ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2014, **50**, 7306

Received 1st April 2014,
Accepted 20th May 2014

DOI: 10.1039/c4cc02398f

www.rsc.org/chemcomm

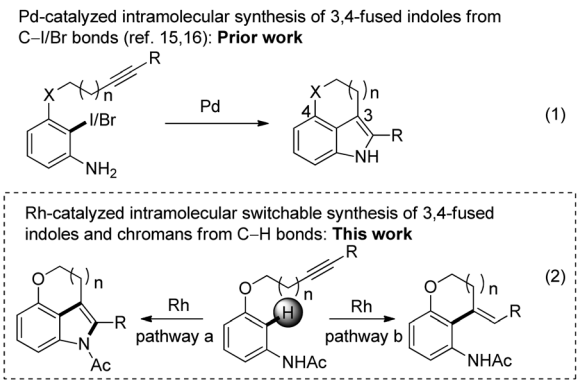
Rhodium(III)-catalyzed intramolecular amidoarylation and hydroarylation of alkyne *via* C–H activation: switchable synthesis of 3,4-fused tricyclic indoles and chromans†

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

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 as fargesine,[1] dehydrobufotenine,[2] welwistatin,[3] lysergic acid,[4] dragmacidin E,[5] decursivine,[6] communesin F,[7] and indolactam V.[8] The formation 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 such polycyclic indoles from 2-bromo- or 2-iodoanilines with an alkyne tethered at the 3-position (eqn (1)).

Due to its high atom- and step-economy, the rhodium(III)-catalyzed C–H activation has gained significant interest in recent years.[18] In 2008, Fagnou and 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, $(Cp^*RhCl_2)_2$ has emerged as an efficient catalyst for alkyne hydroarylation with the aryl C–H bond *via* a novel concerted deprotonation–metalation pathway.[21] Several examples of intermolecular hydroarylation of alkynes have recently 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 the above two pathways of alkyne has 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 acetanilides *via* C–H activation (eqn (2)). It is worth mentioning that the construction of two distinct types of complex molecules from the identical starting materials is achieved simply by a slight change in reaction conditions.



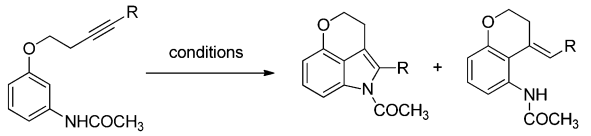
Initially, *N*-(3-((4-(4-methoxyphenyl)but-3-yn-1-yl)oxy)phenyl)-acetamide **1a** was subjected to Fagnou's intermolecular reaction conditions[19a] (Table 1, entry 1). We found that treatment of **1a** with $(Cp^*RhCl_2)_2$ (1 mol%), $AgSbF_6$ (4 mol%) and $Cu(OAc)_2{\cdot}H_2O$ (210 mol%) in *t*-AmOH at 120 °C gave the desired 3,4-fused tricyclic indole **2a** in 87% yield (Table 1, entry 1, 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 has 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. The aprotic solvent acetonitrile increased the yield of tricyclic indole **2d** to 85% (Table 1, entry 3, condition B), and replacement of $Cu(OAc)_2$ with

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

† Electronic supplementary information (ESI) available: Experimental details and spectral data for **3**. CCDC 993319. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4cc02398f

‡ Both authors contributed equally to this work.

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)

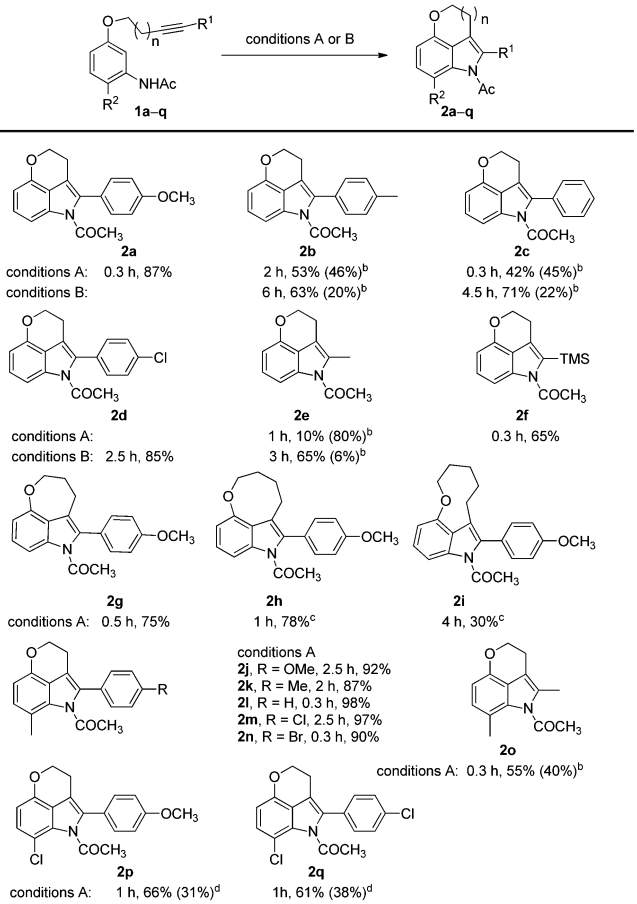
[a] Reactions conducted on a 0.2 mmol scale. Condition A: $(Cp^*RhCl_2)_2$ (1 mol%), $AgSbF_6$ (4 mol%), $Cu(OAc)_2{\cdot}H_2O$ (2.1 equiv.), *t*-AmOH (0.1 M), 120 °C; condition B: $(Cp^*RhCl_2)_2$ (5 mol%), $AgSbF_6$ (20 mol%), $Cu(OAc)_2{\cdot}H_2O$ (2.1 equiv.), CH_3CN (0.1 M), 120 °C; condition C:$(Cp^*RhCl_2)_2$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

pivalic acid (5.0 equiv.)[21] resulted in the hydroarylation product **3d** exclusively (Table 1, entry 4, condition 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 the hydroarylation by-products in the cases of **2b**, **2c** and **2e**. These results reveal that the amidoarylation pathway is 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 condition 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 facilitates 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 catalyst loading (1mol% in most cases *vs.* 20 mol%) without high dilution (0.1 M *vs.* 0.01 M). In addition, the intramolecular reaction could be extended to generate 3,4-medium-ring fused indoles (**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 proceeded smoothly at 120 °C to afford chromans in good to excellent yields (Table 3).

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

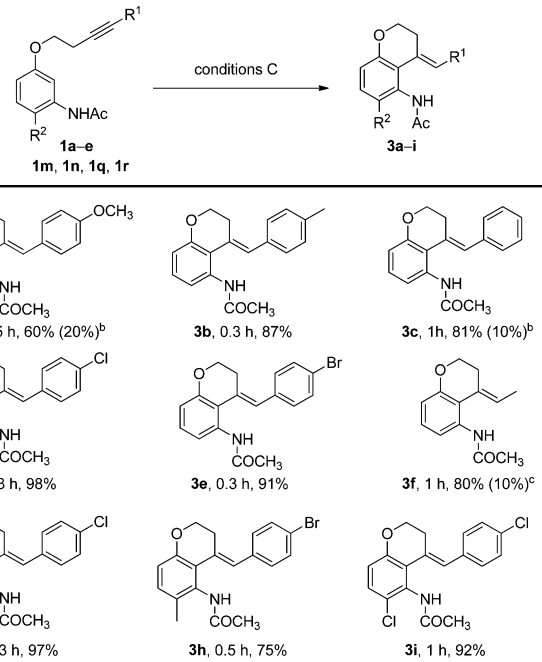


[a] Reactions conducted on a 0.2 mmol scale. Condition A: $(Cp^*RhCl_2)_2$ (1 mol%), $AgSbF_6$ (4 mol%), $Cu(OAc)_2{\cdot}H_2O$ (2.1 equiv.), *t*-AmOH (0.1 M), 120 °C; condition B: $(Cp^*RhCl_2)_2$ (5 mol%), $AgSbF_6$ (20 mol%), $Cu(OAc)_2{\cdot}H_2O$ (2.1 equiv.), CH_3CN (0.1 M), 120 °C. [b] Yields of the corresponding hydroarylation products **3** are in parentheses. [c] Condition 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).

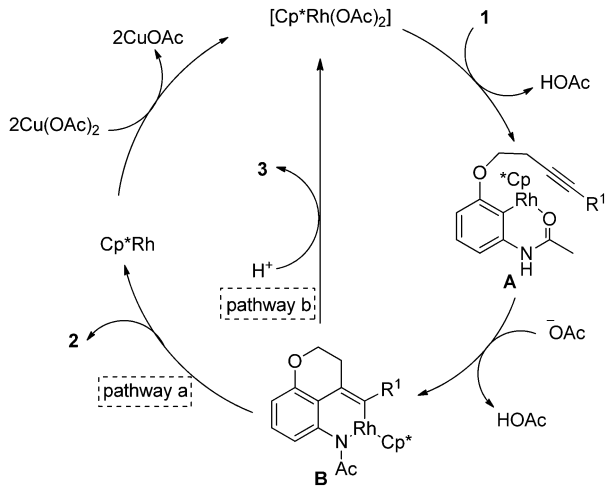
Substrates with different substituents on the alkyne (R^1), such as electron-rich and -deficient aryl, phenyl and alkyl groups, were well tolerated (**3a–f**). Substrates with both electron-donating and electron-withdrawing R^2 groups participated in this reaction (**3g–i**).Unlike the amidoarylation, the hydroarylation pathway has a slight effect on the electronic and steric effect of the R^1 and R^2 substituents. Furthermore, these reactions gave the alkene products with *E* selectivity, and the results are consistent with those obtained from the intermolecular version 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.

On the basis of the above results (Tables 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

Table 3 Synthesis of chromans **3**[a]



[a] Reactions conducted on a 0.2 mmol scale. Condition 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] Condition A, yields of tricyclic indoles **2e** are in parentheses.



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

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** with regeneration of the catalyst. In addition, the hydroarylation product **3g** was treated with the amidoarylation conditions (Tables 1 and 2, condition 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 in the formation of tricyclic indole product **2** from the amidoarylation of **1** under these conditions.

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 bond activation. In this process, two distinct types of complex molecules from the identical starting materials are achieved simply by a slight change of reaction conditions. The reaction features atom- and step-economy, high product yields and a practical procedure. Studies on the synthetic applications of this protocol are being carried out in our laboratory.

Financial support for 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) is 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 and T. Fukuyama, *Org. Lett.*, 2013, **15**, 4230; (*b*) Q. Liu, Y.-A. Zhang, P. Xu and Y. Jia, *J. Org. Chem.*, 2013, **78**, 10885; (*c*) Q. Liu and Y. Jia, *Org. Lett.*, 2011, **13**, 4810; (*d*) A. Iwata, S. Inuki, S. Oishi, N. Fujii and H. Ohno, *J. Org. Chem.*, 2011, **76**, 5506; (*e*) T. Kurokawa, M. Isomura, H. Tokuyama and T. Fukuyama, *Synlett*, 2009, 775.
5 For total synthesis of dragmacidin E, see: K. S. Feldman and 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. Cui and Y. Jia, *Chem. – Eur. J.*, 2013, **19**, 3139; (*c*) M. Mascal, K. V. Modes and A. Durmus, *Angew. Chem., Int. Ed.*, 2011, **50**, 4445; (*d*) H. Qin, Z. Xu, Y. Cui and Y. Jia, *Angew. Chem., Int. Ed.*, 2011, **50**, 4447; (*e*) D. Sun, Q. Zhao and 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. Leduc and M. A. Kerr, *Eur. J. Org. Chem.*, 2007, 237.
7 For total synthesis of communes in F, see: (*a*) J. Belmar and 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. Goetz and N. K. Garg, *J. Am. Chem. Soc.*, 2011, **133**, 3832; (*b*) Z. Xu, F. Zhang, L. Zhang and Y. Jia, *Org. Biomol. Chem.*, 2011, **9**, 2512; (*c*) S. M. Bronner, A. E. Goetz and 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. Park and 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 indoles by the Pictet–Spengler reaction, see: (*a*) H. Schçnherr and J. L. Leighton, *Org. Lett.*, 2012, **14**, 2610; (*b*) D.-J. Cheng, H.-B. Wu and S.-K. Tian, *Org. Lett.*, 2011, **13**, 5636; (*c*) K. Yamada, Y. Namerikawa, T. Haruyama, Y. Miwa, R. Yanada and M. Ishikura, *Eur. J. Org. Chem.*, 2009, 5752.
12 For selected examples of synthesis of 3,4-fused indoles by the intramolecular Friedel–Crafts reaction, see: (*a*) R. J. Rafferty and R. M. Williams, *J. Org. Chem.*, 2012, **77**, 519; (*b*) E. Fillion and 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. Trost and P. J. McDougall, *Org. Lett.*, 2009, **11**, 3782; (*b*) R. Lauchli and K. J. Shea, *Org. Lett.*, 2006, **8**; (*c*) S. K. Bur and 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. 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. Dai and S. You, *Chem. Sci.*, 2013, **4**, 97; (*d*) M. Hellal, S. Singh and 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. Meervelt and E. V. Van der Eycken, *Eur. J. Org. Chem.*, 2011, 1837; (*f*) H. J. Lim, J. C. Gallucci and T. V. RajanBabu, *Org. Lett.*, 2010, **12**, 2162; (*g*) P. S. Baran, J. Thomas, T. J. Maimone and J. M. Richter, *Nature*, 2007, **446**, 404.
15 For synthesis of 3,4-fused indoles by 6π-electrocyclizations, see: T. J. Greshock and 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. Shi and 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 and J.-M. Campagne, *Chem. Rev.*, 2006, **106**, 911; (*b*) T. Gulder and P. S. Baran, *Nat. Prod. Rep.*, 2012, **29**, 899; (*c*) S. Ma and 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**).