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An Unexpected C–C Bond Cleavage of Acetophenones: Synthesis of Bis(heteroaryl)arylmethanes and Triarylmethanes via SeO_2/Lanthanide Chloride Catalyzed Friedel–Crafts Arylation

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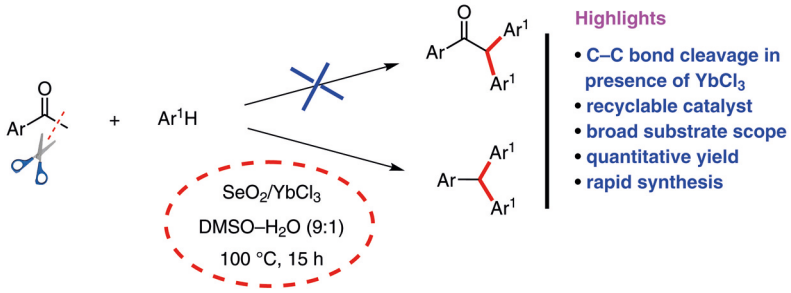

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Abstract A novel synthesis of bisheteroarylaryl methanes and triarylmethanes is described by the selective C–C bond cleavage of acetophenones in the presence of SeO_2/lanthanide chlorides. The present strategy provides an in situ generation of aldehydes from acetophenones followed by a double Friedel–Crafts reaction of electron-rich arenes. Natural product 1,1,1-tris(3-indolyl)methane is synthesized in a single step following the same protocol.

Key words acetophenones, C–C bond cleavage, double Friedel–Crafts reaction

Bis(heteroaryl)arylmethane (BHAAM) and triarylmethane (TRAM) scaffolds containing molecules were found to exhibit important biological activities such as antitubercular, anticancer, analgesic, antimicrobial, antiviral, and antihyperglycemic properties (Figure 1).[1] Many BHAAM derivatives have a wide application in dyes, medicines, copy engineering,[2] agriculture chemistry,[3] food industry,[4] materials, and photochromic agents.[5] Moreover, tetraoxaquaterenes[6] and macromolecules which are used as metal-ion carriers have been synthesized from bis(furyl)methanes.[7] As a result of this prevalence and prominence of BHAAM and TRAM derivatives, various methods have been reported for their synthesis using Lewis and Brønsted acids, solid-supported catalysts, and superacidic systems. For example, $Yb(OTf)_3$,[8] $AuCl_3$,[9] molecular iodine,[10] TMSCl,[11] $FeCl_3$,[12] and $Cu(OTf)_2$[13] have been utilized as Lewis acids for these types of reactions. Subsequently, Brønsted acids such as TfOH,[14] TFA,[15] PTSA,[16] $BF_3{\cdot}H_2O$,[17] and *o*-benzenedisulfonimide[18] have also been used predominately. In addition to this polystyrene-supported sulfonic acid,[19] silica gel supported $NaHSO_4$,[20] silica-sulfuric acid,[21] perfluorinated sulfonic acid resin (Nafion-H),[22] and ionic liquids[23] have also been used for the synthesis of diheteroarylalkane derivatives.

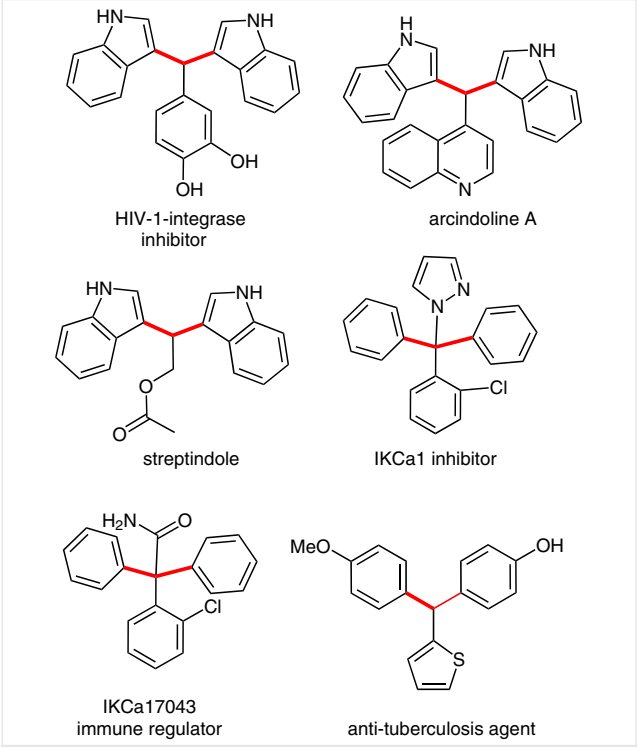
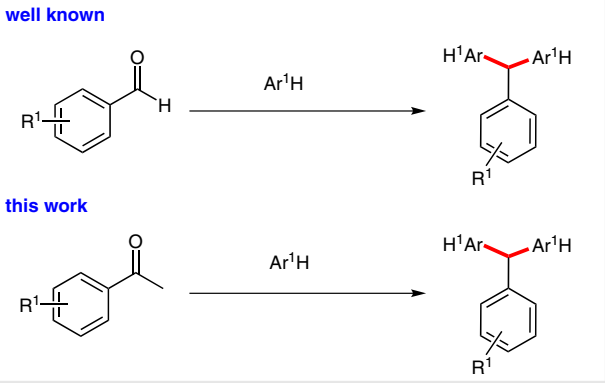


Figure 1 BHAAM- and TRAM-containing drugs

Though the reported methods are satisfactory for the synthesis of BHAAM and TRAM, they have some drawbacks like low yield, high catalyst loadings, and environmental in-

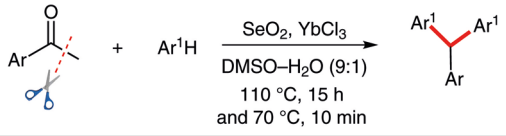
compatibility. In this regard it is desirable to develop general and catalytic method for the synthesis of BHAAM and TRAM (Scheme 1).



Scheme 1 Friedel–Crafts reactions of electron-rich arenes

The selective cleavage of C–C bond can be a challenging, yet offers one of the most powerful and efficient synthetic strategies for chemical transformations.[24] In addition to this, metal-catalyzed C–C bond-cleavage reactions have become the subject of intensive studies.[25] On the other hand, Friedel–Crafts reaction has attracted much attention and emerged as well-accepted method in organic synthesis for C–C bond formation.[26] Till date various electron-rich arenes/heteroarenes are used so far in the Friedel–Crafts reaction with diverse carbonyl compounds. Lanthanide chlorides are used as catalysts for various organic transformations[27] because of certain advantages, like easy availability, water-tolerant and nontoxic nature. Moreover, these catalysts can be recovered and reused without loss of efficiency.[28]

To the best of our knowledge the oxidative coupling of acetophenones with electron-rich arenes to BHAAM and TRAM remain unexplored. In the continuation of our work related to green chemistry[29a–d] and double Friedel–Crafts reactions,[29e–i] herein we wish to report for the first time C–C bond cleavage of acetophenones in the presence of lanthanide chlorides for in situ generation of aldehydes and subsequent Friedel–Crafts reaction with electron-rich arenes/heteroarenes (Scheme 2).



Scheme 2 $YbCl_3$-catalyzed C–C bond cleavage followed by Friedel–Crafts reaction

In order to determine the credibility of our protocol in the initial exploring experiments, we investigated different reaction conditions using 1-(4-chlorophenyl)ethanone (**1e**) and 2-methylfuran (**2**) as the starting substrates (Table 1). We performed the reaction of **1a** with **2** in the presence of SeO_2/YCl_3 (0.3 mmol) in DMSO–H_2O (9:1, 3 mL) at 100 °C. As expected, the above reaction gave the desired product 5,5′-[(4-chlorophenyl)methylene]bis(2-methylfuran) (**4f**) in reasonable yield (75%, Table 1, entry 1). The structure of the product was confirmed by ^1H NMR, ^{13}C NMR, and IR spectroscopic and MS spectrometric analysis. It was presumed that the formation of the desired product occurred may be via C–C bond cleavage followed by double Friedel–Crafts reaction. However, the reaction did not proceed in the absence of catalyst (Table 1, entry 2). Thus, a sequence of catalysts, such as $SeO_2/YbCl_3$, $SeO_2/GdCl_3$, $SeO_2/SmCl_3$, $SeO_2/NdCl_3$, $SeO_2/ErCl_3$, and $SeO_2/LaCl_3$ were tested for the reaction (Table 1, entries 3–8). Among the screened catalysts, $YbCl_3$ was found the most suitable for maximum conversion (80% yield, Table 1, entry 3).

Table 1 Optimization of the Reaction Conditions for the Synthesis of 5,5′-[(4-Chlorophenyl)methylene]bis(2-methylfuran) (**4f**)[a]

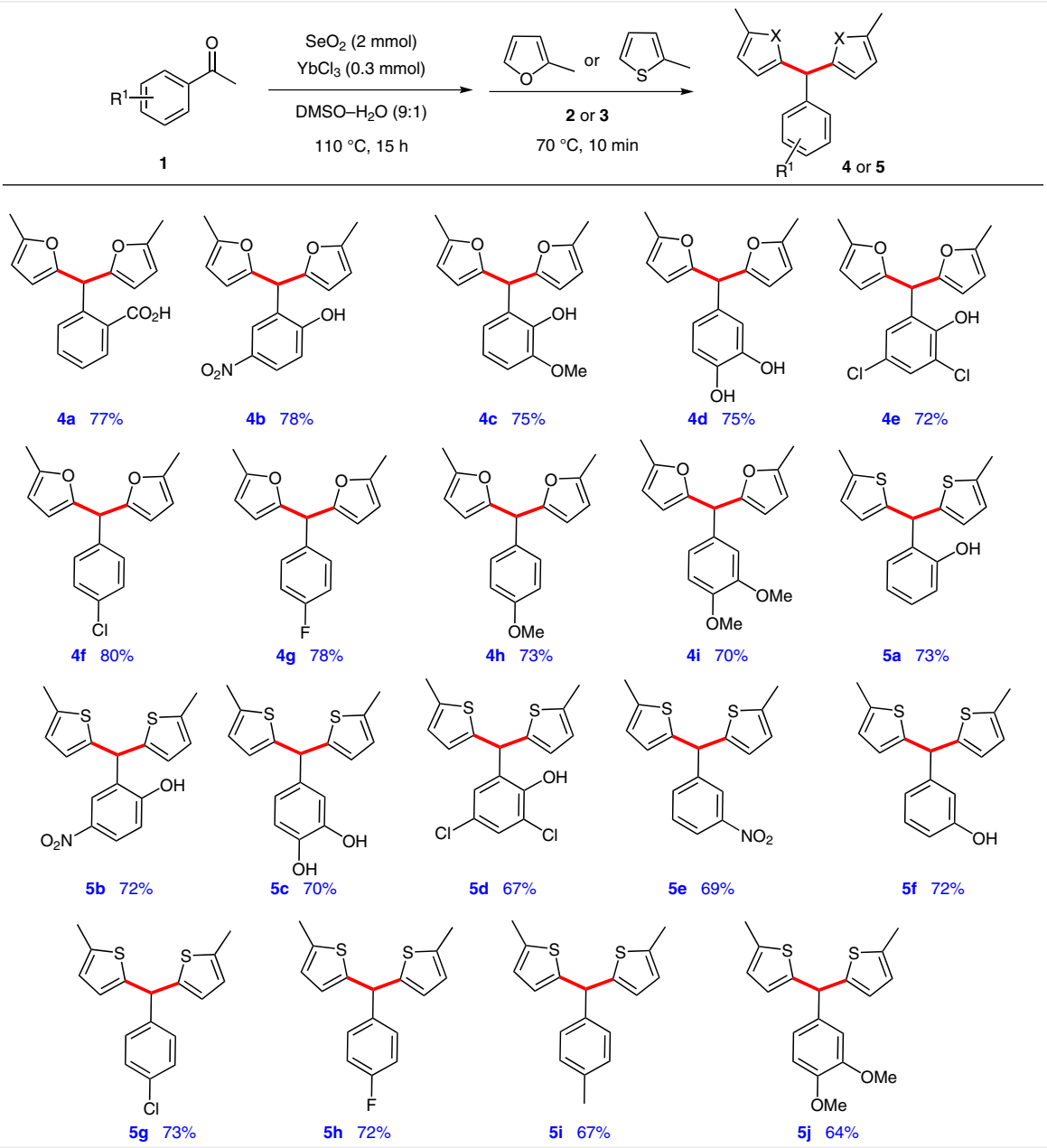
Entry	Catalyst	Solvent	Yield (%)[b]
1	SeO_2/YCl_3	DMSO–H_2O (9:1)	75
2	–	DMSO–H_2O (9:1)	n.r.
3	$SeO_2/YbCl_3$	DMSO–H_2O (9:1)	80
4	$SeO_2/GdCl_3$	DMSO–H_2O (9:1)	68
5	$SeO_2/SmCl_3$	DMSO–H_2O (9:1)	66
6	$SeO_2/NdCl_3$	DMSO–H_2O (9:1)	60
7	$SeO_2/ErCl_3$	DMSO–H_2O (9:1)	57
8	$SeO_2/LaCl_3$	DMSO–H_2O (9:1)	42
9	$SeO_2/YbCl_3$	DMF–H_2O (9:1)	70
10	$SeO_2/YbCl_3$	toluene–H_2O (9:1)	65
11	$SeO_2/YbCl_3$	1,4-dioxane–H_2O (9:1)	60
12	$SeO_2/YbCl_3$	DMSO	n.r.
13	$SeO_2/YbCl_3$	H_2O	n.r.
14	SeO_2	DMSO–H_2O (9:1)	n.r.
15	$YbCl_3$	DMSO–H_2O (9:1)	n.r.

[a] Reaction conditions: 1-(4-chlorophenyl)ethanone (**1e**, 1 mmol), 2-methylfuran (**2**, 2 mmol), and lanthanide chloride (0.3 mmol) in solvent (3 mL) at 110 °C and 70 °C within 15 h and 10 min.
[b] Isolated yield.

Later, various solvent systems such as DMF–H_2O, toluene–H_2O, and 1,4-dioxane–H_2O were examined, and the DMSO–H_2O system was found as solvent of choice in terms of yield (Table 1, entries 9–11). The reaction failed to initiate either in pure DMSO or in pure H_2O (Table 1, entries 12 and 13), indicating that the mixture of solvent was essential for the reaction to proceed. It is noteworthy to mention that the reaction did not proceed with either SeO_2 or $YbCl_3$ alone (Table 1, entries 14 and 15).

With the optimal reaction conditions[33] in hand, the scope of this SeO_2/lanthanide chloride catalyzed protocol was extended to a variety of substituted acetophenones with 2-methylfuran/thiophene, and the results are outlined in the Scheme 3. Acetophenone bearing electron-donating (OH, Me, OMe), or electron-withdrawing (CO_2H, NO_2, F, Cl) groups reacted smoothly under the optimized conditions and gave the desired products in good to high yields (Scheme 3, 4a,c,d,f–i, 5a,c,e–j). In addition to this, both electron-donating and electron-deficient (2-HO-3,5-Cl and 2-HO-5-O_2N) groups containing phenyl ring of acetophenones also underwent smooth reaction and afforded high yield of the corresponding products (Scheme 3, 4b,e, 5b,d).

To expand the scope of the substrates, acetophenones **1** with indoles **6** was examined in optimized conditions. To our delight, the reaction proceeded easily to furnish bisindolylmethanes **7**. The results demonstrated that the electronic nature of the acetophenones had little influence on



Scheme 3 $YbCl_3$-catalyzed synthesis of bisheteroarylaryl methanes. *Reagents and conditions*: acetophenones **1** (1 mmol), 2-methylfuran/thiophene **2**/**3** (2 mmol), SeO_2 (2 mmol), and $YbCl_3$ (0.3 mmol) in DMSO–H_2O (9:1, 3 mL) at 110 °C and 70 °C within 15 h and 10 min. Isolated yields are given.

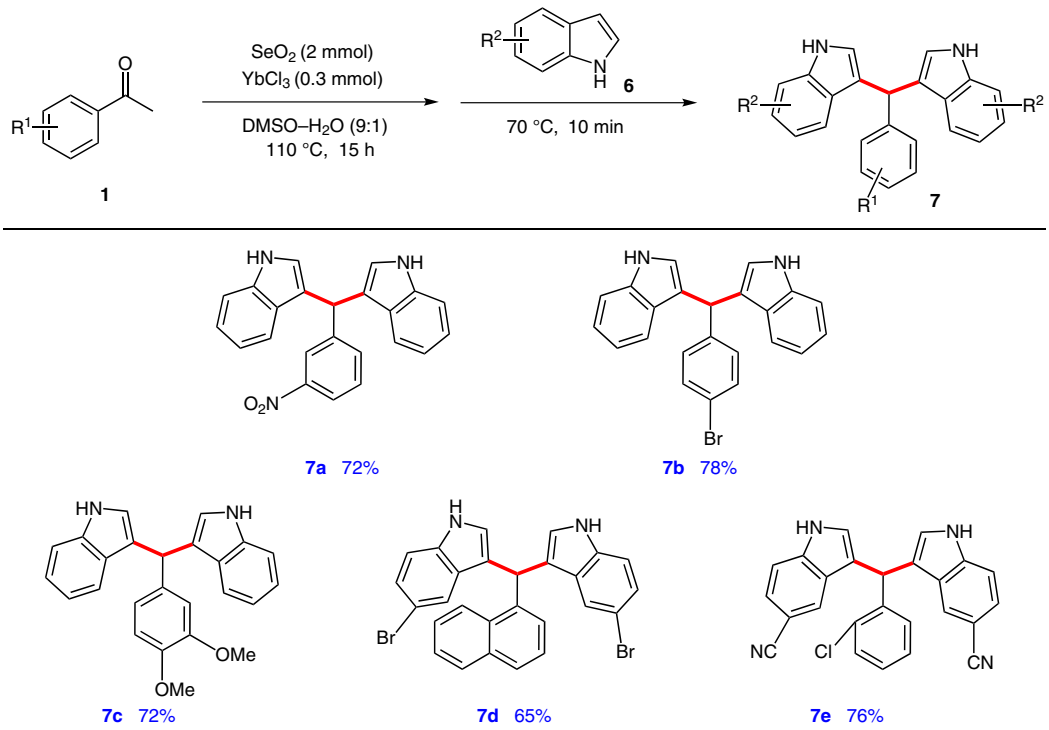
the reaction efficiency, as all the desired products with substituents were obtained in moderate to good yields (Scheme 4, 7a,f).

To further expand the substrate scope, we performed the reactions of acetophenones **1** with different electron-rich arenes **8**, such as 1,3-dimethoxybenzene, 1,3,4-trimethoxybenzene, and 1,3,5-trimethoxybenzene, and they were well tolerated to produce TRAM **9** in good yields (Scheme 5). During the experiments we observed the reactivity profile of electron-rich arenes/heteroarenes is as follows 2-methylfuran > indoles > 2-methylthiophene > arenes.

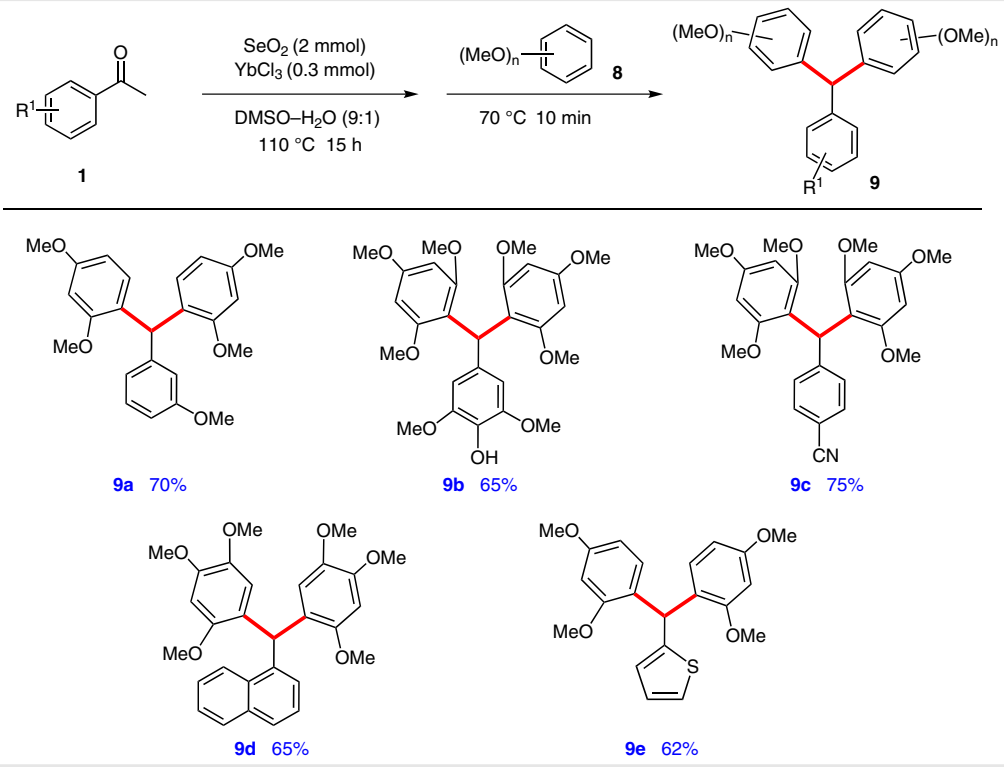
The developed protocol was successfully applied to the rapid and straightforward synthesis of natural product 1,1,1-tris(3-indolyl)methane.[30] When we treated 1-(1*H*-indol-3-yl)ethanone **1r** with indole under the optimized reaction conditions,[31] we directly obtained the 1,1,1-tris(3-indolyl)methane **7f** in 50% yield (Scheme 6).

In order to address the mechanism of the present protocol, we carried out a few control experiments. 1-(4-chlorophenyl)ethanone (**1f**) was converted into 2-(4-chlorophenyl)-2-oxoacetaldehyde **A** in 75% yield using the SeO_2 (Scheme 7). Further the reaction of glyoxal **A** with $YbCl_3$ gave 4-chlorobenzaldehyde **B** in 84% yield by the C–C bond cleavage. Subsequently, glyoxal **A** was subjected to 2-methylfuran (**2**) in the presence of $YbCl_3$, product 5,5′-[(4-chlorophenyl)methylene] bis(2-methylfuran) (**4f**) was observed in 82% yield. Furthermore, aldehyde **B** with 2-methylfuran could be converted into **4f** under the same reaction conditions. These results clearly confirmed the intermediacy of phenylglyoxal **A** and aldehyde **B** in the transformation.

A putative mechanism for this $SeO_2/YbCl_3$-catalyzed C–C bond cleavage followed by double Friedel–Crafts reaction is proposed based on previous reports[32] and illustrated in Scheme 8. Initially, acetophenone was converted into arylglyoxal **A** in the presence of SeO_2, which reacts with water, and reacted to hydrated α,α-bis(hydroxy)acetophenone **B** by grasping one molecule of water. Compound **B** further transformed into intermediate **C** in the presence of $YbCl_3$ by a 1,2-hydrate shift from methyl hydrogen atom to carbonyl carbon in a Cannizaro-type reaction.[33] Subsequently, cleavage of the C–C bond from int-**C** furnishes aldehyde **D** along with the release of formic acid**.** Next, the aldehyde is coordinated by $YbCl_3$ to yield the more electrophilic carbonyl carbon of intermediate **D**. The nucleophilic carbon of arene/heteroarene attacks on the carbonyl carbon of **D** via Friedel–Crafts reaction leading to the formation of the complex **E**, which further converts into the highly stabilized carbocation intermediate **F** by leaving a hydroxyl group. Finally, a second molecule of arene/heteroarene reacts with **F** via Friedel–Crafts reaction to afford the desired BHAAM and TRAM products.



Scheme 4 $YbCl_3$-catalyzed synthesis of bisindolylmethanes. *Reagents and conditions*: acetophenones **1** (1 mmol), indoles **6** (2 mmol), SeO_2 (2 mmol), and $YbCl_3$ (0.3 mmol) in DMSO–H_2O (9:1, 3 mL) at 110 °C and 70 °C within 15 h and 10 min. Isolated yields are given.



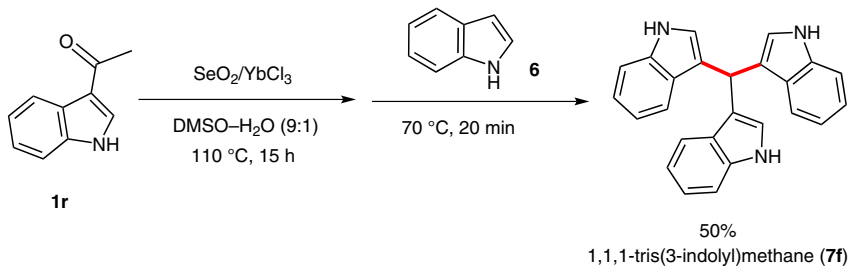
Scheme 5 $YbCl_3$-catalyzed synthesis of triarylmethanes. *Reagents and conditions*: acetophenones **1** (1 mmol), arenes **8** (2 mmol), SeO_2 (2 mmol), and $YbCl_3$ (0.3 mmol) in DMSO–H_2O (9:1, 3 mL) at 110 °C and 70 °C within 15 h and 10 min. Isolated yields are given.

The recovery and reusability of the $YbCl_3$ catalyst was studied for four model products, such as **4f**, **5a**, **7b**, and **9c**. After completion of the reaction, the reaction mixture was filtered through a short pad of Celite®. Excess SeO_2 and other selenium-containing byproducts were removed by adsorption on Celite.

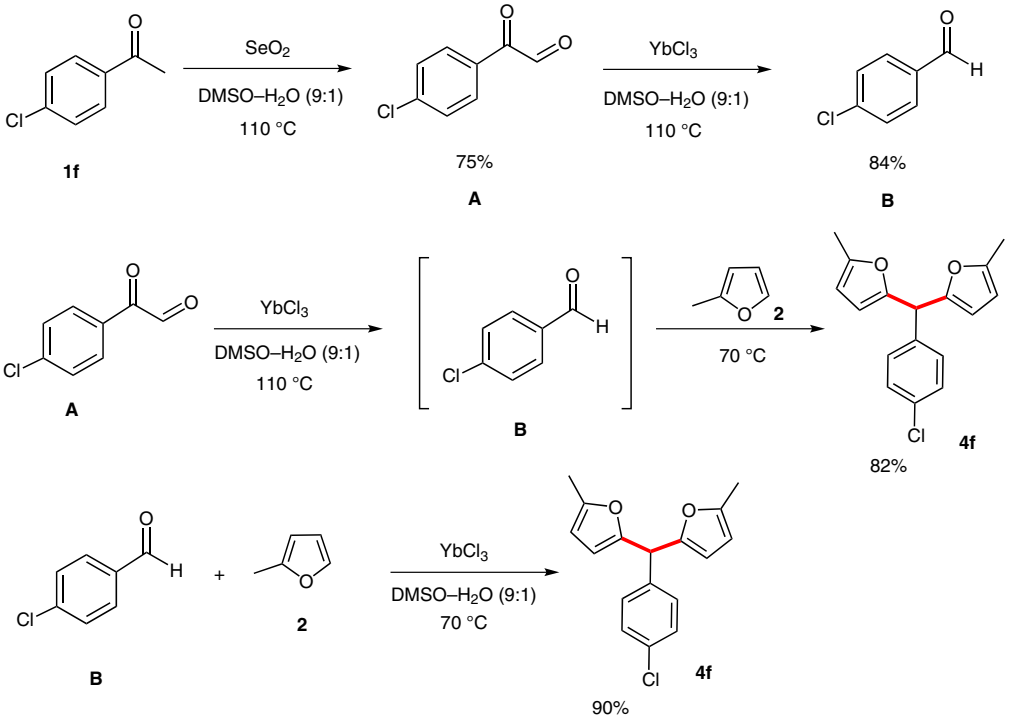
Water was added to the filtrate, and the mixture was extracted with dichloromethane. The catalyst was recovered from the aqueous layer by removing water and then subjected to the next run. The reuse of $YbCl_3$ up to three cycles gave consistent yield of product without any substantial loss in the catalytic activity. These results are summarized in Figure 2. The ease of recovery and reusability of this reaction media may contribute to the development of green strategy for the preparation of BHAAMs and TRAMs.

We believe that the present method may serve as an alternative method for the synthesis of bisheteroarylmethanes/tryarylmethanes, via in situ generation of aldehyde by C–C bond cleavage. Moreover, the present method provides access to bis(heteroaryl)methanes that were not prepared earlier (Scheme 3, 4c–e, 5a–f,h,j).

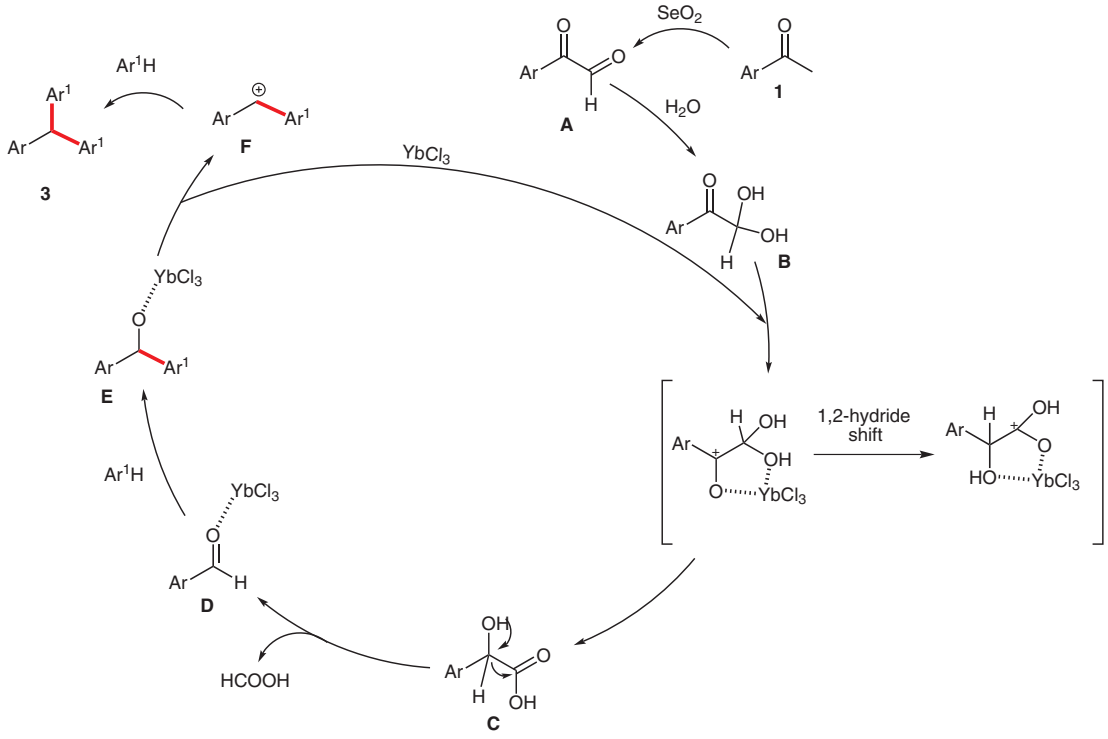
In summary, we have developed a lanthanide chlorides catalyzed novel one-pot synthesis of BHAAMs and TRAMs by the Friedel–Crafts reaction of acetophenones with electron-rich arenes. Our method describes the use of acetophenes for the first time in a one-pot reaction for the synthesis of BHAAMs and TRAMs. The reaction involves an un-



Scheme 6 Synthesis of 1,1,1-tris(3-indolyl)methane **7f**



Scheme 7 Control experiments



Scheme 8 Plausible mechanistic pathway for the formation of BHAAMs and TRAMs

expected cleavage of the C–C bond of acetophenones that yields aldehydes which further participated in a Friedel–Crafts reaction. This is the first report regarding the C–C bond cleavage in the presence of $YbCl_3$. The present method is rapid, convenient, and practical to provide BHAAMs and TRAMs. Moreover, the recovery and reusability of the catalyst makes the procedure environmental friendly.

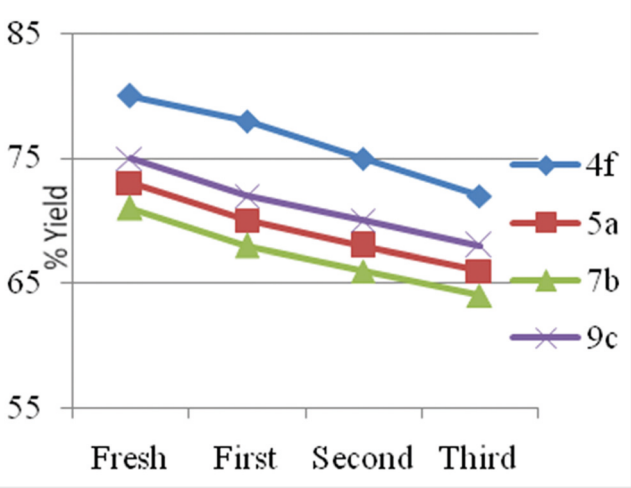


Figure 2 Reusability data for $YbCl_3$

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560808.

References and Notes

(1) (a) Agh-Atabay, N. M.; Dulger, B.; Gucin, F. *Eur. J. Med. Chem.* **2003**, *38*, 875. (b) Mann, J.; Baron, A.; Opoku-Boahen, Y.; Johansson, E.; Parkinson, G.; Kelland, L. R.; Neidle, S. *J. Med. Chem.* **2001**, *44*, 138. (c) Yeung, K. S.; Meanwell, A.; Qiu, Z.; Hernandez, D.; Zhang, S.; McPhee, F.; Weinheimer, S.; Clark, J. M.; Janc, J. W. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2355. (d) Mibu, N.; Yokomizo, K.; Uyeda, M.; Sumoto, K. *Chem. Pharm. Bull.* **2005**, *53*, 1171. (e) Mibu, N.; Yokomizo, K.; Uyeda, M.; Sumoto, K. *Chem. Pharm. Bull.* **2003**, *51*, 1325. (f) Lewis, M. R.; Goland, P. P. *Cancer Res.* **1952**, *12*, 130. (g) Parai, M. K.; Panda, G.; Chaturvedi, V.; Manju, Y. K.; Sinha, S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 289. (h) Panda, G.; Shagufta, ; Mishra, J. K.; Chaturvedi, V.; Srivastava, A. K.; Srivastava, R.; Srivastava, B. S. *Bioorg. Med. Chem.* **2004**, *12*, 5269. (i) Mibu, N.; Sumoto, K. *Chem. Pharm. Bull.* **2000**, *48*, 1810.
(2) Fukuda, M.; Fukunishi, A.; Mori, M. JP 06171214, **1994**.
(3) Nakanishi, M.; Mukai, T.; Inamasu, S. JP 44027990, **1969**.
(4) Stoll, M.; Winter, M.; Gautschi, F.; Flament, I.; Willhalm, B. *Helv. Chim. Acta* **1967**, *50*, 628.
(5) (a) Nair, V.; Thomas, S.; Mathew, S. C.; Abhilash, K. G. *Tetrahedron* **2006**, *62*, 6731. (b) Walsh, C. T.; Garneau-Tsodikova, S.; Howard-Jones, A. R. *Nat. Prod. Rep.* **2006**, *23*, 517. (c) Butin, A. V.; Stroganova, T. A.; Kul'nevich, V. G. *Chem. Heterocycl. Compd.* **1999**, *35*, 757. (d) Shchepinov, M. S.; Korshun, V. A. *Chem. Soc. Rev.* **2003**, *32*, 170. (e) Irie, M. *J. Am. Chem. Soc.* **1983**, *105*, 2078.
(6) Pajewski, R.; Ostaszewski, R.; Ziach, K.; Kulesza, A.; Jurczak, J. *Synthesis* **2004**, 865.
(7) (a) Hall, J. E. US 4429090, **1984**. (b) Gandini, A. EP 0379250, **1990**. (c) Musau, R. M.; Whiting, A. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2881. (d) He, Y.; Chen, Z.; Wu, C. *Chin. J. Synth. Chem.* **1993**, *1*, 123.
(8) Genovese, S.; Epifana, F.; Pelucchini, C.; Curini, M. *Eur. J. Org. Chem.* **2009**, 1132.
(9) (a) Nair, V.; Abhilash, K. G.; Vidya, N. *Org. Lett.* **2005**, *7*, 5857. (b) Nair, V.; Vidya, N.; Abhilash, K. G. *Synthesis* **2006**, *21*, 3647.
(10) Jaratjaroonphong, J.; Tuengpanya, S.; Saeeng, R.; Udompong, S.; Srisook, K. *Eur. J. Med. Chem.* **2014**, *83*, 561.
(11) Gagieva, S. C.; Sukhova, T. A.; Savinov, D. V.; Tuskaev, V. A.; Lyssenko, K. A.; Bravaya, N. M.; Belokon, Yu. N.; Bulychev, B. M. *Russ. Chem. Bull.* **2006**, *55*, 1794.
(12) Thirupathi, P.; Kim, S. S. *J. Org. Chem.* **2010**, *75*, 5240.
(13) (a) Alonso, N.; Esquivias, J.; Omez-Array, R. G.; Carretero, J. C. *J. Org. Chem.* **2008**, *73*, 6401. (b) Temelli, B.; Unaleroglu, C. *Tetrahedron* **2006**, *62*, 10130. (c) Esquivias, J.; Gomez-Array, R. G.; Carretero, J. C. *Angew. Chem. Int. Ed.* **2006**, *45*, 629.
(14) Ohishi, T.; Kojima, T.; Matsuoka, T.; Shiro, M.; Kotsuki, H. *Tetrahedron Lett.* **2001**, *42*, 2493.
(15) Mibu, N.; Yokomizo, K.; Miyata, T.; Sumoto, K. *J. Heterocycl. Chem.* **2010**, *47*, 1434.
(16) Roberts, B. A.; Cave, G. W. V.; Raston, C. L.; Scott, J. L. *Green Chem.* **2001**, *3*, 280.
(17) Prakash, G. K. S.; Panja, C.; Shakhmin, A.; Shah, E.; Mathew, T.; Olah, G. A. *J. Org. Chem.* **2009**, *74*, 8659.
(18) Barbero, M.; Cadamuro, S.; Dughera, S.; Rucci, M.; Spano, G.; Venturello, P. *Tetrahedron* **2014**, *70*, 1818.
(19) An, L. T.; Ding, F. Q.; Zou, J. P. *Dyes Pigm.* **2008**, *77*, 478.
(20) Leng, Y.; Chen, F.; Zuo, L.; Duan, W. *Tetrahedron Lett.* **2010**, *51*, 2370.
(21) Zolfigol, M. A.; Salehi, P.; Shiri, M.; Sayadi, A.; Abdoli, A.; Keypur, H.; Rezaeivala, K.; Niknam, M.; Kolvari, E. *Mol. Diversity* **2008**, *12*, 203.
(22) Prakash, S. G. K.; Fogassy, G.; Olah, G. A. *Catal. Lett.* **2010**, *138*, 155.
(23) (a) Rad-Moghadam, K.; Sharifi-Kiasaraie, M. *Tetrahedron* **2009**, *65*, 8816. (b) Wang, A.; Zheng, X.; Zhao, Z.; Li, C.; Cui, Y.; Zheng, X.; Yin, J.; Yang, G. *Appl. Catal., A* **2014**, *482*, 198.
(24) For reviews and some recent reports on C–C bond cleavage, see: (a) Cai, S.; Zhao, X.; Wang, X.; Liu, Q.; Li, Z.; Wang, D. Z. *Angew. Chem. Int. Ed.* **2012**, *51*, 8050. (b) Liu, H.; Dong, C.; Zhang, Z.; Wu, P.; Jiang, X. *Angew. Chem. Int. Ed.* **2012**, *51*, 12570. (c) Qin, C.; Zhou, W.; Chen, F.; Ou, Y.; Jiao, N. *Angew. Chem. Int. Ed.* **2011**, *50*, 12595. (d) Murakami, M.; Matsuda, T. *Chem. Commun.* **2011**, *47*, 1100. (e) Bonesi, S. M.; Fagnoni, M. *Chem. Eur. J.* **2010**, *16*, 13572. (f) Winter, C.; Krause, N. *Angew. Chem. Int. Ed.* **2009**, *48*, 2460; *Angew. Chem.* **2009**, *121*, 6457. (g) Park, Y. J.; Park, J.-W.; Jun, C. H. *Acc. Chem. Res.* **2008**, *41*, 222. (h) Seiser, T.; Cramer, N. *Org. Biomol. Chem.* **2009**, *7*, 2835.

(25) (a) Zhang, C.; Feng, P.; Jiao, N. *J. Am. Chem. Soc.* **2013**, *135*, 15257. (b) Zhou, W.; Yang, Y.; Liu, Y.; Deng, G. J. *Green Chem.* **2013**, *15*, 76. (c) Bowring, M. A.; Bergman, R. G.; Tilley, T. D. *J. Am. Chem. Soc.* **2013**, *135*, 13121. (d) Souillart, L.; Cramer, N. *Chem. Sci.* **2014**, *5*, 837. (e) Ogata, K.; Shimada, D.; Furuya, S.; Fukuzawa, S. I. *Org. Lett.* **2013**, *15*, 1182. (f) Zhu, Y.; Yan, H.; Lu, L.; Liu, D.; Rong, G.; Mao, J. *J. Org. Chem.* **2013**, *78*, 9898. (g) Bour, J. R.; Green, J. C.; Winton, V. J.; Johnson, J. B. *J. Org. Chem.* **2013**, *78*, 1665. (h) Xu, F.; Tao, T.; Zhang, K.; Wang, X.-X.; Huang, W.; You, X.-Z. *Dalton Trans.* **2013**, *42*, 3631. (i) Ziadi, A.; Correa, A.; Martin, R. *Chem. Commun.* **2013**, *49*, 4286. (j) Chen, F.; Wang, T.; Jiao, N. *Chem. Rev.* **2014**, *114*, 8613. (k) Grenning, A. J.; Tunge, J. A. *J. Am. Chem. Soc.* **2011**, *133*, 14785. (l) Allpress, C. J.; Miłaczewska, A.; Borowski, T.; Bennett, J. R.; Tierney, D. L.; Arif, A. M.; Berreau, L. M. *J. Am. Chem. Soc.* **2014**, *136*, 7821. (m) Huang, X.; Li, X.; Zou, M.; Song, S.; Tang, C.; Yuan, Y.; Jiao, N. *J. Am. Chem. Soc.* **2014**, *136*, 14858. (n) Li, H.; Li, W.; Liu, W.; He, Z.; Li, Z. *Angew. Chem. Int. Ed.* **2011**, *50*, 2975. (o) Tang, C.; Jiao, N. *Angew. Chem. Int. Ed.* **2014**, *53*, 6528. (p) Zhou, W.; Fan, W.; Jiang, Q.; Liang, Y.; Jiao, N. *Org. Lett.* **2015**, *17*, 2542. (q) Zhang, C.; Xu, Z.; Shen, T.; Wu, G.; Zhang, L.; Jiao, N. *Org. Lett.* **2012**, *14*, 2362.

(26) (a) *Friedel–Crafts and Related Reactions*; Vol. 1–4; Olah, G. A., Ed.; Wiley-Interscience: New York, **1963**. (b) Olah, G. A.; Krishnamurti, R.; Prakash, G. K. S. In *Comprehensive Organic Synthesis*; Vol. 3; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, **1991**, 293. (c) Jorgensen, K. A. *Synthesis* **2003**, 1117. (d) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 550. (e) Bandini, M.; Melloni, A.; Tommasi, S.; Umani-Ronchi, A. *Synlett* **2005**, 1199. (f) Poulsen, T. B.; Jorgensen, K. A. *Chem. Rev.* **2008**, *108*, 2903. (g) Bandini, M.; Umani-Ronchi, A. *Catalytic Asymmetric Friedel–Crafts Alkylations*; Wiley-VCH: Weinheim, **2009**.

(27) Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W. W. L. *Chem. Rev.* **2002**, *102*, 2227.

(28) Xu, F.; Luo, Y.; Wu, J.; Shen, Q.; Chen, H. *Heteroat. Chem.* **2006**, *17*, 389.

(29) (a) Santosh Kumar, G.; Pushpa Ragini, S.; Sanjeeva Kumar, S.; Meshram, H. M. *RSC Adv.* **2015**, *5*, 51576. (b) Madhu Babu, B.; Santosh Kumar, G.; Thakur, P. B.; Bangade, V. M. *Tetrahedron Lett.* **2014**, *55*, 3473. (c) Santosh Kumar, G.; Pushpa Ragini, S.; Meshram, H. M. *Tetrahedron Lett.* **2013**, *54*, 5974. (d) Meshram, H. M.; Ramesh, P.; Santosh Kumar, G.; Reddy, B. C. K. *Tetrahedron Lett.* **2010**, *51*, 4313. (e) Raghavender Reddy, M.; Nageswara Rao, N.; Ramakrishna, K.; Meshram, H. M. *Tetrahedron Lett.* **2014**, *55*, 1898. (f) Nageswara Rao, N.; Raghavende Reddy, M.; Ramakrishna, K.; Meshram, H. M. *Helv. Chim. Acta* **2014**, *97*, 744. (g) Swetha, A.; Kumar, G. S.; Kumar, A. S.; Meshram, H. M. *Tetrahedron Lett.* **2014**, *55*, 4705. (h) Madhu Babu, B.; Thakur, P. B.; Rao, N. N.; Kumar, G. S.; Meshram, H. M. *Tetrahedron Lett.* **2014**, *55*, 1868. (i) Madhu Babu, B.; Thakur, P. B.; Bangade, V. M. *Tetrahedron Lett.* **2014**, *55*, 766.

(30) Ravikanth, V.; Imelda, O.; Irene, W.; Hartmut, L. *J. Nat. Prod.* **2003**, *66*, 1520.

(31) **General Procedure for the Synthesis of Compounds 4 or 5**

A solution of acetophenone **1** (1 mmol), SeO_2 (2 mmol), and $YbCl_3$ (0.3 mmol) in DMSO–H_2O (9:1, 3 mL) was well stirred at 110 °C for 15 h. Then the 2-methylfuran (**2**) or 2-methylthiophene (**3**) was added to the reaction mixture at r.t. and stirred again for 10 min at 70 °C. After completion of the reaction, the reaction mixture brought to r.t., and it was filtered through a short pad of Celite, excess SeO_2, and other selenium-containing byproducts were removed by adsorption on Celite. Water was added to the filtrate, and the mixture was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by chromatography on silica gel to afford required products **4** or **5**. The recovered catalyst was obtained from the aqueous layer after removing water.

^{1}H NMR, ^{13}C NMR, MS, and IR spectral data for the new products are given below.

2-[Bis(5-methylfuran-2-yl)methyl]-6-methoxyphenol (4c, Scheme 3)

Dark-brown viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.23 (s, 6 H), 3.86 (s, 3 H), 4.01 (s, 1 H), 5.86 (s, 4 H), 6.73–6.83 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.6, 37.6, 55.9, 105.9, 107.9, 109.1, 119.2, 121.3, 123.3, 125.6, 142.9, 146.3, 151.1, 152.4, ppm. IR (KBr): ν = 731, 790, 1023, 1232 1290, 1481, 1608, 3521 cm^{-1}. ESI-MS: *m/z* = 321 [M + Na]$^+$. ESI-HRMS: *m/z* calcd for $C_{18}H_{18}O_4Na$ [M + Na]$^+$: 321.1098; found: 321.1092.

4-[Bis(5-methylfuran-2-yl)methyl]benzene-1,2-diol (4d, Scheme 3)

Dark-brown viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.24 (s, 6 H), 5.21 (s, 1 H), 5.83–5.88 (m, 4 H), 6.68 (dd, *J* = 1.88, 8.12 Hz, 1 H), 6.75 (d, *J* = 1.88 Hz, 1 H), 6.80 (d, *J* = 8.30 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.5, 44.3, 106.0, 107.9, 115.2, 115.4, 120.9, 132.9, 142.5, 143.3, 151.3, 152.9 ppm. IR (KBr): ν = 750, 801, 1107, 1269, 1519, 1603, 3387cm^{-1}. ESI-MS: *m/z* = 307 [M + Na]$^+$. ESI-HRMS: *m/z* calcd for $C_{17}H_{16}O_4Na$ [M + Na]$^+$: 307.0945; found: 307.0939.

2-[Bis(5-methylfuran-2-yl)methyl]-4,6-dichlorophenol (4e, Scheme 3)

Dark-brown viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.24 (s, 6 H), 5.73–5.76 (m, 1 H), 5.87–5.93 (m, 4 H), 7.01–7.04 (m, 1 H), 7.22 (d, *J* = 2.13 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.5, 38.4, 106.1, 108.6, 120.4, 125.2, 127.1, 128.3, 128.9, 147.6, 150.8, 151.7 ppm. IR (KBr): ν = 735, 811, 1051, 1182, 1240, 1321, 1465, 1679, 3509 cm^{-1}. ESI-MS: *m/z* = 360 [M + Na]$^+$. ESI-HRMS: *m/z* calcd for $C_{17}H_{14}Cl_2O_3Na$ [M + Na]$^+$: 360.0214; found: 360.0210.

2-[Bis(5-methylthiophen-2-yl)methyl]phenol (5a, Scheme 3)

Dark-brown viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.40 (s, 6 H), 5.94 (s, 1 H), 6.56–6.58 (m, 2 H), 6.63 (d, *J* = 3.35 Hz, 2 H), 6.77 (dd, *J* = 1.22, 8.54 Hz, 1 H), 6.88 (td, *J* = 1.22, 7.47 Hz, 1 H), 7.12–7.16 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.3, 41.6, 116.2, 120.8, 124.6, 125.8, 128.3, 129.3, 130.1, 139.3, 143.7, 153.0 ppm. IR (KBr): ν = 754, 810, 1042, 1227, 1270, 1455, 1593, 3504 cm^{-1}. ESI-MS: *m/z* = 301 [M + H]$^+$. ESI-HRMS: *m/z* calcd for $C_{17}H_{17}OS_2$ [M + H]$^+$: 301.0719; found: 301.0714.

2-[Bis(5-methylthiophen-2-yl)methyl]-4-nitrophenol (5b, Scheme 3)

White solid; mp 196–198 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.44 (s, 6 H), 5.94 (s, 1 H), 6.61 (dd, *J* = 0.94, 3.39 Hz, 2 H), 6.65 (d, *J* = 3.39 Hz, 2 H), 6.90 (q, *J* = 6.04 Hz, 1 H), 8.07–8.12 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.3, 41.6, 116.5, 124.7, 124.9, 125.5, 126.4, 131.0, 140.2, 141.7, 158.8 ppm. IR (KBr): ν = 639, 1071, 1278, 1327, 1486, 1588, 3317 cm^{-1}. ESI-MS: *m/z* = 368 [M + Na]$^+$. ESI-HRMS: *m/z* calcd for $C_{17}H_{16}NO_3S_2$ [M + Na]$^+$: 368.0390; found: 368.0387.

4-[Bis(5-methylthiophen-2-yl)methyl]benzene-1,2-diol (5c, Scheme 3)

Dark-brown viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.40 (s, 6 H), 5.55 (s, 1 H), 6.53–6.60 (m, 4 H), 6.72–6.82 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.3, 47.0, 115.1, 115.4, 120.9, 124.4, 125.5, 136.9, 138.9, 142.4, 143.2, 145.3 ppm. IR (KBr): ν = 765, 806, 1111, 1282, 1518, 1607, 3392 cm^{-1}. ESI-MS: *m/z* = 317

[M + H]$^+$. ESI-HRMS: *m/z* calcd for $C_{17}H_{17}O_2S_2$ [M + H]$^+$: 317.0668; found: 317.0666.

2-[Bis(5-methylthiophen-2-yl)methyl]-4,6-dichlorophenol (5d, Scheme 3)

Dark-brown viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.42 (s, 6 H), 5.71 (s, 1 H), 6.04 (br s, 1 H), 6.57 (s, 4 H), 7.09 (d, *J* = 2.45 Hz, 1 H), 7.24 (d, *J* = 2.45 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.3, 40.7, 120.4, 124.6, 125.2, 126.0, 127.1, 128.0, 133.0, 139.3, 142.9, 147.2 ppm. IR (KBr): ν = 757, 800, 1039, 1161, 1227, 1321, 1460, 1667, 3521 cm^{-1}. ESI-MS: *m/z* = 370 [M + H]$^+$. ESI-HRMS: *m/z* calcd for $C_{17}H_{18}Cl_2OS_2$ [M + H]$^+$: 370.3362; found: 370.3358.

5,5′-[(3-Nitrophenyl)methylene]bis(2-methylthiophene) (5e, Scheme 3)

Dark-brown viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.40 (s, 6 H), 5.77 (s, 1 H), 6.54–6.62 (m, 4 H), 7.44 (t, *J* = 8.30 Hz, 1 H), 7.64 (d, *J* = 7.55 Hz, 1 H), 8.08 (d, *J* = 8.30 Hz, 1 H), 8.16 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.1, 47.0, 121.9, 123.0, 124.6, 126.0, 129.1, 134.2, 139.6, 143.2, 145.7, 148.1 ppm. IR (KBr): ν = 730, 800, 1229, 1350, 1530 cm^{-1}. ESI-MS: *m/z* = 352 [M + Na]$^+$. ESI-HRMS: *m/z* calcd for $C_{17}H_{15}NO_2S_2Na$ [M + Na]$^+$: 352.0347; found: 352.0342.

3-[Bis(5-methylthiophen-2-yl)methyl]phenol (5f, Scheme 3)

Dark-brown viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.39 (s, 6 H), 5.25 (br s, 1 H), 5.60 (s, 1 H), 6.49–6.61 (m, 4 H), 6.63–6.77 (m, 2 H), 6.82–6.89 (m, 1 H), 7.09–7.18 (m, 1 H) ppm. IR (KBr): ν = 703, 754, 803, 1040, 1227, 1263, 1451, 1598, 3393 cm^{-1}. ESI-MS: *m/z* = 301 [M + H]$^+$. ESI-HRMS: *m/z* calcd for $C_{17}H_{17}O_2S_2$ [M + H]$^+$: 301.0717; found: 301.0712.

5,5′-[(4-Fluorophenyl)methylene]bis(2-methylthiophene) (5h, Scheme 3)

Dark-brown viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.40 (s, 6 H), 5.64 (s, 1 H), 6.56 (s, 4 H), 6.97 (t, *J* = 3.50 Hz, 2 H), 7.22–7.28 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.0, 46.8, 115.1, 124.4, 125.5, 129.6, 138.9, 144.8, 159.9, 163.1 ppm. IR (KBr): ν = 537, 803, 842, 1158, 1227, 1505, 1603 cm^{-1}. ESI-MS: *m/z* = 303 [M + H]$^+$. ESI-HRMS: *m/z* calcd for $C_{17}H_{16}FS_2$ [M + H]$^+$: 303.0673; found: 303.0670.

5,5′-[(3,4-Dimethoxyphenyl)methylene]bis(2-methylthiophene) (5j, Scheme 3)

Brown solid; mp 112–114 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.40 (s, 6 H), 3.81 (s, 3 H), 3.84 (s, 3 H), 5.61 (s, 1 H), 6.55 (dd, *J* = 0.94, 3.39 Hz, 2 H), 6.59 (d, *J* = 3.21 Hz, 2 H), 6.80–6.86 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.2, 47.3, 55.7, 110.8, 111.6, 120.2, 124.3, 125.4, 136.3, 138.8, 145.4, 147.9, 148.7 ppm. IR (KBr): ν = 721, 759, 1038, 1251, 1302, 1491, 1572, 1692 cm^{-1}. ESI-MS: *m/z* = 367 [M + Na]$^+$. ESI-HRMS: *m/z* calcd for $C_{19}H_{20}O_2S_2Na$ [M + H]$^+$: 367.0899; found: 367.0894.

(32) (a) Zhang, L.; Bi, X.; Guan, X.; Li, X.; Liu, Q.; Barry, B. D.; Liao, P. *Angew. Chem. Int. Ed.* **2013**, *52*, 11303. (b) Koito, Y.; Nakajima, K.; Kitano, M.; Hara, M. *Chem. Lett.* **2013**, *42*, 873.

(33) (a) Assary, R. S.; Curtiss, L. A. *J. Phys. Chem. A* **2011**, *115*, 8754. (b) Sugimura, T.; Futagawa, T.; Mori, A.; Ryu, I.; Sonoda, N.; Tai, A. *J. Org. Chem.* **1996**, *61*, 6100.