Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: X. Zhou, W. Fu, H. Jiang, C. Wang, C. Ju, W. chu and Z. sun, *Org. Biomol. Chem.*, 2017, DOI: 10.1039/C6OB02707E.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/obc

DOI: 10.1039/C6OB02707E

Organic & Biomolecular Chemistry

COMMUNICATION

Synthesis of 8-azaprotosappanin A derivatives via intramolecular palladium-catalyzed ortho C–H activation/C–C cyclization and antibacterial activity

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/C6CC01149G

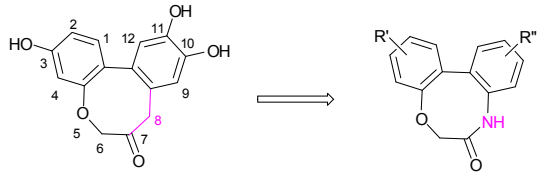
www.rsc.org/

Xuan Zhou, Wanyong Fu, Hongshuo Jiang, Chenglong Wang, Chao Ju, Wenyi Chu*and Zhizhong Sun*

A novel synthetic protocol for the construction of eight-numbered heterocycle by intramolecular Palladium-catalyzed ortho C-H activation/C-C cyclization was proposed. With protosappanin A as the lead compoundm, 25 derivatives of 8-azaprotosappanin A were prepared in good yields by this protocol. Besides, a plausible reaction mechanism of the intramolecular cyclization was proposed. This strategy could be widely used in the synthesis of some natural products and drugs with large heterocycle due to the fast reaction rate and the mild condition. In vitro antimicrobial activities of the synthesized compounds were assessed against strains of Gram-positive bacteria and select the linezolid and ciprofloxcin as standard drugs. Some of the synthesized compounds were found to have excellent antibacterial activities.

Benzoheterocyclic fragment is a key structural motif in some natural products,[1] which are often used as lead compounds in drug designing and screening due to their good biological activities.[2] Protosappanin A, as a natural product containing dibenzoheterocyclic fragment, was found in the extraction of Caesalpinia in 1986[3] and first total synthesized by our research group in 2016.[4] Some studies of biological activities indicated that Protosappanin A has anti-bacterial,[5] inhibition of xanthine oxidase,[6] anti-inflammation,[7] anti-HIV-1,[8] organ transplantation immunosuppressive,[9] vasorelaxant activity[10] and so on. In view of the great value of Protosappanin A, more extensive exploration on its derivatives would be interesting and meaningful.

The dibenzoheterocyclic fragment in Protosappanin A belongs to a biaryl skeleton (**Scheme 1**). We attempted to transform the heterocyclic fragment of Protosappanin A to design its derivatives. An imino group (-NH-) was introduced to replace the methylene group (C-8) of the heterocyclic fragment to get 8-azaprotosappanin A (**Scheme 1**). The 8-azaprotosappanin A contains a dibenzoxazinone fragment which is widely found in natural products and important intermediates in organic synthesis and drug synthesis. The dibenzoxazinone structure analogues have potential antibacterial,[11] histone deacetylase inhibition,[12] HIV-1 reverse transcriptase inhibition[13] and other activities.



Scheme 1 Design of 8-azaprotosappanin A derivatives with Protosappanin A as lead compound.

The biaryl skeleton of 8-azaprotosappanin A derivatives is often constructed by C–C bond cross coupling reaction. For the synthesis of 8-azaprotosappanin A derivatives, one of the most important steps is the construction of dibenzoxazinone via intramolecular cyclization.[14] However, the previous cyclization methods were mainly used to synthesize five, six or seven-membered rings.[15] The 8-azaprotosappanin A derivatives containing an eight-membered ring were not easy to be obtained by intramolecular cyclization. The present methods to synthesize this complex dibenzoheterocyclic fragment always need complicated reaction process, harsh reaction conditions and get low product yields.

In recent years, the transition-metal-catalyzed C–H coupling has emerged as a powerful and ideal method for the construction of carbon-carbon skeleton.[16] Transition-metal-catalyzed C(sp^2)–H coupling[17] is an improved method preceding traditional cross-couplings[18] and direct arylations.[19] This method makes it possible to synthesize some large ring compounds directly, which attracts more interests in organic synthesis.

In this manuscript, a Pd-catalyzed ortho C–H activation/C–C cyclization for intramolecular C–H arylation strategy, as an economical, green and efficient approach for the synthesis of

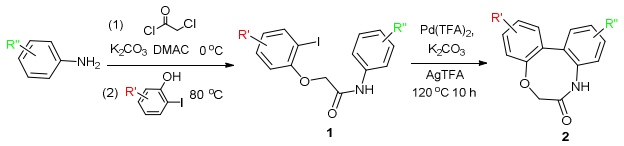
School of Chemistry and Materials Science, Heilongjiang University, Harbin, Heilongjiang 150080, PR China. E-mail: wenyichu@hlju.edu.cn; sunzz@hlju.edu.cn; Fax: (+) 86-451-86609135.

† Electronic Supplementary Information (ESI) available: experimental procedures and compound characterization data, and ^{1}H and ^{13}C NMR spectra of new compounds (PDF). See DOI: 10.1039/x0xx00000x

View Article Online
DOI: 10.1039/C6OB02707E

large ring compounds, was applied to synthesize a serial of 8-azaprotosappanin A derivatives.

In order to obtain 8-azaprotosappanin A derivatives, the steps of this strategy was detailed in **Scheme 2**. Firstly, α-(2-iodoaryloxy)-N-arylacetamides **1** were obtained in good yields by the continuous reactions in N, N-dimethylacetamide (DMAC) in the presence of K_2CO_3 including acylation of arylamines with chloroacetyl chloride at 0 °C[20] and etherification of using 2-iodo-phenols at 80 °C.[21] Then, compounds **1** were used as the key intermediate to synthesize 8-azaprotosappanin A derivatives **2** through intramolecular cyclization of Pd-catalyzed ortho C–H activation/C–C cyclization.



Scheme 2 Synthesis of 8-azaprotosappanin A derivatives.

α-(2-Iodophenoxy)-N-phenylacetamide **1u** was chosen as the model substrate to investigate the reaction conditions of ortho C–H activation/C–C cyclization. The reaction conditions such as catalyst, oxidant, solvent and temperature were screened. The experimental results were shown in **Table 1**.

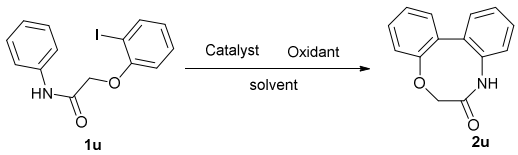
For the ortho C-H activation, the catalyst plays a crucial role. Firstly, different catalysts such as Pd(0), Pd(II), Ru(III), Ru(0) and Cu(II) salts were screened respectively. The results showed that $Pd(TFA)_2$ (**Table 1**, 84% for entry 3) was superior to $Pd(OAc)_2$, $Pd(PPh)_3Cl_2$ and $Pd(PPh_3)_4$ (**Table 1**, entries 1-4). While $RuCl_3$ and $Ru(PPh_3)_3$ as catalysts exhibited low catalytic activity with the yields of 61% and 50%, respectively (**Table 1**, entries 5-6). Also, $Cu(TFA)_2$ and $Cu(OAc)_2$ as catalyst or without catalyst, no desired product was obtained (**Table 1**, entries 7-9).

For the ortho C–H activation, the oxidant is also an important factor. The effect of different silver compounds such as AgTFA, AgOAc, Ag_2O and AgF was examined. AgTFA gave a good yield of 84%, while AgOAc, Ag_2O and AgF gave 74%, 68% and 62%, respectively (**Table 1**, entries 3 and 10-12). $Cu(OAc)_2$ and $K_2S_2O_8$ produced an inferior result (**Table 1**, entries 13-14). DDQ as the oxidant or without oxidant, the reaction didn't occur (**Table 1**, entries 15-16).

Different solvents such as N,N-Dimethylformamide (DMF), 1,4-dioxane, acetonitrile (CH_3CN), N-Methylpyrolidone (NMP), N,N-Dimethylacetamide (DMAC), Dimethylsulfoxide (DMSO) and Tetrahydrofuran (THF) were also investigated (**Table 1**, entries 3 and 17-22). For the amide solvents, DMF, DMAC and NMP were better than DMSO (**Table 1**, entries 3 and 17-19). The low-boiling point solvents gave the reaction a low yield (**Table 1**, entries 20-22). The results showed that DMAC was efficient for the synthesis of **2u** in excellent yields (**Table 1**, entry 3).

Simultaneously, the reaction time and temperature were investigated. When the reaction time was 8, 10 and 12 hours, the yield was 74%, 84% and 84%，respectively (**Table 1**, entry 3). When the reaction temperature was 100 °C and 120 °C, the yield was 51% and 84% (**Table 1**, entries 3 and 23). When the reaction temperature reached to 140 °C, the yield was 65% (**Table 1**, entry 24). Obviously, there was no product detected when the reaction temperature increased to reflux temperature 166 °C (**Table 1**, entry 25), because high reaction temperature was helpful for iodine removal reaction and not conducive to the cyclization reaction.

Table 1 Optimization of reaction conditions[a]



Entry	Catalyst	Oxidant	Solvent	Temp(°C)	Yield(%)[b]
1	$Pd(PPh_3)_4$	AgTFA	DMAC	120	63
2	$Pd(OAc)_2$	AgTFA	DMAC	120	71
13	$Pd(TFA)_2$	AgTFA	DMAC	120	84, 74[c], 84[d]
4	$Pd(PPh)_3Cl_2$	AgTFA	DMAC	120	66
5	$RuCl_3$	AgTFA	DMAC	120	61
6	$Ru(PPh_3)_3$	AgTFA	DMAC	120	50
7	$Cu(TFA)_2$	AgTFA	DMAC	120	-
8	$Cu(OAc)_2$	AgTFA	DMAC	120	-
9	-	AgTFA	DMAC	120	-
10	$Pd(TFA)_2$	AgOAc	DMAC	120	74
11	$Pd(TFA)_2$	AgF	DMAC	120	62
12	$Pd(TFA)_2$	Ag_2O	DMAC	120	68
13	$Pd(TFA)_2$	$Cu(OAc)_2$	DMAC	120	47
14	$Pd(TFA)_2$	$K_2S_2O_8$	DMAC	120	43
15	$Pd(TFA)_2$	DDQ	DMAC	120	-
16	$Pd(TFA)_2$	-	DMAC	120	-
17	$Pd(TFA)_2$	AgTFA	DMF	120	73
18	$Pd(TFA)_2$	AgTFA	NMP	120	70
19	$Pd(TFA)_2$	AgTFA	DMSO	120	65
20	$Pd(TFA)_2$	AgTFA	CH_3CN	reflux	58
21	$Pd(TFA)_2$	AgTFA	dioxane	reflux	37
22	$Pd(TFA)_2$	AgTFA	THF	reflux	trace
23	$Pd(TFA)_2$	AgTFA	DMAC	100	51,
24	$Pd(TFA)_2$	AgTFA	DMAC	140	65
25	$Pd(TFA)_2$	AgTFA	DMAC	reflux	-

[a] Reaction conditions: (0.4 mmol), catalyst (15 mol%), oxidant (2eq) and additive K_2CO_3 (2 eq) in solvent (6 mL) for 10 hours. [b] Isolated yields after silica gel column chromatography. [c] For 8 h. [d] For 12 h.

Based on the above research, the optimized condition for C–H activation/C–C cyclization reaction was 15 mol% $Pd(TFA)_2$ as the catalyst, 2 equiv of AgTFA as the oxidant and 2 equiv of K_2CO_3 as the additive in DMAC at 120 °C for 10 hours.

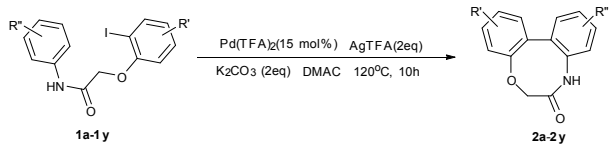
The scope of substrates was further investigated by above optimized synthetic process. A series of 8-azaprotosappanin A derivatives were successfully synthesized by this method and

View Article Online
DOI: 10.1039/C6OB02707E

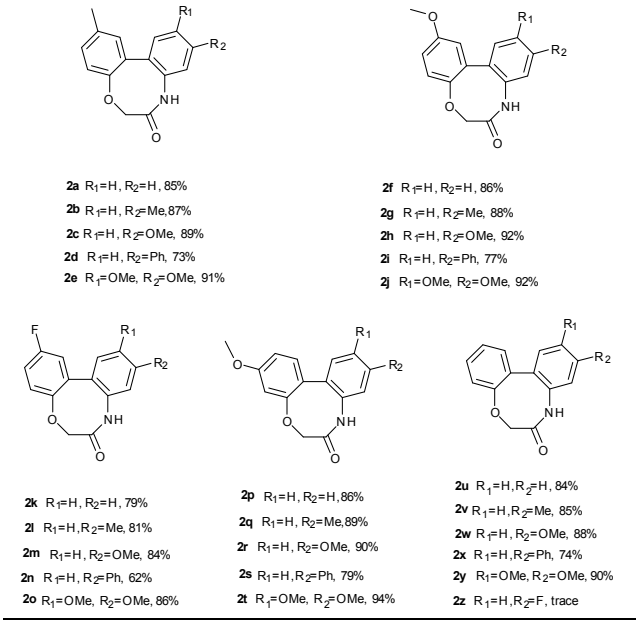
shown in **Table 2**. The substrates **1a**-**y** were prepared by the continuous reactions through arylamines and 2-iodo-phenols.

Under the optimized conditions, α-(2-iodoaryloxy)-N-arylacetamides with different electron-donating and electron-withdrawing groups were catalyzed to undergo intramolecular cyclization smoothly to afford corresponding 8-azaprotosappanin A derivatives **2** in excellent yields.

Table 2 Synthesis of variously substituted **2**

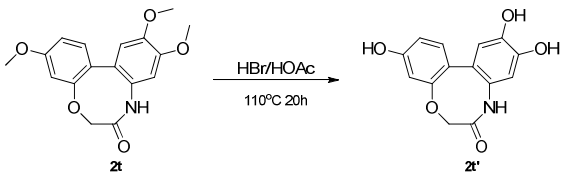


1a-1y 2a-2y



The group R' on the aryl ring with iodo-group could be electron-donating groups, electron-withdrawing group -F and -H. When the electron-donating groups such as -OMe and -Me were at the para position, the cyclization showed high reaction activities and afforded good yields of 73-92% (**Table 2**, entries **2a**-**2j**). Compared with the electron-donating groups, the electron-withdrawing group -F at the para position showed slightly low reaction activities and the yields of 62-86% (**Table 2**, entries **2k**-**2o**). When the electron-donating group -OMe was at the para or meta position, the reaction activities and the yields had little effect (**Table 2**, 77%-92% for entries **2f**-**2j** and 79%-94% for entries **2p**-**2t**).

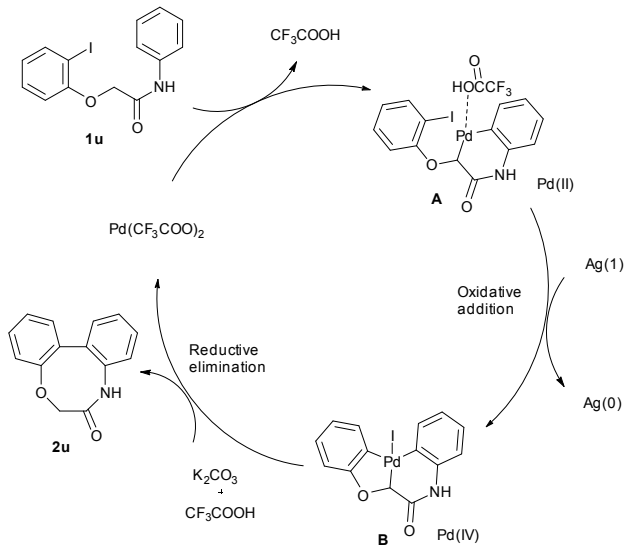
Another group R" on the aryl ring with amino-group could be -Me, -OMe, -Ph, -H and so on. When the electron-donating groups such as -OMe and -Me were at the meta position, the cyclization showed highly reaction activities and afforded good yields of 81-92% (**Table 2**, entries **2b**, **2c**, **2g**, **2h**, **2l**, **2m**, **2q**, **2r**, **2v** and **2w**). The group -Ph was at meta position, the reaction activities and the yields slightly decreased to 62%-79% (**Table 2**, entries **2d**, **2i**, **2n**, **2s** and **2x**). Compared with the electron-donating groups, the electron-withdrawing group -F at the meta position showed obviously low reaction activity and yield (**Table 2**, entry **2z**).



2t 2t' 8-azaprotosappanin A

Scheme 3 Synthesis of 8-azaprotosappanin A

In order to get 8-azaprotosappanin A (**2t'**), the methyl protecting group of compound **2t** was removed by demethylation (**Scheme 3**). Finally, 8-azaprotosappanin A was achieved through the cleavage of **2t** with 40% HBr in AcOH at 110 °C in 80% yield.



Scheme 4 Proposed mechanism for compound **2u**.

A feasible mechanism for intramolecular ortho C–H activation/C–C cyclization is proposed and shown in **Scheme 4**. α-(2-Iodophenoxy)-N-phenylacetamide **1u** undergoes a cyclopalladation to generate intermediate **A**. Then the intermediate **A** is oxidized by AgTFA to give Pd(IV) intermediate **B** containing a five-membered and a six-membered palladacycle[22] via oxidative addition. At last, the intermediate **B** is reduced to obtain the compound **2u** by the reductive elimination in the present of CF_3COOH and K_2CO_3. Then a catalytic reaction cycle is completed and the Pd(II) salt will continue to participate next reaction cycle.

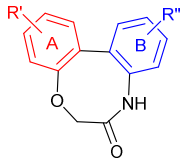
Biological activity

In vitro antibacterial activities of compounds **2a-2y** and protosappanin A (**PA**) were studied against a panel of Gram-positive bacteria. The antibacterial activities of the compounds were examined against a panel of susceptible and resistant

View Article Online
DOI: 10.1039/C6OB02707E

strains of Gram-positive bacteria, including Staphylococcus aureus (ATCC 25923), methicillin-resistant Staphylococcus aureus (MRSA, clinical isolate), Staphylococcus epidermidis (ATCC 12228) and Enterococcus faecalis (ATCC 29212). E. coli (ATCC 25922) was also used as a Gram-negative bacteria.

Table 3 Antibacterial activities (MIC, μg/mL) of 8-azaprotosappanin A derivatives.



8-azaprotosappanin A derivatives

Entry	Compound	SA	MRSA	SE	EF	EC
1	**2a**	16	16	32	32	>32
2	**2b**	16	32	16	32	>32
3	**2c**	**2**	8	**4**	16	>32
4	**2d**	32	>32	>32	>32	>32
5	**2e**	**4**	8	16	**4**	>32
6	**2f**	32	32	>32	32	>32
7	**2g**	16	16	8	16	>32
8	**2h**	**4**	16	32	16	>32
9	**2i**	32	>32	>32	>32	>32
10	**2j**	8	16	**4**	16	>32
11	**2k**	8	16	16	8	>32
12	**2l**	16	8	8	16	>32
13	**2m**	8	**2**	**2**	8	>32
14	**2n**	32	>32	32	>32	>32
15	**2o**	**2**	8	**4**	**2**	>32
16	**2p**	32	16	32	32	>32
17	**2q**	16	16	8	16	>32
18	**2r**	**4**	8	16	8	>32
19	**2s**	>32	32	>32	32	>32
20	**2t**	**4**	**2**	**2**	8	>32
21	**2u**	>32	>32	>32	>32	>32
22	**2v**	32	32	32	32	>32
23	**2w**	16	16	32	16	>32
24	**2x**	>32	>32	>32	>32	>32
25	**2y**	**4**	16	8	16	>32
26	**2t'**	**2**	**1**	**4**	**1**	>32
27	**PA**	**4**	**8**	**4**	**4**	>32
28	**Linezolid**	4	2	4	2	>32
29	**Ciprofloxacin**	-	-	1	2	1

[a]MRSA = methicillin-resistant Staphylococcus aureus (clinical isolate); SA = Staphylococcus aureus (ATCC 25923); SE = Staphylococcus epidermidis (ATCC 12228); EF = Enterococcus faecalis (ATCC 29212); EC = E. coli (ATCC 25922); PA = protosappanin A [b]Bold indicating for significant antibacterial activity.

Linezolid and Ciprofloxacin were used as a positive control in the experiments. The minimum inhibitory concentration (MIC) is defined as the lowest concentration of a drug that inhibits the visible bacterial growth after incubation at 37 °C for 24 h. MICs were determined by agar dilution method as outlined as following (the clinical and laboratory standards institute). The experiment results of in vitro evaluation were summarized in **Table 3**.

According to the obtained anti-bacterial data (**Table 3**), most of the tested compounds were appropriate active against Gram-positive bacteria. Among the tested compounds for antibacterial activity against Staphylococcus aureus, **2c**, **2o** and **2t'** showed low inhibitory concentration (MIC) of 2 (μg/mL); **2e**, **2h**, **2r**, **2t**, and **2y** MIC of 4 (μg/mL) were found. The compounds **2m**, **2t**, and **2t'** exhibited significant activity against methicillin-resistant Staphylococcus aureus, the compounds **2c**, **2j**, **2m**, **2o**, **2t** and **2t'** showed excellent activity against Staphylococcus epidermidis and compounds **2e**, **2o** and **2t'** exhibited significant activity against enterococcus faecalis. In particular, 8-azaprotosappanin A (**2t'**) had better activities against Gram-positive bacteria than linezolid against Staphylococcus aureus and Ciprofloxacin against Enterococcus faecalis; and 8-azaprotosappanin A (**2t'**) had higher active aganist methicillin-resistant Staphylococcus aureus and methicillin-resistant Staphylococcus aureus than Protosappanin A. Therefore, it is meaningful work that an imino group (-NH-) was introduced to replace the methylene group (C-8) of the heterocyclic fragment to get 8-azaprotosappanin A (**2t'**). Unfortunately, all tested compounds did not show any inhibitive activity against E. coli. The experimental results indicated that the compounds **2c**, **2e**, **2m**, **2o**, **2t** and **2t'** showed good antibacterial activities, especially the compound **2t'**.

Notably, the substituent of the aryl ring had a certain influence on the anti-bacterial activities of the compounds. The compound **2u** without substituent on the aryl ring showed no activities against Gram-positive bacteria. The compounds **2k**, **2l** and **2m** with -F substitution on aromatic ring **A** exhibited higher anti-microbial activity than that with -H (**2u**, **2v** and **2w**), -Me (**2a**, **2b** and **2c**) and -OMe (**2f**, **2g**, **2h**, **2p**, **2q** and **2r**). The compounds **2e**, **2j**, **2o**, **2t** and **2y** with double -OMe substitution on aromatic ring **B** had higher anti-microbial activity, whereas the compounds **2d**, **2i**, **2n, 2s** and **2x** with -Ph substitution showed no anti-microbial activity. However, the compound **2t'** with three -OH substitutions exhibited the most significant anti-bacterial activity because of the presence of -OH group to improve the bioavailability of the molecule. The results indicated that -F and -OH groups on aryl rings of the compounds were helpful to the antibacterial activity.

Conclusion

A novel synthetic protocol for the construction of eight-numbered heterocycle by intramolecular Pd-catalyzed ortho C–H Activation/C–C cyclization was proposed. A series of 8-azaprotosappanin A derivatives were obtained in good yields. This protocol could be used in the synthesis of central skeleton of some natural products and drugs due to its fast reaction rate and naturally benign condition. Most of the synthesized compounds showed promising activities against Gram-positive bacteria, wherein the compounds **2c**, **2e**, **2m**, **2o**, **2t** and **2t'** showed good antibacterial activities, especially 8-azaprotosappanin A (**2t'**). Further research on other biological activities and structure-activity relationship of these compounds is going on. Some other natural products containing the framework will be synthesized through our synthetic approach in the future.

View Article Online
DOI: 10.1039/C6OB02707E

Acknowledgements

This work was supported by Fund of Natural Science Foundation of Heilongjiang Province of China (No. 201207 and No. 201208), for which we are thankful.

Notes and references

1 (a) C. Junbiao, J. Reiner, and J. X. Xie, *Chem. Rev.,* 2005, **105**, 4581–4609; (b) A. W. Schmidt, K. R. Reddy and H. J. Knölker, *Chem. Rev.*, 2012, **112**, 3193–3328.

2 (a) K. Ohmori, M. Tamiya, M. Kitamura, H. Kato, M. Oorui and K. Suzuki, *Angew. Chem., Int. Ed*., 2005, **44**, 3871–3874; (b) S. Strych, G.Journot, R. P. Pemberton, S. C. Wang, D. J. Tantillo and D. Trauner, *Angew. Chem., Int. Ed*., 2015, **54**, 5079–5083.

3 N. Masahiro, N. Seiji, L. Shumei, E. Ikuyo and K. Kenichi, *Biol. Pharm. Bull*., 1986, **34**, 1.

4 J. Q. Liu, X. Zhou, C. L. Wang, W. Y. Fu, W. Y. Chu and Z. Z. Sun, *Chem. Comm*., 2016, **52**, 5152-5155.

5 I. Batubara, T. Mitsunaga and H. Ohashi, *J. Wood. Sci*., 2010, **56**, 77–81.

6 M. T. T. Nguyen, S. Awale, Y. Tezuka, Q. L. Tran and S. Kadota, *Chem. Pharm. Bull*., 2005, **53**, 984–988.

7 (a) B. S. Min, T. D. Cuong, T. M. Hung, B. K. Min, B. S. Shin and M. H. Woo, *Bioorg. Med. Chem. Lett*., 2012, **22**, 7436–7439; (b) J. H. Lyu, K. H. Kim, H. W. Kim, S. I. Cho, K. T. Ha, J. Y. Choi, C. W. Han, H. S. Jeong, H. K. Lee, K. S. Ahn, S. R. Oh, R. T. Sadikot, J. W. Christman and M. J Joo, *Ethnopharmacol*., 2012, **140**, 107-116.

8 S. Tewtrakul, P. Chaniad, S. Pianwanit, C. Karalai, C. Ponglimanont and O. Yodsaoue, *Phytother. Res*., 2015, **29**, 724–729.

9 (a) J. Wu, M. Zhang, H. Jia, X. T. Huang, Q. Zhang and J. B. Hou, *N-S Arch Pharmaco*., 2010, **381**, 83-92; (b) M. Zhang, J. He, J. Hou, J. Wu, M. Sun, J. Cui, J. Tian, M. Jiang and B. Yu, *PLoS. One*., 2014, **9**, e96138.

10 Y. Sasaki, Suzuki, M. T. Matsumoto, T. Hosokawa, T. Kobayashi, K. Kamata and S. Nagumo, *Biol. Pharm. Bull.,* 2010, **33**, 1555–1560.

11 (a) O. Baudoin, M. Cesario, D. Guenard and F. Guéritte, *J. Org. Chem*., 2002, **67**, 1199–1207; (b) Z. H. Chohan, M. H. Youssoufi, A. Jarrahpour and T. B. Hadda, *Eur. J. Med. Chem.*, 2010, **45**, 1189-1199; (c) B. P. Mathew, A. Kumar, S. Sharma, P. K. Shukla and M. Nath, *Eur. J. Med. Chem.*, 2010, **45**, 1502-1507; (d) V. S. Patil, V. S. Padalkar, K. R. Phatangare, P. G. Umape, B. N. Borase and N. Sekar, *J. Heterocyclic. Chem*., 2015, **52**, 124-129; (e) S. Konda, S. Raparthi, K. Bhaskar, R. K. Munaganti, V. Guguloth, L. Nagarapu and D. M. Akkewar, *Bioorg. Med. Chem. Let*., 2015, **25**, 1643-1646.

12 M. Binaschi, A. Boldetti, M. Gianni, C. Alberto, M, M. Gensini, M. Bigioni, M. Parlani, A. Giolitti, M. Fratelli, C. Valli, M. Terao and E. Garattini, *ACS. Med. Chem. Lett*., 2010, **1**, 411–415.

13 (a) L. Yang, G. Deng, D. X. Wang, Z. T. Huang, J. P. Zhu and M. X. Wang, *Org. Let*t., 2007, **9**, 1387–1390; (b) J. M. Klunder, K, D. Hargrave, M. West, E. Cullen, K. M. Pal, L. S. Behnke, R, D. Kapadia, W. J. McNeil, C. Wu and G. C.Chow, *J. Med. Chem*., 1992, **35**, 1887–1897.

14 (a) G. Zeni and R. C. Larock, *Chem. Rev*., 2006, **106**, 4644-4680; (b) A, B. El and H. Alper, *Synlett*., 2000, **2000**, 161–171.

15 (a) O. Baudoin, M. Cesario, D. Guenard and F. Guéritte, *J. Org. Chem*., 2002, **67**, 1199–1207; (b) R. Bernini, S. Cacchi, G. Fabrizi and A. Sferrazza, *Synthesis*, 2008, **2008**, 729-738; (c) A. Putey, F. Popowycz, Q. T. Do, P. Bernard, S. K. Talapatra, F. Kozielski, C. M. Galmarini and B. Joseph, *J. Med. Chem*., 2009, **52**, 5916–5925; (d) L. Basolo, E. M. Beccalli, E. Borsini and G. Brogginib, *Tetrahedron*, 2009. **65**, 3486-349; (e) K. C. Majumdar, N. De and S. Chakravorty, *Synthetic. Commun*., 2010, **41**, 121–130; (f) H. Tabata, H. Suzuki, K. Akiba, H. Takahashi, H. Natsugari, *J. Org. Chem*., 2010, **75**, 5984–5993; (g) M. R. Tatton, I. Simpson and T. J. Donohoe, *Chem. Commun.*, 2014, **50**, 11314–11316; (h) J. K. Laha, K. P. Jethava and N Dayal. *J. Org. Chem*., 2014, **79**, 8010–8019; (i) A. R. Pérez, L. D. Miranda and A. Garcia. *Tetrahedron. Lett*., 2015, **56**, 6669–6673; (j) C. Liu, J. Yuan, M. Gao, S. Tang, W. Li, R. Shi and A. Lei, *Chem. Rev*., 2015, **115**, 12138–12204.

16 (a) F. Bellina and R. Rossi, *Chem. Rev*., 2009, **110**, 1082–1146; (b) B. Li and P. H. Dixneuf, *Chem. Soc. Rev*., 2013, **42**, 5744–5767; (c) J. Laroche, K. Beydoun, V. Guerchais and H. Doucet, *Catal. Sci. Technol*., 2013, **3**, 2072–2080; (d) Y. Yamamoto, *Chem. Soc. Rev*., 2014, **43**, 1575–1600; (e) A. H. Cherney, N. T. Kadunce and S. E. Reisman, *Chem. Rev*., 2015, **115**, 9587–9652; (f) Z. Huang, H. N. Lim, F. Mo, C. Y. Michael and G. B. Dong, *Chem. Soc. Rev*., 2015, **44**, 7764–7786; (g) T. Gensch, M. N. Hopkinson, F. Glorius and J. Wencel-Delord, *Chem. Soc. Rev*., 2016, **45**, 2900–2936.

17 J. Yamaguchi, A. D. Yamaguchi and K. Itami, *Angew. Chem. Int. Ed*., 2012, **51**, 8960–9009.

18 (a) C. Liu, H. Zhang, W. Shi and A. Lei, *Chem. Rev*., 2011, **111**, 1780–1824; (b) S. G. V. Modha, P. Mehtaz and V. Eycken, *Chem. Soc. Rev*., 2013, **42**, 5042–5055; (c) F. S. Han, *Chem. Soc. Rev*., 2013, **42**, 5270–5298.

19 (a) L. Ackermann, *Chem. Rev*., 2011, **111**, 1315–1345; (b) L. McMurray, F. O. Hara and M. J. Gaunt, *Chem. Soc. Rev*., 2011, **40**, 1885–1898; (c) O. Baudoin, *Chem. Soc. Rev*., 2011, **40**, 4902–4911; (d) P. B. Arockiam, C. Bruneau, P. H. Dixneuf, *Chem. Rev*., 2012, **112**, 5879–5918.

20 (a) H. Zou, H. Wu, X. Zhang, Y. Zhao, J. Stöckigta and Y. J. Lou, *Bioorgan. Med. Chem*., 2010, **18**, 6351–6359; (b) D. Kumar, G. Khare, S. Kidwai, A. K. Tyagi, R. Singh and D. S. Rawat, *Med. Chem. Comm*., 2015, **6**, 131–137.

21 N. Sachan, S. Thareja, R. Agarwal, S. Shivajirao, M. K. Vithal and M. Kulkarni, *Int. J. PharmTech. Res*., 2009, **1**, 1625–1631.

22 (a) L. Grande, E. Serrano, L. Cuesta and E. P. Urriolabeitia, *Organometallics*, 2011, **31**, 394–404; (b) M. Chicote, C. Rubio, D. Bautista and J. Vicente, *Dalton. Trans*., 2014, **43**, 15170–15182.