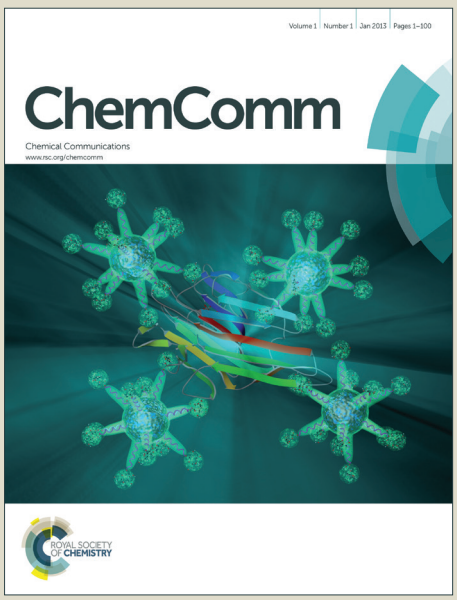
ChemComm

Accepted Manuscript



This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this *Accepted Manuscript* with the edited and formatted *Advance Article* as soon as it is available.

You can find more information about *Accepted Manuscripts* in the Information for Authors.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard Terms & Conditions and the Ethical guidelines still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

COMMUNICATION

Rhodium(III)-catalyzed intramolecular amidoarylation and hydroarylation of alkyne via C–H activation: Switchable synthesis of 3,4-fused tricyclic indoles and chromans†

Xue Zhang,‡ Yifei Li,‡Hui Shi, Lunan Zhang, Shanshan Zhang, Xianxiu Xu* and Qun Liu*

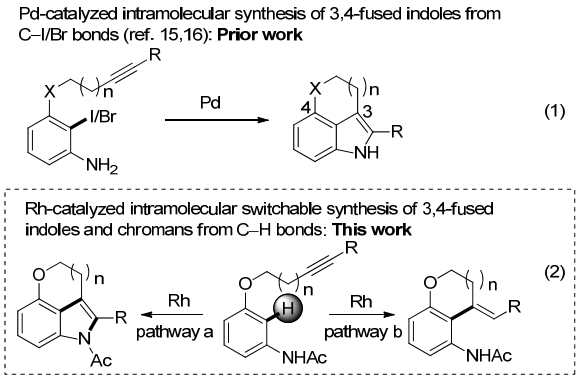
Received (in XXX, XXX) Xth XXXXXXXXX 200X, Accepted Xth XXXXXXXXX 200X

DOI: 10.1039/b000000x

The controllable intramolecular amidoarylation and hydroarylation of alkynes has been achieved via rhodium(III)-catalyzed C–H activation. The merger of two distinct reaction pathways allows for the development of atom- and step-economic protocols for the switchable synthesis of 3,4-fused indoles and chromans, respectively.

The 3,4-fused tricyclic indole structural motif forms the core of many natural products with pharmacological relevance, such asfargesine, [1] dehydrobufotenine,[2] welwistatin,[3] lysergic acid,[4]dragmacidin E,[5] decursivine,[6] communesin F,[7]and indolactam V.[8]Theformation of the 3,4-fused indole framework generally involves building the third ring onto a preformed indole moiety.[2-15] Very recently, Boger[16] and Jia[17] independently reported a palladium-catalyzed intramolecular Larock indole process for the preparation of suchpolycyclic indoles from 2-bromo- or 2-iodoanilines with an alkyne tethered at 3-position (Eqn. 1).

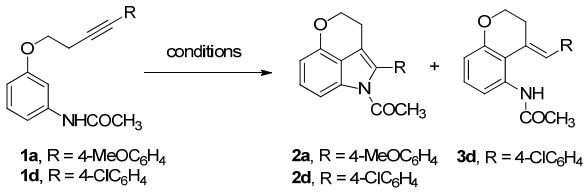
Due to its highatom- and step-economy, the rhodium(III)-catalyzed C−H activation has received significant interest in recent years.[18] In 2008, Fagnouand co-workers reported a novel strategy for indole synthesis via a Rh-catalyzed intermolecular amidoarylation of internal alkynes with acetanilides.[19] Other directing strategies for the divergent synthesis of N-H and N-alkyl indoles were later developed.[20] On the other hand, $(Cp^*RhCl_2)_2$ hasemerged as an efficient catalystfor alkyne hydroarylationwith aryl C–H bond via a novel concerted deprotonation–metalation pathway.[21] Several examples of intermolecular hydroarylationof alkynes haverecently been reported.[21,22] Although the Rh(III)-catalyzed intramolecular amidoarylation and hydroarylation of alkenes were documented last year,[23] to our knowledge, the controllable intramolecular version of above two pathways of alkyne have been remained unexplored. As part of our continuing interest in the development of Rh(III)-catalyzed C−H activation,[24] herein, we present the Rh(III)-catalyzed intramolecular amidoarylation and hydroarylation for the switchable synthesis of 3,4-fused tricyclic



indoles (pathway a) and chromans (pathway b) from alkyne tethered acetanilidesvia C−H activation (Eqn. 2). It is worth to mention that the construction of two distinct types of complex moleculesfrom the identical starting materials areachieved simply by a slight change of reaction conditions.

Initially, *N*-(3-((4-(4-methoxyphenyl)but-3-yn-1-yl)oxy)phenyl)acetamide**1a** was subjected to the Fagnou's intermolecular reaction conditions[19a] (Table 1, entry 1). We found that treatment of **1a** with $(Cp^*RhCl_2)_2$ (1 mol%), $AgSbF_6$ (4

Table 1 Optimization of reaction conditions[a]



entry	substrates	conditions	Time (h)	Yield (%)[b] 2	3
1	**1a**	A	0.3	**2a** (87)	---
2	**1d**	A	0.3	**2d** (26)	**3d** (51)
3	**1d**	B	3.0	**2d** (85)	---
4	**1d**	C	0.3	---	**3d**(98)

[a]Reactions conducted on 0.2 mmol scale. Conditions A: $(Cp^*RhCl_2)_2$ (1 mol%), $AgSbF_6$ (4 mol%), $Cu(OAc)_2•H_2O$ (2.1 equiv), *t*-AmOH (0.1 M), 120 °C; conditions B: $(Cp^*RhCl_2)_2$ (5 mol%), $AgSbF_6$ (20 mol%), $Cu(OAc)_2•H_2O$ (2.1 equiv), CH_3CN (0.1 M), 120 °C; conditions C:$(Cp^*RhCl_2)_2$ (2.5 mol%), $AgSbF_6$ (10 mol%), PivOH (5.0 equiv), *t*-AmOH (0.1 M), 120 °C. [b]Yields ofIsolated products.

Department of Chemistry, Northeast Normal University, Changchun 130024, China. Fax: 86 431 85099759; Tel: 86 431 85099759; E-mail: xuxx677@nenu.edu.cn; liuqun@nenu.edu.cn

†Electronic Supplementary Information (ESI) available: Experimental details and spectral data for **3** are included in the supporting information. For ESI data see DOI: 10.1039/b000000x/

‡ Both authors contributed equally to this work.

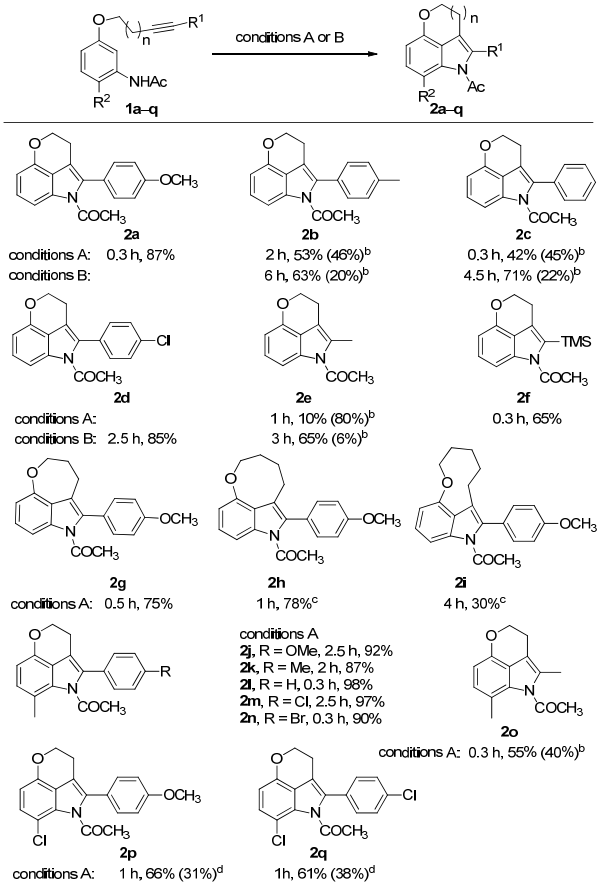
ChemComm Accepted Manuscript

mol%) and $Cu(OAc)_2•H_2O$ (210 mol%) in *t*-AmOH at 120°C gave the desired 3,4-fused tricyclic indole **2a** in 87%yield(Table 1, entry1, condition A). However, under the identical conditions the substrate *N*-(3-((4-(4-chlorophenyl)but-3-yn-1-yl)oxy)phenyl)acetamide**1d** gave the amidoarylation product**2d** only in 26% yield along with the hydroarylation product **3d** in 51% yield (Table 1, entry 2). These results indicated that the electronic effect of the aryl groups attached to the triple bond have a strong effect on the pathways of amidoarylation and hydroarylation. Then, the reaction conditions of both the amidoarylation product **2d** and the hydroarylation product **3d** were further optimized. Aprotic solvent, acetonitrile increased the yield of tricyclic indole **2d** to 85% (Table 1, entry 3, conditions B), and replacement of $Cu(OAc)_2$ with pivalic acid (5.0 equiv)[21] resulted in the hydroarylation product **3d** exclusively (Table 1, entry 4, conditions C).

With the optimal conditions in hand, we surveyed various substrates to determine the scope of the amidoarylation reaction. Under the reaction conditions A or B, the reactions proceeded smoothly to afford tricyclic indoles **2** in good to excellent yields (Table 2). The substituents on the alkyne (R^1 group) were well tolerated with electron-rich and electron-deficient aryl, phenyl, alkyl and trimethylsilyl groups and gave the tricyclic indoles in good to high yield (**2a**–**f**)along with thehydroarylation by-products in the cases of **2b**, **2c** and **2e**. These results reveal that the amidoarylation pathwayis quite sensitive to the electronic effect of the substituents on the alkyne.In comparison, substrates with both electron-rich and electron-deficient R^2 groups resulted in the amidoarylation products exclusively in excellent yields under conditions A,no matter which substituents were attached to the alkyne group (**2j**–**q**). It is most likely that the steric effect of the R^2 groups facilitate this amidoarylation process. Compared with the palladium-catalyzed 3,4-fused tricyclic indole synthesis,[17] the rhodium(III)-catalyzed protocol is more practical due to its low catalystloading (1 mol% in most cases vs 20 mol%) and without high dilution (0.1 M vs 0.01 M). In addition, The intramolecular reaction could be extended togenerate 3,4-medium-ring fusedindoles (**2g**–**i**), which are especially difficult to prepare.[25]

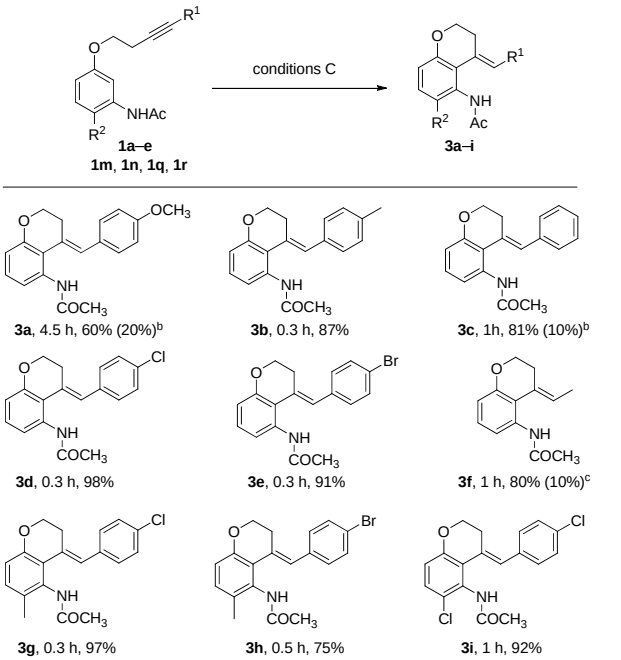
The intramolecular amidoarylation process mentioned above represents a very simple and efficient methodology for the construction of 3,4-fused tricyclic indoles which is highly atom- and step-economic. Since the construction of distinct types of complex molecules from identical starting materials is an attractive and challenging task in organic synthesis,[26] the preparation of chromans **3** from the hydroarylation reactions of *N*-(3-((but-3-yn-1-yl)oxy)phenyl)acetamides**1**was also investigated. In the presence of $(Cp^*RhCl_2)_2$ (2.5 mol%), $AgSbF_6$ (10 mol%) and pivalic acid (5.0 equiv), the reactions smoothly proceeded at 120 °C to afford chromans in good to excellent yields(Table 3). Substrates with different substituents on the alkyne (R^1), such as electron-rich and -deficient aryl, phenyl and

Table 2 Synthesis of tricyclic indoles **2a**



[a]Reactions conducted on 0.2 mmol scale. Conditions A: $(Cp^*RhCl_2)_2$ (1 mol%), $AgSbF_6$ (4 mol%), $Cu(OAc)_2•H_2O$ (2.1 equiv), *t*-AmOH (0.1 M), 120 °C; Conditions B: $(Cp^*RhCl_2)_2$ (5 mol%), $AgSbF_6$ (20 mol%), $Cu(OAc)_2•H_2O$ (2.1 equiv), CH_3CN (0.1 M), 120 °C. [b]Yields of the corresponding hydroarylation products **3** are in parentheses. [c]Conditions A, $(Cp^*RhCl_2)_2$ (10 mol%), 0.01 M. [d]Yields of products **2a** and **2d** are in parentheses (from the dechlorination of **2p** and **2q** respectively).

Table 3 Synthesis of chromans **3**



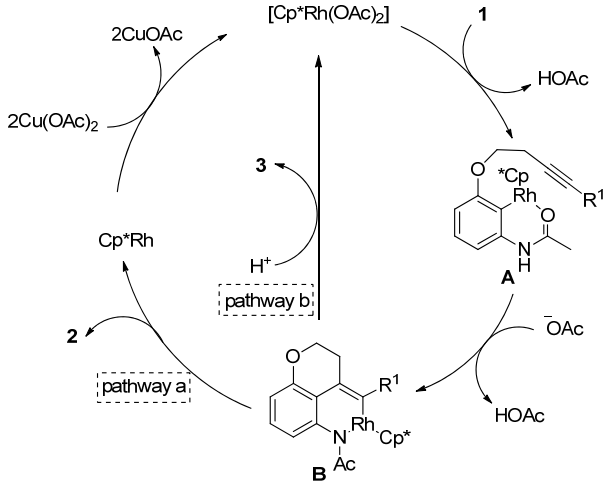
[a]Reactions conducted on 0.2 mmol scale. Conditions C: $(Cp^*RhCl_2)_2$ (2.5 mol%), $AgSbF_6$ (10 mol%), PivOH (5.0 equiv), *t*-AmOH (0.1 M), 120°C. [b]PivOH (1.0 equiv), yields of the corresponding tricyclic indoles **2** are in parentheses. [c]Conditions A, yields of tricyclic indoles **2e** is in parentheses.

ChemComm Accepted Manuscript

This journal is © The Royal Society of Chemistry [year]

alkyl groups were well tolerated (**3a**–**f**). Substrates with both electron-donating and electron-withdrawing R^2groups participated in this reaction (**3g**–**i**).Unlike the amidoarylation, the hydroarylation pathway has slight effect on the electronic and steric effectof the R^1 and R^2 substituents. Furthermore, thesereactionsgave the alkene products with *E* selectivity, and the results are consistent with those from the intermolecularversion of the hydroarylation reaction.[21] The configuration of **3f** was established by the X-ray single crystal analysis,[27] and others were determined by analogy with their NMR spectra.Migratoryinsertion of alkyne to form an alkenylrhodium intermediate,

On the basis of the above results (Table 1–3) and the related work,[19,21,23] a mechanistic pathway is proposed (Scheme 1). First, C–H bond cleavage of **1** occurs to produce a six-membered rhodacycle intermediate **A**. Next, Alkyne coordination to rhodium and migratory insertion of alkyne into the rhodium−carbon bond results in the formation of intermediate **B**. Then two pathways may exist,in pathway a, the carbon-nitrogen bond is formed to produce the tricyclic indoles **2** after reductive elimination, at which time the Rh(III) is reduced to Rh(I), reoxidation of the reduced catalyst with the copper(II) oxidant restores the catalytically active rhodium(III)-complex. In pathway b, intermediate **B** is protonated by the pivalic acid to give the corresponding alkene derivative **3**withregeneration of the catalyst.In addition, the hydroarylation product **3g** was treated with the amidoarylation conditions (Table 1 and 2, conditions A) for 10 h, the corresponding tricyclic indole product **2m** could not be detected. This result indicates that the hydroarylation product **3** is not the intermediate for the formation of tricyclic indole product **2** from the amidoarylation of **1** under these conditions.



Scheme 1 Proposed mechanism for the formation of **2** and **3**.

In summary, we have developed a Rh(III)-catalyzed intramolecular amidoarylation and hydroarylation for the switchable syntheses of 3,4-fused tricyclic indoles and chromans from alkyne tethered acetanilides via aryl C−H bonds activation. In this process, two distinct types of complex moleculesfrom the identical starting materials areachieved simply by a slight change of reaction conditions. The reaction features atom- and step-economy, high product yields and practical procedure. The synthetic applications of this protocol are being carried out in our laboratory.

Financial supports of this research provided by the NNSFC (21172030 and 21272034), the Young Scientific Research Foundation of Jilin Province (20140520083JH) and the Fundamental Research Funds for the Central Universities (12QNJJ010) are greatly acknowledged.

Notes and references

1 S. Qu, Q. Liu, C. Tan, S. Jiang and D. Zhu, *Planta Med.*, 2006, **72**, 264.

2 For a recent synthesis, see: A. J. Peat and S. L. Buchwald, *J. Am. Chem. Soc.*,1996, **118**, 1028.

3 For total synthesis of N-methylwelwitindolinone, see: (a) V. Bhat, K. M. Allan and V. H. Rawal, *J. Am. Chem. Soc.*,2011, **133**, 5798; (b) A. D. Huters, K. W. Quasdorf, E. D. Styduhar and N. K. Garg, *J. Am. Chem. Soc.*,2011, **133**, 15797.

4 For recent total synthesis of lysergic acid, see: (a) S. Umezaki, S. Yokoshima, T. Fukuyama, *Org. Lett.,* 2013, **15**, 4230; (b) Q. Liu, Y.-A. Zhang, P. Xu, Y. Jia, *J. Org. Chem.,* 2013, **78**, 10885;(c) Q. Liuand Y. Jia, *Org. Lett.,* 2011, **13**, 4810; (d) A. Iwata, S. Inuki, S. Oishi, N. Fujiiand H. Ohno, *J. Org. Chem.,* 2011, **76**, 5506; (e) T. Kurokawa, M. Isomura, H. Tokuyamaand T. Fukuyama, *Synlett,* 2009, 775.

5 For total synthesis of dragmacidin E, see: K. S. Feldmanand P. Ngernmeesri, *Org. Lett.,* 2011, **13**, 5704.

6 For total synthesis of decursivine, see: (a) L. Guo, Y. Zhang, W. Hu, L. Li and Y. Jia, *Chem. Commun.*,**2014**, *50*, 3299; (b) W. Hu, H. Qin, Y. Cuiand Y. Jia, *Chem. Eur. J.*,2013, **19**, 3139;(c) M. Mascal, K. V. Modesand A. Durmus, *Angew. Chem. Int. Ed.*, 2011, **50**, 4445; (d) H. Qin, Z. Xu, Y. Cuiand Y. Jia, *Angew. Chem. Int. Ed.*, 2011, **50**, 4447; (e) D. Sun, Q. Zhaoand C. Li, *Org. Lett.,* 2011, **13**, 5302; (f) Y. Koizumi, H. Kobayashi, T.Wakimoto, T. Furuta, T. Fukuyama and T. Kan, *J. Am. Chem. Soc.,* 2008, **130**, 16854; (g) A. B. Leducand M. A. Kerr, *Eur. J. Org. Chem.*, 2007, 237.

7 For total synthesis of communesin F, see: (a) J. Belmarand R. L. Funk, *J. Am. Chem. Soc.*, 2012, **134**, 16941; (b) Z. Zuo,W. Xie and D. Ma, *J. Am. Chem. Soc.*, 2010, **132**, 13226; (c) P. Liu, J. H. Seo and S. M. Weinreb, *Angew. Chem. Int. Ed.,* 2010, **49**, 2000; (d) J. Yang, H. Wu, L. Shen and Y. Qin, *J. Am. Chem. Soc.,* 2007, **129**, 13794.

8 For total synthesis of indolactam V, see:(a) S. M. Bronner, A. E. Goetzand N. K. Garg, *J. Am. Chem. Soc.,* 2011, **133**, 3832; (b) Z. Xu, F. Zhang, L. Zhangand Y. Jia, *Org. Biomol. Chem.*, 2011, **9**, 2512; (c) S. M. Bronner, A. E. Goetzand N. K. Garg, *Synlett*, 2011, 2599.

9 For a review for the synthesis of 3,4-Fused tricyclic indoles, see: D. Shan and Y. Jia, *Chin. J. Org. Chem.,* 2013, **33**, 1144.

10 For synthesis of 3,4-fused indoles by intramolecular Fischer indole syntheses, see: (a) I.-K. Park, J. Parkand C.-G. Cho, *Angew. Chem. Int. Ed.*, 2012, **51**, 2496; (b) J. Park, S.-Y. Kim, J.-E. Kim and C.-G. Cho, *Org. Lett.,* 2014, **16**, 178.

11 For selected examples of synthesis of 3,4-fused indolesby the Pictet–Spengler reaction, see: (a) H.Schçnherrand J. L. Leighton, *Org. Lett.*,2012, **14**, 2610; (b) D.-J. Cheng, H.-B. Wuand S.-K. Tian, *Org. Lett.,* 2011, **13**, 5636;(c) K. Yamada, Y. Namerikawa, T. Haruyama, Y. Miwa, R.Yanadaand M. Ishikura, *Eur. J. Org. Chem.*, 2009, 5752.

12 For selected examples of synthesis of 3,4-fused indolesby the intramolecular Friedel–Craftsreaction, see: (a) R. J. Raffertyand R. M. Williams, *J. Org. Chem.*,2012, **77**, 519; (b) E. Fillionand A. M. Dumas, *J. Org. Chem.*,2008, **73**, 2920.

13 For selected examples of synthesis of 3,4-fused indoles by the intramolecular Diels–Alder reaction, see: (a) B. M. Trostand P. J. McDougall, *Org. Lett.,* 2009,**11**, 3782; (b) R. Lauchliand K. J. Shea, *Org. Lett.,* 2006, **8**,5287; (c) S. K. Burand A. Padwa, *Org. Lett.,*2002, **4**, 4135.

14 For selected examples of synthesis of 3,4-fused indoles by transition metal catalyzed reactions, see: (a) T. Miura, Y. Funakoshi and M.

ChemComm Accepted Manuscript

Murakami, *J. Am. Chem. Soc.*, 2014, **136**, 2272; (b) C. Zheng, J. J. Chen and R. Fan, *Org. Lett.,* 2014, *16*, 816; (c) Q. Xu, L. Daiand S. You, *Chem. Sci.* 2013, **4**, 97; (d) M. Hellal, S. Singhand G. D. Cuny, *J. Org. Chem.*, 2012, **77**, 4123; (e) V. A. Peshkov, S. V. Hove, P. A. Donets,O. P. Pereshivko, K. V. Hecke, L. V. Meerveltand E. V. Van der Eycken, *Eur. J. Org. Chem.*, 2011, 1837; (f) H. J. Lim, J. C. Gallucciand T. V. RajanBabu, *Org. Lett.,* 2010, **12**, 2162; (g) P. S. Baran, J. Thomas, T. J. Maimoneand J. M. Richter, *Nature,* 2007, **446**, 404.

15 For synthesis of 3,4-fused indoles by 6π-electrocyclizations, see: T. J. Greshockand R. L. Funk, *J. Am. Chem. Soc.*, 2006, **128**, 4946.

16 S. P. Breazzano, Y. B. Poudel and D. L. Boger, *J. Am. Chem. Soc.,* 2013, **135**, 1600.

17 D. Shan, Y. Gao and Y. Jia, *Angew. Chem. Int. Ed.,*2013, **52**, 4902.

18 Reviews on rhodium(III)-catalyzed C−H activation: (a) G. Song, F.Wang and X. Li, *Chem. Soc. Rev.*, 2012, **41**, 3651; (b) F. W. Patureau, J. Wencel-Delord and F. Glorius, *Aldrichimica Acta,* 2012, **45**, 31; (c) T. Satoh and M. Miura, *Chem.Eur. J.*,2010, **16**, 11212; (d) D. A. Colby, A. S. Tsai, R. G. Bergman and J. A. Ellman, *Acc. Chem. Res.*,2011, **45**, 814.

19 (a) D. R. Stuart, M. Bertrand-Laperle, K. M. N. Burgess, and K. Fagnou, *J. Am. Chem. Soc.*, 2008, **130**, 16474; (b) D. R. Stuart, P. Alsabeh, M. Kuhn, and K. Fagnou, *J. Am. Chem. Soc.,* 2010, **132**, 18326.

20 (a) C.Wang, H.Sun, Y.Fang and Y.Huang, *Angew. Chem. Int. Ed.,* 2013, **52**, 5795; (b) C. Wang and Y. Huang, *Org. Lett.,* 2013, **15**, 5294; (c) B. Liu, C. Song, C. Sun, S. Zhou and J. Zhu, *J. Am. Chem. Soc.,* 2013, **135**, 16625; (d) D. Zhao, Z. Shiand F. Glorius, *Angew. Chem. Int. Ed.,* 2013, **52**, 12426.

21 For Rh(III)-catalyzed hydroarylation, see: (a) D. J. Schipper, M. Hutchinson and K. Fagnou, *J. Am. Chem. Soc.* 2010, **132**, 6910; (b) F. Wang, Z. Qi, J. Sun, X. Zhang and X. Li, *Org. Lett.,*2013, **15**, 6290.

22 For Ru-catalyzed hydroarylation, see: (a) M. C. Reddy and M. Jeganmohan, *Chem. Commun.,* 2013, **49**, 481; (b) Y. Hashimoto, K. Hirano, T. Satoh, F. Kakiuchi and M. Miura, *Org. Lett.,* 2012, **14**, 2058; (c) P. Zhao, R. Niu, F. Wang, K. Han and X. Li, *Org. Lett.,* 2012, **14**, 4166.

23 Very recently, Rh(III)-catalyzed intramolecular hydroarylation and amidoarylation of alkenes by an amide directing group were reported, see: (a) T. A. Davis, T. K. Hyster and T. Rovis, *Angew. Chem. Int. Ed.,* 2013, **52**, 14181; (b) B. Ye, P. A. Donets and N. Cramer, *Angew. Chem. Int. Ed.,* 2014, **53**, 507; (c) Z. Shi, M. Boultadakis-Arapinis, D. C. Koester and F. Glorius, *Chem. Commun.,* 2014,**50**, 2650.

24 (a) X. Xu, Y. Liu and C.-M. Park, *Angew. Chem. Int. Ed.,* 2012, **51**, 9372; (b)W. Yang, J. Sun, X. Xu, Q. Zhang and Q. Liu, *Chem. Commun.*, 2014, **50**, 4420.

25 (a) A. Parenty, X. Moreau, J.-M. Campagne, *Chem. Rev.*,2006, **106**, 911; (b) T. Gulder, P. S. Baran, *Nat. Prod. Rep.*, 2012, **29**, 899; (c) S. Ma, E.-I. Negishi, *J. Am. Chem. Soc.,* 1995, **117**, 6345.

26 For recent reports, see: (a) B. Alcaide, P. Almendros and T. M. del Campo, *Angew. Chem. Int. Ed.,* 2007, **46**, 6684; (b) X. Jiang, X. Ma, Z. Zheng and S. Ma, *Chem.–Eur. J.,* 2008, **14**, 8572; (c) L. Liu and J. Zhang, *Angew. Chem. Int. Ed.,* 2009, **48**, 6093; (d) A. S. Dudnik, Y. Xia, Y. Li and V. Gevorgyan, *J. Am. Chem. Soc.,* 2010, **132**, 7645; (e) P. A. Evans, J. R. Sawyer and P. A. Inglesby, *Angew. Chem. Int. Ed.,* 2010, **49**, 5746.

27 CCDC 993319 (**3f**) contain the supplementarycrystallographic data for this paper. These data can be obtainedfree of charge from The Cambridge Crystallographic DataCentre via www.ccdc.cam.ac.uk/data_request/cif.

ChemComm Accepted Manuscript

 This journal is © The Royal Society of Chemistry [year]