. Rovis, *J. Am. Chem. Soc.*, 2013, **135**, 5364.

9 Q. Li, Y.-N. Yan, X.-W. Wang, B.-W. Gong, X.-B. Tang, J.-J. Shi, H. E. Xu and W. Yi, *RSC Adv.*, 2013, **3**, 23402.

10 (*a*) Z. Ding and N. Yoshikai, *Beilstein J. Org. Chem.*, 2012, **8**, 1536; (*b*) S.-G. Xu, X.-M. Huang, X.-H. Hong and B. Xu, *Org. Lett.*, 2012, **14**, 4614; (*c*) Z. Wang, F. Song, Y. Zhao, Y. Huang, L. Yang, D. Zhao, J. Lan and J. You, *Chem. – Eur. J.*, 2012, **18**, 16616; (*d*) J. Ryu, K. Shin, S. H. Park, J. Y. Kim and S. Chang, *Angew. Chem., Int. Ed.*, 2012, **51**, 9904; (*e*) C. Pan, H. Jin, P. Xu, X. Liu, Y. Cheng and C. Zhu, *J. Org. Chem.*, 2013, **78**, 9494; (*f*) Z. Shi, M. Boultadakis-Arapinis and F. Glorius, *Chem. Commun.*, 2013, **49**, 6489; (*g*) M. Schinkel, I. Marek and L. Ackermann, *Angew. Chem., Int. Ed.*, 2013, **52**, 3977; (*h*) V. P. Reddy, R. Qiu, T. Iwasaki and N. Kambe, *Org. Lett.*, 2013, **15**, 1290.

11 For selected examples, see: (*a*) Y. Lamotte, P. Martres, N. Faucher, A. Laroze, D. Grillot, N. Ancellin, Y. Saintillan, V. Beneton and R. T. Gampe Jr., *Bioorg. Med. Chem. Lett.*, 2010, **20**, 1399; (*b*) J. H. Choi, A. S. Banks, T. M. Kamenecka, S. A. Busby, M. J. Chalmers, N. Kumar, D. S. Kuruvilla, Y. Shin, Y. He, J. B. Bruning, D. P. Marciano, M. D. Cameron, D. Laznik, M. J. Jurczak, S. C. Schurer, D. Vidovic, G. I. Shulman, B. M. Spiegelman and P. R. Griffin, *Nature*, 2011, **477**, 477.

12 J. Huang, L. Zhao, Y. Liu, W. Cao and X. Wu, *Org. Lett.*, 2013, **15**, 4338.

13 For the deprotection procedure, see ref. 2*c*, 6*d*, *e*, *g* and 10 and the ESI†.

