Tetrahedron Letters 54 (2013) 5162–5166

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of 1,5-diphenylpent-3-en-1-yne derivatives utilizing an aqueous *B*-alkyl Suzuki cross coupling reaction

Da-Wei Chuang [a], Mohamed El-Shazly [a,b], Chin-Chau Chen [c], Yu-Ming Chung [a], Balaji D. Barve [d], Ming-Jung Wu [c], Fang-Rong Chang [a,*], Yang-Chang Wu [a,e,f,g,*]

[a] *Graduate Institute of Natural Products, College of Pharmacy, Kaohsiung Medical University, Kaohsiung 807, Taiwan*
[b] *Department of Pharmacognosy and Natural Products Chemistry, Faculty of Pharmacy, Ain-Shams University, Organization of African Unity Street, Abassia, Cairo 11566, Egypt*
[c] *Department of Chemistry, National Sun Yat-sen University, Kaohsiung 804, Taiwan*
[d] *Department of Medicinal and Applied Chemistry, Kaohsiung Medical University, Kaohsiung 807, Taiwan*
[e] *School of Chinese Medicine, College of Chinese Medicine, China Medical University, Taichung 404, Taiwan*
[f] *Natural Medicinal Products Research Center, China Medical University Hospital, Taichung 404, Taiwan*
[g] *Center for Molecular Medicine, China Medical University Hospital, Taichung 404, Taiwan*

ARTICLE INFO

Article history:
Received 13 May 2013
Revised 21 June 2013
Accepted 3 July 2013
Available online 10 July 2013

Keywords:
Henna
Palladium
B-Benzyl-9-BBN
B-Alkyl Suzuki coupling
Aqueous reaction

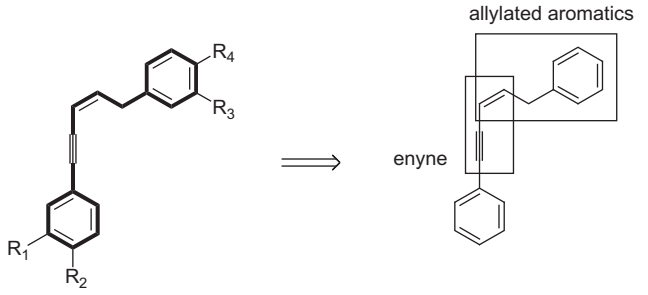
ABSTRACT

1,5-Diphenylpent-3-en-1-yne derivatives were isolated in minor quantities from terrestrial plants and exhibited strong anti-inflammatory activity. A cross coupling reaction between *B*-benzyl-9-BBN and chloroenynes under mild condition was developed resulting in the formation of different 1,5-diphenylpent-3-en-1-yne derivatives with a full control on the *E*/*Z* selectivity. Several substrates bearing electron-donating and electron-withdrawing substituents were tolerable under the reaction conditions affording the corresponding products in good yields. This is the first study to report the synthesis of a vast array of novel 1,5-diphenylpent-3-en-1-yne derivatives paving the way for the preparation of tailored derivatives on mass scale necessary for biological studies and drug development.

Introduction

Human beings' fascination with natural products and their curative effect go back to the early days of human history.[1] Henna (*Lawsonia inermis*) is a perfect example of an ancient and globally used herb with a myriad of medicinal and cosmetic uses. Several biologically active components have been isolated from henna and some of them have been synthetically prepared.[1] Our group has recently reported the isolation of novel 1,5-diphenylpent-3-en-1-yne derivatives from henna possessing impressive anti-inflammatory activity (Fig. 1).[2] These derivatives are unique from different perspectives because they were isolated for the first time from nature and only two reports in the early nineties discussed the synthesis of a single 1,5-diphenylpent-3-en-1-yne derivative.[3] The significant biological activity and limited isolated quantities encouraged us to envisage the development of a simple and high yielding methodology for their synthesis.

From a retrosynthetic perspective, 1,5-diphenylpent-3-en-1-ynes can be considered as a combination of enynes and allylated aromatics. The enyne moiety and allylated aromatics represent important structural motifs which are found in many synthetic precursors.[4–10] Despite the fact that 1,3-enyne synthesis has been established through different efficient methodologies,[4] the synthe-

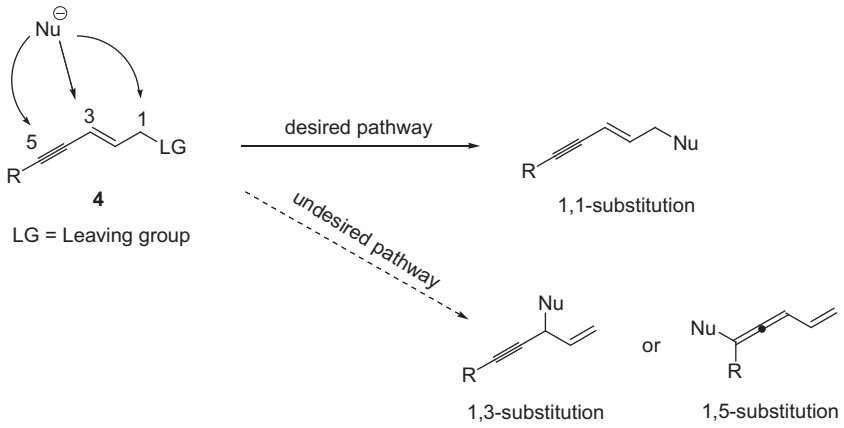


1: $R_1 = R_3 = H$, $R_2 = R_4 = OH$
2: $R_1 = R_2 = R_4 = OH$, $R_3 = H$
3: $R_1 = H$, $R_2 = R_4 = OH$, $R_3 = OCH_3$

Figure 1. New 1,5-diphenylpent-3-en-1-ynes isolated from henna.

* Corresponding authors at: Graduate Institute of Natural Products, College of Pharmacy, Kaohsiung Medical University, Kaohsiung 807, Taiwan. Tel.: +886 7 3121101x2162; fax: +886 7 3114773.
E-mail address: aaronfrc@kmu.edu.tw (F.-R. Chang).

0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.07.020



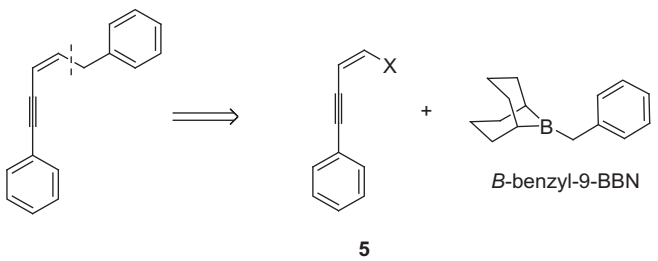
Scheme 1. Desired and undesired products from S_N reaction of organometallic nucleophiles with enynes.

sis of 1,5-diphenylpent-3-en-1-yne derivatives did not receive such success. Masuyama et al. used a palladium catalyzed dehydration of propynyl alcohols with $SnCl_2$. However, the product was formed as a mixture of *E*/*Z* isomers (20/80) and the yield was only 53%.[3a] Yoshimatsu et al. developed a mild dehydration process using polyphosphoric acid trimethylsilyl ester (PPSE), but the method also provided 1,5-diphenylpent-3-en-1-yne as a mixture of *E*/*Z* isomers (33/67) with mediocre yield (54%).[3b]

Nucleophilic substitution of an organometallic reagent on the allylic position of an enyne (**4**) was proposed as an alternative route for the preparation of 1,5-diphenylpent-3-en-1-ynes, however other side reactions such as 1,3-substitution or 1,5-substitution are inevitable (Scheme 1).[11] Additionally, the use of highly reactive and moisture-sensitive organometallic reagents adds to the reaction limitations. In order to establish an easy access to 1,5-diphenylpent-3-en-1-yne derivatives, a mild and selective method must be introduced. The recent advances in C–C bond formation reactions, suggested that *B*-alkyl Suzuki coupling could offer a solution to this problem.[12]

The *B*-alkyl Suzuki reaction differs from the typical Suzuki reactions, in which alkyl boranes are utilized instead of vinyl or aryl boranes to react with aryl or vinyl halides.[13] In the *B*-alkyl Suzuki reaction, the hydroboration of an olefin is followed by a metal-catalyzed coupling reaction with the organic halides. However, these procedures cannot be applied for the synthesis of 1,5-diphenylpent-3-en-1-ynes because it will result in the formation of products with additional methylene bridge.[14] Therefore, we proposed an alternative pathway for the synthesis of 1,5-diphenylpent-3-en-1-ynes from two synthons, an enyne (**5**), and *B*-benzyl-9-BBN (Scheme 2).

most of the organometallic coupling reactions. Some studies reported the preparation of benzylboranes using bis(pinacolato)diboron and benzyl halides with palladium or other metal catalysts as well as *B*-OMe-9-BBN with benzyl metal species.[15]



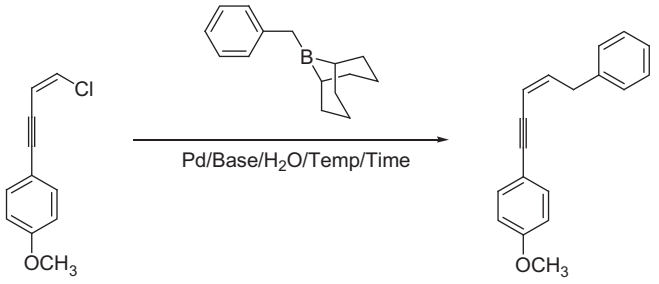
Scheme 2. Retro-synthetic analysis of 1,5-diphenylpent-3-en-1-yne.

However, the subsequent use of this reagent in related cross coupling reactions is seldom described in the literature.[16,17] Based on the aforementioned structural analysis of 1,5-diphenylpent-3-en-1-ynes, we developed a versatile synthetic protocol for their synthesis in which (*E*)- and (*Z*)-chloroenynes were utilized for the first time as the coupling partners with *B*-benzyl-9-BBN.

Results and discussion

The preparations of (*E*)- and (*Z*)-chloroenynes were achieved through a typical sonogashira coupling reaction.[18] With different chloroenynes in hand, we proceeded to examine the optimum cou-

Table 1
Optimization of the *B*-alkyl Suzuki cross coupling reactions using water as the sole solvent[a]

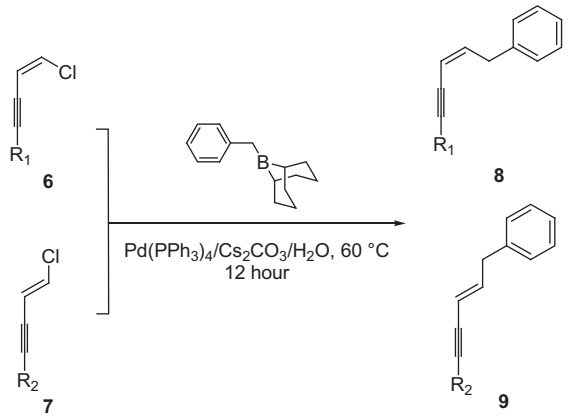


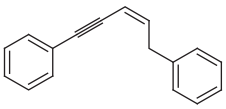
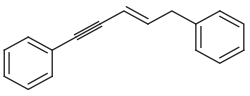
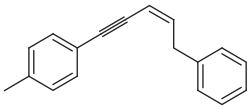
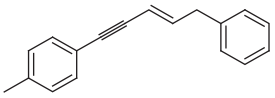
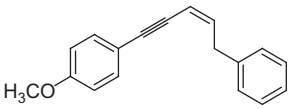
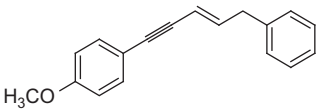
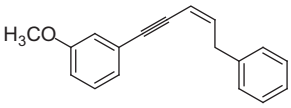
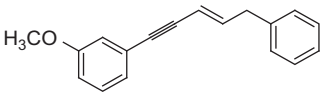
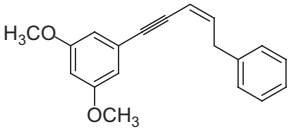
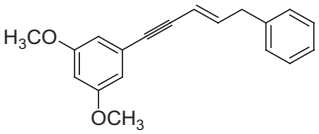
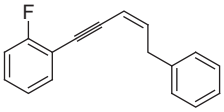
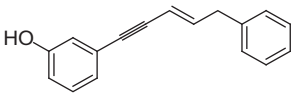
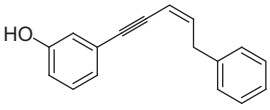
6c **8c**

Entry	Catalyst (3 mol %)	Base (3 equiv)	Time (h)	Temp (°C)	Yield[b] (%)
1	$Pd(OAc)_2$	K_3PO_4	6	60	Trace
2	$PdCl_2$	K_3PO_4	6	60	Trace
3	$Pd_2(dba)_3$	K_3PO_4	6	60	Trace
4	$PdCl_2(dppf)$	K_3PO_4	6	60	20
5	$PdCl_2(PPh_3)_2$	K_3PO_4	6	60	65
6	$Pd(OAc)_2(PPh_3)_2$	K_3PO_4	6	60	68
7	$Pd(PPh_3)_4$	K_3PO_4	6	60	75
8	$Pd(PPh_3)_4$	K_2CO_3	6	60	62
9	$Pd(PPh_3)_4$	KOH	6	60	75
10	$Pd(PPh_3)_4$	KF	6	60	Trace
11	$Pd(PPh_3)_4$	Et_3N	6	60	68
12	$Pd(PPh_3)_4$	Cs_2CO_3	6	60	77
13	$Pd(PPh_3)_4$	Cs_2CO_3	12	60	82
14	$Pd(PPh_3)_4$	Cs_2CO_3	24	60	79
15	$Pd(PPh_3)_4$	Cs_2CO_3	12	rt	Trace
16[c]	$Pd(PPh_3)_4$	Cs_2CO_3	12	60	45

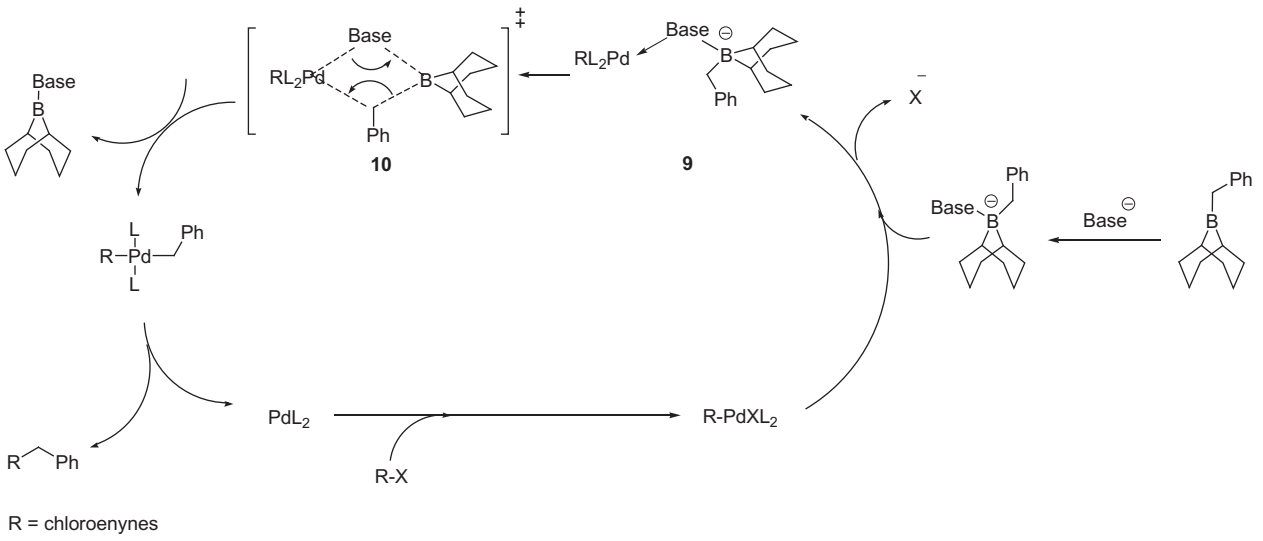
[a] Conditions: **6c** (80 mg), BBN (2 equiv), catalyst (3 mol %), base (3 equiv), H_2O (6 mL).
[b] Isolated yields.
[c] Reaction without nitrogen.

Table 2
Synthesis of 1,5-diphenylpent-3-en-1-yne derivatives[a]



Entry	Product	Entry	Product
1	 **8a** (65%)[b]	8	 **9h** (73%)
2	 **8b** (71%)	9	 **9i** (76%)
3	 **8c** (82%)	10	 **9j** (65%)
4	 **8d** (68%)	11	 **9k** (83%)
5	 **8e** (72%)	12	 **9l** (65%)
6	 **8f** (70%)	13	 **9m** (64 %)
7	 **8g** (50%)		

[a] Conditions: **6** or **7** (80 mg), BBN (2.0 equiv), $Pd(PPh_3)_4$ (3.0 mol %), Cs_2CO_3 (3.0 equiv), H_2O (6.0 mL), 60 °C, 12 h.
[b] Isolated yields.



Scheme 3. Plausible mechanism of *B*-alkyl Suzuki cross coupling reactions.

pling condition with *B*-benzyl-9-BBN.[19] Initially, we used (*Z*)-chloroenynes **6c** (1.0 equiv) as a model substrate with 2.0 equiv of *B*-benzyl-9-BBN, 3.0 mol % of $Pd(PPh_3)_4$, and 3.0 equiv of K_3PO_4 in dry THF at 60 °C for 6 h. Under this condition, the desired (*Z*)-product **8c** was obtained in 65% yield without the formation of the opposite geometrical isomer. Higher yield (78%) was obtained upon using a mixture of THF and water (3:1). This improvement in the product yield encouraged us to examine the use of water as the sole solvent, which to our delight resulted in similar yield (75%).

After selecting water as the coupling reaction solvent, we examined the effect of changing other reaction conditions on the product yield. Different palladium salts were tested aiming to select the optimum catalyst for the coupling reaction. The use of $Pd(OAc)_2$, $PdCl_2$, and $Pd_2(dba)_3$, failed to provide any product (Table 1, entries 1–3). $PdCl_2(dppf)$ resulted in poor yield (20%, Table 1, entry 4). However, the use of $PdCl_2(PPh_3)_2$ improved the yield significantly (65%, Table 1, entry 5), and $Pd(OAc)_2(PPh_3)_2$ also resulted in a similar outcome (68%, Table 1, entry 6). The most commonly utilized palladium catalyst in organic synthesis, $Pd(PPh_3)_4$ afforded the best result (75%, Table 1, entry 7). These screening reactions suggested that PPh_3 is the ideal ligand compared to other ligands such as dppf or dba; and Pd(0) is the optimum catalyst compared to Pd(II). Following the catalyst optimization, we examined the effect of using different bases on the reaction yield. The use of K_3PO_4 and KOH resulted in similar yields (75%, Table 1, entry 7 and 9), while K_2CO_3 provided slightly a lower yield (62%, Table 1, entry 8). KF, another base used frequently in Suzuki coupling reactions, failed to yield the desired compound (Table 1, entry 10). Interestingly, the organic base Et_3N afforded the product in 68% yield (Table 1, entry 11), providing an additional evidence of the versatility of *B*-alkyl-Suzuki coupling, since organic amines are not frequently used in Suzuki cross coupling reactions.[20]

However, the highest yield was obtained using Cs_2CO_3, which was selected as the optimum base (77%, Table 1, entry 12).[21] The effect of running the reaction under inert or ambient atmosphere on the product yield was also studied. Under ambient atmosphere, the reaction mixture turned black and the yield decreased to 45% (Table 1, entry 16); suggesting the necessity of inert condition for the optimal yield. The effect of temperature was also examined showing that conducting the reaction at room temperature led to the formation of the product in trace amounts (Table 1, entry 15).

Optimizing the reaction time was the final step in the screening experiments, which was achieved through comparing product yields after 6, 12, and 24 h. After 12 h the yield increased to 82% (Table 1, entry 13) compared to 77% yield obtained after 6 h (Table 1, entry 12), however after 24 h it dropped slightly (79%, Table 1, entry 14) indicating that the optimum reaction time is 12 h. This finding was supported by a time-course NMR experiment (see Supplementary data). Based on the aforementioned screening results, entry 13 was selected as the most optimum condition.

The optimized cross coupling conditions were applied for the preparation of different 1,5-diphenylpent-3-en-1-yne derivatives. Several (*Z*)-chloroenynes bearing alkoxy groups (Table 2, entries 3–5) reacted selectively and smoothly yielding the corresponding (*Z*)-1,5-diphenylpent-3-en-1-ynes without the formation of the (*E*)-isomers. This strict stereoselectivity was also achieved for the (*E*)-chloroenynes (Table 2, entries 8–13). Interestingly, chloroenynes bearing a free hydroxy group were tolerable under this basic aqueous condition and afforded the products with moderate yields (Table 2, entries 7 and 13).

From a mechanistic point of view, the *B*-alkyl-Suzuki reaction is slightly different from the typical Suzuki coupling reaction. Soderquist and Matos have reported a pioneer investigation on the mechanism of cross coupling reaction involving *B*-alkyl-9-BBN derivatives.[22] The base used in the reaction plays a critical role in the whole mechanistic cycle, especially in the conversion of the *B*-alkyl-9-BBN into a more reactive species (**9**) (Scheme 3). They suggested a formation of four-centered hydroxo-μ_2-bridged transition state (**10**) which collapses facilitating the transfer of an alkyl group to the palladium catalyst. Finally through the reductive elimination step, the desired product is generated. The use of water in our condition improved base solubility pushing the conversion of *B*-benzyl-9-BBN to the corresponding active species (**9**).

Conclusion

A mild and selective *B*-alkyl Suzuki cross coupling protocol for the synthesis of 1,5-diphenylpent-3-en-1-yne derivatives was developed. In this study, we present not only the first cross coupling reaction between *B*-benzyl-9-BBN and chloroenynes, but also the use of pure water as the reaction solvent for this type of reactions. A number of 1,5-diphenylpent-3-en-1-yne derivatives were synthesized successfully under this condition with moderate to

good yields with a full control of stereoselectivity. The developed protocol is working in concert with the ongoing research projects investigating the biological activity and mechanism of action of henna active constituents. A series of biological studies for the prepared derivatives are underway in our laboratory.

Acknowledgments

This study was supported by NSC grants (NSC 102-2911-I-002-303 and NSC 101-2325-B-039-004 to Y.C. Wu), and a grant from the Department of Health, Executive Yuan, R.O.C. (Taiwan) (DOH102-TD-C-111-002).

Supplementary data

Supplementary data (^{1}H and ^{13}C NMR copies of all the compounds are available, time-course NMR experiment) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.07.020.

References and notes

1. (a) Nicolaou, K. C.; Vourloumis, D.; Winssinger, N.; Baran, P. S. *Angew. Chem., Int. Ed.* **2000**, *39*, 44–122; (b) Borade, A. S.; Babasaheb, N. K.; Shete, R. V. *Int. J. Pharm. Life Sci.* **2011**, *2*, 536–541; (c) Miczak, M. A. *Henna's Secret History*; Writers Club Press: New York, 2001; (d) Siddiqui, B. S.; Kardar, M. N.; Ali, S. T.; Khan, S. *Helv. Chim. Acta* **2003**, *86*, 2164–2169; (e) Bufford, D. E.; Hsieh, C. F.; Huang, T. C.; Kao, M. T.; Lievens, A. W.; Ohashi, H.; Peng, C. I. Flora of Taiwan *Tah Jinn Printing Company, Ltd.* **1993**, *3*, 872–885; (f) Alam, M. S.; Niwa, M.; Sakai, T.; Gupta, S.; Ali, M. *Phytochemistry* **1992**, *31*, 2558–2560; (g) Muhammad, A.; Al-Oriquat, G.; Al-Hassan, J. M.; Muhammad, N. *Heterocycles* **1984**, *22*, 813–816; (h) Muhammad, A.; Al-Oriquat, G.; Al-Hassan, J. M.; Muhammad, N. *Heterocycles* **1980**, *14*, 1973–1976; (i) Hart, D. J. *Organic Synthesis Via Examination of Selected Natural Products*; World Scientific Publishing Company, 2011; (j) Osbourn, A. E.; Lanzotti, V. *Plant-derived Natural Products*; Springer Science Business Media, L.L.C, 2009.
2. Liou, J. R.; El-Shazly, M.; Du, Y. C.; Tseng, C. N.; Hwang, T. L.; Chuang, Y. L.; Hsu, Y. M.; Hsieh, P. W.; Wu, C. C.; Chen, S. L.; Hou, M. F.; Chang, F. R.; Wu, Y. C. *Phytochemistry* **2012**, *88*, 67–73.
3. (a) Masuyama, Y.; Takahara, J. P.; Hashimoto, K.; Kurusu, Y. *J. Chem. Soc., Chem. Commun.* **1993**, 1219–1220; (b) Yoshimatsu, M.; Yamada, H.; Shimizu, H.; Kataoka, T. *J. Chem. Soc., Chem. Commun.* **1994**, 2107–2108.
4. (a) Wu, H. C.; Yang, C. W.; Hwang, L. C.; Wu, M. J. *Org. Biomol. Chem.* **2012**, *10*, 6640–6648; (b) Yu, X.; Zhou, G.; Zhang, J. *Chem. Commun.* **2012**, 4002–4004; (c) Chen, C. C.; Yang, S. C.; Wu, M. J. *J. Org. Chem.* **2011**, *76*, 10269–10274; (d) Chen, Z. Y.; Wu, M. J. *Org. Lett.* **2005**, *7*, 475–477; (e) Zhang, Y.; Herndon, J. W. *Org. Lett.* **2003**, *5*, 2043–2045; (f) Wu, M. J.; Lee, C. Y.; Lin, C. F. *Angew. Chem., Int. Ed.* **2002**, *41*, 4077–4079.
5. (a) Adachi, Y.; Kamei, N.; Yokoshima, S.; Fukuyama, T. *Org. Lett.* **2011**, *13*, 4446–4449; (b) Sinclair, A.; Stockman, R. A. *Nat. Prod. Rep.* **2007**, *24*, 298–326.
6. (a) Aydogmuş, Z.; Imre, S.; Ersoy, L.; Wray, V. *Nat. Prod. Res.* **2004**, *18*, 43–49; (b) Kozikowski, A. P.; Lee, J. *J. Org. Chem.* **1990**, *55*, 863–870.
7. (a) Chandler, C. L.; Phillips, A. J. *Org. Lett.* **2005**, *7*, 3493–3495; (b) Gadikota, R. R.; Callam, C. S.; Lowary, T. L. *J. Org. Chem.* **2001**, *66*, 9046–9051.
8. (a) Kharkar, P. S.; Deodhar, M. N.; Kulkarni, V. M. *Med. Chem. Res.* **2009**, *18*, 421–432; (b) Gokhale, V. M.; Kulkarni, V. M. *J. Med. Chem.* **1999**, *42*, 5348–5358; (c) Nussbaumer, P.; Leitner, I.; Mraz, K.; Stuetz, A. *J. Med. Chem.* **1995**, *38*, 1831–1836.
9. Krasovskaya, V.; Krasovskiy, A.; Bhattacharjya, A.; Lipshutz, B. H. *Chem. Commun.* **2011**, 5717–5719.
10. (a) Shanbhag, G. V.; Devassy, B. M.; Halligudi, S. B. *J. Mol. Catal. A-Chem.* **2004**, *218*, 67–72; (b) Mazza, G.; Kiehn, F. A. *J. Essent. Oil Res.* **1992**, *4*, 295–299.
11. Li, H.; Alexakis, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 1055–1058.
12. Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2001**, *40*, 4544–4568.
13. For different reviews of typical Suzuki cross coupling please refer to the following articles: (a) Suzuki, A.; Yamamoto, Y. *Chem. Lett.* **2011**, *40*, 894–901; (b) Kambe, N.; Iwasakia, T.; Terao, J. *Chem. Soc. Rev.* **2011**, *40*, 4937–4947; (c) Li, H.; Johansson Seechurn, C. C. C.; Colacot, T. J. *ACS Catal.* **2012**, *2*, 1147–1164; (d) Seidel, G.; Furstner, A. *Chem. Commun.* **2012**, 2055–2070; (e) Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chem., Int. Ed.* **2012**, *51*, 5062–5085.
14. For the explanatory scheme please refer to the Supplementary data.
15. (a) Bej, A.; Srimani, D.; Sarkar, A. *Green Chem.* **2012**, *14*, 661–667; (b) Christian, K.; Dang, L.; Li, Z. Y.; Todd, B. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 5350–5354; (c) Giroux, A. *Tetrahedron Lett.* **2003**, *44*, 233–235; (d) Ishiyama, T.; Oohashi, Z.; Ahiko, T. A.; Miyaura, N. *Chem. Lett.* **2002**, *31*, 780–781; (e) Fang, G. Y.; Wallner, O. A.; Blasio, N. D.; Ginesta, X.; Harvey, J. N.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2007**, *129*, 14632–14639.
16. (a) Tatamidani, H.; Kakiuchi, F.; Chatani, N. *Org. Lett.* **2004**, *6*, 3597–3599; (b) Tatamidani, H.; Yokota, K.; Kakiuchi, F.; Chatani, N. *J. Org. Chem.* **2004**, *69*, 5615–5621; (c) Fuwa, H.; Sasaki, M. *Org. Biomol. Chem.* **2007**, *5*, 2214–2218; (d) Zhu, Q.; Wu, J.; Fathi, R.; Yang, Z. *Org. Lett.* **2002**, *4*, 3333–3336.
17. Flaherty, A.; Trunkfield, A.; Barton, W. *Org. Lett.* **2005**, *7*, 4975–4978.
18. (a) Tikad, A.; Hamze, A.; Provot, O.; Brion, J. D.; Alami, M. *Eur. J. Org. Chem.* **2010**, 725–731; (b) For different conditions for Sonogashira coupling please refer to the following reviews: (i) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874–922; (ii) Doucet, H.; Hierso, J. C. *Angew. Chem., Int. Ed.* **2007**, *46*, 834–871; (iii) Chinchilla, R.; Nájera, C. *Chem. Soc. Rev.* **2011**, *40*, 5084–5121; (iv) Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chem., Int. Ed.* **2012**, *51*, 5062–5085; (v) Bakherad, M. *Appl. Organomet. Chem.* **2013**, *27*, 125–140.
19. For the preliminary optimization studies please refer to the Supplementary data.
20. (a) Klingensmith, L. M.; Leadbeater, N. E. *Tetrahedron Lett.* **2003**, *44*, 765–768; (b) Grasa, G. A.; Viciu, M. S.; Huang, J.; Zhang, C.; Trudell, M. L.; Nolan, S. P. *Organometallics* **2002**, *21*, 2866–2873; (c) Zim, D.; Gruber, A. S.; Ebeling, G.; Dupont, J.; Monteiro, A. L. *Org. Lett.* **2000**, *2*, 2881–2884; (d) Zhang, C.; Huang, J.; Trudell, M. L.; Nolan, S. P. *J. Org. Chem.* **1999**, *64*, 3804–3805; (e) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483.
21. It is noteworthy to mention that the use of the more expensive base Cs_2CO_3 resulted in 2% increase in the product yield compared to K_3PO_4. However, our main focus is to introduce the most optimum conditions which result in the highest possible yield so we decided to select Cs_2CO_3 as the optimum base.
22. Matos, K.; Soderquist, J. A. *J. Org. Chem.* **1998**, *63*, 461–470.