Tetrahedron Letters 55 (2014) 6274–6276

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Proton transfer-assisted host–guest complexation between a difunctional pillar[5]arene and amine-based guests

Bin Hua, Guocan Yu *

Department of Chemistry, Zhejiang University, Hangzhou 310027, PR China

ARTICLE INFO

Article history:
Received 29 June 2014
Revised 12 September 2014
Accepted 19 September 2014
Available online 28 September 2014

Keywords:
Pillararene
Proton transfer
Host–guest system
Supramolecular chemistry

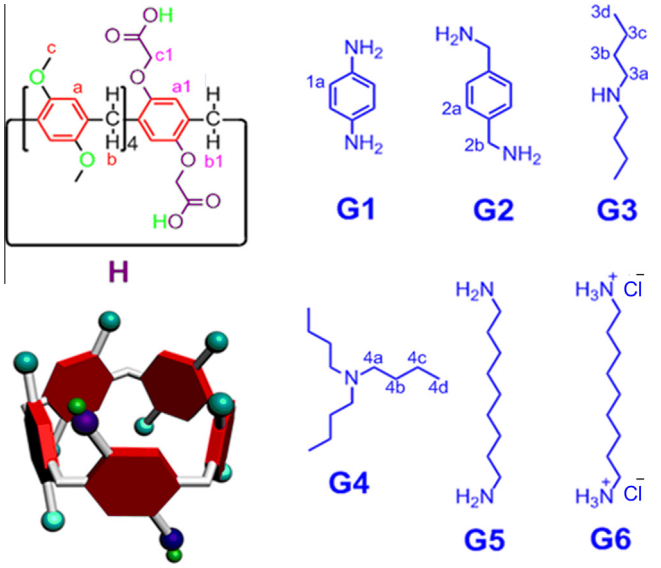
ABSTRACT

Proton transfer from a difunctional pillar[5]arene containing two carboxylic acid moieties to amine-based guests occurs in the host–guest complexation. The binding affinities are enhanced effectively due to the existence of electrostatic interactions.

The arrival of any novel generation of macrocycles can accelerate the development of supramolecular chemistry and provide new opportunities for materials science. Macrocycles such as crown ethers,[1] cyclodextrins,[2] calixarenes,[3] and cucurbiturils[4] have attracted much interest over the past few decades. Pillar[*n*]arenes, mainly including pillar[5]arenes[5] and pillar[6]arenes,[6] are a new family of macrocyclic host molecules. They have acted as useful platforms for the fabrication of various interesting supramolecular systems, including cyclic dimers,[7] liquid crystals,[8] chemosensors,[9] supramolecular polymers,[10] drug delivery systems,[11] cell glue,[12] transmembrane channels[13], and selective adsorption porous material.[14]

The amine derivatives are present in a vast number of naturally occurring complex structures, such as proteins, peptides, and alkaloids, which have been widely utilized in supramolecular chemistry and aroused remarkable interests. Moreover, amines are extremely useful building blocks in organic synthesis, and they serve as precursors for many valuable compounds, including pharmaceuticals, dyes, agrochemicals, and organic materials. However, most amine derivatives exhibit slight toxicity, which limit their applications to some extent. For example, methylhexanamine and tuaminoheptane are stimulants banned by the World Anti-Doping Agency. With the aim to prepare large supramolecular systems efficiently from small building blocks, as well as to encapsulate and detect the presence of amine derivatives, searching for novel host–guest molecular recognition motifs with high binding affinities is desired by the design of optimized hosts (Scheme 1).

Herein, a difunctional pillar[5]arene bearing two carboxyl units (**H**)[15] was employed as a macrocyclic host to investigate the host–guest complexation with various amine-based guests



Scheme 1. Chemical structures of a difunctional pillar[5]arene (**H**) and the amine-based guests (**G1**–**G6**).

* Corresponding author.
E-mail address: guocanyu@zju.edu.cn (G. Yu).

http://dx.doi.org/10.1016/j.tetlet.2014.09.092
0040-4039/

(**G1**–**G6**) both in solution and in the solid state by using ^{1}H NMR, isothermal titration calorimetric (ITC), 2D NOESY and X-ray crystallographic analysis. Proton transfer from the carboxylic acid groups to the amine units occurred in the principle of undergoing an acid–base reaction, resulting in the achievement of electrostatic interactions, which played a significant role in the host–guest complexation. Furthermore, the influences of the shapes and basicities of the guests on the binding affinities were studied.

The host–guest complexation was firstly investigated by ^{1}H NMR spectroscopy in a mixture of chloroform-*d* and methanol-d_4 (1:1, v/v). The ^{1}H NMR spectra of the host–guest complexes showed only one set of peaks, indicating fast-exchange complexation between **H** and **G** (**G1**–**G4**) on the ^{1}H NMR time scale. Compared with the spectrum of dibutylamine (**G3**) shown in Figure 1e, the signals related to protons H_{3a}, H_{3b}, H_{3c} and H_{3d} shifted upfield significantly ($\Delta\delta$ = −0.61, −0.79, −0.69 and −0.27 ppm for H_{3a}, H_{3b}, H_{3c} and H_{3d}, respectively) in the presence of equimolar **H** (Fig. 1d). This phenomenon demonstrated that **G3** threaded deeply into the cavity of **H** and protons on **G3** were shielded by the electron-rich cyclic structure upon formation of an inclusion complex.[5b] Meanwhile, broadening effects for the peaks corresponding to the protons on **G3** were observed due to complexation dynamics.[6e] On the other hand, the resonances of protons H_{a1}, H_b and H_c on **H** exhibited slight downfield shifts, whereas the peaks of protons H_{a1}, H_b, and H_c shifted upfield upon complexation with **G3**. These observations indicated that host–guest interactions between **H** and **G3** were achieved successfully, associated with the formation of a stable inclusion complex.[5h] Similar complexation-induced chemical shift changes were observed for **G1**, **G2,** and **G4** (Figs. 1 and S1–S4), indicating the host–guest complexation between **H** and **G1** (**G2** or **G4**). It should be noted that the signals related to H_{4a} on **G4** and H_{1a} on **G1** shifted downfield upon the addition of equimolar **H** (Figs. 1b and S1). These chemical shift changes were caused by the protonation of the nitrogen atoms on the guests.[16] Proton transfer from the carboxylic acid groups to the amine units on the guests occurred in the principle of undergoing an acid-base reaction.[15] Mainly driven by the electrostatic interactions between **H** and the guests, stable 1:1 [2]pseudorotaxane-type inclusion complexes formed.

2D NOESY NMR spectroscopy was utilized to study the relative positions of the components in host–guest inclusion complexes (Figs. S9–S11). As shown in Figure S10, nuclear Overhauser effect (NOE) correlations between the resonances corresponding to the aromatic protons (H_a and H_{a1}) of the pillar[5]arene framework of **H** and protons H_{3a}, H_{3b}, H_{3c}, and H_{3d} on **G3** were observed, demonstrating that **G3** was threaded into the cavity of **H**. Similarly, NOE correlations were also observed for host–guest systems **H**⊃**G2** and **H**⊃**G4**, verifying the formation of threaded inclusion complexes.

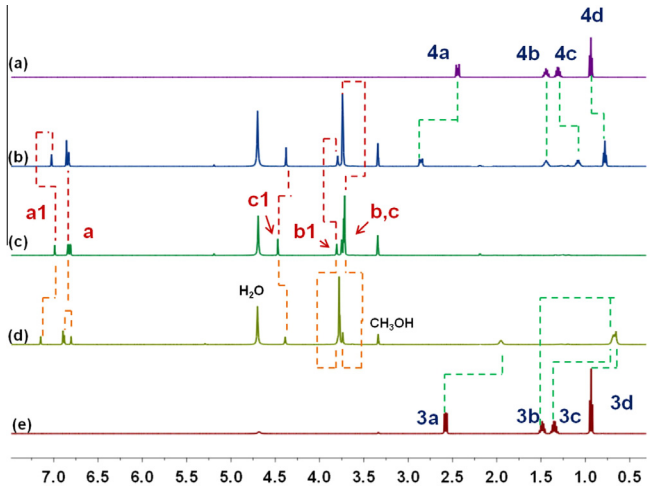


Figure 1. ^{1}H NMR spectra (500 MHz, chloroform-*d*/methanol-d_4 = 1:1, 295 K): (a) **G4** (5.00 mM); (b) **H** (5.00 mM) and **G4** (5.00 mM); (c) **H** (5.00 mM); (d) **H** (5.00 mM) and **G3** (5.00 mM); and (e) **G3** (5.00 mM).

Moreover, ITC measurements were performed to determine association constants as well as thermodynamic parameters, such as enthalpy changes ($\Delta H°$) and entropy changes ($\Delta S°$). In all cases, the titration data were well fitted by computer simulation using the 'one set of binding sites' model, demonstrating 1:1 complexations between **H** and the guests (Figs. S12–S16). Notably, the thermodynamic data (**G1**–**G4**) listed in Table 1 have the same feature ($\Delta H° < 0$; $T\Delta S° < 0$; $|\Delta H°| > |T\Delta S°|$), indicating that these complexations are all driven by enthalpy changes.[17] The association constant of **H**⊃**G3** was determined to be $(3.03 \pm 0.151) \times 10^5$ M^{-1}, about 7.5 times that of **H**⊃**G4**. The reason was that tributylamine (**G4**) possessed a three-armed structure and the relatively large size inhibited its effective complexation with **H**. The corresponding cationic guest interacted with the carboxylate anion on **H** through electrostatic interaction due to the proton transfer from **H** to **G4**. One alkyl chain penetrated into the cavity of **H** in the presence of C–H···π interaction, whereas the rest of the two alkyl chains appended on the rim of the host. In comparison to **H**⊃**G1**, **H** exhibited stronger binding affinity to **G2**, because the pK_a value of *p*-xylylenediamine (**G2**) was higher than that of *p*-phenylenediamine (**G1**). The difference in pK_a values affected the proton transfer behavior, thus influencing the association constant significantly. This selectivity emphasized that proton transfer from the carboxylic acid groups to the amine units associated with the formation of salt bridge played an important role in the host–guest complexation. In order to verify this conclusion, **G6** with two cationic groups was selected as a model guest where proton transfer could not occur. Compared with that, $(3.45 \pm 0.23) \times 10^5$ M^{-1}, of **H**⊃**G5**,[15] the association constant related to **H**⊃**G6** decreased to $(1.78 \pm 0.28) \times 10^4$ M^{-1}, because proton transfer from **H** to the guest assisted the host–guest complexation for **H**⊃**G5**. It should be noted that the entropy change for **H**⊃**G6** was different from those of the other host–guest systems (Table 1), which attributed to the protonation of the amine groups, thus affecting the host–guest interactions. Moreover, undecane and *n*-decylamine (*n*-$C_{10}H_{21}NH_2$) were employed as guest molecules to demonstrate that electrostatic interactions enhanced the binding affinities of these host–guest systems effectively (Figs. S17 and S18). The binding affinity between **H** and undecane was too weak to be calculated by ITC, because proton transfer could not realize in this host–guest system. The main driving forces were C–H···π interactions, which were much weaker than the electrostatic interactions. The association constant of **H** and *n*-decylamine was calculated to be $(1.01 \pm 0.13) \times 10^5$ M^{-1}, which was lower than that of **H**⊃**G5**. The reason was that cooperative electrostatic interactions between **G5** and **H** could be achieved on both sides of the pillar[5]arene platform. These results were in good agreement with our previous work.[15]

Table 1
Association constants K_a, enthalpy changes $\Delta H°$, and entropy changes $\Delta S°$ obtained from ITC experiments for 1:1 complexes of **H** with guests **G1**–**G4**[a]

	pK_a	K_a (M^{-1})	$\Delta H°$ (cal/mol)	$\Delta S°$ (cal/mol/deg)
G1	6.17 ± 0.10	(9.93 ± 1.92)E3	−(1.05 ± 0.623)E4	−17.1
G2	9.46 ± 0.10	(5.89 ± 1.43)E5	−(1.76 ± 0.043)E4	−32.7
G3	11.0 ± 0.19	(3.03 ± 0.15)E5	−(1.61 ± 0.009)E4	−29.0
G4	9.99 ± 0.50	(4.14 ± 0.34)E4	−(1.65 ± 0.049)E4	−34.2
G5	10.9 ± 0.10	(3.45 ± 0.23)E5	−(2.51 ± 0.031)E4	−57.6
G6	/	(1.78 ± 0.28)E4	−(3.29 ± 0.35)E3	8.58

[a] Microcalorimetric titration experiments were conducted in a mixture of chloroform and methanol (1:1, v/v) at 303.15 K by titration of **G** (2.00 mM, 10 μL per injection) into the solution of **H** (0.100 mM).

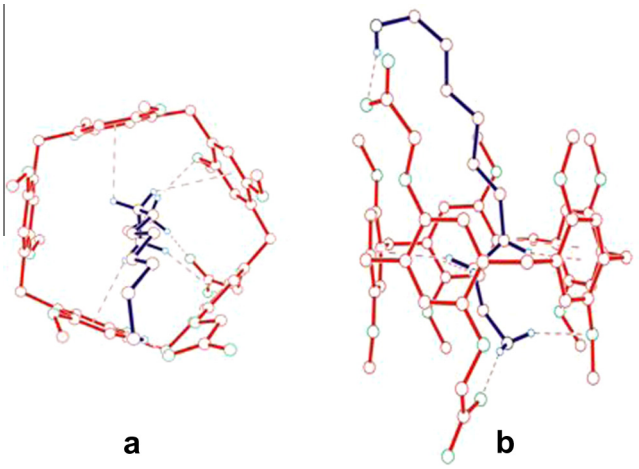


Figure 2. Ball-stick views of the crystal structure of **H**⊃**G5** (a and b). Hydrogens except the ones participating in the formation of C–H···π interactions and hydrogen bonds were omitted for clarity. The purple dotted lines indicate C–H···π interactions and hydrogen bonds.

Further evidence for the formation of host–guest complexes was obtained from ESI mass spectra. Peaks at *m*/*z* 947.2, 975.2, 968.5, and 1024.2 corresponding to [**H**⊃**G1** + H]$^+$, [**H**⊃**G2** + H]$^+$, [**H**⊃**G3** + H]$^+$ and [**H**⊃**G4** + H]$^+$, respectively, were monitored. These results further confirmed the formation of inclusion complexes in the 1:1 binding mode, in agreement with the results obtained from ITC experiments. In terms of the cavity size, the diameter of the internal cavity of **H** is 4.7 Å,[18] enabling the host to encapsulate one alkyl chain or a benzene ring.

Single crystal X-ray analysis provided convincing evidence for the proton transfer-assisted host–guest complexation process. The crystal structure of **H**⊃**G5** was obtained by slow diffusion of *iso*-propylether into its dichloromethane/methanol mixture. As shown in Figure 2, **G5** threaded into the cavity of **H** to form a [2]pseudortaxane-type inclusion complex. The length of **G5** is longer than the height of **H**, so the alkyl chain bends to make the length suitable for the host. On the other hand, the C–H···π distances were shorter than 3.05 Å, and the C–H···π angles were larger than 90°, confirming the existence of multiple C–H···π interactions between **H** and **G5**.[5c] Besides, hydrogen bonds formed between the methylene protons and the oxygen atoms of the hydroquinone moiety. Furthermore, protons transferred from the carboxyl groups to the amines, resulting in the formation of corresponding carboxylate anions and alkylammonium cations inside its cavity. The guest locates inside the cavity of **H** with ammonium groups pointing at the carboxylate anion to achieve electrostatic interactions, which plays a critical role in the formation of **H**⊃**G5** in the solid state.

In conclusion, the host–guest complexation between a difunctional pillar[5]arene (**H**) and various amine-based guests (**G1**–**G6**) with different shapes or basicities was investigated. Proton transfer from the carboxylic acid groups to the amine units occurred in the principle of undergoing an acid–base reaction associated with the achievement of electrostatic interactions, which played a significant role in the host–guest complexation. The structures and pK_a values of the guests also influenced the host–guest interactions. This novel host–guest recognition motif can be applied in the construction of mechanically interlocked molecules, such as pseudorotaxanes, rotaxanes, and catenanes.

Acknowledgments

This work was supported by the Fundamental Research Funds for the Central Universities.

Supplementary data

Supplementary data (^{1}H NMR, 2D NOESY spectra and ESI mass spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.09.092.

References and notes

1. (a) Huang, F.; Fronczek, F. R.; Gibson, H. W. *J. Am. Chem. Soc.* **2003**, *125*, 9272; (b) Huang, F.; Jones, J. W.; Slebodnick, C.; Gibson, H. W. *J. Am. Chem. Soc.* **2003**, *125*, 14458; (c) Huang, F.; Nagvekar, D. S.; Slebodnick, C.; Gibson, H. W. *J. Am. Chem. Soc.* **2005**, *127*, 484; (d) Wang, F.; Han, C.; He, C.; Zhou, Q.; Zhang, J.; Wang, C.; Li, N.; Huang, F. *J. Am. Chem. Soc.* **2008**, *130*, 11254; (e) Jiang, W.; Schäfer, A.; Mohr, P. C.; Schalley, C. A. *J. Am. Chem. Soc.* **2010**, *132*, 2309; (f) Wang, F.; Zhang, J.; Ding, X.; Dong, S.; Liu, M.; Zheng, B.; Li, S.; Zhu, K.; Wu, L.; Yu, Y.; Gibson, H. W.; Huang, F. *Angew. Chem., Int. Ed.* **2010**, *49*, 1090; (g) Dong, S.; Luo, Y.; Yan, X.; Zheng, B.; Ding, X.; Yu, Y.; Ma, Z.; Zha, Q.; Huang, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 1905; (h) Dong, S.; Zheng, B.; Xu, D.; Yan, X.; Zhang, M.; Huang, F. *Adv. Mater.* **2012**, *24*, 3191; (i) Zhang, M.; Xu, D.; Yan, X.; Chen, J.; Dong, S.; Zheng, B.; Huang, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 7011; (j) Chen, L.; Tian, Y.-K.; Ding, Y.; Tian, Y.-J.; Wang, F. *Macromolecules* **2012**, *45*, 8412; (k) Zhu, K.; Vukotic, V. N.; Loeb, S. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 2168; (l) Yan, X.; Xu, D.; Chi, X.; Chen, J.; Dong, S.; Ding, X.; Yu, Y.; Huang, F. *Adv. Mater.* **2012**, *24*, 362; (m) Tian, Y.-J.; Meijer, E. W.; Wang, F. *Chem. Commun.* **2013**, 9197; (n) Ji, X.; Yao, Y.; Li, J.; Yan, X.; Huang, F. *J. Am. Chem. Soc.* **2013**, *135*, 74.
2. (a) Harada, A. *Acc. Chem. Res.* **2001**, *34*, 456; (b) Chen, G.; Jiang, M. *Chem. Soc. Rev.* **2011**, *40*, 2254.
3. Guo, D.-S.; Liu, Y. *Chem. Soc. Rev.* **2012**, *41*, 5907.
4. Kim, K.; Selvapalam, N.; Ko, Y. H.; Park, K. M.; Kim, D.; Kim, J. *Chem. Soc. Rev.* **2007**, *36*, 267.
5. (a) Ogoshi, T.; Kanai, S.; Fujinami, S.; Yamagishi, T. A.; Nakamoto, Y. *J. Am. Chem. Soc.* **2008**, *130*, 5022; (b) Li, C.; Zhao, L.; Li, J.; Ding, X.; Chen, S.; Zhang, Q.; Yu, Y.; Jia, X. *Chem. Commun.* **2010**, 9016; (c) Zhang, Z.; Xia, B.; Han, C.; Yu, Y.; Huang, F. *Org. Lett.* **2010**, *12*, 3285; (d) Zhang, Z.; Luo, Y.; Xia, B.; Han, C.; Yu, Y.; Chen, X.; Huang, F. *Chem. Commun.* **2011**, 2417; (e) Ma, Y.; Ji, X.; Xiang, F.; Chi, X.; Han, C.; He, J.; Abliz, Z.; Chen, W.; Huang, F. *Chem. Commun.* **2011**, 12340; (f) Ogoshi, T.; Demachi, K.; Kitajima, K.; Yamagishi, T. *Chem. Commun.* **2011**, 7164; (g) Han, C.; Zhang, Z.; Yu, G.; Huang, F. *Chem. Commun.* **2012**, 9876; (h) Zhang, Z.; Han, C.; Yu, G.; Huang, F. *Chem. Sci.* **2012**, *3*, 3026; (i) Li, C.; Han, K.; Li, J.; Zhang, H.; Ma, J.; Shu, X.; Chen, Z.; Weng, L.; Jia, X. *Org. Lett.* **2012**, *14*, 42; (j) Yao, Y.; Xue, M.; Chen, J.; Zhang, M.; Huang, F. *J. Am. Chem. Soc.* **2012**, *134*, 15712; (k) Li, C.; Ma, J.; Zhao, L.; Zhang, Y.; Yu, Y.; Shu, X.; Li, J.; Jia, X. *Chem. Commun.* **2013**, 1924; (l) Li, H.; Chen, D.-X.; Sun, Y.-L.; Zheng, Y.; Tan, L.-L.; Weiss, P. S.; Yang, Y.-W. *J. Am. Chem. Soc.* **2013**, *135*, 1570; (m) Xu, J.-F.; Chen, Y.-Z.; Wu, L.-Z.; Tung, C.-H.; Yang, Q.-Z. *Org. Lett.* **2013**, *15*, 6148; (n) Dong, S.; Zheng, B.; Yao, Y.; Han, C.; Yuan, J.; Antonietti, M.; Huang, F. *Adv. Mater.* **2013**, *25*, 6864; (o) Yao, Y.; Xue, M.; Zhang, Z.; Zhang, M.; Wang, Y.; Huang, F. *Chem. Sci.* **2013**, *4*, 3667; (p) Li, Z.-Y.; Zhang, Y.; Zhang, C.-W.; Chen, L.-J.; Wang, C.; Tan, H.; Yu, Y.; Li, X.; Yang, H.-B. *J. Am. Chem. Soc.* **2014**, *136*, 8577.
6. (a) Cao, D.; Kou, Y.; Liang, J.; Chen, Z.; Wang, L.; Meier, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 9721; (b) Han, C.; Ma, F.; Zhang, Z.; Xia, B.; Yu, Y.; Huang, F. *Org. Lett.* **2010**, *12*, 4360; (c) Yu, G.; Xue, M.; Zhang, Z.; Li, J.; Han, C.; Huang, F. *J. Am. Chem. Soc.* **2012**, *134*, 13248; (d) Xue, M.; Yang, Y.; Chi, X.; Zhang, Z.; Huang, F. *Acc. Chem. Res.* **2012**, *45*, 1294; (e) Yu, G.; Han, C.; Zhang, Z.; Chen, J.; Yan, X.; Zheng, B.; Liu, S.; Huang, F. *J. Am. Chem. Soc.* **2012**, *134*, 8711; (f) Yu, G.; Zhou, X.; Zhang, Z.; Han, C.; Mao, Z.; Gao, C.; Huang, F. *J. Am. Chem. Soc.* **2012**, *134*, 19489; (g) Chen, W.; Zhang, Y.; Li, J.; Lou, X.; Yu, Y.; Jia, X.; Li, C. *Chem. Commun.* **2013**, 7956; (h) Zhang, H.; Zhao, Y. *Chem. Eur. J.* **2013**, *19*, 16862.
7. (a) Zhang, Z.; Yu, G.; Han, C.; Liu, J.; Ding, X.; Yu, Y.; Huang, F. *Org. Lett.* **2011**, *13*, 4818; (b) Liu, L.; Wang, L.; Liu, C.; Fu, Z.; Meier, H.; Cao, D. *J. Org. Chem.* **2012**, *77*, 9413.
8. Nierengarten, I.; Guerra, S.; Holler, M.; Karmazin-Brelot, L.; Barberá, J.; Deschenaux, R.; Nierengarten, J.-F. *Eur. J. Org. Chem.* **2013**, *18*, 3675.
9. Strutt, N. L.; Forgan, R. S.; Spruell, J. M.; Botros, Y. Y.; Stoddart, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 5668.
10. (a) Zhang, Z.; Luo, Y.; Chen, J.; Dong, S.; Yu, Y.; Ma, Z.; Huang, F. *Angew. Chem. Int. Ed.* **2011**, *50*, 1397; (b) Hu, X.-Y.; Wu, X.; Duan, Q.; Xiao, T.; Lin, C.; Wang, L. *Org. Lett.* **2012**, *14*, 4826.
11. Duan, Q.; Cao, Y.; Li, Y.; Hu, X.; Xiao, T.; Lin, C.; Pan, Y.; Wang, L. *J. Am. Chem. Soc.* **2013**, *135*, 10542.
12. Yu, G.; Ma, Y.; Han, C.; Yao, Y.; Tang, G.; Mao, Z.; Gao, C.; Huang, F. *J. Am. Chem. Soc.* **2013**, *135*, 10310.
13. (a) Si, W.; Chen, L.; Hu, X.-B.; Tang, G.; Chen, Z.; Hou, J.-L.; Li, Z.-T. *Angew. Chem., Int. Ed.* **2011**, *50*, 12564; (b) Hu, X.-B.; Chen, Z.; Tang, G.; Hou, J.-L.; Li, Z.-T. *J. Am. Chem. Soc.* **2012**, *134*, 8384.
14. Zhang, Z.; Zhao, Q.; Yuan, J.; Antonietti, M.; Huang, F. *Chem. Commun.* **2014**, 2595.
15. Yu, G.; Hua, B.; Han, C. *Org. Lett.* **2014**, *16*, 2486.
16. (a) Capici, C.; Gattuso, G.; Notti, A.; Parisi, M. F.; Pappalardo, S.; Brancatelli, G.; Geremia, S. *J. Org. Chem.* **2012**, *77*, 9668; (b) Brancatelli, G.; Gattuso, G.; Geremia, S.; Notti, A.; Pappalardo, S.; Parisi, M. F.; Pisagatti, I. *Org. Lett.* **2014**, *16*, 2354.
17. Wei, P.; Yan, X.; Li, J.; Ma, Y.; Huang, F. *Chem. Commun.* **2013**, *49*, 1070.
18. Han, C.; Zhang, Z.; Chi, X.; Zhang, M.; Yu, G.; Huang, F. *Acta Chim. Sinica* **2012**, *70*, 1775.