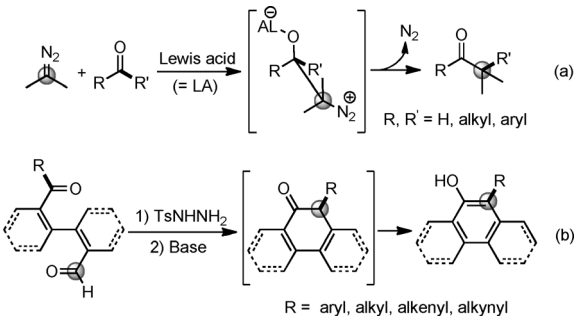
Synthetic Methods

DOI: 10.1002/ange.201209269

Catalyst-Free Intramolecular Formal Carbon Insertion into σ-C–C Bonds: A New Approach toward Phenanthrols and Naphthols**

*Ying Xia, Peiyuan Qu, Zhenxing Liu, Rui Ge, Qing Xiao, Yan Zhang, and Jianbo Wang**

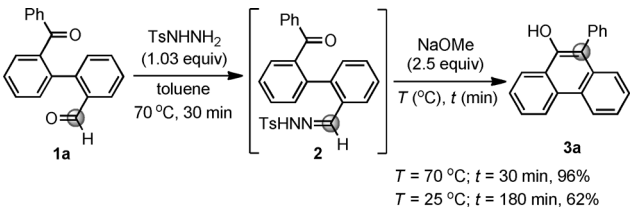
The formal diazo carbon insertion into the carbonyl group is a valuable tool for the homologation of aldehydes and ketones.[1,2] The reaction follows two steps: 1) nucleophilic addition of diazo compound to ketone or aldehyde; 2) 1,2-shift of R or R′ with instantaneous release of N_2 (Scheme 1a).[3] The formal carbon insertion into the formyl C–H bond has become a general method for ketone synthesis because of the high efficiency of both steps (Scheme 1a, when R′ = H). On the other hand, the corresponding formal C–C bond insertion (Scheme 1a, when R′ = alkyl or aryl) is more challenging because of the relatively low reactivity and the difficulty associated with the selectivity of the 1,2-shift. Recently, the studies by Kingsbury,[1g,2e,h,j] Maruoka,[1f,2d,f,g,i] Feng,[1h,2k] and other groups have significantly promoted the development of this area, particularly the stereocontrol of the reaction.



Scheme 1. Formal diazo carbon insertion into carbonyl group.

A major limitation for the widespread application of this type of reaction is the use of usually unstable diazo compounds as nucleophiles. The strategy of in situ generation of diazo compounds from *N*-tosylhydrazones, which are easily available from the corresponding ketones or aldehydes, is a useful way to circumvent this problem.[4–6] The use of *N*-tosylhydrazones as diazo precursors for formal carbon insertion into formyl C–H bonds in the synthesis of ketones has been reported.[7] However, to the best of our knowledge, the use of *N*-tosylhydrazones as diazo precursors for the formal carbon insertion into a keto C–C bond is without precedent. Ketones are less reactive than aldehydes, therefore, a Lewis acid is usually needed to activate the carbonyl group of a ketone. However, this method is not compatible with the basic reaction conditions for the in situ generation of diazo compounds from *N*-tosylhydrazones. We conceived that this problem may be circumvented through an intramolecular reaction, in which the reactivity of the ketone toward the diazo nucleophile is enhanced because of steric proximity, so that activation by a Lewis acid is no longer necessary. In connection to our recent study on Rh^{II}-catalyzed carbene dimerization,[6] we herein report a catalyst-free intramolecular formal σ-C–C bond insertion with the internal aldehyde as the carbon unit, which leads to the efficient formation of phenanthrol and naphthol derivatives (Scheme 1b).

At the outset, we investigated the reaction of 2′-benzoylbiphenyl-2-carbaldehyde (**1a**) with $TsNHNH_2$ (1.03 equiv) in toluene at 70 °C for 30 min (Scheme 2). As expected, only the aldehyde carbonyl group is cleanly converted to the corresponding *N*-tosylhydrazone **2** because of the reactivity difference of the two carbonyl groups. Subsequently, NaOMe (2.5 equiv) was added to the same reaction mixture and heating was continued for another 30 min at 70 °C. To our delight, 10-phenylphenanthren-9-ol (**3a**) could be isolated in 96% yield. Surprisingly, the conversion of *N*-tosylhydrazone **2** to **3a** can also be carried out at room temperature, although with diminished yield.



Scheme 2. Selective *N*-tosylhydrazone formation and subsequent cyclization.

Hydroxy-substituted polycyclic aromatic compounds (PACs), such as **3a**, are highly useful, because they have wide applications in material science[8a] and medicinal chemistry[8b] and are abundant in natural products.[9] Moreover, the phenolic hydroxy group can be further transformed to various functional groups.[10,13] However, systematical studies on the synthesis of hydroxy-substituted PACs are still rare.[11,12] The experiments shown in Scheme 2 demonstrate the potential of

[*] Y. Xia, P. Qu, Z. Liu, R. Ge, Q. Xiao, Dr. Y. Zhang, Prof. Dr. J. Wang
Beijing National Laboratory of Molecular Sciences (BNLMS) and Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education
College of Chemistry, Peking University
Beijing 100871 (China)
E-mail: wangjb@pku.edu.cn

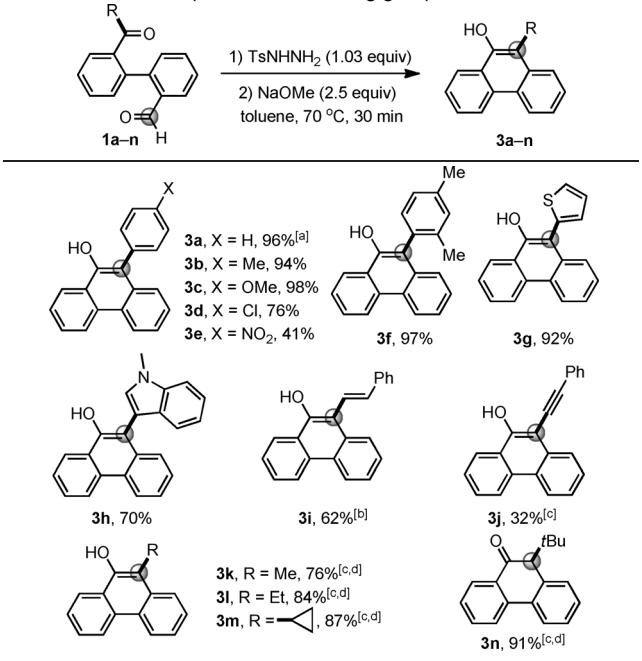
[**] The project is supported by the National Basic Research Program of China (973 Program, No. 2009CB825300), NSFC (Grant No. 21272010, 20832002).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201209269.

intramolecular C–C bond insertion in the efficient and regioselective synthesis of hydroxy-substituted PACs. Consequently, we decided to study the scope of this transformation.

The scope of this reaction was first explored by testing a series of 1,2-shifting R group in the biaryl keto aldehyde substrates. A series of biaryl ketoaldehydes **1a–n** can be easily prepared by Suzuki–Miyaura cross-coupling reactions, starting from readily available starting materials.[13] A variety of R groups, including aryl, alkenyl, alkynyl, and alkyl groups, were examined, and the expected formal C–C bond insertion process occurred smoothly in all cases (Table 1). When the

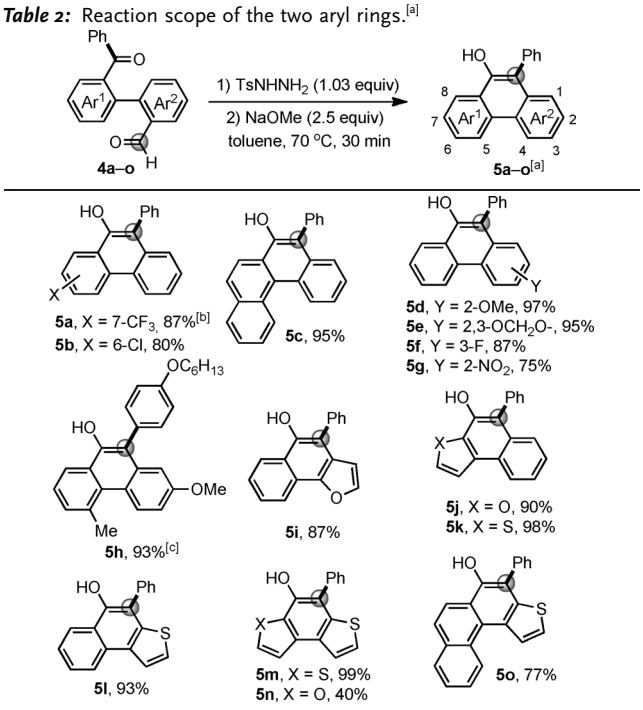
Table 1: Reaction scope of the 1,2-shifting group.[a]



[a] Yields of isolated products after purification by column chromatography on silica gel. [b] The second step was carried out at 90 °C. [c] LiO*t*Bu was used instead of NaOMe in the second step. [d] The first step was carried out at 40 °C.

1,2-shifting group is an phenyl group that bears electron-donating substituents, the reaction provided the corresponding products in excellent yields (**3a–c**). On the other hand, the substrates that bear electron-withdrawing groups afforded the products in diminished yields (**3d**,**e**). Notably, the *ortho*-substituted phenyl group on the substrate does not hinder the C–C bond migration process (**3f**). The heteroaryl, vinyl, and alkynyl groups also undergo 1,2-shifts to afford the desired products (**3g–j**). The low yield after the 1,2-alkynyl shift may be attributed to the electron deficiency of the alkynyl carbon atom. To our delight, the reaction with alkyl-substituted substrates proceeded well by lowering the temperature of the first step to 40 °C in order to avoid the formation of *N*-tosylhydrazone at the ketone moiety (**3k–n**). When R is a bulky *tert*-butyl group, the anticipated C–C bond insertion occurs smoothly, while the subsequent aromatization does not occur (**3n**).

Table 2: Reaction scope of the two aryl rings.[a]



[a] Yields of isolated products after purification by column chromatography on silica gel. [b] The second step was carried out at 90 °C. [c] LiO*t*Bu was used instead of NaOMe in the second step.

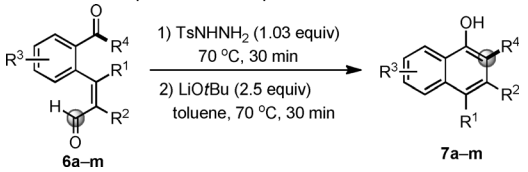
Next, we examined the substrates with two different parent aromatic rings (Table 2). The reaction was found marginally affected by the substituents on the two phenyl rings. Both electron-withdrawing (**5a–b**,**f**,**g**) and electron-donating (**5d–e**,**h**) groups were tolerated, giving the corresponding substituted 9-phenanthrols in good to excellent yields. Furthermore, the reaction with substrates that contain a heteroaryl skeleton afforded the corresponding cyclization products in good to excellent yields (**5i–o**).

This method was further applied in the regioselective formation of polysubstituted naphthols. Both α- and β-naphthol derivatives could be synthesized with this method by simply switching the positions of carbonyl groups in the corresponding ketoaldehyde substrates (Tables 3 and 4). Here, LiO*t*Bu was proved to be a more suitable base than NaOMe for the second step. A series of polysubstituted α-naphthols could be synthesized in good to excellent yields (Table 3). The substituents on the vinyl aldehyde moiety (R^1 and R^2) show marginal impact on this transformation, affording the corresponding isomeric α-naphthols **7a** and **7b** in good yields. With regard to the substituents on the aryl ketone moiety (R^3), the reactions also proceed well (**7c–f**). Moreover, this methodology can be a good choice for the formation of carbocyclic ring-fused naphthols (**7g–m**).

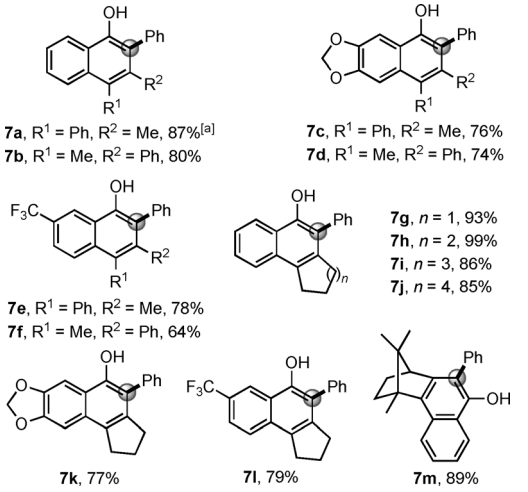
By changing the position of the formyl and keto carbonyl group on the substrates, β-naphthol derivatives could be obtained similarly (Table 4). Remarkably, this method can also be applied in the formation of hydroxy-substituted benzothiophenes (**9n–q**).

A plausible mechanism to rationalize this cyclization is depicted in Scheme 3. The substrate **1a** is first converted to

Table 3: Reaction scope of the α-naphthols.[a]

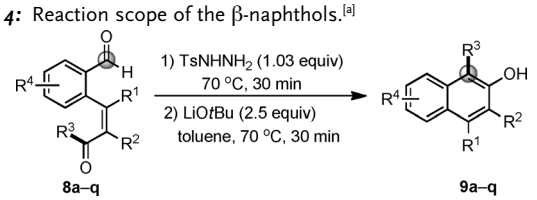


6a–m **7a–m**

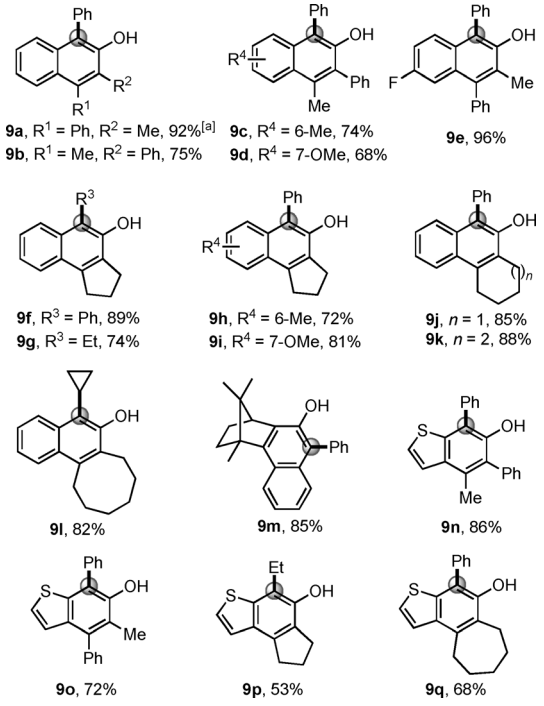


[a] Yields of isolated products after purification by column chromatography on silica gel.

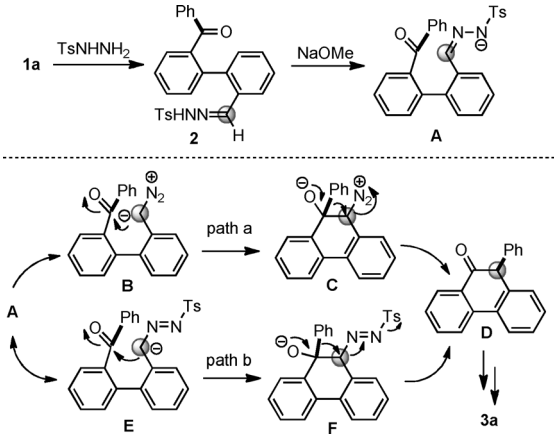
Table 4: Reaction scope of the β-naphthols.[a]



8a–q **9a–q**



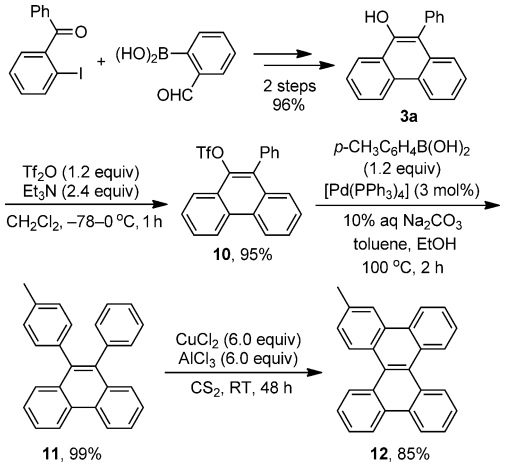
[a] Yields of isolated products after purification by column chromatography on silica gel.



Scheme 3. Mechanistic rationale.

the mono(*N*-tosylhydrazone) **2**, which undergoes deprotonation to form tosylhydrazone salt **A**. From **A**, two pathways are possible: a) the corresponding diazo compound **B** is generated,[4a,7] then a nucleophilic attack on the keto carbonyl group forms **C**, and a 1,2-shift with release of N_2 subsequently affords **D**; b) **A** undergoes intramolecular carbon alkylation (through resonance structure **E**), which is then followed by 1,2-shift. Current experimental observations indicate that path b is more likely: 1) the solution does not show the characteristic red color of diazo intermediate during the reaction; 2) the reaction can take place at room temperature, whereas the generation of diazo intermediate from tosylhydrazone needs elevated temperatures (usually above 60 °C).[4a,7] However, rigorous investigation is necessary to unambiguously establish the reaction mechanism.

The phenolic hydroxy group can undergo various synthetically useful transformations.[13] To illustrate the potential application of the products, **3a** was converted to dibenzochrysene (DBC).[14] Staring from commercially available materials, DBC derivative **12** could be readily synthesized in five steps with an overall yield of 77 % (Scheme 4). Derivatives of DBC can be applied to the preparation of sensors,



Scheme 4. Synthesis of dibenzochrysene derivative.

nonlinear optical and liquid–crystalline materials. Thus, preparation of such compounds has recently attracted attention.[15]

In conclusion, we have developed a new cyclization process with an intramolecular carbon insertion into a C–C bond as the key step. This catalyst-free transformation occurs under very mild conditions, and affords a general and efficient approach to various hydroxy-substituted PACs, including phenanthrol and naphthol derivatives and their heteroatom-containing analogues. In view of the easy availability of the starting substrates, the high efficiency and the excellent functional-group tolerance, this method is expected to find wide applications in organic synthesis.

Received: November 20, 2012
Published online: January 29, 2013

Keywords: 1,2-shift · cyclization · diazo compounds · insertion · hydrocarbons

[1] Formal diazo carbon insertion into carbonyl C–H bond: a) C. A. Loeschorn, M. Nakajima, P. J. McCloskey, J.-P. Anselme, *J. Org. Chem.* **1983**, *48*, 4407; b) C. R. Holmquist, E. J. Roskamp, *J. Org. Chem.* **1989**, *54*, 3258; c) R. M. Werner, O. Shokek, J. T. Davis, *J. Org. Chem.* **1997**, *62*, 8243; d) S. J. Mahmood, A. K. Saha, M. M. Hossain, *Tetrahedron* **1998**, *54*, 349; e) E. L. Dias, M. Brookhart, P. S. White, *J. Am. Chem. Soc.* **2001**, *123*, 2442; f) T. Hashimoto, H. Miyamoto, Y. Naganawa, K. Maruoka, *J. Am. Chem. Soc.* **2009**, *131*, 11280; g) A. J. Wommack, D. C. Moebius, A. L. Travis, J. S. Kingsbury, *Org. Lett.* **2009**, *11*, 3202; h) W. Li, J. Wang, X. L. Hu, K. Shen, W. T. Wang, Y. Y. Chu, L. L. Lin, X. H. Liu, X. M. Feng, *J. Am. Chem. Soc.* **2010**, *132*, 8532; i) L. Gao, B. C. Kang, G.-S. Hwang, D. H. Ryu, *Angew. Chem.* **2012**, *124*, 8447; *Angew. Chem. Int. Ed.* **2012**, *51*, 8322.

[2] Formal diazo carbon insertion to carbonyl C–C bond: a) W. S. Johnson, M. Neeman, S. P. Birkeland, N. A. Fedoruk, *J. Am. Chem. Soc.* **1962**, *84*, 989; b) K. Maruoka, A. B. Concepcion, H. Yamamoto, *Synthesis* **1994**, 1283; c) K. Maruoka, A. B. Concepcion, H. Yamamoto, *J. Org. Chem.* **1994**, *59*, 4725; d) T. Hashimoto, Y. Naganawa, K. Maruoka, *J. Am. Chem. Soc.* **2008**, *130*, 2434; e) D. C. Moebius, J. S. Kingsbury, *J. Am. Chem. Soc.* **2009**, *131*, 878; f) T. Hashimoto, Y. Naganawa, K. Maruoka, *J. Am. Chem. Soc.* **2009**, *131*, 6614; g) T. Hashimoto, Y. Naganawa, K. Maruoka, *Chem. Commun.* **2010**, *46*, 6810; h) J. A. Dabrowski, D. C. Moebius, A. J. Wommack, A. F. Kornahrens, J. S. Kingsbury, *Org. Lett.* **2010**, *12*, 3598; i) T. Hashimoto, Y. Naganawa, K. Maruoka, *J. Am. Chem. Soc.* **2011**, *133*, 8834; j) V. L. Rendina, D. C. Moebius, J. S. Kingsbury, *Org. Lett.* **2011**, *13*, 2004; k) W. Li, X. Liu, X. Hao, Y. Cai, L. Lin, X. Feng, *Angew. Chem.* **2012**, *124*, 8772; *Angew. Chem. Int. Ed.* **2012**, *51*, 8644.

[3] Y. Zhang, J. Wang, *Chem. Commun.* **2009**, 5350.

[4] For reviews on the application of *N*-tosylhydrazones in diazo-related transformations, see: a) J. R. Fulton, V. K. Aggarwal, J. d. Vicente, *Eur. J. Org. Chem.* **2005**, 1479; b) J. Barluenga, C. Valdés, *Angew. Chem.* **2011**, *123*, 7626; *Angew. Chem. Int. Ed.* **2011**, *50*, 7486; c) Z. Shao, H. Zhang, *Chem. Soc. Rev.* **2012**, *41*, 560; d) Y. Zhang, J. Wang, *Top. Curr. Chem.* **2012**, *327*, 239.

[5] For a report on the use of *N*-tosylhydrazones in metal-free C–C bond formation, see: J. Barluenga, M. Tomás-Gamasa, F. Aznar, C. Valdés, *Nat. Chem.* **2009**, *1*, 494.

[6] For our recent related study on Rh^{II}-catalyzed intramolecular carbene dimerization, see: Y. Xia, Z. Liu, Q. Xiao, P. Qu, R. Ge, Y. Zhang, J. Wang, *Angew. Chem.* **2012**, *124*, 5812; *Angew. Chem. Int. Ed.* **2012**, *51*, 5714.

[7] a) S. R. Angle, M. L. Neitzel, *J. Org. Chem.* **2000**, *65*, 6458; b) V. K. Aggarwal, J. d. Vicente, B. Pelotier, I. P. Holmes, R. V. Bonnert, *Tetrahedron Lett.* **2000**, *41*, 10327.

[8] For examples, see: a) R. Mitsuhashi, Y. Suzuki, Y. Yamanari, H. Mitamura, T. Kambe, N. Ikeda, H. Okamoto, A. Fujiwara, M. Yamaji, N. Kawasaki, Y. Maniwa, Y. Kubozono, *Nature* **2010**, *464*, 76; b) M. G. Banwell, A. Bezos, C. Burns, I. Kruszelnicki, C. R. Parish, S. Su, M. O. Sydnes, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 181.

[9] For an example, see: a) A. Fürstner, M. M. Domostoj, B. Scheiper, *J. Am. Chem. Soc.* **2006**, *128*, 8087; b) K. Okano, H. Fujiwara, T. Noji, T. Fukuyama, H. Tokuyama, *Angew. Chem.* **2010**, *122*, 6061; *Angew. Chem. Int. Ed.* **2010**, *49*, 5925; c) D. Mal, A. K. Jana, P. Mitra, K. Ghosh, *J. Org. Chem.* **2011**, *76*, 3392.

[10] For an example, see: J. Cao, M. Miao, W. Chen, L. Wu, X. Huang, *J. Org. Chem.* **2011**, *76*, 9329.

[11] For selected examples of the synthesis of phenanthrols, see: a) J.-M. Fu, M. J. Sharp, V. Snieckus, *Tetrahedron Lett.* **1988**, *29*, 5459; b) J.-M. Fu, V. Snieckus, *Can. J. Chem.* **2000**, *78*, 905; c) X. Cai, S. Brown, P. Hodson, V. Snieckus, *Can. J. Chem.* **2004**, *82*, 195; d) S. Lin, T. You, *Tetrahedron Lett.* **2008**, *64*, 9906; e) Y. B. Zhao, B. Mariampillai, D. A. Candito, B. Laleu, M. Li, M. Lautens, *Angew. Chem.* **2009**, *121*, 1881; *Angew. Chem. Int. Ed.* **2009**, *48*, 1849.

[12] For selected examples of the synthesis of naphthols, see: a) P. Turnbull, H. W. Moore, *J. Org. Chem.* **1995**, *60*, 644; b) X. Huang, J. Xue, *J. Org. Chem.* **2007**, *72*, 3965; c) Z.-Q. Wang, Y. Liang, Y. Lei, M.-B. Zhou, J.-H. Li, *Chem. Commun.* **2009**, 5242; d) G. Chai, Z. Lu, C. Fu, S. Ma, *Chem. Eur. J.* **2009**, *15*, 11083; e) H. Xu, S. Li, H. Liu, H. Fu, Y. Jiang, *Chem. Commun.* **2010**, *46*, 7617; f) S. A. Shahzad, C. Vivant, T. Wirth, *Org. Lett.* **2010**, *12*, 1364; g) Y. E. Türkmen, T. J. Montavon, S. A. Kozmin, V. H. Rawal, *J. Am. Chem. Soc.* **2012**, *134*, 9062.

[13] For details, see the Supporting Information.

[14] C. Kübel, K. Eckhardt, V. Enkelmann, G. Wegner, K. Müllen, *J. Mater. Chem.* **2000**, *10*, 879.

[15] For examples, see: a) S. Yamaguchi, T. M. Swager, *J. Am. Chem. Soc.* **2001**, *123*, 12087; b) C.-W. Li, C.-I. Wang, H.-Y. Liao, R. Chaudhuri, R.-S. Liu, *J. Org. Chem.* **2007**, *72*, 9203; c) R. Chaudhuri, M.-Y. Hsu, C.-W. Li, C.-I. Wang, C.-J. Chen, C. K. Lai, L.-Y. Chen, S.-H. Liu, C.-C. Wu, R.-S. Liu, *Org. Lett.* **2008**, *10*, 3053; d) M. Shimizu, I. Nagao, Y. Tomioka, T. Hiyama, *Angew. Chem.* **2008**, *120*, 8216; *Angew. Chem. Int. Ed.* **2008**, *47*, 8096; e) K. Mochida, K. Kawasumi, Y. Segawa, K. Itami, *J. Am. Chem. Soc.* **2011**, *133*, 10716; f) T. S. Navale, K. Thakur, R. Rathore, *Org. Lett.* **2011**, *13*, 1634.

