Nitrogen Heterocycles

Direct Synthesis of Protoberberine Alkaloids by Rh-Catalyzed C–H Bond Activation as the Key Step

Jayachandran Jayakumar and Chien-Hong Cheng*[a]

Abstract: A one-pot reaction of substituted benzaldehydes with alkyne–amines by a Rh-catalyzed C–H activation and annulation to afford various natural and unnatural protoberberine alkaloids is reported. This reaction provides a convenient route for the generation of a compound library of protoberberine salts, which recently have attracted great attention because of their diverse biological activities. In addition, pyridinium salt derivatives can also be formed in good yields from α,β-unsaturated aldehydes and amino–alkynes. This reaction proceeds with excellent regioselectivity and good functional group compatibility under mild reaction conditions by using O_2 as the oxidant.

Introduction

Protoberberine derivatives, including palmatines and berberines,[1] are found in many natural products and have attracted great attention, because of their diverse biological activities, such as antimalarial, anti-arrhythmic, antitumor, inhibitory, antileukemia, antibacterial, anti-inflammatory, and cytotoxicity (see Figure 1).[2,3] Although a few approaches are available for the synthesis of protoberberines, most of the approaches are limited by the scope and lengthy synthetic sequences (Scheme 1 a).[3] As a result, most of the protoberberines used for biological studies are still obtained from the extract of the related plants.

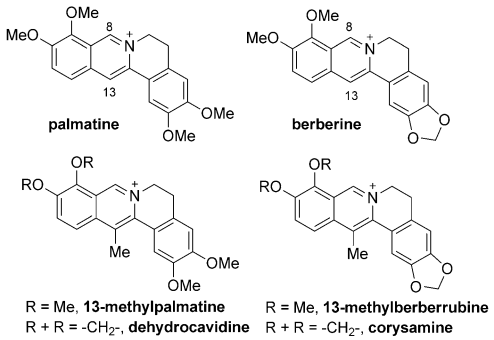
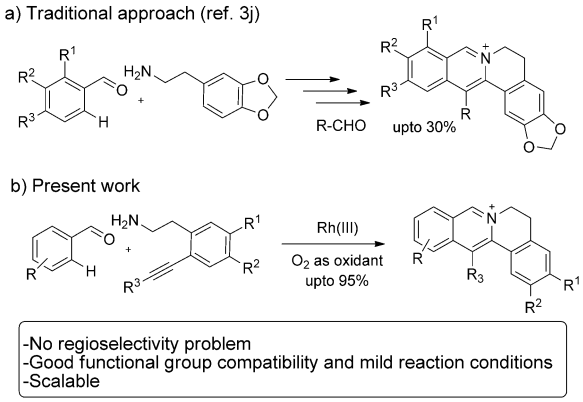


Figure 1. Typical protoberberine natural products.



Scheme 1. Methods for the synthesis of isoquinoline derivatives.

The transition-metal-catalyzed C–H activation reactions offer great opportunities for the synthesis of complex molecules from halide-free starting materials.[4] In recent years, the intermolecular Rh^{III} or Ru^{II}-catalyzed C–H activation and cyclization with alkynes represent a powerful tool for the synthesis of highly functionalized heterocycles.[5–7] However, in most cases, the reactions with unsymmetrical alkynes show low regioselectivity. Consequently, intramolecular reactions are highly attractive in terms of regioselectivity, high efficiency, and versatility for fused heterocyclic compounds. A highly enantioselective intramolecular hydroarylation of alkene tethers by Rh^{III}-catalyzed *ortho*-directed C–H bond activations is known.[8] However, only two intramolecular reactions for alkyne tethers have been reported recently. Park and co-workers revealed a Rh^{III}-catalyzed intramolecular annulation of alkyne-tethered hydroxamic esters to afford 3-hydroxyalkylisoquinolones and 6-hydroxyalkyl-2-pyridones,[9] while Mascareñas, Gulías and co-workers reported a Rh-catalyzed synthesis of tricyclic isoquinolines by the intramolecular annulations of alkyne-tethered benzamides.[10].

Our continuous interest in the metal-catalyzed C–H bond activation/cyclization reactions[11] and our experience in isoquinolinium salt synthesis[12] stimulated us to develop a highly effi-

[a] Dr. J. Jayakumar, Prof. Dr. C.-H. Cheng
Department of Chemistry
National Tsing Hua University
Hsinchu 30013 (Taiwan)
Fax: (+886) 35724698
E-mail: chcheng@mx.nthu.edu.tw
Homepage: http://mx.nthu.edu.tw/%7Echcheng

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201504378.

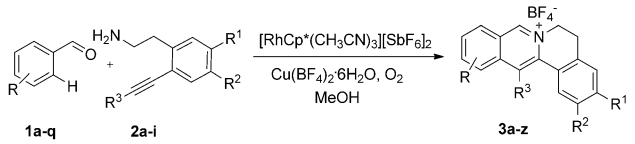
cient methodology for the synthesis of various protoberberine salts, including five 13-substituted protoberberine alkaloids (Scheme 1b), by a Rh-catalyzed C–H bond activation reaction as the key step. The catalytic reaction features the in situ formation of an imine moiety, as the directing group, for the C–H bond activation and intramolecular annulation, thus providing a convenient route for the generation of a compound library of protoberberine salts and natural products for screening their biological activities. Recently, a few examples of Rh^{III}-catalyzed synthesis of isoquinolinium and cinnolinium salts have been reported.[13] Our present strategy involves a one-pot synthesis of protoberberine salts by the Rh^{III}-catalyzed C–H activation and annulations of substituted benzaldehydes with 1-(2-aminoethyl)-2-alkynylarenes (Scheme 1b).

Results and Discussion

We started the optimization studies for the one-pot reaction of benzaldehyde (**1a**) with alkyne–amine **2a** to give protoberberine salt **3a** using various rhodium(III) and ruthenium(II) complexes as the catalysts. After careful investigation of the reaction conditions, we found that treating benzaldehyde (**1a**; 0.36 mmol) with alkyne–amine (**2a**; 0.30 mmol) in the presence of $[RhCp^*(CH_3CN)_3][SbF_6]_2$ (2.5 mol%) and $Cu(BF_4)_2{\cdot}6H_2O$ (60.0 mol%) in MeOH at 60 °C under O_2 (1 atm) for 6 h afforded protoberberine salt **3a** in 94% isolated yield (see Table S1 in the Supporting Information for details). It is worth noting that dioxygen, an inexpensive oxidant, can be used even though the catalytic reaction required some copper source. The structure of **3a** containing an isoquinolinium cation and tetrafluoroborate anion was confirmed by its ^1H, ^{13}C, ^{19}F, and ^{11}B NMR, and mass data. Substrate **2** was prepared from commercially available 2-aminoethylarene in four steps in 80–88 yields (see the Supporting Information).[14] The above conditions were then employed as the standard conditions for the reactions of various substituted benzaldehydes with amino–alkynes to form the corresponding protoberberine salts **3**.

To understand the substrate scope of this catalytic reaction, we investigated the reactions of *p*-substituted benzaldehydes **1b–k** with alkyne–amine **2a** under the standard reaction conditions (Table 1). The reactions of electron-donating 4-*tert*-butyl-, 4-*N*,*N*′-dimethyl-, and 4-methoxy-substituted benzaldehydes (**1b–d**) with **2a** smoothly afforded **3b–d** in 82–94% yields (entries 2–4). Similarly, the reactions of electron-withdrawing 4-fluoro-, 4-chloro-, 4-bromo-, 4-trifluoromethyl, 4-methylester, and 4-nitro-substituted benzaldehydes (**1e–j**) with **2a** smoothly afforded **3e–j** in 78–90% yields (entries 5–10). The reaction of 4-phenylbenzaldehyde (**1k**) afforded **3k** in 84% yield (entry 11) and 2,4-dimethylbenzaldehyde (**1l**) gave **3l** in 86% yield (entry 12). Highly substituted 3,4,5-trimethoxybenzaldehyde (**1m**) underwent cyclization with **2a** efficiently to afford **3m** in 95% yield (entry 13). However, the reaction of

Table 1. Results of the reaction of benzaldehydes with alkyne–amines.[a]



1a-q **2a-i** **3a-z**

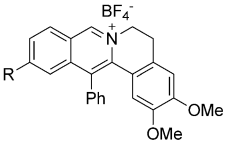
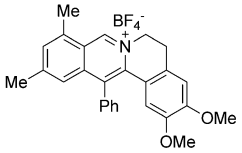
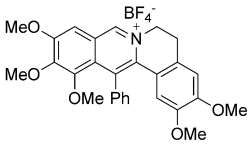
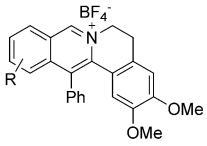
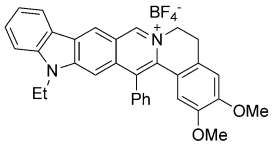
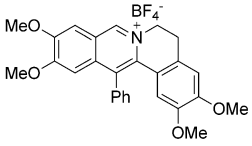
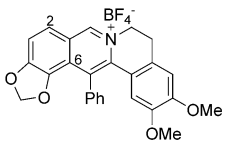
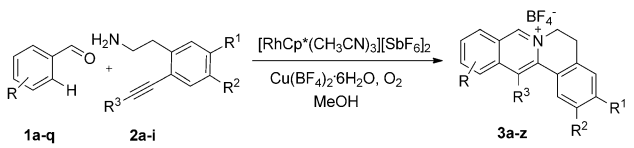
			Product		Yield [%][b]
1	**1a**	**2a**		**3a**: R = 4-H	94
2	**1b**	**2a**		**3b**: R = 4-*t*Bu	85
3	**1c**	**2a**		**3c**: R = 4-*N*(CH_3)$_2$	82
4	**1d**	**2a**		**3d**: R = 4-OMe	94
5	**1e**	**2a**		**3e**: R = 4-F	86
6	**1f**	**2a**		**3f**: R = 4-Cl	80
7	**1g**	**2a**		**3g**: R = 4-Br	82
8	**1h**	**2a**		**3h**: R = 4-CF_3	78
9	**1i**	**2a**		**3i**: R = 4-CO_2Me	85
10	**1j**	**2a**		**3j**: R = 4-NO_2	90
11	**1k**	**2a**		**3k**: R = 4-Ph	84
12	**1l**	**2a**		**3l**	86
13	**1m**	**2a**		**3m**	95
14	**1n**	**2a**		**3n**: R = 3-OMe **3n′**: R = 5-OMe	86 (1:1)
15	**1o**	**2a**		**3o**	90
16	**1p**	**2c**		**3p**	85
17	**1q**	**2a**		**3q**	82

Table 1. (Continued)



1a-q 2a-i 3a-z

			Product	Yield [%][b]
18		**2b**	**3r**: R^3 = 3-thiophene	82
19		**2c**	**3s**: R^3 = Me	88
20	**1a**	**2d**	**3t**: R^3 = *t*Bu	84
21		**2e**	**3u**: R^3 = *n*-Pr	80
22		**2f**	**3v**: R^3 = cyclopropyl	78
23	**1a**	**2g**	**3w**: R^3 = cyclohex-1-enyl	81
24	**1a**	**2h**	**3x**: R^3 = *n*-octyl	76
25	**1a**	**2i**	**3y** R^1,R^2 = O-CH_2-O	85
26	**1a**	**2j**	**3z** R^1R^2 = H	88

[a] All reactions were carried out using aryl aldehyde **1** (0.36 mmol), alkyne–amine **2** (0.30 mmol), $[RhCp^*(CH_3CN)_3][SbF_6]_2$ (2.5 mol%), $Cu(BF_4)_2{\cdot}6H_2O$ (60 mol%), O_2 (1 atm), and MeOH (2.5 mL) at 60 °C for 6 h. [b] Isolated yields.

m-substituted 3-methoxy benzaldehyde (**1n**) with **2a** provided two regioisomeric products **3n** and **3n'** in a 1:1 ratio in 86% combined yield (entry 14). *meta*- and *para*-Disubstituted benzaldehydes were also viable substrates; thus, the reactions of 9-ethyl-9*H*-carbazole-3-carbaldehyde (**1o**) and 3,4-dimethoxybenzaldehyde (**1p**) with **2a** afforded **3o** and **3p** in 90 and 85% yields, respectively, with high regioselectivities (entries 15 and 16). Surprisingly, the reaction of 3,4-methylenedioxybenzaldehyde (**1q**) with **2a** proceeded with opposite regioselectivity to afford **3q** in 82% yield (entry 17). It is worth noting that two possible C–H bond activation sites are present at the C2 and C6 of **1q**; the activation occurred at the sterically hindered C6 position. The structure of **3q** was further confirmed by single-crystal X-ray diffraction.[15]

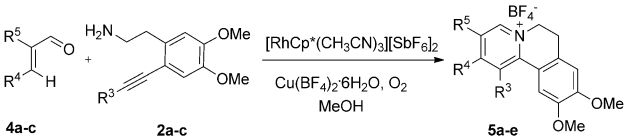
In addition to **2a**, other alkyne–amines (**2b–h**) were also investigated. The reaction of 3-thiophene alkyne–amine **2b** with **1a** afforded the salt product **3r** in 82% yield (entry 18). Similarly, the reactions of methyl-, *tert*-butyl-, *n*-propyl-, cyclopropyl-, octylalkynyl , and cyclohex-1-enyl amines **2c–h** afforded the corresponding protoberberine salts **3s–x** in 76–88% yields (entries 19–24). The reaction of benzaldehyde (**1a**) with alkyne–amine **2i** having a methyl group attached to the alkynyl group and a methylenedioxy moiety connected to the aryl ring afforded **3y** in 85% yield (entry 25). Interestingly, 2-(2-phenylethynyl)phenylethanamine **2j** also reacted smoothly with **1a** to afford **3z** in 88% yield (entry 26).

The present rhodium-catalyzed C–H activation reaction also can be applied to α,β-unsaturated aldehydes and the results are summarized in Table 2. Treatment of methacrylaldehyde (**4a**) with **2a** in the presence of $[RhCp^*(CH_3CN)_3][SbF_6]_2$ (2.5 mol%) and $Cu(BF_4)_2{\cdot}6H_2O$ (60.0 mol%) in MeOH at 60 °C under O_2 (1 atm) for 6 h afforded pyridinium salt **5a** in 88% yield. Under similar reaction conditions, **4a** reacted with **2b** and **2c** having a *tert*-butyl and *n*-octyl groups, respectively, attached to the alkyne carbon to give the corresponding pyridinium salts **5b** (82%) and **5c** (70%). The reaction of cinnamaldehyde **4b** with **2a** afforded **5d** in 84% yield. It is interesting to note that even α-methylcinnamaldehyde **4c** reacted smoothly with **2a** to give the expected highly substituted pyridinium salt **5e** in 82% yield.

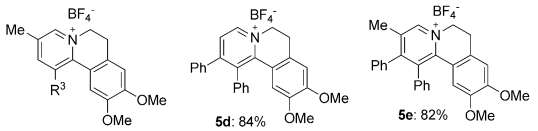
Based on the known metal-catalyzed directing group-assisted C–H bond activation/annulation reactions,[4–10] a plausible reaction mechanism is proposed for this catalytic reaction (Scheme 2). The catalytic cycle is probably initiated by the coordination of the imine nitrogen, which is generated in situ from **1a** and **2a**, to Rh^{III}, followed by the ortho C–H bond activation to form the five-membered rhodacycle **I**. Next, the coordination of the alkynyl group in **I** to the Rh center affords intermediate **II**. Further insertion of the alkynyl group into the Rh–C bond affords the bicyclic seven-membered rhodacycle **III**. The reductive elimination of **III** then affords the final salt **3a** and Rh^{I}. The Rh species is reoxidized by Cu^{II} or O_2 to regenerate the active Rh^{III} species for the next catalytic cycle.

The significance of this Rh-catalyzed C–H activation and annulation reaction was further demonstrated by its application to the direct synthesis of 13-substituted protoberberine salts. The synthesis of these natural products using this methodology is shown in Scheme 3. The reaction of aldehydes **1r** (0.36 mmol) and **1s** (0.36 mmol) with alkyne–amine **2c** (0.30 mmol) in the presence of $[RhCp^*(CH_3CN)_3][SbF_6]_2$ (2.5 mol%) and $Cu(BF_4)_2{\cdot}6H_2O$ (60 mol%) in MeOH under O_2

Table 2. Results of rhodium-catalyzed C–H activation and annulation of α,β-unsaturated aldehydes and alkyne–amines.[a,b]



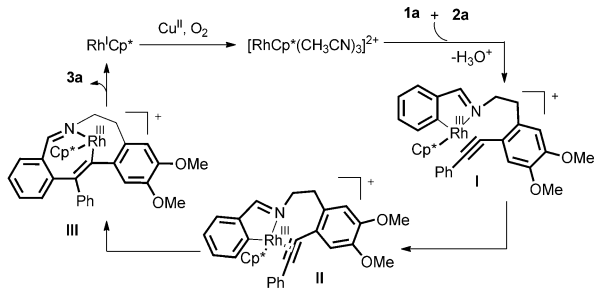
4a-c 2a-c 5a-e



5a: R^3 = Ph (88%)
5b: R^3 = ^{t}Bu (82%)
5c: R^3 = $(CH_2)_7CH_3$ (70%)

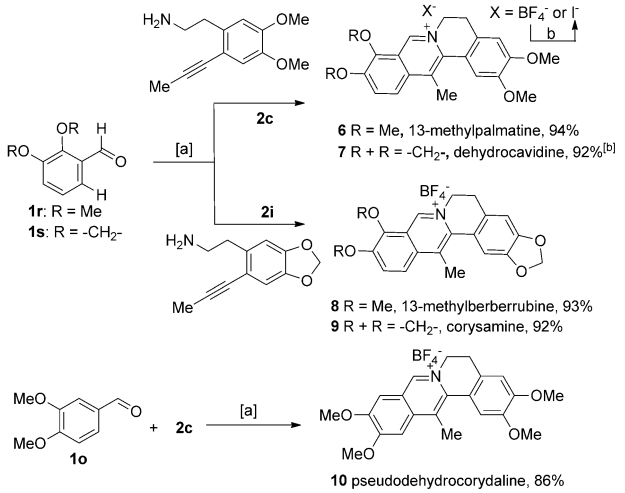
5d: 84% **5e**: 82%

[a] Unless otherwise mentioned, all reactions were carried out using α,β-unsaturated aldehyde **4** (0.36 mmol), alkyne–amine **2** (0.30 mmol), $[RhCp^*(CH_3CN)_3][SbF_6]_2$ (2.5 mol%), $Cu(BF_4)_2{\cdot}6H_2O$ (60 mol%), O_2 (1 atm), and MeOH (2.5 mL) at 60 °C for 6 h. [b] Isolated yields.

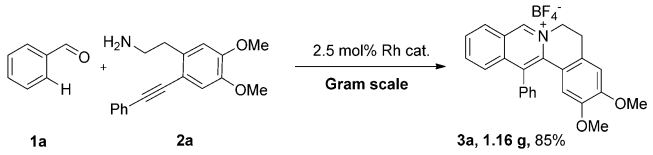


Scheme 2. Proposed mechanism for the formation of protoberberine salt derivatives.

(1 atm) at 60 °C for 6 h afforded the BF_4^- salts of 13-methylpamatine **6** and dehydrocavidine **7** in 94% and 92% isolated yields, respectively. Similarly, the reactions of **1r** and **1s** with **2i** smoothly afforded 13-methylberberrubine **8** and corysamine **9**, respectively, in excellent yields. Furthermore, the reaction of 3,4-dimethoxybenzaldehyde (**1o**) with **2c** gave **10** in 86% yield with high regioselectivity. To the best of our knowledge, this is the first step-economic and high-yielding method for the formation of protoberberine salts by the Rh-catalyzed C–H activation and annulation using aldehydes and alkyne–amines in a one-pot reaction. It is worth noting that 13-methylpamatine **8** has been previously synthesized in five steps with an overall yield of 12% from 3,4-dimethoxyisoquinoline and dimethoxybenzyl chloride.[3a,c] Very recently Donohoe and co-workers reported a synthesis of protoberberine alkaloids by a Pd-catalyzed sequential enolate arylation of aryl bromides with ketones followed by aromatization and cyclization in overall 47% yield.[16] The total synthesis of other protoberberine alkaloids, which have been isolated in low yields from plants, were not reported.[3b] To the best of our knowledge, we appear to be the first one for the total synthesis of natural products **6**,**7**, **9,** and **10**.



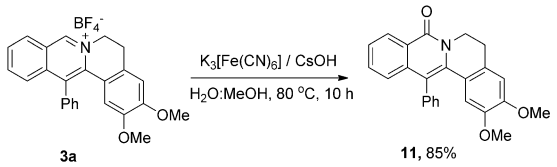
Scheme 3. One-pot synthesis of protoberberine natural products. Reaction conditions: [a] aryl aldehyde **1** (0.36 mmol), alkyne–amine **2** (0.30 mmol), $[RhCp^*(CH_3CN)_3][SbF_6]_2$ (2.5 mol%), $Cu(BF_4)_2{\cdot}6H_2O$ (60 mol%), O_2 (1 atm), and MeOH (2.5 mL) at 60 °C for 6 h. [b] NaI (2.0 equiv) and MeOH (3.0 mL) at 30 °C for 0.5 h. For the crystal structure of compound **7**, see the Supporting Information.



Scheme 4. Gram-scale reaction. Conditions: benzaldehyde **1a** (3.60 mmol), alkyne–amine **2a** (3.00 mmol), $[RhCp^*(CH_3CN)_3][SbF_6]_2$ (2.5 mol%), $Cu(BF_4)_2{\cdot}6H_2O$ (60 mol%), O_2 (1 atm), and MeOH (25 mL) at 60 °C for 6 h.

Further, we also investigated the scalability of this C–H activation/annulation reaction (Scheme 4). Thus, benzaldehyde (**1a**) was treated with **2a** in the presence of $[RhCp^*(CH_3CN)_3][SbF_6]_2$ (2.5 mol%) and $Cu(BF_4)_2{\cdot}6H_2O$ (60 mol%) in MeOH under O_2 (1 atm) at 60 °C for 6 h to afford protoberberinium salt **3a** in 85% isolated yield.

An important synthetic application of the protoberberine salt is its transformation into 8-oxyprotoberberine. An example is demonstrated in Scheme 5. The protoberberine salt **3a** (0.30 mmol) was treated with $K_3[Fe(CN)_6]$ (1.80 mmol) and CsOH (1.20 mmol) in a mixture of H_2O and MeOH (1:1) at 80 °C for 10 h to afford 8-oxyprotoberberine **11** in 85% isolated yield.[17]



Scheme 5. Synthesis of 8-oxyprotoberberine **11**. Reaction conditions: salt **3a** (0.30 mmol), $K_3[Fe(CN)_6]$ (1.80 mmol), and CsOH (1.20 mmol) in H_2O:MeOH (1:1; 5 mL) at 80 °C for 10 h.

Conclusion

In conclusion, we have developed a novel method for the synthesis of substituted protoberberine salts in high yields by a Rh^{III}-catalyzed intramolecular C–H bond activation/annulation of aldehydes and alkyne–amines in one-pot reactions. In addition, pyridinium salts were also formed in good yields from α,β-unsaturated aldehydes and alkyne–amines. The protocol was successfully applied to the synthesis of natural products, such as 13-methylpalmatine (**6**), dehydrocavidine (**7**), 13-methylberberrubine (**8**), corysamine (**9**), and pseudohydrocorydaline (**10**), with 65–75% overall yields under mild reaction conditions by using O_2 as the oxidant. To the best of our knowledge, this is the first step-economic synthesis of highly substituted protoberberine alkaloids.

Experimental Section

General procedure for the synthesis of substituted protoberberine salts (3)

A sealed tube containing $[RhCp^*(CH_3CN)_3][SbF_6]_2$ (2.5 mol%) and $Cu(BF_4)_2{\cdot}6H_2O$ (60 mol%) was degassed and purged with oxygen gas. Then, a mixture of aryl aldehyde **1** (0.36 mmol) and alkyne–

amine **2** (0.30 mmol) in MeOH (2.5 mL) was added to the system by syringe. The reaction mixture was stirred under an oxygen atmosphere (1 atm) at 60 °C for 6 h, and was then cooled to room temperature and diluted with CH_2Cl_2 (10 mL). The mixture was filtered through a Celite pad, which was washed with CH_2Cl_2 (50 mL). The combined filtrate was concentrated in vacuum and the residue was carefully washed with ethyl acetate and *n*-hexane to afford the desired pure product **3**.

Acknowledgements

We thank the Ministry of Science and Technology of the Republic of China (MOST 103-2633M-007-001) for supporting this research.

Keywords: aldehydes · alkaloids · C–H activation · copper · rhodium

[1] For reviews on berberine synthesis, see: a) J. Stöckigt, A.-P. Antonchick, F. Wu, H. Waldmann, *Angew. Chem. Int. Ed.* **2011**, *50*, 8538; *Angew. Chem.* **2011**, *123*, 8692; b) D.-Z. Wu, J.-Y. Yuan, H.-L. Shi, Z.-B. Hu, *Br. J. Pharmacol.* **2009**, *153*, 1203; c) T. Hashimoto, Y. Yamada, *Annu. Rev. Med. Annu. Rev. Plant. Physiol. Mol. Biol.* **1994**, *45*, 257.

[2] a) L. Grycová, J. Dostal, R. Marek, *Phytochemistry* **2007**, *68*, 150; b) K. Iwasa, M. Moriyasu, T. Yamori, T. Turuo, D.-U. Lee, W. Wiegrebe, *J. Nat. Prod.* **2001**, *64*, 896; c) A. Singh, S. Duggal, N. Kaur, J. Singh, *J. Nat. Prod.* **2010**, *3*, 64; d) X. Bian, G. Yang, L. He, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1380; e) T.-M. Hung, P.-T. Thuong, N.-T. Nhan, N.-T. Thanh Mai, T.-L. Quan, J.-S. Choi, M.-H. Woo, B.-S. Min, K.-W. Bae, *Nat. Prod. Sci.* **2011**, *17*, 108; f) G. Lahm, J.-G. Deichmann, A.-L. Rauen, T. Opatz, *J. Org. Chem.* **2015**, *80*, 2010.

[3] For synthesis and bioactivity of protoberberine alkaloids, see: a) M. Hanaoka, S. Yoshida, C. Mukai, *J. Chem. Soc. Chem. Commun.* **1985**, 1257; b) X.-Y. Cheng, Y. Shi, S.-L. Zhen, H. Sun, W. Jin, *J. Chromatogr. Sci.* **2010**, *48*, 441; c) Z. Iparissiderso, B. Fichtnerja, N. Plawskbia, L. Nalliah, D. B. Maclean, *Can. J. Chem.* **1980**, *58*, 2770; d) Y.-H. Li, P. Yang, W.-J. Kong, Y.-X. Wang, C.-Q. Hu, Z.-Y. Zuo, Y.-M. Wang, H. Gao, L.-M. Gao, Y.-C. Feng, N.-N. Du, Y. Liu, D.-Q. Song, J.-D. Jiang, *J. Med. Chem.* **2009**, *52*, 492; e) D.-U. Lee, Y.-J. Kang, M.-K. Park, Y.-S. Lee, H.-G. Seo, T.-S. Kim, C.-H. Kim, K.-C. Chang, *Life. Sci.* **2003**, *73*, 1401; f) L. Chen, L. Feng, Y. Li, G. Wu, US 2010/0286396 A1, **2010**; g) Y.-X. Liu, C.-L. Xiao, Y.-X. Wang, Y.-H. Li, Y.-H. Yang, Y.-B. Li, C.-W. Bi, L.-M. Gao, J.-D. Jiang, D.-Q. Song, *Eur. J. Med. Chem.* **2012**, *52*, 151; h) J.-B. Bremner, S. Samosorn, *Aust. J. Chem.* **2003**, *56*, 871; i) G.-E. Lee, H.-S. Lee, S.-D. Lee, J.-H. Kim, W.-K. Kim, Y.-C. Kim, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 954; j) X. Bian, L. He, G. Yang, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1380.

[4] For recent reviews on the C–H functionalization, see: a) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 624; b) T. Satoh, M. Miura, *Chem. Eur. J.* **2010**, *16*, 11212; c) D.-H. Wang, K. M. Engle, B.-F. Shi, J.-Q. Yu, *Science* **2010**, *327*, 315; d) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147; e) C. S. Yeung, V. M. Dong, *Chem. Rev.* **2011**, *111*, 1215; f) J. Le Bras, J. Muzart, *Chem. Rev.* **2011**, *111*, 1170; g) K. M. Engle, T.-S. Mei, M. Wasa, J.-Q. Yu, *Acc. Chem. Res.* **2012**, *45*, 788; h) M. Mewald, J. A. Schiffner, M. Oestreich, *Angew. Chem. Int. Ed.* **2012**, *51*, 1763; *Angew. Chem.* **2012**, *124*, 1797.

[5] a) M. V. Pham, N. Cramer, *Angew. Chem. Int. Ed.* **2014**, *53*, 3484; *Angew. Chem.* **2014**, *126*, 3552; b) J. Wencel-Delord, T. Droge, F. Liu, F. Glorius, *Chem. Soc. Rev.* **2011**, *40*, 4740; c) G. Song, F. Wang, X. Li, *Chem. Soc. Rev.* **2012**, *41*, 3651; d) P. B. Arockiam, C. Bruneau, P. H. Dixneuf, *Chem. Rev.* **2012**, *112*, 5879; e) L. Ackermann, *Acc. Chem. Res.* **2014**, *47*, 281; f) F. W. Patureau, J. Wencel-Delord, F. Glorius, *Aldrichimica Acta* **2012**, *45*, 31.

[6] For selected examples of Rh^{III}-catalyzed annulations, see: a) N. Umeda, H. Tsurugi, T. Satoh, M. Miura, *Angew. Chem. Int. Ed.* **2008**, *47*, 4019; *Angew. Chem.* **2008**, *120*, 4083; b) D. R. Stuart, M. Bertrand-Laperle, K. M. N. Burgess, K. Fagnou, *J. Am. Chem. Soc.* **2008**, *130*, 16474; c) S. Mochida, K. Hirano, T. Satoh, M. Miura, *J. Org. Chem.* **2009**, *74*, 6295; d) Y. Su, M. Zhao, K. Han, G. Song, X. Li, *Org. Lett.* **2010**, *12*, 5462; e) K. Morimoto, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2010**, *12*, 2068; f) D. R. Stuart, P. Alsabeh, M. Kuhn, K. Fagnou, *J. Am. Chem. Soc.* **2010**, *132*, 18326; g) T. K. Hyster, T. Rovis, *J. Am. Chem. Soc.* **2010**, *132*, 10565; h) S. Rakshit, F. W. Patureau, F. Glorius, *J. Am. Chem. Soc.* **2010**, *132*, 9585; i) N. Guimond, C. Gouliaras, K. Fagnou, *J. Am. Chem. Soc.* **2010**, *132*, 6908; j) S. Mochida, M. Shimizu, K. Hirano, T. Satoh, M. Miura, *Chem. Asian J.* **2010**, *5*, 847; k) X. Wei, M. Zhao, Z. Du, X. Li, *Org. Lett.* **2011**, *13*, 4636; l) Y. Yang, M.-B. Zhou, X.-H. Ouyang, R. Pi, R.-J. Song, J.-H. Li, *Angew. Chem. Int. Ed.* **2015**, *54*, 6595; *Angew. Chem.* **2015**, *127*, 6695; m) H. Wang, F. Glorius, *Angew. Chem. Int. Ed.* **2012**, *51*, 7318; *Angew. Chem.* **2012**, *124*, 7430; n) W. Dong, L. Wang, K. Parthasarathy, F. F. Pan, C. Bolm, *Angew. Chem. Int. Ed.* **2013**, *52*, 11573; *Angew. Chem.* **2013**, *125*, 11787; o) J. Jayakumar, K. Parthasarathy, Y. H. Chen, T. H. Lee, S. C. Chuang, C.-H. Cheng, *Angew. Chem. Int. Ed.* **2014**, *53*, 9889; *Angew. Chem.* **2014**, *126*, 10047.

[7] For selected examples of Ru^{II}-catalyzed annulations, see: a) L. Ackermann, A. V. Lygin, N. Hofmann, *Angew. Chem. Int. Ed.* **2011**, *50*, 6379; *Angew. Chem.* **2011**, *123*, 6503; b) B. Li, H. Feng, S. Xu, B. Wang, *Chem. Eur. J.* **2011**, *17*, 12573; c) L. Ackermann, A. V. Lygin, N. Hofmann, *Org. Lett.* **2011**, *13*, 3278; d) L. Ackermann, S. Fenner, *Org. Lett.* **2011**, *13*, 6548; e) R. K. Chinnagolla, M. Jeganmohan, *Chem. Commun.* **2012**, *48*, 2030; f) L. Ackermann, L. Wang, A. V. Lygin, *Chem. Sci.* **2012**, *3*, 177; g) R. K. Chinnagolla, M. Jeganmohan, *Eur. J. Org. Chem.* **2012**, 417; h) L. Ackermann, J. Pospech, K. Graczyk, K. Rauch, *Org. Lett.* **2012**, *14*, 930; i) R. K. Chinnagolla, S. Pimparkar, M. Jeganmohan, *Org. Lett.* **2012**, *14*, 3032; j) B. Li, H. Feng, N. Wang, J. Ma, H. Song, S. Xu, B. Wang, *Chem. Eur. J.* **2012**, *18*, 12873; k) S. Reddy Chidipudi, I. Khan, H. W. Lam, *Angew. Chem. Int. Ed.* **2012**, *51*, 12115; *Angew. Chem.* **2012**, *124*, 12281; l) L. Wang, L. Ackermann, *Org. Lett.* **2013**, *15*, 176.

[8] For intramolecular alkene C–H annulations, see: a) T. A. Davis, T. K. Hyster, T. Rovis, *Angew. Chem. Int. Ed.* **2013**, *52*, 14181; *Angew. Chem.* **2013**, *125*, 14431; b) Z. Shi, C. Grohmann, F. Glorius, *Angew. Chem. Int. Ed.* **2013**, *52*, 5393; *Angew. Chem.* **2013**, *125*, 5503; c) B. Ye, P. A. Donets, N. Cramer, *Angew. Chem. Int. Ed.* **2014**, *53*, 507; *Angew. Chem.* **2014**, *126*, 517; d) Z. Shi, M. Boultadakis-Arapinis, F. Glorius, D. C. Koester, *Chem. Commun.* **2014**, *50*, 2650; e) R. K. Thalji, K. A. Ahrendt, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2001**, *123*, 9692.

[9] X. Xu, Y. Liu, C.-M. Park, *Angew. Chem. Int. Ed.* **2012**, *51*, 9372; *Angew. Chem.* **2012**, *124*, 9506.

[10] N. Quiñones, A. Seoane, R. Garcia-Fandino, J. L. Mascarenas, M. Gulias, *Chem. Sci.* **2013**, *4*, 2874.

[11] a) K. Parthasarathy, N. Senthilkumar, J. Jayakumar, C.-H. Cheng, *Org. Lett.* **2012**, *14*, 3478; b) C.-Z. Luo, P. Gandeepan, J. Jayakumar, K. Parthasarathy, Y.-W. Chang, C.-H. Cheng, *Chem. Eur. J.* **2013**, *19*, 14181; c) C.-Z. Luo, P. Gandeepan, C.-H. Cheng, *Chem. Commun.* **2013**, *49*, 8528; d) C.-Z. Luo, J. Jayakumar, P. Gandeepan, Y.-C. Wu, C.-H. Cheng, *Org. Lett.* **2015**, *17*, 924.

[12] J. Jayakumar, K. Parthasarathy, C.-H. Cheng, *Angew. Chem. Int. Ed.* **2012**, *51*, 197; *Angew. Chem.* **2012**, *124*, 201.

[13] a) L. Li, W. W. Brennessel, W. D. Jones, *J. Am. Chem. Soc.* **2008**, *130*, 12414; b) G. Zhang, L. Yang, Y. Wang, Y. Xie, H. Huang, *J. Am. Chem. Soc.* **2013**, *135*, 8850; c) D. Zhao, Q. Wu, X. Huang, F. Song, T. Lv, J. You, *Chem. Eur. J.* **2013**, *19*, 6239.

[14] a) C. Shi, I. Ojima, *Tetrahedron* **2007**, *63*, 8563; b) D. Mujahidin, S. Doye, *Eur. J. Org. Chem.* **2005**, 2689; c) K. Ito, S. Akashi, B. Saito, T. Katsuk, *Synlett* **2003**, *12*, 1809; d) C. White, A. Yates, P. M. Maitlis, *Inorg. Synth.* **1992**, *29*, 228.

[15] CCDC 975533 (**7**), 975534 (**3 i**), and 995756 (**3 q**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre

[16] a) A.-E. Gatland, B.-S. Pilgrim, P.-A. Procopiou, T.-J. Donohoe, *Angew. Chem. Int. Ed.* **2014**, *53*, 14555; *Angew. Chem.* **2014**, *126*, 14783.

[17] R. P. Korivi, W.-J. Wu, C.-H. Cheng, *Chem. Eur. J.* **2010**, *16*, 282.

Received: October 31, 2015
Published online on December 22, 2015