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Facile $Sc(OTf)_3$-Catalyzed Generation and Successive Aromatization of Isobenzofuran from *o*-Dicarbonylbenzenes

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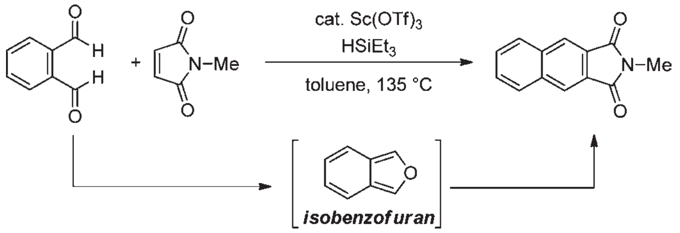
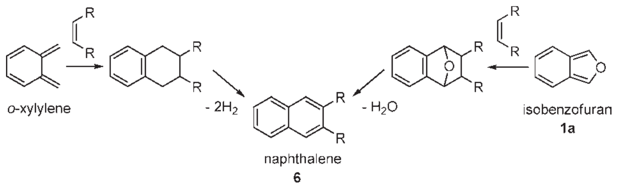
ABSTRACT



Isobenzofuran can be prepared from *o*-phthalaldehyde using hydrosilane. The formed isobenzofuran is trapped by an alkene via a Diels–Alder reaction. Further dehydration proceeds to furnish the conjugated aromatic compound. This multistep reaction was promoted by catalytic amounts of $Sc(OTf)_3$.

Isobenzofuran (**1a**) has been referred to as the most reactive isolated diene toward cycloadditions.[1] Although **1a** has been characterized spectroscopically, it has a short lifetime at room temperature. The reactivity of **1a** can be attributed to its *o*-xylylenoid nature and readily undergoes Diels–Alder reactions with a wide range of dienophiles to achieve aromaticity. **1a** and its derivatives are commonly used to construct six-membered π-conjugate systems in natural products and functional materials (Scheme 1).[2]

Scheme 1. Synthesis of Naphthalene **6** from *o*-Xylylene or Isobenzofuran **1a**



There have been many reports concerning the synthesis of isobenzofurans **1**,[3] but catalytic methods for their construction have been limited to only a few examples.[4] Isobenzofurans are traditionally synthesized via the partial

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(1) (a) Tobia, D.; Rickborn, B. *J. Org. Chem.* **1987**, *52*, 2611–2615. (b) Whitney, S. E.; Rickborn, B. *J. Org. Chem.* **1988**, *53*, 5595–5596. (c) Thibault, M. E.; Pacarynuk, L. A.; Closson, T. L. L.; Dibble, P. W. *Tetrahedron Lett.* **2001**, *42*, 789–791.

(2) (a) Levy, L. A.; Pruitt, L. *J. Chem. Soc., Chem. Commun.* **1980**, 227–228. (b) Rodrigo, R. *Tetrahedron* **1988**, *44*, 2093–2135. (c) Chew, S.; Wang, P.; Hong, Z.; Kwong, H. L.; Tang, J.; Sun, S.; Lee, C. S.; Lee, S.-T. *J. Lumin.* **2007**, *124*, 221–227. (d) Paraskar, A. S.; Reddy, A. R.; Patra, A.; Wjjsboom, Y. H.; Gidron, O.; Shimon, L. J. W.; Leitus, G.; Bendikov, M. *Chem.—Eur. J.* **2008**, *14*, 10639–10647. (e) Chun, D.; Cheng, Y.; Wudl, F. *Angew. Chem., Int. Ed.* **2008**, *47*, 8380–8385. (f) Ma, X. M.; Wu, W. J.; Zhang, Q.; Guo, F. L.; Meng, F. S.; Hua, J. L. *Dyes Pigm.* **2009**, *82*, 353–359. (g) Wu, W. J.; Guo, F. L.; Li, J.; He, J. X.; Hua, J. L. *Synth. Met.* **2010**, *160*, 1008–1014.

(3) (a) Cava, M. P.; Mitchell, M. J.; Deana, A. A. *J. Org. Chem.* **1960**, *25*, 1481–1483. (b) Naito, K.; Rickborn, B. *J. Org. Chem.* **1980**, *45*, 4062–4063. (c) Kappe, C. O.; Cochran, J. E.; Padwa, A. *Tetrahedron Lett.* **1995**, *36*, 9285–9288. (d) Jiang, D.; Herndon, J. W. *Org. Lett.* **2000**, *2*, 1267–1269. (e) Yamana, K.; Ibata, T.; Nakano, H. *Synthesis* **2006**, *24*, 4124–4130. (f) Jacq, J.; Einhorn, C.; Einhorn, J. *Org. Lett.* **2008**, *10*, 3757–3760. (g) Wang, F.; Wang, Y.; Cai, L.; Miao, Z.; Chen, R. *Adv. Synth. Catal.* **2008**, *350*, 2733–2739.

(4) (a) Mikami, K.; Ohmura, H. *Org. Lett.* **2002**, *4*, 3355–3357. (b) Kuninobu, Y.; Nishina, Y.; Nakagawa, C.; Takai, K. *J. Am. Chem. Soc.* **2006**, *128*, 12376–12377.

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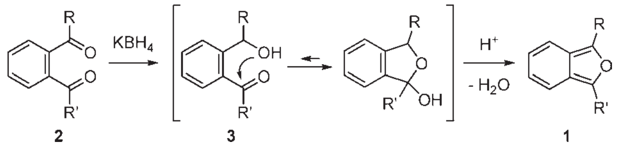
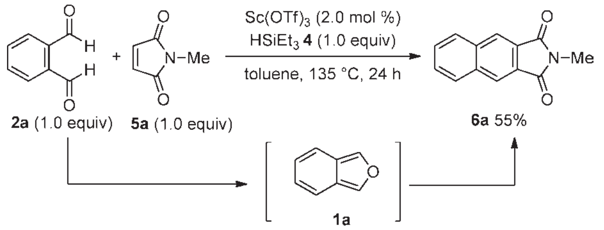
reduction of *o*-dicarbonylbenzene **2** with KBH_4 and subsequent acid treatment (Scheme 2).[3a] Unstable isobenzofuran (**1a**) is decomposed during this procedure; therefore, a one-step synthesis of **1** under neutral conditions is highly desirable.[4a,5] To develop a more convenient approach to **1**, we have focused on *o*-carbonylbenzylalcohol **3** as a key intermediate. The formation of analogue **3** has been investigated using hydrosilane as a reductant instead of KBH_4. Herein, we have developed a novel method for a $Sc(OTf)_3$-catalyzed generation of isobenzofuran (**1a**) from *o*-phthalaldehyde **2a** and triethylsilane (**4**). The generated **1a** was immediately trapped using *N*-methylmaleimide (**5a**). Owing to the Lewis acid character of $Sc(OTf)_3$, successive dehydration occurred to yield the corresponding naphthalene derivative **6a** in 55% yield (Scheme 3). Metal triflates have been known to keep their Lewis acidity active even in the presence of water,[6] which enabled this multistep reaction catalytic. The same reaction can be promoted by other metal triflates, such as $Cu(OTf)_2$ (50%), AgOTf (51%), $In(OTf)_3$ (53%), and $Bi(OTf)_3$ (38%), but we have focused on $Sc(OTf)_3$ in this manuscript.

Scheme 2. Multistep Formation of Isobenzofuran **1** from *o*-Dicarbonylbenzene **2**

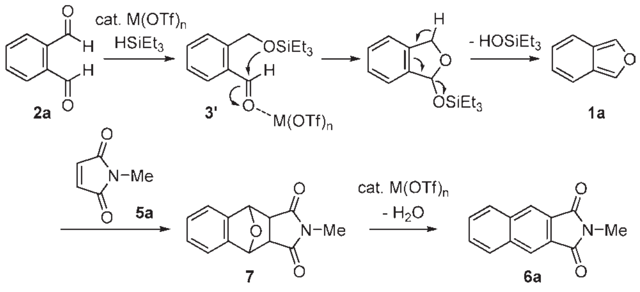


Scheme 3. Generation and Aromatization of Isobenzofuran in situ



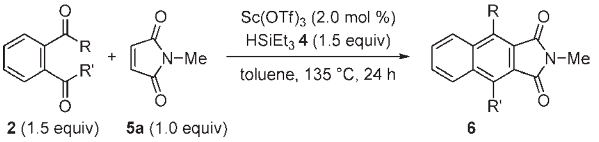
The proposed reaction mechanism for the formation of **6a** is shown in Scheme 4. Initially, the hydrosilylation of a carbonyl group occurs to give silyl ether **3′**.[7] The intramolecular cyclization and elimination of hydroxysilane then gives isobenzofuran (**1a**). Successive Diels–Alder reaction with maleimide **5a** and dehydration furnishes naphthalene **6a**. Only catalytic amounts of metal triflate can promote these multistep reactions in one-pot.[8]

Scheme 4. Possible Reaction Mechanism



The influence of the substituents on dicarbonylbenzene **2** is of interest because the stability of isobenzofuran **1** strongly depends on R and R′. The nature of R and R′ were varied as shown in Table 1. The naphthalene derivative **6a** was obtained in 65% yield upon the addition of 1.5 equivalents of **2a** and **4** (entry 1). When *o*-acetylbenzaldehyde (**2b**) was used, the corresponding naphthalene **6b** was obtained in low yields (entry 2). Conversely, *o*-carbonylbenzaldehyde **2c**, having phenyl group instead of methyl group, was efficiently converted into **6b** in 82% yield (entry 3). It is proposed that the phenyl group stabilizes the isobenzofuran intermediate **1**.[3,8] *o*-Diacetylbenzene (**2d**) gave a complex mixture (entry 4). When *o*-dibenzoylbenzene (**2e**) was used, the corresponding naphthalene derivative **6e** was formed in 69% yield (entry 5). These results are strongly associated with the reactivity of the carbonyl groups toward hydrosilylation and the stability of the isobenzofuran intermediates **1**. Formyl groups (R or R′ = H) are more susceptible to hydrosilylation than keto groups,[9]

Table 1. Survey of Substituents on **2**[a]



entry	2		yield of **6**/%[b]
1	**2a** (R = H, R′ = H)	**6a**	65
2	**2b** (R = H, R′ = Me)	**6b**	18
3	**2c** (R = H, R′ = Ph)	**6c**	82
4	**2d** (R = Me, R′ = Me)	**6d**	trace
5	**2e** (R = Ph, R′ = Ph)	**6e**	69
6	**2f** (R = H, R′ = 2-thienyl)	**6f**	60
7	**2g** (R = H, R′ = 2-furyl)	**6g**	66

[a] Reaction conditions: $Sc(OTf)_3$ (2.0 mol %), **2** (0.375 mmol), **4** (0.375 mmol), **5a** (0.250 mmol), toluene (0.25 mL), under argon atmosphere. [b] Isolated yield after recrystallization.

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(5) Gabriele, B.; Salerno, G.; Fazio, A.; Pittelli, R. *Tetrahedron* **2003**, *59*, 6251–6259.

(6) (a) Kobayashi, S.; Hachiya, I.; Araki, M.; Ishitani, H. *Tetrahedron Lett.* **1993**, *34*, 3755–3758. (b) Kobayashi, S.; Nagayama, S.; Busujima, T. *J. Am. Chem. Soc.* **1998**, *120*, 8287–8288.

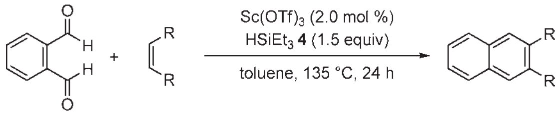
(7) The hydrosilylation is promoted in the presence of metal triflates. See: (a) Bach, P.; Albright, A.; Laali, K. K. *Eur. J. Org. Chem.* **2009**, 1961–1966. (b) Wile, B. M.; Stradiotto, M. *Chem. Commun.* **2006**, 4104–4106. (c) Roy, A. K. *Adv. Organomet. Chem.* **2008**, *55*, 1–59.

(8) (a) Genovese, S.; Epifano, F.; Pelucchini, C.; Curini, M. *Eur. J. Org. Chem.* **2009**, 1132–1135. (b) Sakai, H.; Tsutsumi, K.; Morimoto, T.; Kakiuchi, K. *Adv. Synth. Catal.* **2008**, *350*, 2498–2502.

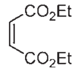
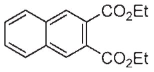
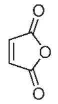
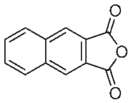
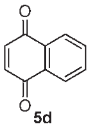
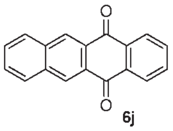
and isobenzofurans bearing an aryl group are stable enough to undergo the subsequent Diels–Alder reaction with **5a**.[10] Heteroaryl-substituted *o*-dicarbonylbenzenes were also applicable to give the naphthalenes having a thienyl (**6f**, entry 6) or furyl (**6g**, entry 7) group.

The scope with respect to dienophile (**5**) was also examined (Table 2). Simple alkenes such as cyclooctene did not give the corresponding naphthalene derivative due to its lack of reactivity toward **1a**. Diethyl maleate (**5b**) gave the corresponding product **6h**, but only in low yield (entry 1). Cyclic alkenes bearing carbonyl groups successfully promoted the reaction. Acid anhydride **5c** and quinone **5d** usually act as poisons toward Lewis acid catalysis, but both maleic anhydride (**5c**) and benzoquinone (**5d**) were applicable in the $Sc(OTf)_3$-catalyzed system (entries 2 and 3).

Table 2. Effect of Dienophiles in Sc-Catalyzed Synthesis of **6**[a]

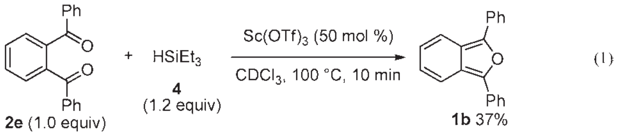


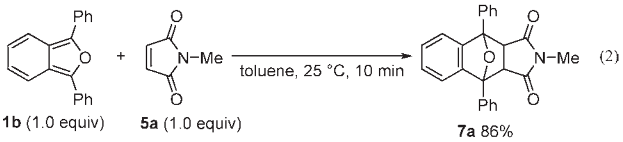
2a (1.5 equiv) **5** (1.0 equiv) **6**

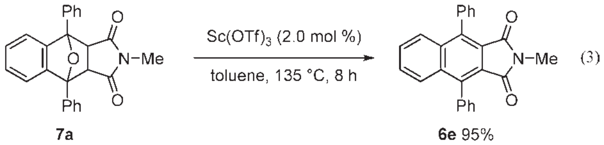
entry	5	product	yield / %[b]
1	 **5b**	 **6h**	18
2[c]	 **5c**	 **6i**	40
3	 **5d**	 **6j**	78

[a] Reaction conditions: $Sc(OTf)_3$ (2.0 mol %), **2a** (0.375 mmol), **4** (0.375 mmol), **5** (0.250 mmol), toluene (0.25 mL), under argon atmosphere. [b] Isolated yield after recrystallization. [c] Dichloroethane was used as solvent.

The reaction pathway was further explored using the following investigations. *o*-Dibenzoylbenzene (**2e**) was subjected to the reaction conditions shown in eq 1 without dienophile **5**. The isobenzofuran derivative **1b** was obtained in 37% yield (eq 1). To obtain the isobenzofuran **1b**, the reaction conditions were modified as necessary. When the amount of $Sc(OTf)_3$ was reduced, longer reaction times were required. Consequently, **1b** was consumed by decomposition and/or polymerization. In the case of *o*-phthalaldehyde (**2a**), isobenzofuran (**1a**) was not observed due to its instability.[11] After separation, **1b** was allowed to react with **5a**, then gave adduct **7a** in 86% yield via a Diels–Alder reaction immediately, even without any catalyst (eq 2). The dehydration of **7a** proceeded with catalytic $Sc(OTf)_3$, to give the naphthalene derivative **6e** in 95% yield (eq 3). $Sc(OTf)_3$ can act as a catalyst for both the synthesis of isobenzofuran **1** and the dehydration of **7**. Previously, the synthesis of naphthalene **6e** from **7a** has required a stoichiometric or excess amount of Brønsted acid.[12]







To reuse the catalyst, we wanted to immobilize the scandium onto a solid support.[13] $Sc(OTf)_3$ (10 wt%) was dissolved in THF, immobilized on several kinds of solid supports by the evaporation to dryness method, and washed with diethyl ether to remove any formed trifluoromethanesulfonic acid. The screening revealed Amberlyst-15[14] to be the optimum support for the catalysis: silica-supported scandium catalyst gave **6a** in 5% yield, and DOWEX- or zeolite-supported scandium did not work as a catalyst. EDX analysis of the prepared catalyst confirmed that scandium was supported on Amberlyst-15, and the fluorine atom from the trifluoromethanesulfonyl group was not detected. This suggests that a ligand exchange reaction on scandium occurred between the trifluoromethanesulfonyl group and the sulfo group of Amberlyst-15.[15]

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(9) (a) Benderradji, F.; Nechab, M.; Einhorn, C.; Einhorn, J. *Synlett* **2006**, *13*, 2035–2038. (b) Chan, S.-H.; Yick, C.-Y.; Wong, H. N. C. *Tetrahedron* **2002**, *58*, 9413–9422. (c) Shang, M.; Butler, D. N.; Warrener, R. N. *Chem. Commun.* **2001**, 1550–1551.

(10) Diarylisobenzofurans are frequently used as the diene moiety in Diels-Alder reaction. See recent reports: (a) Uchiyama, M.; Kobayashi, Y.; Furuyama, T.; Nakamura, S.; Kajihara, Y.; Miyoshi, T.; Sakamoto, T.; Kondo, Y.; Morokuma, K. *J. Am. Chem. Soc.* **2008**, *130*, 472–480. (b) Tran, B. L.; Pink, M.; Mindiola, D. J. *Organometallics* **2009**, *28*, 2234–2243. (c) Ehm, C.; Lentz, D. *Chem. Commun.* **2010**, *46*, 2399–2401.

(11) (a) Wiersum, U. E.; Mijs, W. J. *J. Chem. Soc., Chem. Commun.* **1972**, 347–348. (b) Wege, D. *Tetrahedron Lett.* **1971**, 2337–2338. (c) Warrener, R. N. *J. Am. Chem. Soc.* **1971**, *93*, 2346–2348.

(12) (a) Allen, C. F. H.; Bell, A.; Gates, J. W., Jr. *J. Org. Chem.* **1943**, *8*, 373–379. (b) Tobia, D.; Rickborn, B. *J. Org. Chem.* **1986**, *51*, 3849–3858. (c) Cafeo, G.; Giannetto, M.; Kohnke, F. H.; La Torre, G. L.; Parisi, M. F.; Menzer, S.; White, A. J. P.; Williams, D. J. *Chem.—Eur. J.* **1999**, *5*, 356–368.

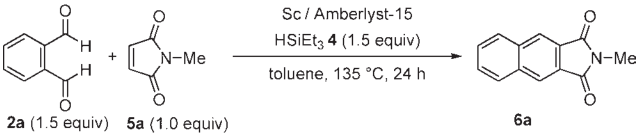
(13) Polymer supported scandium catalyst has been developed, see: (a) Kobayashi, S.; Nagayama, S. *J. Org. Chem.* **1996**, *61*, 2256–2257. (b) Kobayashi, S.; Nagayama, S. *J. Am. Chem. Soc.* **1996**, *118*, 8977–8978. (c) Takeuchi, M.; Akiyama, R.; Kobayashi, S. *J. Am. Chem. Soc.* **2005**, *127*, 13096–13097.

(14) Only Amberlyst-15 promoted the reaction, but **6a** was obtained in a low yield (17%).

(15) (a) Yu, L.; Chen, D.; Li, J.; Wang, P. G. *J. Org. Chem.* **1997**, *62*, 3575–3581. (b) Nagayama, S.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 567–569.

The catalyst was found to be recyclable in the reaction (Table 3). The EDX measurement revealed that the atom ratio of sulfur (derived from sulfo group of Amberlyst) and scandium was 8:2, before and after the reaction. This suggests that any leaching of scandium is minimal.

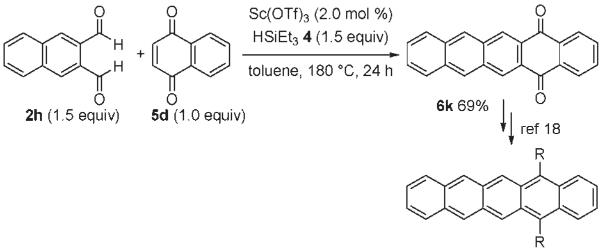
Table 3. Recycle of the Catalyst Supported on Amberlyst-15[a]



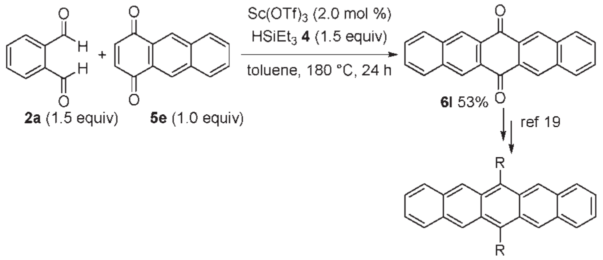
cycle	1	2	3	4	5	6
yield/%[b]	67	59	65	57	65	67

[a] Reaction conditions: catalyst (28 mg, Sc: 0.005 mmol), **2a** (0.375 mmol), **4** (0.375 mmol), **5** (0.250 mmol), toluene (0.25 mL), under argon atmosphere. [b] Isolated after recrystallization.

Having established a new and efficient Sc-catalyzed system, its application toward functional materials was investigated. Pentacene derivatives are often used as organic electronics materials such as in organic field-effect transistors and solar cells.[16] We wanted to synthesize pentacenediones, which are used as precursors to pentacenes. The reaction of *o*-bisformylnaphathalene (**2h**) with benzoquinone (**5d**) yielded 5,14-pentacenedione (**6k**) in 69% yield (eq 4). Similarly, 6,13-pentacenedione (**6l**) was synthesized from *o*-phthalaldehyde (**2a**) and anthracenedione **5e** (eq 5). The successive dehydration is convenient, since, in some cases, the retro-Diels–Alder reaction occurs in equilibrium between the isobenzofuran and the corresponding endoxide adduct, then the yield of the product decreases.[17] This technique can allow pentacenes having substituents at different positions to be synthesized in few steps.[18,19]



(4)



(5)

In conclusion, we have developed a novel method for the preparation of isobenzofuran derivatives **1**. These isobenzofurans were trapped by a dienophile **5** via a Diels–Alder reaction and finally converted to the corresponding naphthalene derivative **6** via dehydration. We have also confirmed that the Sc/Amberlyst-15 catalyst is efficient and recyclable. The 5,14- and 6,13-pentacenediones, **6k** and **6l**, were also synthesized as precursors to substituted pentacenes.

Acknowledgment. Financial support for this study was provided by Special Coordination Funds for Promoting Science and Technology of MEXT.

Supporting Information Available. Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) (a) Watkins, N. J.; Yan, L.; Gao, Y. *Appl. Phys. Lett.* **2002**, *80*, 4384–4386. (b) Chu, C.-W.; Li, S.-H.; Chen, C.-W.; Shrotriya, V.; Yang, Y. *Appl. Phys. Lett.* **2005**, *87*, 193508. (c) DiBenedetto, S. A.; Frattarlli, D.; Rantner, M. A.; Facchetti, A.; Marks, T. J. *J. Am. Chem. Soc.* **2008**, *130*, 7528–7529.

(17) (a) Christopfel, W. C.; Miller, L. L. *J. Org. Chem.* **1986**, *51*, 4169–4175. (b) Yick, C.-Y.; Chan, S.-H.; Wong, H. N. C. *Tetrahedron Lett.* **2000**, *41*, 5957–5961.

(18) Recent reports on synthesis of 5,14-substituted pentacenes. See: (a) Lin, Y. -C.; Lin, C.-H. *Org. Lett.* **2007**, *9*, 2075–2078. (b) Palayangoda, S. S.; Mondal, R.; Shah, B. K.; Neckers, D. C. *J. Org. Chem.* **2007**, *72*, 6584–6587. (c) Vets, N.; Dilien, H.; Toppet, S.; Dehaen, W. *Synlett* **2006**, 1359–1362.

(19) Recent reports on synthesis of 6,13-substituted pentacenes. See: (a) Lehnherr, D.; Murray, A. H.; McDonald, R.; Ferguson, M. J.; Tykwinski, R. R. *Chem.—Eur. J.* **2009**, *15*, 12580–12584. (b) Huang, Z.; Jiang, Y.; Yang, X.; Fu, Y.; Cao, W.; Zhang, J. *Synth. Met.* **2009**, *159*, 1552–1556. (c) Wang, J.; Liu, K.; Liu, Y.-Y.; Song, C.-L.; Shi, Z.-F.; Peng, J.-B.; Zhang, H.-L.; Cao, X.-P. *Org. Lett.* **2009**, *11*, 2563–2566. (d) Tang, M. L.; Oh, J. H.; Reichardt, A. D.; Bao, Z. *J. Am. Chem. Soc.* **2009**, *131*, 3733–3740.