

RSC Advances



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

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

You can find more information about *Accepted Manuscripts* in the [Information for Authors](#).

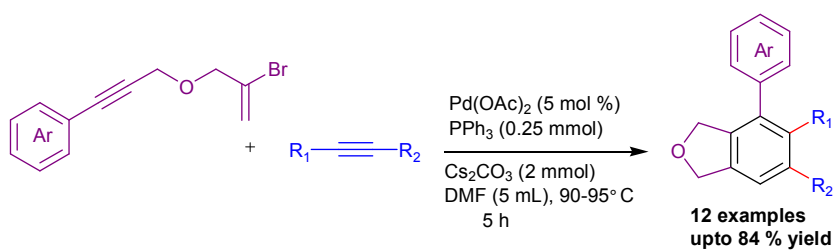
Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard [Terms & Conditions](#) and the [Ethical guidelines](#) still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions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

Graphical Abstract

Synthesis of 4,5,6-trisubstituted-1,3-dihydroisobenzofurans by virtue of palladium-catalyzed domino carbopalladation of bromoenynes and internal alkynes

Munmun Ghosh, Raju Singha, Shubendu Dhara and Jayanta K. Ray*

An efficient hetero-annulation protocol has been developed for the construction of 4,5,6-trisubstituted-1,3-dihydroisobenzofurans *via* palladium-catalyzed domino carbopalladation of bromoenynes and internal alkynes.





Synthesis of 4,5,6-trisubstituted-1,3-dihydroisobenzofurans by virtue of palladium-catalyzed domino carbopalladation of bromoenynes and internal alkynes

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

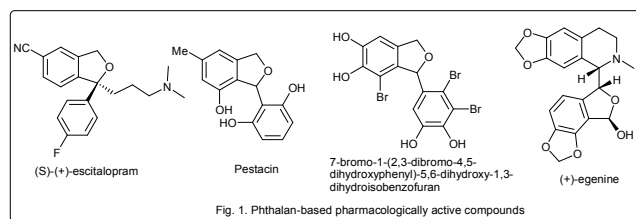
DOI: 10.1039/x0xx00000x

www.rsc.org/

Mummun Ghosh^a, Raju Singha^a, Shubhendu Dhara^a and Jayanta K. Ray^{*a}

An efficient hetero-annulation protocol has been developed for the construction of 4,5,6-trisubstituted-1,3-dihydroisobenzofurans via palladium-catalyzed domino carbopalladation of bromoenynes and internal alkynes. The reaction followed domino intramolecular Heck cyclization (5-*exo-dig*) and termination of the resulting diene with internal alkyne to give highly substituted isobenzofurans in moderate to good yields.

1,3-dihydroisobenzofurans (phthalans) contribute to the family of a considerable number of natural products demonstrating fascinating pharmacological activities including antidepressive, antioxidant, antifungal, antibacterial, antitumor and cardiovascular disease, anti-inflammatory, cytotoxicity against human cancer cell and so on.¹ They are also important in terms of industrial applications² and as major building blocks in organic synthesis.³ Figure 1 represents some selected bioactive phthalans.^{1a-g}



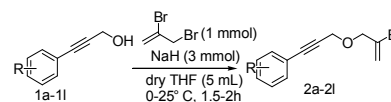
Owing to such versatile pharmacological, industrial as well as synthetic applications, development of efficient and economic methods for the synthesis of phthalans has attracted a number of chemists over the last few decades. A plethora of transition metal catalyzed⁴ as well as metal free⁵ strategies have been reported for the construction of substituted 1,3-dihydroisobenzofurans.

Cyclization of 2-bromo-1,*n,m*-enynes and 2-bromo-1,*m,n*-dienynes, more particularly, 2-bromo-1,6-enynes via sequential carbopalladation leading to the formation of a “living” alkenylpalladium intermediate and consecutive termination of this “living” intermediate via further intra- or intermolecular carbopalladation to other double or triple bonds have gained considerable attention of a number of chemists.⁶ Following the same strategy, herein we report synthesis of previously unexplored class of highly substituted 1,3-dihydroisobenzofurans from bromoenynes and internal alkynes via palladium-catalyzed domino carbopalladation. Although some reports on other metal-catalyzed synthesis of 4,5,7-triphenyl-1,3-dihydroisobenzofurans,^{7a-c} 4-methyl-5,6-diphenyl-1,3-dihydroisobenzofurans,^{7a} 4,5,6,7-tetraphenyl-1,3-dihydroisobenzofurans^{7a,7d} or 4,7-dimethyl-5,6-diphenyl-1,3-dihydroisobenzofurans^{7a,7e} are available, no such work has been reported so far for the palladium-catalyzed synthesis of 4,5,6-triphenyl-1,3-dihydroisobenzofurans. Therefore, we targeted to synthesize 4,5,6-triphenyl-1,3-dihydroisobenzofurans using domino carbopalladation (Heck reaction followed by termination) strategy. During the course of the study, we also successfully synthesized 5-hexyl-4,6-diphenyl-1,3-dihydroisobenzofuran along with the other regioisomer.

The Heck precursor [3-(2-Bromo-allyloxy)-prop-1-ynyl]-benzenes (2-bromo-1,6-enynes) (**2a-2l**) were synthesized from the corresponding iodo/bromo-benzenes (1 mmol) by Sonogashira coupling with propargyl alcohol (1.2 mmol) using PdCl₂(PPh₃)₂ (5 mol %) and CuI (5 mol %) in refluxing Et₃N (6 mL) for 4-5 h (in case of iodides) or 8-10 h (in case of bromides)⁸ followed by allylation of the 3-Phenyl-2-propynyl alcohols (**1a-1l**) using NaH (3 mmol) and 2,3-dibromopropene (1 mmol) in dry THF (5 mL) (0°C-25°C) for 1.5-2 h (Table 1).^{6c,6g}

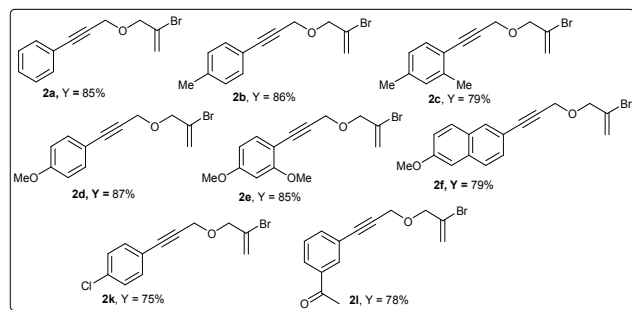
Table 1

Synthesis of [3-(2-Bromo-allyloxy)-prop-1-ynyl]-benzenes^a (**2a-2l**)



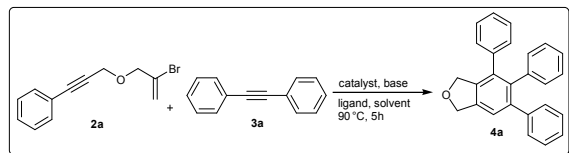
^a Department of Chemistry, Indian Institute of Technology, Kharagpur 721302, India. E-mail: jkray@chem.iitkgp.ernet.in; Fax: +91 3222282252; Tel: +91 322228332

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x



^a Isolated yields after purification through column chromatography.

Table 2
Optimization studies^a



Entry	Catalyst	Ligand	Base	Solvent	Temp (°C)	Yield (%) ^b
1	Pd(OAc) ₂	PPh ₃	Et ₃ N	DMF	90	48
2	Pd(OAc) ₂	PPh ₃	Na ₂ CO ₃	DMF	90	64
3	Pd(OAc) ₂	PPh ₃	K ₂ CO ₃	DMF	90	61
4	Pd(OAc)₂	PPh₃	Cs₂CO₃	DMF	90	82
5	Pd(OAc) ₂	PPh ₃	Cs ₂ CO ₃	DMF	70	56
6	Pd(OAc) ₂	PPh ₃	NaOAc	DMF	90	46
7	Pd(OAc) ₂	PPh ₃	KOBu ^t	DMF	90	55
8	Pd(OAc) ₂	PPh ₃	HCOONa	DMF	90	26
9	Pd(OAc) ₂	PPh ₃	Cs ₂ CO ₃	DMA	90	77
10	Pd(OAc) ₂	PPh ₃	Cs ₂ CO ₃	DMSO	90	72
11	Pd(OAc) ₂	PPh ₃	Cs ₂ CO ₃	1,4-dioxane	90	46
12	Pd(OAc) ₂	-	Cs ₂ CO ₃	DMF	90	44
13	Pd(OAc) ₂	PCy ₃	Cs ₂ CO ₃	DMF	90	33
14	Pd(OAc) ₂	BINAP	Cs ₂ CO ₃	DMF	90	40
15	PdCl ₂	PPh ₃	Cs ₂ CO ₃	DMF	90	54
16	PdCl ₂ (CH ₃ CN) ₂	-	Cs ₂ CO ₃	DMF	90	46
17	Pd(PPh ₃) ₄	-	Cs ₂ CO ₃	DMF	90	50
18	Pd ₂ (dba) ₃	-	Cs ₂ CO ₃	DMF	90	36

^a Reagents and conditions: **2a** (1 mmol), diphenylacetylene **3a** (1.5 mmol), Pd catalyst (5 mol %), base (2 mmol), ligand (0.25 mmol) and solvent (5 mL) for 5 h.

^b Yields refer to the isolated yields after purification through column chromatography.

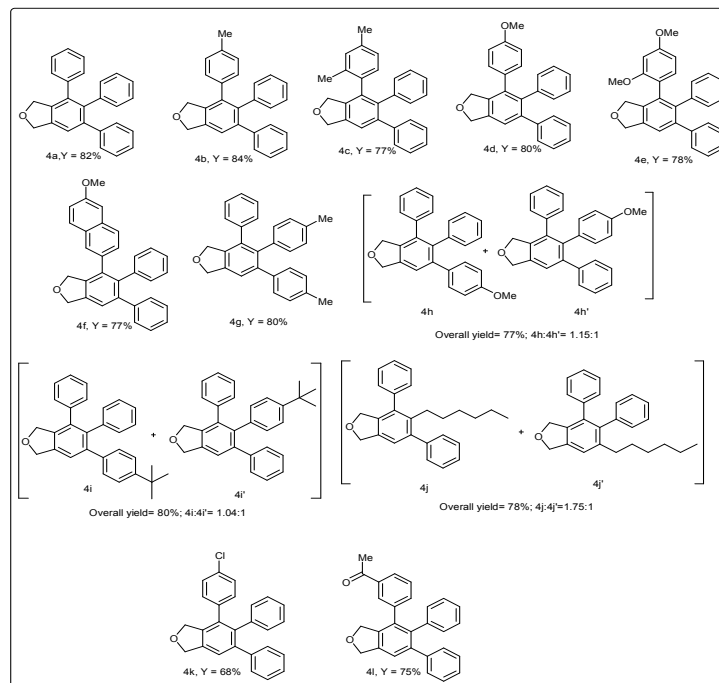
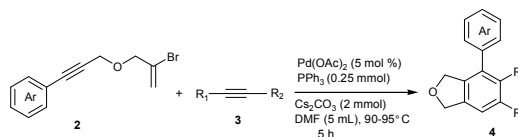
The bromoalkyne **2a** was then initially reacted with diphenylacetylene **3a** in presence of Pd(OAc)₂ catalyst, Et₃N base and PPh₃ ligand in DMF at 90 °C for 5 h to give 4,5,6-triphenyl-1,3-dihydroisobenzofuran **4a** in 48 % yield. After screening through a number of reaction conditions, the domino carbopalladation reaction was found to be most effective with Pd(OAc)₂ (5 mol %), PPh₃ (0.25 mmol), Cs₂CO₃ (2 mmol) when 1 mmol of **2a** was reacted with 1.5 mmol of **3a** in DMF (5 mL) at 90 °C for 5 h resulting in the formation of 82 % of 4,5,6-triphenyl-1,3-dihydroisobenzofuran **4a** as the only isolable product (Table 2, Entry 4).

We next attempted to investigate the general applicability of this methodology and a number of variously functionalised (both

electron donating and electron withdrawing) 2-bromo-1,6-enynes **2a-2l** were reacted with symmetrical as well as unsymmetrical internal alkynes **3** under the optimized reaction condition. The results are summarized in Table 3.

Table 3

Synthesis of 4,5,6-trisubstituted-1,3-dihydroisobenzofuran^{a,b} (**4a-4l**)



^a Reagents and conditions: all the reactions were carried out under the following conditions: substrates **2** (1 mmol), **3** (1.5 mmol), Pd(OAc)₂ (5 mol %), PPh₃ (0.25 mmol), Cs₂CO₃ (2 mmol), DMF (5 mL), 90-95 °C, 5 h

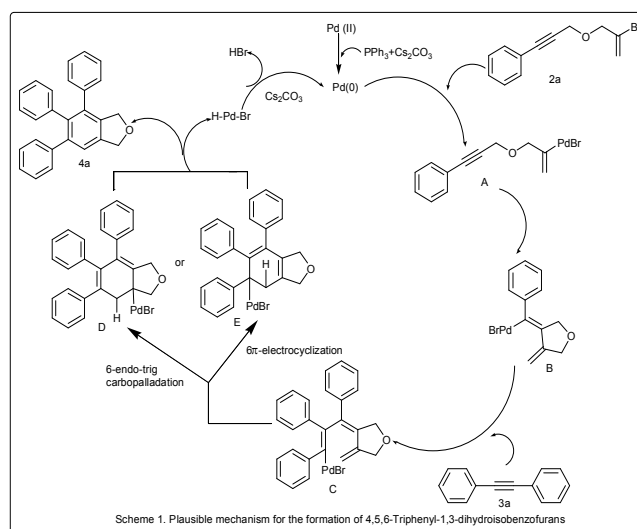
^b Isolated yield (after purification through column chromatography) after 5 h.

The reaction was found to be relatively high yielding in case of electron donating groups present either in **2** or **3** [resulting in **4b-4j-4j'**] compared to those with electron withdrawing groups (resulting in **4k** and **4l**). However, when the reaction was carried out with diethyl acetylenedicarboxylate (R₁ = R₂ = CO₂Et) and 1,1'-(1,2-ethylenediyl)bis[4-nitro-benzene] (R₁ = R₂ = 4-NO₂-C₆H₄), the starting material and/or the product probably could not persist under the applied reaction condition leading to no fruitful result.

With unsymmetrical internal alkynes a regioisomeric mixture was obtained in each case. As indicated by NMR data, **4h** and **4h'** were obtained in a ratio of 1.15:1 (**4h:4h'** ≈ 1.15:1). Similarly, according to NMR data, **4i:4i'** ≈ 1.04:1 and **4j:4j'** ≈ 1.75:1. However, geometry optimization was carried out for (**4h** and **4h'**), (**4i** and **4i'**) and (**4j** and **4j'**) by using the DFT method at the (U)B3LYP level in the Gaussian 09 program⁹ and 6-311G* basis set was used for all the

elements. The DFT calculation shows that between **4h** and **4h'**, **4h** is more stable by 0.21 KJ/mol of energy and hence they were obtained in almost equimolar ratio (**4h:4h'**≈**1.15:1** from NMR data). Between **4i** and **4i'**, **4i** is more stable only by 0.1 KJ/mol and thus they were also obtained in equimolar ratio (**4i:4i'**≈**1.04:1** from NMR data). Again, between **4j** and **4j'**, **4j** is more stable by 6.67 KJ/mol of energy and hence **4j** was obtained as the major product (**4j:4j'**≈**1.75:1** from NMR data). Thus the DFT calculation supports the results obtained experimentally. The results thus obtained also stand consistent with the regiochemical consequences reported by Negishi *et al.* in 1993.^{6c}

To explain mechanistically, it would be rationalized that Pd(II) is initially reduced by PPh₃ to Pd(0) which enters the catalytic cycle by oxidative addition to the sp²-C-Br bond of the bromoenyne **2a** leading to the formation of the alkenylpalladium intermediate **A**. This intermediate then undergoes intramolecular carbopalladation to the triple bond forming a "living" alkenylpalladium intermediate **B**. Carbopalladation of diphenylacetylene **3a** to **B** furnishes intermediate **C** which is then converted to the desired product **4a** either via **D** (6-endo-trig carbopalladation) or via **E** (6π-electrocyclization) followed by β-dehydropalladation sequence.^{6b,10}



Conclusions

In summary, we have developed an easy access to highly substituted 1,3-dihydroisobenzofurans using domino carbopalladation of bromoenynes and internal alkynes. Our methodology is advantageous with respect to good yield and substrate versatility. Moreover, the starting materials are readily accessible. Hope this methodology may find successful application in the construction of phthalan-containing natural products and also help in materials, pharmaceutical as well as in industrial research.

Acknowledgement

M.G. thanks CSIR, New Delhi for the fellowship. The DST, India is also thanked for providing funds for the project and creating 200 and 600 MHz NMR facility under the IRPHA programme.

Notes and references

1 (a) R. Karmakar, P. Pahari and D. Mal, *Chem. Rev.*, 2014, **114**, 6213. (b) K. Dorell, M. A. Cohen, S. S. Huprikar, J. M. Gorman and M. Jones, *Psychosomatics*, 2005, **46**, 91. (c) T. Giridhar, G. Srinivasulu and K. S. Rao, US 2011/ 0092719 A1, 2011. (d) J. K. Harper, A. M. Arif, E. J. Ford, G. A. Strobel, J. A. Porco Jr., D. P. Tomer, K. L. Oneill, E. M. Heider and D. M. Grant, *Tetrahedron*, 2003, **59**, 2471. (e) U. Holler, J. B. Gloer and D. T. Wicklow, *J. Nat. Prod.*, 2002, **65**, 876. (f) D. Shi, X. Fan, L. Han, F. Xu and Z. Yuan, *Faming Zhuanli Shenqing Gongkai Shuomingshu* 2008, CN 101283998 A 20081015. (g) B. Gozler, T. Gozler and M. Shamma, *Tetrahedron*, 1983, **39**, 577. (h) Z. P. Xie, H. Y. Zhang, F. C. Li, B. Liu, S. X. Yang, H. P. Wang, Y. Pu, Y. Chen and S. Qin, *Chin. Chem. Lett.*, 2012, **23**, 941.

2 (a) J. F. DeBernardis, D. L. Arendsen, J. J. Kyncl and D. J. Kerkman, *J. Med. Chem.*, 1987, **30**, 178. (b) H. Feichtinger and H. Linden, (A.-G. Ruhrchemie), U.S. Patent US31, 76, 024, 1965; Chem. Abstr 1965, 62, 16192. (c) D. D. Phillips and S. B. Soloway (Shell Oil Co.) U.S. Patent 30, 36, 092, 1962; Chem. Abstr. 1962, 57, 13724.

3 (a) R. Rodrigo, *Tetrahedron*, 1988, **44**, 2093. (b) D. Garcia, F. Foubelo and M. Yus, *Tetrahedron* 2008, **64**, 4275 (c) A. Lifshitz, A. Suslensky and C. Tamburu, *J. Phys. Chem. A*, 2001, **105**, 3148. (c) T.-Y. Yuen, S.-H. Yang and M. A. Brimble, *Angew. Chem. Int. Ed.*, 2011, **50**, 8350. (d) S. E. Denmark, C. S. Regens and T. Kobayashi, *J. Am. Chem. Soc.*, 2007, **129**, 2774.

4 (a) Y. Shibata and K. Tanaka, *Synthesis*, 2012, **44**, 323 references therein. (b) B. Panda and T. K. Sarkar, *Tetrahedron Lett.*, 2008, **49**, 6701. (c) Z. Chai, Z.-F. Xie, X.-Y. Liu, G. Zhao and J.-D. Wang, *J. Org. Chem.*, 2008, **73**, 2947. (d) L. Lu, X.-Y. Liu, X.-Z. Shu, K. Yang, K.-G. Ji, and Y.-M. Liang, *J. Org. Chem.*, 2009, **74**, 474. (d) J. Das, R. Mukherjee and A. Basak, *J. Org. Chem.*, 2014, **79**, 3789. (e) P. Novak, R. Pohl, M. Kotor, and M. Hocek, *Org. Lett.*, 2006, **8**, 2051. (f) N. D. Ca, F. Campanini, B. Gabriele, G. Salerno, C. Massera and M. Costa, *Adv. Synth. Catal.*, 2009, **351**, 2423. (g) B. V. S. Reddy, S. Jalal, P. Borkar, J. S. Yadav, P. G. Reddy and A. V. S. Sarma *Tetrahedron Lett.*, 2013, **54**, 1519. (h) B. Martin-Matute., C. Nevado, D. J. Cárdenas and A. M. Echavarren, *J. Am. Chem. Soc.*, 2003, **125**, 5757.

5 (a) I. Coric, J. H. Kim, T. Vlaar, M. Patil, W. Thiel and B. List, *Angew. Chem. Int. Ed.*, 2013, **52**, 3490. (b) J. M. Robinson, T. Sakai, K. Okano, T. Kitawaki and R. L. Danheiser, *J. Am. Chem. Soc.*, 2010, **132**, 11039. (c) M. Guiso, A. Betrow and C. Marra *Eur. J. Org. Chem.*, 2008, 1967. (d) V. Capriati, S. Florio, R. Luisi, F. M. Perna and A. Salomone, *J. Org. Chem.*, 2006, **71**, 3984. (e) B. Ravindra, B. G. Das and P. Ghorai, *Org. Lett.*, 2014, **16**, 5580. (f) F.

COMMUNICATION

RSC ADVANCES

A. Luzzio and O. E. Okoromoba, *Tetrahedron Lett.*, 2011, **52**, 6530. (g) K. Tomooka, L.-F. Wang, F. Okazaki and T. Nakai, *Tetrahedron Lett.*, 2000, **41**, 6121. (i) H.-J. Wu, C.-H. Yen and C.-T. Chuang, *J. Org. Chem.*, 1998, **63**, 5064.

6 (a) E. Negishi, C. Coperet, S. Ma, S. -Y. Liou and F. Liu, *Chem. Rev.*, 1996, **96**, 365. (b) S. Bräse and A. D. Meijere, *Handbook of Organopalladium Chemistry for Organic Synthesis* (Eds.: E. Negishi and A. de Meijere), Wiley, New York, 2002, 1369 (see pp. 1376). (c) E. Negishi, M. Ay and T. Sugihara, *Tetrahedron*, 1993, **49**, 5471. (d) F. E. Meyer and A. D. Meijere, *Synlett*, 1991, 777. (e) G. Poli, G. Giambastiani and A. Heumann, *Tetrahedron*, 2000, **56**, 5959. (f) F. E. Meyer, P. J. Parsons and A. D. Meijere, *J. Org. Chem.*, 1991, **56**, 6487. (g) P. J. Parsons, M. Stefinovic, P. Willis and F. E. Meyer, *Synlett*, 1992, 864. (g) M. Schelper and A. D. Meijere, *Eur. J. Org. Chem.*, 2005, 582.

7 (a) A. Scheller, W. Winter and E. Mueller, *Justus Liebigs Annalen der Chemie*, 1976, **7-8**, 1448. (b) X. Fang, J. Sun and X. Tong, *Chem. Commun.*, 2010, **46**, 3800. (c) T. Matsuda and K. Suzuki, *Eur. J. Org. Chem.*, 2015, 3032. (d) S. Li, L. Zhou, Z. Song, F. Bao, K.-i. Kanno and T. Takahashi, *Heterocycles*, 2007, **73**, 519. (e) R. N. Warrener, G. M. Elsey, I. G. Pitt and A. R. Russell, *Australian Journal of Chemistry*, 1995, **48**, 241.

8 (a) Y.-F. Qiu, F. Yang, Z.-H. Qiu, M.-J. Zhong, L.-J. Wang, Y.-Y. Ye, B. Song and Y.-M. Liang, *J. Org. Chem.*, 2013, **78**, 12018. (b) J. Panteleev, R. Y. Huang, E. K. J. Lui and M. Lautens, *Org. Lett.*, 2011, **13**, 5314.

9. Gaussian 09, Revision C.01, Frisch, M. J.; Trucks, W. G.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A. *et al.* Gaussian, Inc., Wallingford CT, 2010.

10 (a) E. Negishi, L. S. Harring, Z. Owczarczyk, M. M. Mohamud, and M. Ay, *Tetrahedron Lett.*, 1992, **33**, 3253. (b) E. Negishi and L. Anastasia, *Chem. Rev.*, 2003, **103**, 1979. (c) A. D. Meijere, P. V. Zezschwitz and S. Brase, *Acc. Chem. Res.*, 2005, **38**, 413.