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Synthesis of 2-substituted benzo[*b*]thiophene via a Pd-catalyzed coupling of 2-iodothiophenol with phenylacetylene†

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A Pd(II)-catalyzed Sonogashira type cross-coupling reaction between 2-iodothiophenol and phenylacetylene has been developed. A series of 2-substituted benzo[*b*]thiophenes were obtained in moderate to good yield (up to 87%). The application of this method was demonstrated by the synthesis of 2-(4-(*tert*-butyl)phenyl)benzo[*b*]thiophene 1,1-dioxide and (4-methoxyphenyl)(2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl)methanone, which exhibit a fluorescence quantum yield of up to 1 and can be used as a cannabinoid receptor ligand, respectively.

Introduction

As a crucial class of heterocyclic compounds, 2-substituted benzo[*b*]thiophenes have broad biological properties¹ and diversified applications in the field of materials science.² They are usually considered as important structural motifs in pharmaceuticals and biologically active molecules. For example, as shown in Fig. 1, Bi-BTBT, raloxifene, and *i*Pr-BTBT are examples of commercial drugs and organic semiconductors containing benzo[*b*]thiophene cores.³

The normal approaches to synthesize 2-substituted benzo[*b*]thiophenes are normally focused on a coupling cyclization

reaction of *o*-bromoalkynylbenzenes with various thiol surrogates upon lithium halogen exchange at $-78\text{ }^{\circ}\text{C}$ (Scheme 1a)⁴ or the annulation of alkynylbenzenes (Scheme 1b).⁵ While in the process of reporting this study, a similar study was reported by Fu and co-workers using the electrophilic cyclization of *o*-alkynyl thioanisole (Scheme 1c).⁶ However, the major obstacles of these methods are a result of the harsh reaction conditions or the limitation of the starting materials used.

On the other hand, the Sonogashira cross-coupling reaction⁷ between aryl or alkenyl halides with terminal alkynes in the presence of a transition-metal catalyst has become one of the most powerful methods to prepare alkyl-aryl and diaryl-substituted acetylenes.⁸ In a continuation of our study on catalytic Sonogashira cross-coupling reaction and synthesis of sulfur-containing heterocyclic compounds,⁹ herein we report

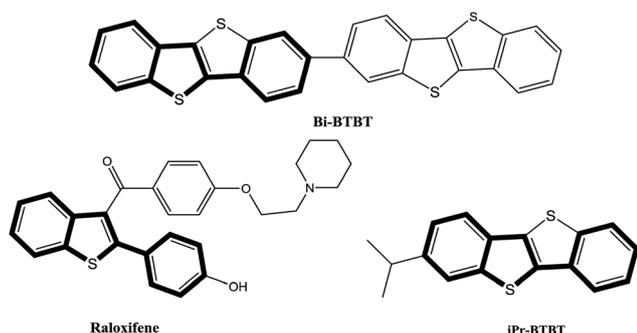
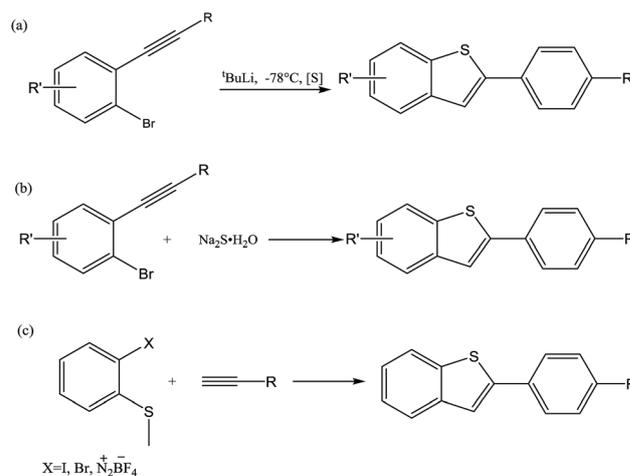


Fig. 1 Selected pharmaceutical and biologically active 2-substituted benzo[*b*]thiophenes.

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Scheme 1 Selected examples of the commonly used synthetic methods to prepare 2-substituted benzo[*b*]thiophenes.



the palladium-catalyzed synthesis of 2-substituted benzo[*b*]thiophenes using 2-halothiophenols and phenylacetylenes as starting materials.

Results and discussion

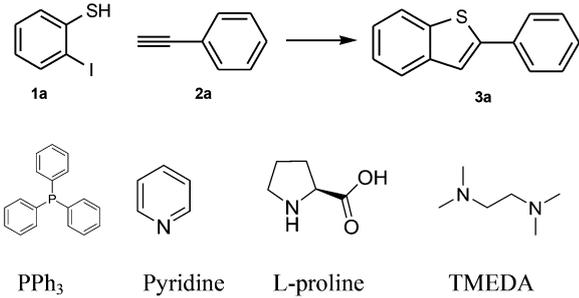
Our investigation started with the model substrates 2-iodothiophenol **1a** and phenylacetylene **2a**. As shown in Table 1, a variety of transition metal salts were tested and palladium acetate exhibited the best catalytic ability with a yield of 34% (Entries 1–8). Moreover, other metals including nickel, cobalt, and iron salts gave much less yields of 4%, 8%, and 5%, respectively (Entries 3, 4, and 5). In the case of copper salt, the coupling product between the alkyne was found to be the major product (Entries 1 and 2).¹⁰ The blank experiment further confirmed that no reaction occurred in the absence of a catalyst

and ligand (Entry 9). Furthermore, silver salts were found to be beneficial to the reaction. In addition, AgTFA was shown to be the best one with a yield of 71% (Entries 10–12). Moreover, the ligand was also proved to promote the catalysis by up to 81% yield in the case of TMEDA (Entries 13–16). Lastly, screening the reaction temperature and catalyst loading indicated that 110 °C and 15 mol% catalyst were optimal for the reaction with yields up to 87% (Entries 17–23). Hence, it was concluded that the best conditions were 15 mol% Pd(OAc)₂, 20 mol% TMEDA, and 1.1 equiv. AgTFA in DMF at 110 °C for 24 h.

With the optimal reaction conditions in hand, we then explored the scope of 2-iodothiophenols and alkynes. As shown in Scheme 2, different alkynes with either electron-withdrawing groups (–F, –Br) or electron-donating groups (–*t*Bu, –OCH₃) can generate the desired products in yields from 41 to 78% under the standard conditions (**3b–3e**). Moreover, 2-iodothiophenols with various functional groups (such as –F, –Cl, and –CF₃) can also be successfully applied in this method and novel compounds such as **3g**, **3h**, and **3i** were also obtained in around 50% yield, which have great potential, especially in pharmaceutical compounds and materials synthesis.

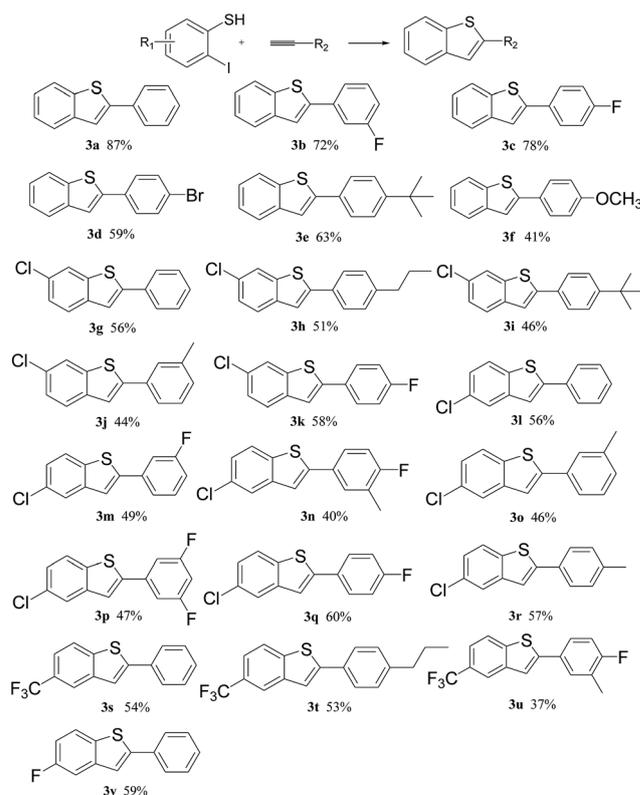
To further explore the potential application of this method, the reaction of **1a** and **2a** was scaled up to 10.0 mmol in a 50 mL one-necked flask and the same efficiency was maintained (Scheme 3). The desired product can be obtained in 75% yield, which confirms its suitability for large-scale reaction.

Table 1 Optimization of the reaction conditions^a



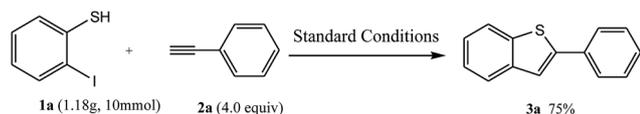
| Entry | Catalyst | Ligand | Additive | T/°C | Yield ^b (%) |
|-----------------|--------------------------------------|------------------|---------------------------------|------|------------------------|
| 1 | CuI | — | — | 100 | 14 |
| 2 | CuCl | — | — | 100 | Trace |
| 3 | NiCl ₂ | — | — | 100 | 4 |
| 4 | CoCl ₂ ·6H ₂ O | — | — | 100 | 8 |
| 5 | FeSO ₄ | — | — | 100 | 5 |
| 6 | Pd(PPh ₃)Cl ₂ | — | — | 100 | 28 |
| 7 | Pd(PPh ₃) ₄ | — | — | 100 | 21 |
| 8 | Pd(OAc) ₂ | — | — | 100 | 34 |
| 9 | — | — | — | 100 | Trace |
| 10 | Pd(OAc) ₂ | — | AgOAc | 100 | 68 |
| 11 | Pd(OAc) ₂ | — | Ag ₂ CO ₃ | 100 | 66 |
| 12 | Pd(OAc) ₂ | — | AgTFA | 100 | 71 |
| 13 | Pd(OAc) ₂ | PPh ₃ | AgTFA | 100 | 75 |
| 14 | Pd(OAc) ₂ | TMEDA | AgTFA | 100 | 81 |
| 15 | Pd(OAc) ₂ | L-Proline | AgTFA | 100 | 69 |
| 16 | Pd(OAc) ₂ | Pyridine | AgTFA | 100 | 72 |
| 17 | Pd(OAc) ₂ | TMEDA | AgTFA | 105 | 82 |
| 18 | Pd(OAc) ₂ | TMEDA | AgTFA | 110 | 85 |
| 19 | Pd(OAc) ₂ | TMEDA | AgTFA | 115 | 84 |
| 20 | Pd(OAc) ₂ | TMEDA | AgTFA | 120 | 84 |
| 21 ^c | Pd(OAc) ₂ | TMEDA | AgTFA | 110 | 87 |
| 22 ^d | Pd(OAc) ₂ | TMEDA | AgTFA | 110 | 87 |
| 23 ^e | Pd(OAc) ₂ | TMEDA | AgTFA | 110 | 86 |

^a Reaction conditions: 2-iodothiophenol **1a** (0.5 mmol), phenylacetylene **2a** (4 equiv.), catalyst (10 mol%), ligand (20 mol%), and additive (1.1 equiv.) in DMF (2 mL) under N₂ for 24 h. ^b Isolated yields. ^c Pd(OAc)₂ (15 mol%). ^d Pd(OAc)₂ (20 mol%). ^e Pd(OAc)₂ (25 mol%).

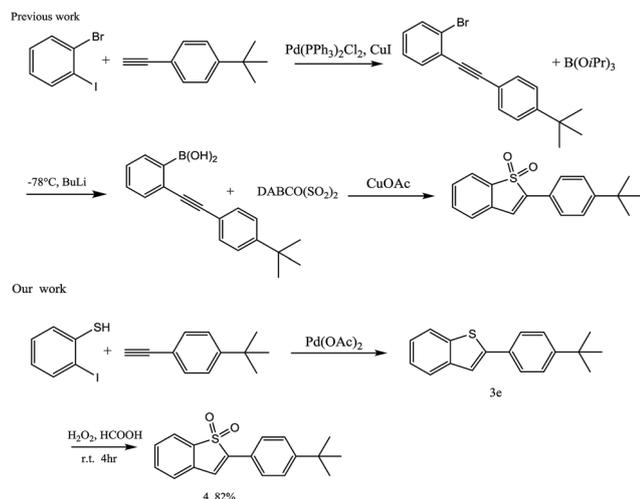


Scheme 2 The synthesis of different benzo[*b*]thiophenes.^{a,b} ^a Reaction conditions: 2-iodothiophenol (0.5 mmol), alkyne (4 equiv.), Pd(OAc)₂ (15 mol%), TMEDA (20 mol%), and AgTFA (1.1 equiv.) in DMF (2 mL) under N₂ at 110 °C for 24 h. ^b Isolated yield.





Scheme 3 The gram scale reaction performed under the standard conditions.



Scheme 4 A comparison of the synthesized compounds **4** and **5**.



Fig. 2 Images of compound **4** in MeCN ($1.0 \times 10^{-5} \text{ mol L}^{-1}$) and the solid state under sunlight (left) and under 360 nm UV light (right).

Furthermore, 2-(4-(*tert*-butyl)phenyl)benzo[*b*]thiophene 1,1-dioxide **4** can be easily obtained after adding H_2O_2 into **3e** at room temperature, which could shorten one step and uses milder reaction conditions when compared with those reported in the literature (Scheme 4).¹¹ Furthermore, Fig. 2 shows images of the compound **4** in MeCN and the solid state under sunlight (left) and under 360 nm UV light (right). Fig. 3 displays the absorption and emission spectra of compound **4** in MeCN ($1.0 \times 10^{-5} \text{ mol L}^{-1}$). Note that compound **4** in MeCN exhibited an

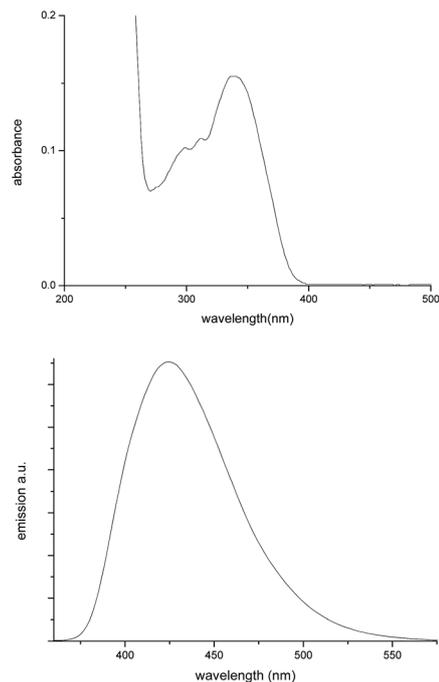
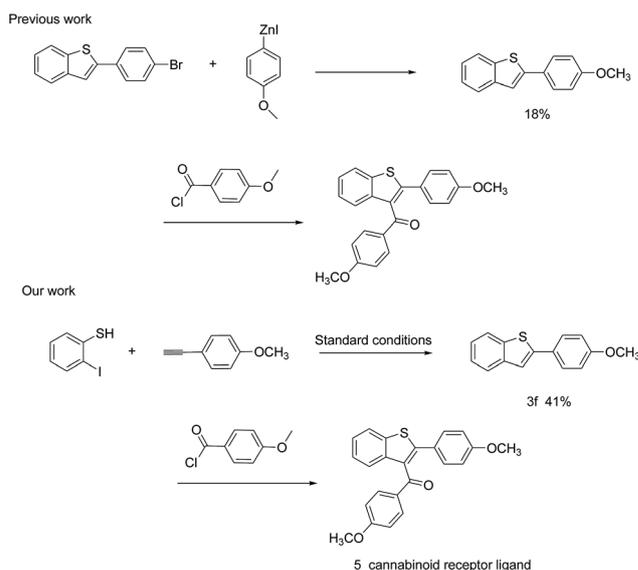
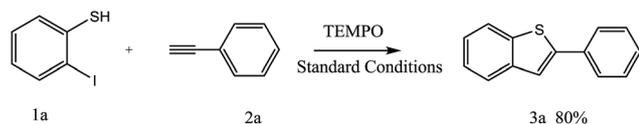


Fig. 3 The absorption and emission spectra of compound **4** in MeCN ($1.0 \times 10^{-5} \text{ mol L}^{-1}$).

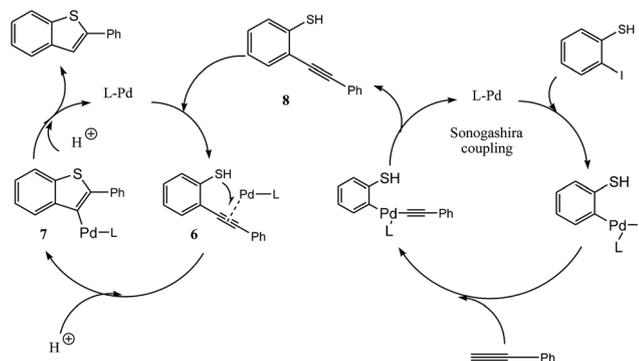
unexpectedly high fluorescence quantum yield of up to 1 that was measured using quinine sulfate as a standard (quinine in $5.0 \times 10^{-5} \text{ mol L}^{-1}$ sulfuric acid), which would show broad prospects for use in organic light-emitting diodes (OLEDs).

Besides this, we also tried to synthesize the benzothiophene derivative (4-methoxyphenyl)(2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl)methanone **5** using product **3f** as the starting material in a higher yield than that reported in the literature. Compound **5** has been reported as a new cannabinoid receptor ligand and an intermediate of thrombin inhibitor.¹²





Scheme 5 The radical/electron trapping experiment.



Scheme 6 The proposed reaction pathway.

To explore the reaction pathway, a radical trapping experiment was carried out by the addition of a typical radical scavenger TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl). Almost the same yield (80%) indicated that the reaction did not involve a radical intermediate (Scheme 5). Furthermore, the intermediate 2-(phenylethynyl)benzenethiol **8** was observed by GC/MS in the reaction between 2-iodothiophenol and phenylacetylene after 3 hours.

Based on the experimental and literature data, we proposed a reaction pathway for the palladium-catalyzed synthesis of 2-substituted benzo[*b*]thiophenes from 2-halophenols and alkynes, which consists of two steps: the Sonogashira coupling of 2-halothiophenol with the alkyne and the subsequent cyclization of 2-alkynylthiophenol (Scheme 6). First, the Pd-catalyzed Sonogashira coupling of 2-halothiophenol with the alkyne affords intermediate **8**. Then, coordination of Pd with intermediate **8** may provide complex **6**, whose subsequent addition to the C–C triple bond gave intermediate **7**. Protonation of intermediate **7** results in the formation of benzo[*b*]thiophene and the regenerated Pd-catalyst.

Conclusions

In summary, we developed an efficient catalytic system using 2-iodothiophenols as the starting material for the synthesis of a variety of 2-substituted benzo[*b*]thiophenes. This protocol involves the following advantages: easily available starting materials and simple operations with moderate to good yields, and will contribute a new optional route for the construction the benzo[*b*]thiophene ring. Moreover, the application of this method was considered as an example by the synthesis of 2-(4-(*tert*-butyl)phenyl)benzo[*b*]thiophene 1,1-dioxide and (4-methoxyphenyl)(2-(4-methoxyphenyl)benzo[*b*]thiophen-3-yl) methanone, which exhibit a fluorescence quantum yield up to 1 and use as a cannabinoid receptor ligand, respectively.

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Notes and references

- For selected recent examples, see: (a) L. Berrade, B. Aisa, M. Ramirez, S. Galiano, S. Guccione, L. Moltzau, F. Levy, F. Nicoletti, G. Battaglia, G. Molinaro, I. Aldana, A. Monge and S. Perez-Silanes, *J. Med. Chem.*, 2007, **50**, 5644; (b) A. Venturelli, D. Tondi, L. Cancian, F. Morandi, G. Cannazza, B. Segatore, F. Prati, G. Amicosante, B. Shoichet and M. Costi, *J. Med. Chem.*, 2011, **54**, 3086; (c) R. Romagnoli, P. Baraldi, M. Carrion, C. Cara, D. Preti, F. Fruttarolo, M. Pavani, M. Tabrizi, M. Tolomeo, S. Grimaudo, A. Cristina, J. Balzarini, J. Hadfield, A. Brancale and E. Hamel, *J. Med. Chem.*, 2007, **50**, 2273; (d) J. Chabert, B. Marquez, L. Neville, L. Joucla, S. Broussous, P. Bouhours, E. David, S. Pellet-Rostaing, B. Marquet, N. Moreau and M. Lemaire, *Bioorg. Med. Chem.*, 2007, **15**, 4482.
- (a) J. Gao, R. Li, L. Li, Q. Meng, H. Jiang, H. Li and W. Hu, *Adv. Mater.*, 2007, **19**, 3008; (b) V. Bren, A. Dubonosov, V. Minkin, A. Tsukanov, T. Gribanova, E. Shepelenko, Y. Revinsky and V. Rybalkin, *J. Phys. Org. Chem.*, 2007, **20**, 917; (c) T. Zhang, J. O'toole and C. Proctor, *J. Sulfur Chem.*, 1999, **22**, 1.
- (a) M. Abe, T. Mori, I. Osaka, K. Sugimoto and K. Takimiya, *Chem. Mater.*, 2015, **27**, 5049; (b) B. Fox and S. Olson, *J. Med. Chem.*, 2015, **58**, 5256; (c) G. Schweicher, V. Lemaure, Y. Geerts and Z. Bao, *Adv. Mater.*, 2015, **27**, 3066; (d) E. Yamaguchi, C. Wang, A. Fukazawa, T. Higashiyama and S. Yamaguchi, *Angew. Chem., Int. Ed.*, 2015, **54**, 4539; (e) E. Amir, M. Murai and C. Hawker, *Chem. Sci.*, 2014, **5**, 4483; (f) X. Peng, J. Deng and H. Xu, *RSC Adv.*, 2013, **3**, 24146; (g) S. Kawai, T. Nakashima and T. Kawai, *J. Mater. Chem.*, 2009, **19**, 3606; (h) S. Chen, W. Li, X. Li and W. Zhu, *RSC Adv.*, 2015, **5**, 87626.
- (a) H. Sashida, K. Sadamori and T. Tsuchiya, *Synth. Commun.*, 1998, **28**, 713; (b) Y. Wang, S. Parkin and M. Watson, *Org. Lett.*, 2008, **10**, 4421; (c) K. Takimiya, Y. Konda, H. Ebata, N. Niihara and T. Otsubo, *J. Org. Chem.*, 2005, **70**, 10569.
- (a) T. Kashiki, S. Shinamura, M. Kohara, E. Miyazaki, K. Takimiya, M. Ikeda and H. Kuwabara, *Org. Lett.*, 2009, **11**, 2473; (b) L. Sun, C. Den, R. Tang and X. Zhang, *J. Org. Chem.*, 2011, **76**, 7546.
- L. Gao, B. Chang, W. Qiu, L. Wang and X. Fu, *Adv. Synth. Catal.*, 2016, **358**, 1202.
- (a) K. Sonogashira, Y. Tohda and N. Hagihara, *Tetrahedron Lett.*, 1975, **16**, 4467; (b) H. Diek and F. Heck, *Organomet. Chem.*, 1975, **93**, 295; (c) L. Cassar, *Organomet. Chem.*, 1975, **93**, 253; (d) M. Miller and C. Johnson, *J. Org. Chem.*, 1997,



- 62, 1582; (e) S. Thorand and N. Krause, *J. Org. Chem.*, 1998, **63**, 8551; (f) A. Chandra and B. Singh, *Tetrahedron*, 2008, **64**, 11680.
- 8 (a) T. Magdesieva, O. Nikitin, A. Yakimansky, M. Goikhman and I. Podeshvo, *Electrochim. Acta*, 2011, **56**, 3666; (b) L. Wu, X. Shi, X. Xu, F. Liang and G. Huang, *J. Chem. Sci.*, 2011, **123**, 697; (c) Y. Liang, S. Tang, X. Zhang, L. Mao, Y. Xie and J. Li, *Org. Lett.*, 2006, **8**, 3017.
- 9 (a) L. Yu and X. Zhou, *Eur. J. Org. Chem.*, 2010, **29**, 5560; (b) F. Ke, Z. Li and X. Zhou, *Org. Lett.*, 2011, **13**, 454; (c) H. Deng, Z. Li and X. Zhou, *Chem.–Eur. J.*, 2012, **18**, 4840; (d) R. Che, Z. Li and X. Zhou, *Chem.–Eur. J.*, 2014, **20**, 7258.
- 10 (a) C. Meng and R. Yuan, *ACS Catal.*, 2015, **5**, 3760; (b) P. Röse, K. Harms and G. Hilt, *J. Org. Chem.*, 2015, **80**, 7311; (c) Y. Liu and J. Wan, *Tetrahedron Lett.*, 2013, **54**, 3953.
- 11 (a) J. Liu, A. Narita, S. Osella, W. Zhang, D. Schollmeyer, D. Beljonne, X. Feng and K. Müllen, *J. Am. Chem. Soc.*, 2016, **138**, 2602; (b) R. Mao, D. Zheng, H. Xia and J. Wu, *Org. Chem. Front.*, 2016, **3**, 693.
- 12 (a) J. Romero-Parra, J. Mella-Raipa, M. Torres, R. Escobar, M. Faúndez and C. David Pessoa-Mahana, *Eur. J. Med. Chem.*, 2016, **124**, 17; (b) D. J. Sall, D. L. Bailey, J. A. Bastian and M. Zhang, *J. Med. Chem.*, 2000, **43**, 649.

