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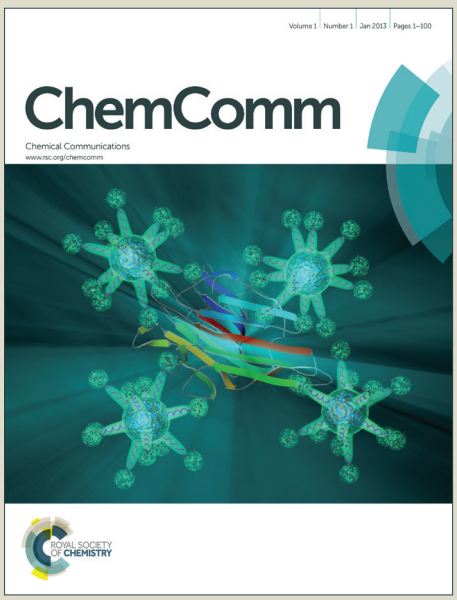

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Cite this: DOI: 10.1039/c0xx00000x

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Communication

Synthesis of 2-phenylnaphthalenes from styryl-2-methoxybenzenes†‡

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Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

A new simple and efficient method for the synthesis of 2-phenylnaphthalenes from electron-rich 1-styryl-2-methoxybenzenes has been described. The reaction proceeds via TFA catalyzed C-C bond cleavage followed by intermolecular [4+2]-Diels-Alder cycloaddition of *in situ* formed styrenyl trifluoroacetate intermediate. The quantum chemical calculations identified the transition state for the cycloaddition reaction and helped in tracing reaction mechanism. The method has been efficiently utilized for synthesis of phenanthrene skeleton and a naphthalene-based potent and selective ER-β agonist.

The naphthalene scaffold has a great utility in synthetic, medicinal and material chemistry.[1] Several natural products (e.g. rifampicin/ rifamycin, gossypol, etc.) which possess a naphthalene core in their structures exhibit promising biological activities.[2] The 2-phenylnaphthalenes have been reported to exhibit potent estrogen receptor (ER-β) agonistic activity.[1d, 1e, 3] There exist several methods for the preparation of naphthalene core including [4+2] Diels-Alder cycloaddition, benzannulations, metal-mediated cyclizations, rearrangement of strained rings, and Lewis acid-catalyzed intramolecular cyclization reactions.[4] For synthesis of the 2-phenylnaphthalene scaffold, most of the reports involve use of a naphthalene core as a starting material. This includes metal-catalyzed cross-coupling of aryl boron compounds,[5] aryl Grignard reagents[6] and aryl halides with existing naphthalene core structures.[2, 7] However, very few methods are reported for the direct construction of 2-phenylnaphthalenes from non-naphthalene starting materials (Figure 1).[4b, 4f, 4g, 4i-k, 8] These methods are metal-catalyzed reactions and involve substrates which require either multiple steps to prepare or a metal-catalyst for their synthesis. In this communication, we report a new method for direct synthesis of biologically important 2-phenylnaphthalenes from electron-rich 1-styryl-2-methoxybenzenes (Scheme of Table 1). The substrates, 1-styryl-2-methoxybenzenes, can be easily synthesized in one-step from corresponding commercially available aldehydes and phosphine salts. The method is simple and efficient with wide-substrate scope, excellent yields and does not require any metal catalyst.

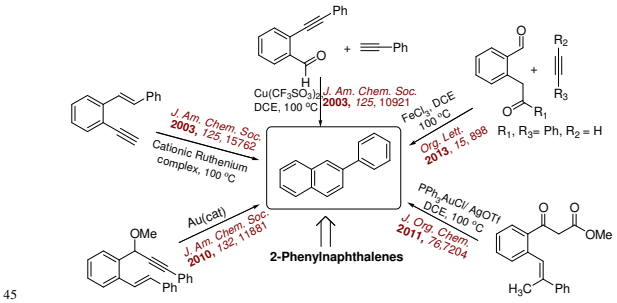
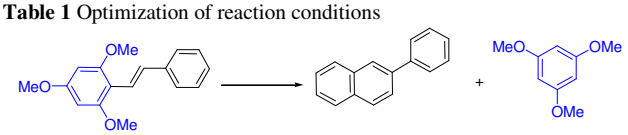


Figure 1. Methods for preparation of 2-phenylnaphthalene scaffold

In continuation of our work on devinylation of 2,4,6-trimethoxy vinylbenzenes,[9] the reaction of 1-styryl-2,4,6-trimethoxybenzene **1a** with TFA led to the formation of a new product **2a** along with 1,3,5-trimethoxybenzene **3a**. The spectral characterization of the new product **2a** revealed it as a 2-phenylnaphthalene. The formation of product **2a** with the release of 1,3,5-trimethoxybenzene **3a** indicated that the reaction must involve C-C bond cleavage followed by intermolecular [4+2]-Diels-Alder cycloaddition. In order to optimize the reaction conditions, and to investigate the effect of using solvents (rather than only TFA) in the reaction medium, a series of experiments using 1-styryl-2,4,6-trimethoxybenzene (**1a**) were carried out as shown in Table 1. A brief examination of variation in TFA amount in combination with various organic solvents and water, indicated that 50% TFA in water is an optimum reaction medium producing desired product **2a** in excellent yield. The HPLC analysis of reaction mixture also indicated formation of only products **2a** and **3a** (Section S7 of ESI). These optimized conditions (Table 1, entry 6) were used for further reactions.

Table 1 Optimization of reaction conditions



1a **2a** **3a**

Entry	Reaction medium[a]	Temp	Time (h)	% yield of **2a**[bc]
1	TFA	rt	1	70
2	TFA	80 °C	0.5	95
3	50% TFA in ACN	80 °C	1	72
4	50% TFA in DCM	60 °C	1	74
5	50% TFA in MeOH	80 °C	1	70
6[d]	**50% TFA in H_2O**	**80 °C**	**0.5**	**94**
7	50% TFA in H_2O	80 °C	1	94

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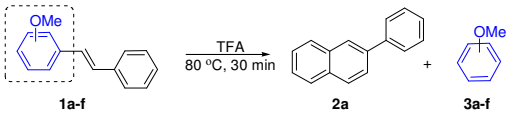
‡*Electronic supplementary information (ESI) available: NMR spectra of all compounds. See DOI: 10.1039/xxxx*

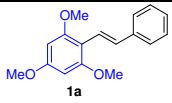
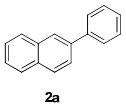
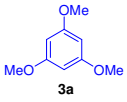
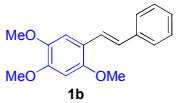
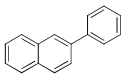
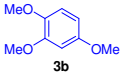
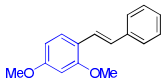
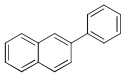
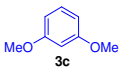
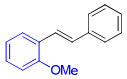
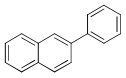
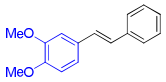
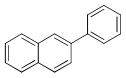
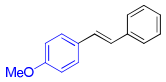
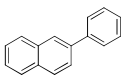
8	25% TFA in H_2O	80 °C	1	0
9	25% TFA in H_2O	80 °C	10	50
10	10% TFA in H_2O	80 °C	10	0
11	H_2O	80 °C	6	0

[a]For 100 mg reaction, 1 mL solvent used; [b] isolated yield; [c]yield calculation is shown in ESI (Section S8); [d]optimized reaction condition.

Next, the effect of variation in leaving-group moiety (methoxybenzene) was studied using different 1-styryl-methoxybenzenes **1a-1f** as starting materials (Table 2). Like substrate **1a** (entry 1), under optimized reaction conditions, the 2,4,5-trimethoxy and 2,4-dimethoxy substrates **1b** and **1c** produced product **2a** in excellent yields (entries 2 and 3). Similarly, the reaction of 1-styryl-2-methoxybenzene (**1d**) with TFA also led to the formation of desired product **2a**, however comparatively less yield was obtained (entry 4). Interestingly, reaction does not proceed with 1-styryl-3,4-dimethoxy and 1-styryl-4-methoxybenzenes (**1e-1f**, entries 5-6), indicating that the presence of an *ortho*-methoxy on the leaving group moeity is essential for the reaction to proceed. Thus, among 2-methoxybenzenes, following reactivity trend was observed: 2,4,6-trimethoxy > 2,4,5-trimethoxy > 2,4-dimethoxy > 2-methoxy.

Table 2. Scope of the reaction for various 1-styryl-methoxybenzenes for synthesis of 2-phenylnaphthalene **2a**

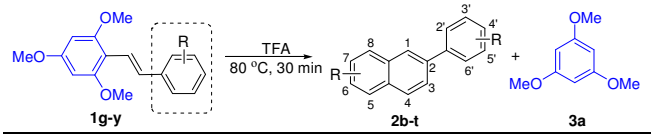


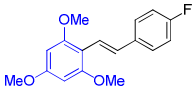
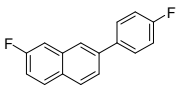
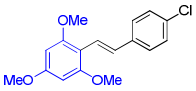
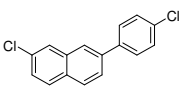
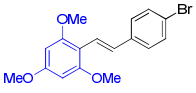
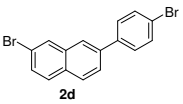
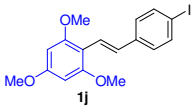
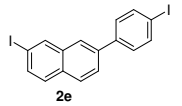
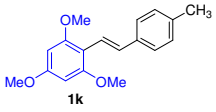
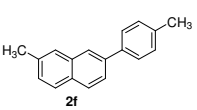
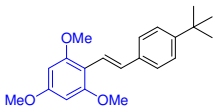
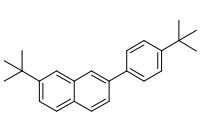
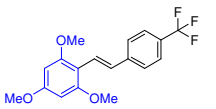
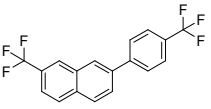
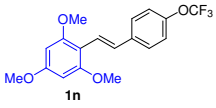
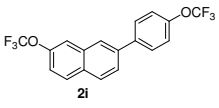
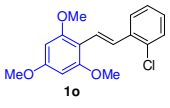
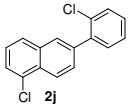
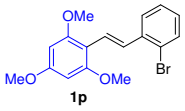
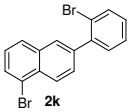
Entry	styryl methoxy-benzenes **1a-f**	product **2a**	methoxybenzene products **3a-f**	% yield[b] of **2a**
1	 **1a**	 **2a**	 **3a**	94
2	 **1b**	 **2a**	 **3b**	90
3	 **1c**	 **2a**	 **3c**	87
4	 **1d**	 **2a**	 **3d**	80
5	 **1e**	 **2a**	 **3e**	0
6	 **1f**	 **2a**	 **3f**	0

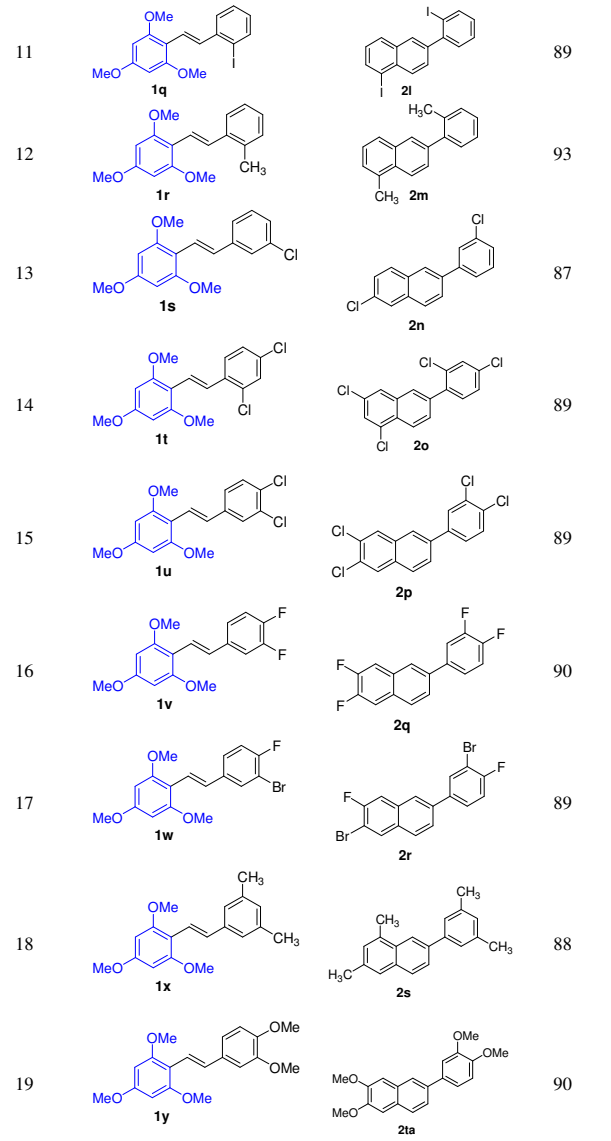
[a] Reagents and conditions: styrylbenzene (100 mg), 50% TFA in water (1 mL), 80 °C, 30 min; [b] isolated yield.

Next, the scope of the reaction for various substituted styryl methoxybenzenes (prepared by Wittig reaction of 2,4,6-tri methoxybenzaldehyde with aryl triphenylphosphine salts)[10] was investigated with variation in substitution on the styryl moiety (Table 3). First the substrates with mono-substituted styryl-2,4,6-trimethoxybenzenes **1g-1s** were investigated. The *para*-substituted styryl-2,4,6-trimethoxybenzenes **1g-1n** led to formation of 7,4´-disubstituted 2-phenylnaphthalenes as products (entries 1-8). The reaction of *ortho*- **1o-1r** (entries 9-12) and *meta*- **1s** (entry 13) substituted styryl-2,4,6-trimethoxybenzenes produced the desired 5,2´-disubstituted **2j-2m** and 6,3´-disubstituted **2n** 2-phenylnaphthalene products, respectively. In the later case, the formation of another possible product (8,3´-disubstituted 2-phenylnaphthalene) was not observed, which may be due to the fact that the intermolecular cycloaddition step occurs from less-hindered side.

Table 3. Scope of the reaction for synthesis of substituted 2-phenylnaphthalenes[a]



Entry	styryl methoxybenzenes **1g-y**	2-phenylnaphthalenes **2b-t**	% yield[b]
1	 **1g**	 **2b**	98
2	 **1h**	 **2c**	90
3	 **1i**	 **2d**	92
4	 **1j**	 **2e**	97
5	 **1k**	 **2f**	92
6	 **1l**	 **2g**	90
7	 **1m**	 **2h**	90
8	 **1n**	 **2i**	99
9	 **1o**	 **2j**	90
10	 **1p**	 **2k**	87



[a] Reagents and conditions: styrylbenzene (100 mg), 50% TFA in water (1 mL), 80 °C, 0.5 h; [b] isolated yield of 2-phenylnaphthalenes.

Next, reactions of disubstituted styryl-2,4,6-trimethoxybenzenes *viz.* 2,4-, 3,4- and 3,5-disubstituted substrates **1t-1y** were investigated (entries 14-19). In these reactions, 2-phenylnaphthalene products **2o-2t** were formed via intermolecular cycloaddition of styryl intermediates from the less hindered side. For example, in the case of 3,4-dimethoxystyryl-2,4,6-trimethoxybenzene (**1y**), the product 6,7,3´,4´-tetramethoxy-2-phenylnaphthalene **2ta** (Table 2, entry 19) was formed. The formation of product **2ta** was further confirmed by HMBC correlations (Figure S1 of ESI). Further, the scope of the established protocol was investigated for synthesis of phenanthrene scaffolds. Treatment of 2-(2,4,6-trimethoxystyryl)naphthalene **1z** with TFA led to the formation of 3-(naphthalen-2-yl)phenanthrene **2u** in 92% yield. In this reaction, the phenanthrene product **2u** was formed selectively over other possible anthracene product (Figure 2).

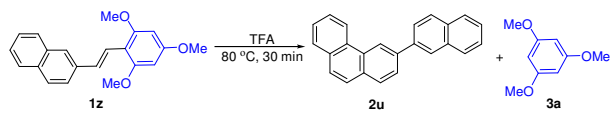


Figure 2. Synthesis of phenanthrene product **2u**

To understand the mechanism of TFA-mediated synthesis of 2-phenylnaphthalenes from 1-styryl-2-methoxybenzenes, quantum chemical studies on the reactants, intermediates, products and the important transition states of the reaction path have been carried out using B3LYP/6-311+G (d,p) methods. Figure 3 shows the reaction scheme with the enthalpy and activation energy values. The first step of the reaction involves the saturation of the double bond in the presence of trifluoroacetic acid. It is an exothermic reaction (3-4 kcal/mol), leading to two products (the *S*-isomer is 1.37 kcal/mol more stable than the *R*-isomer). The next step is the proton-assisted elimination of methoxybenzene to give **V** (in a trans arrangement) which is an endothermic reaction requiring about 17.25 kcal/mol. This step is facilitated by the proton through an intermediate **IV**. The dimerization step involves a concerted mechanism with a barrier of 40.58 kcal/mol and an endothermicity of 9.27 kcal/mol. The non-isolable intermediate **VI** is unstable due to lack of aromaticity and it quickly rearranges through a 1,3-H-shift to a more stable intermediate **VII**, a process which is exothermic by 27.39 kcal/mol. Thus, the dimerization process can be considered to be a thermodynamically favorable process involving a concerted mechanism and immediate 1,3-H-shift. The final step of formation of the naphthalene ring with a loss of two molecules of trifluoroacetic acid is also an exothermic reaction with about 22.84 kcal/mol energy release. This last step probably is the driving force, providing thermodynamical stability due to aromaticity. The overall reaction is exothermic by about 15 kcal/mol and thus very favorable even though it involves a transition state for the concerted Diels-Alder reaction with a barrier of about 40.58 kcal/mol.

Further, the newly established protocol was utilized for the synthesis of 7,4´-dihydroxy-2-phenylnaphthalene **2vh** which has been reported as a potent and selective agonist of estrogen receptor-β (IC_{50} 44 nM).[1d] The synthetic scheme for the preparation of ER-β agonist **2vh** is depicted in Figure 4.

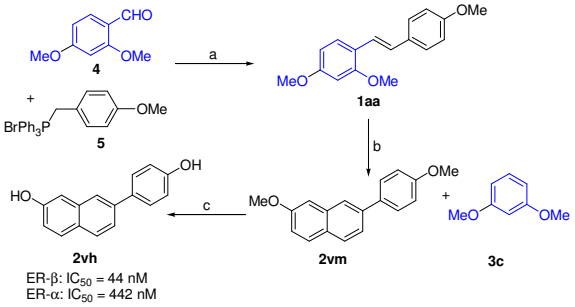


Figure 4. Synthesis of ER-β agonist **2vh**. Reagents and conditions: (a) n-BuLi, THF, 30 min, 80 °C, 92%; (b) 50% TFA in water, 80 °C, 0.5 h, 92%; (c) BBr_3, anhydrous DCM, rt, 3 h, 84%.

In conclusion, we have developed a new method for the synthesis of the 2-phenylnaphthalenes from 1-styryl-methoxybenzenes. Using quantum chemical calculations, the mechanism of the reaction has been established. The utility of the established protocol for synthesis of the phenanthrene scaffold and potent naphthalene-based selective ER-β agonist has been demonstrated.

Acknowledgements

Authors thanks analytical department IIIM for analytical support. RM, RS and SA are thankful to CSIR, DST and UGC for research fellowships. The financial support from DST-SERB is gratefully acknowledged (grant no. SR/FT/CS-168/2011).

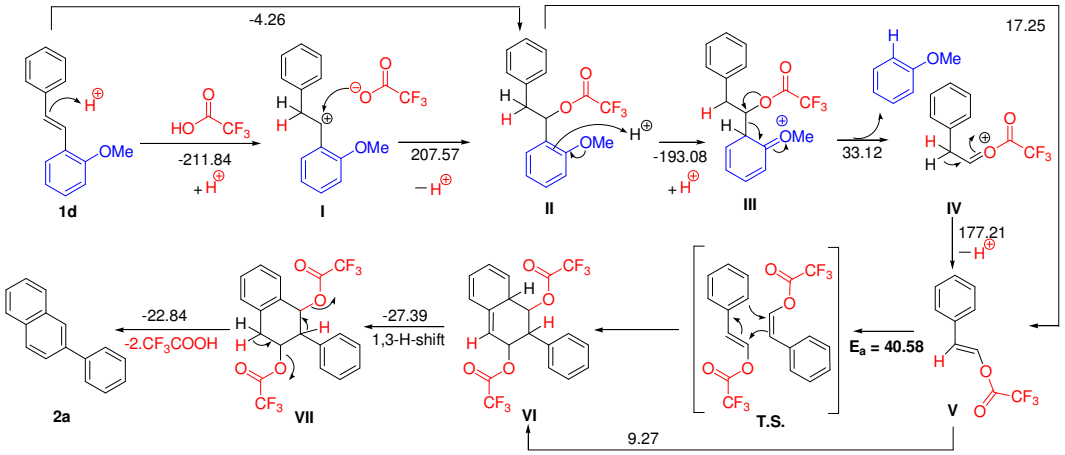


Figure 3 Reaction mechanism showing energy calculations at each step

References and notes

1. For applications of naphthalene scaffold, see: (a) S. V. Bhosale, C. H. Janiab and S. J. Langford, *Chem. Soc. Rev.*, 2008, **37**, 331–342; (b) J. F. Gil, D. J. Ramh and M. Yus, *Tetrahedron*, 1993, **49**, 9535-9546; (c) S. Akutagawa, *Appl. Catal. A: Gen.*, 1995, **128**, 171-207; (d) R. E. Mewshaw, R. J. Edsall, C. Yang, E. S. Manas, Z. B. Xu, R. A. Henderson, J. C. Keith and H. A. Harris, *J. Med. Chem.* , 2005, **48**, 3953-3979; (e) S. Marchais-Oberwinkler, M. Wetzel, E. Ziegler, P. Kruchten, R. Werth, C. Henn, R. W. Hartmann and M. Frotscher, *J. Med. Chem.* , 2011, **54**, 534–547.
2. C. B. de Koning, A. L. Rousseau and W. A. L. van Otterlo, *Tetrahedron*, 2003, **59**, 7-36.
3. M. Frotscher, E. Ziegler, S. Marchais-Oberwinkler, P. Kruchten, A. Neugebauer, L. Fetzer, C. Scherer, U. Müller-Vieira, J. Messinger, H. Thole and R. W. Hartmann, *J. Med. Chem.*, 2008, **51**, 2158–2169.
4. (a) N. Asao and H. Aikawa, *J. Org. Chem.*, 2006, **71**, 5249-5253; (b) N. Asao, T. Nogami, S. Lee and Y. Yamamoto, *J. Am. Chem. Soc.*, 2003, **125**, 10921-10925; (c) N. Asao, K. Sato, Menggenbateer and Y. Yamamoto, *J. Org. Chem.*, 2005, **70**, 3682-3685; (d) C. K. Bradsher, *Chem. Rev.*, 1987, **87**, 1277-1297; (e) L.-X. Shao, Y.-P. Zhang, M.-H. Qi and M. Shi, *Org. Lett.*, 2007, **9**, 117-120; (f) H.-C. Shen, S. Pal, J.-J. Lian and R.-S. Liu, *J. Am. Chem. Soc.*, 2003, **125**, 15762-15763; (g) C. R. Solorio-Alvarado and A. M. Echavarren, *J. Am. Chem. Soc.*, 2010, **132**, 11881–11883; (h) X. Zhang, S. Sarkar and R. C. Larock, *J. Org. Chem.*, 2006, **71**, 236-243; (i) S. Zhu, Y. Xiao, Z. Guo and H. Jiang, *Org. Lett.*, 2013, **15**, 898-901; (j) C. Maurin, F. Bailly and P. Cotelle, *Tetrahedron*, 2005, **61**, 7054–7058; (k) P. Cotelle and J.-P. Catteau, *Tetrahedron Lett.*, 1997, **38**, 2969-2972.
5. (a) J. L. Bolliger and C. M. Frech, *Adv. Synth. Catal.*, 2010, **352**, 1075-1080; (b) T. Tu, H. Mao, C. Herbert, M. Xu and K. H. Dotz, *Chem. Commun.*, 2010, **46**, 7796-7798; (c) Y. Yu, T. Hu, X. Chen, K. Xu, J. Zhang and J. Huang, *Chem. Commun.*, 2011, **47**, 3592-3594; (d) C.-W. Zhao, J.-P. Ma, Q.-K. Liu, Y. Yu, P. Wang, Y.-A. Li, K. Wang and Y.-B. Dong, *Green Chem.*, 2013, **15**, 3150-3154; (e) S.-Y. Ding, J. Gao, Q. Wang, Y. Zhang, W.-G. Song, C.-Y. Su and W. Wang, *J. Am. Chem. Soc.*, 2011, **133**, 19816-19822.
6. (a) E. Shirakawa, Y. Hayashi, K.-i. Itoh, R. Watabe, N. Uchiyama, W. Konagaya, S. Masui and T. Hayashi, *Angew. Chem. Int. Ed.*, 2012, **51**, 218-221; (b) D.-G. Yu, B.-J. Li, S.-F. Zheng, B.-T. Guan, B.-Q. Wang and Z.-J. Shi, *Angew. Chem. Int. Ed.*, 2010, **49**, 4566-4570; (c) N. Yoshikai, H. Matsuda and E. Nakamura, *J. Am. Chem. Soc.*, 2009, **131**, 9590-9599.
7. (a) B.-T. Guan, Y. Wang, B.-J. Li, D.-G. Yu and Z.-J. Shi, *J. Am. Chem. Soc.*, 2008, **130**, 14468–14470; (b) P. Leowanawat, N. Zhang and V. Percec, *J. Org. Chem.* , 2012, **77**, 1018−1025; (c) M. Tobisu, T. Shimasaki and N. Chatani, *Angew. Chem. Int. Ed.*, 2008, **47** 4866 –4869; (d) D.-G. Yu, B.-J. Li, S.-F. Zheng, B.-T. Guan, B.-Q. Wang and Z.-J. Shi, *Angew. Chem. Int. Ed.*, 2010, **49**, 4566 –4570.
8. A. R. Jagdale, J. H. Park and S. W. Youn, *J. Org. Chem.*, 2011, **76**, 7204.
9. S. B. Bharate, R. Mudududdla, R. Sharma and R. A. Vishwakarma, *Tetrahedron Lett.*, 2013, **54**, 2913–2915.
10. B. I. Roman, L. M. De Coen, S. T. F. C. Mortier, T. De Ryck, B. W. A. Vanhoecke, A. R. Katritzky, M. E. Bracke and C. V. Stevens, *Bioorg. Med. Chem.*, 2013, **21**, 5054–5063.