Organic LETTERS

Letter

pubs.acs.org/OrgLett

Activation-Enabled Syntheses of Functionalized Pillar[5]arene Derivatives

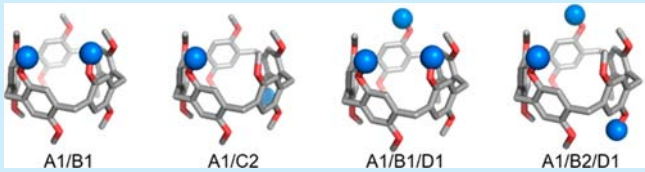
Jie Han,[†,‡] Xisen Hou,[†] Chenfeng Ke,[†] Huacheng Zhang,[†] Nathan L. Strutt,[†] Charlotte L. Stern,[†] and J. Fraser Stoddart*[,†]

[†]Department of Chemistry, Northwestern University, 2145 Sheridan Road, Evanston, Illinois 60208-3113, United States

[‡]College of Chemistry, Nankai University, Tianjin 300071, China

Supporting Information

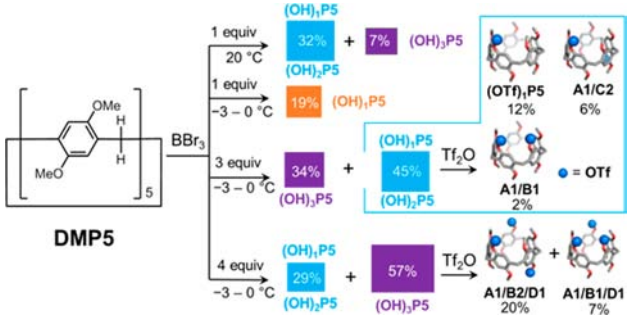
ABSTRACT: A series of regioselective di- and trifunctionalized pillar[5]arene derivatives have been synthesized by a deprotection-followed-by-activation strategy, and their constitutions have been established as a result of having access to their solid-state structures. De-*O*-methylation occurs in a stepwise manner at lower temperatures under kinetic control, affording the desired oligo-substituted pillar[5]arene derivatives. In addition, the regioisomers of these derivatives can be isolated by installing triflate groups on the free hydroxyl groups.



Macrocyclic compounds, such as cyclodextrins,[1] crown ethers,[2] cucurbiturils,[3] calixarenes,[4] and pillar[*n*]arenes,[5] have been developed as host molecules to bind selectively a variety of guests, based on noncovalent bonding interactions, e.g., hydrophobic bonding, donor−acceptor interactions, hydrogen bonding, electrostatic interactions, halogen bonding, and van der Waals interactions. Chemical modification of these macrocyclic compounds enables the installation of functional groups which enhance their ability to express molecular recognition and promote their uses in areas as diverse as molecular sensing,[6] molecular electronics,[7] and drug delivery.[8] Despite success[5b,9] in synthesizing mono- and per-substituted macrocycles, the development of approaches to the regioselective oligo-substitution of macrocycles remains a considerable challenge.

Among these macrocycles, pillar[5]arene (**P5**)—which is composed of five hydroquinone units bridged by methylene groups at their *para* positions—has attracted considerable attention since its introduction by Ogoshi et al.[5a] in 2008, on account of its facile synthesis[10] and its ability to bind cationic[11] and neutral molecules,[12] in addition to its applications in the production of supramolecular assemblies and hybrid materials.[13] A number of synthetic strategies have been developed that make it possible to obtain regioselectively mono-, di-, and tetrafunctionalized **P5** derivatives. These strategies include (i) direct deprotection,[9b,14] (ii) cocyclization,[10a,b,13c] (iii) oxidation-followed-by-reduction,[15] and (iv) *in situ* cyclization-followed-by-deprotection[16] protocols. Among these protocols, the direct deprotection of the alkoxyl groups on **P5** can, in principle, provide all of the possible regioisomers. In practice, however, this strategy was accompanied by challenges, when it came to separations and purifications, for the simple reason that these regioisomers exhibit almost identical properties during column chromatography. Up until now, chromatographic separation has been employed mainly in the preparation of monofunctionalized **P5**. Herein, we report the syntheses (Scheme 1) and solid-state structures of a series of di- and tritriflated **P5** regioisomers by means of a deprotection-followed-by-activation strategy. Thus, de-*O*-methylation, in tandem with triflation of the 1,4-dimethoxypillar[5]arene (**DMP5**), has led to the separation and isolation of four regioisomers in reasonable amounts, i.e., percentage yields in the range of 2−20%.

Scheme 1. Synthesis of Mono-, Di-, and Trifunctionalized Pillar[5]arenes



De-*O*-methylation of **DMP5** yields consecutively the monohydroxylated pillar[5]arene **(OH)$_1$P5**, the dihydroxylated pillar[5]arene **(OH)$_2$P5**, the trihydroxylated pillar[5]arene **(OH)$_3$P5**, and all the way up to the perhydroxylated pillar[5]arene **(OH)$_{10}$P5**. In the ideal situation, where de-*O*-methylation occurs in a stepwise manner, varying the stoichiometry of the deprotecting reagent can, in principle, enrich selectively the desired oligo-substituted **P5** derivatives.

Received: May 14, 2015
Published: June 17, 2015

DOI: 10.1021/acs.orglett.5b01418
Org. Lett. 2015, 17, 3260−3263

Table 1. Summary of Reaction Conditions and Isolated Yields of Di- and Trifunctionalized Pillar[5]arenes Obtained by a Deprotection-Followed-by-Activation Strategy

entry	[DMP5]:[BBr_3]	temperature (°C)	time (h)	yield (%)[a] $(OTf)_1P5$	$(OTf)_2P5$	$(OTf)_3P5$	DMP5 recycled (%)
1	1:1	20	1	18	11[c]	6[e]	50
2	1:1	−3−0	1	8[b]	trace	trace	83
3	1:1	−20	1	1[b]	trace	trace	90
4	1:1	−3−0	2	18[b]	trace	trace	67
5	1:2	−3-0	2	38	26[c] **A1/C2** (5)[d] **A1/B1** (3)[d]	5[f]	15
6	1:3	−3−0	2	12	42[c] **A1/C2** (6)[d] **A1/B1** (2)[d]	21[e] **A1/B2/D1** (9)[d] **A1/B1/D1** (4)[d]	0
7	1:4	−3−0	2	2	26[c] **A1/C2** (4)[d] **A1/B1** trace	46[e] **A1/B2/D1** (20)[d] **A1/B1/D1** (7)[d]	0

[a]Overall yield of the two-step reaction. The isolated percentage yields of the regioisomers are shown in parentheses. [b]Yield of $(OH)_1P5$. [c]Yield of all isomers of $(OTf)_2P5$. [d]Yield of single regioisomer. [e]Yield of the all isomers of $(OTf)_3P5$. [f]Yield of $(OH)_3P5$.

In practice, de-*O*-methylation of **DMP5** with 1 equiv of BBr_3 in $CHCl_3$ at 20 °C afforded (Figure S3) a mixture of $(OH)_1P5$, $(OH)_2P5$, and $(OH)_3P5$. Although $(OH)_3P5$ could be isolated by silica gel chromatography, the separation of $(OH)_2P5$ from $(OH)_1P5$ is not as easy to achieve since both species possess nearly identical polarities and solubilities. In order to have a good understanding of the proportions of $(OH)_1P5$, $(OH)_2P5$, and $(OH)_3P5$, we attempted to separate each regioisomeric mixture by means of appending bulky substituents onto the hydroxyl groups. Since the versatility of organotriflate reagents has been demonstrated previously in nucleophilic substitutions[17] and various coupling reactions,[18] we sought to transform the mixture of $(OH)_1P5$ and $(OH)_2P5$ to the mono- and ditriflate derivatives of **P5**, namely, $(OTf)_1P5$ and $(OTf)_2P5$, by reacting the hydroxylated compounds with trifluoromethanesulfonic anhydride. The larger difference in R_f values between $(OTf)_1P5$ and $(OTf)_2P5$, as compared with the corresponding hydroxylated pillararenes, permitted their isolation by silica gel column chromatography. Since the triflation takes place efficiently in ∼85% yield, the isolated yields of the triflated products should closely reflect those of the corresponding $(OH)_1P5$, $(OH)_2P5$, and $(OH)_3P5$.

De-*O*-methylation of **DMP5** with 1 equiv of BBr_3 at 20 °C, followed by triflation (Table 1, entry 1), afforded $(OTf)_1P5$, $(OTf)_2P5$, and $(OTf)_3P5$ in 18%, 11%, and 6% yields, respectively. When de-*O*-methylation was carried out just below 0 °C (Table 1, entry 2), $(OH)_1P5$ (8% yield) was the major product, while only trace amounts of $(OH)_2P5$ and none of the $(OH)_3P5$ were detected by thin layer chromatography. On lowering the reaction temperature to −20 °C, the deprotection was slowed down considerably (Table 1, entry 3). These results confirm that de-*O*-methylation occurs under kinetic control. Decreasing the reaction temperature reduces the propensity for unwanted side reactions and enables the deprotection to take place in a stepwise manner. Increasing the reaction time to 2 h led (Table 1, entry 4) to the efficient production of $(OH)_1P5$. By comparing the results in entries 1−4 in Table 1, it is found that the reaction conditions in entry 4 are the best to control the yield and regioselectivity. The effect of the stoichiometry of the deprotecting reagent (BBr_3) on the results was investigated under the same reaction conditions. As expected, increasing the amount of BBr_3 could enhance the formation of both $(OTf)_2P5$ and $(OTf)_3P5$. For example, adding 2 equiv of BBr_3 to the reaction mixture (Table 1, entry 5) increases the production of $(OTf)_2P5$, affording a 26% yield, while increasing the amount of BBr_3 to 3 equiv (Table 1, entry 6) raises the yield[19] of $(OTf)_2P5$ to 42%. When the amount of BBr_3 is increased yet further to 4 equiv (Table 1, entry 7), the yield of $(OTf)_3P5$ rises to 46%, and the yields of $(OTf)_1P5$ and $(OTf)_2P5$ decrease significantly. It is noteworthy that, upon addition of 3 or 4 equiv of BBr_3, all the **DMP5** is consumed within 2 h and a small fraction of methylated **P5** derivatives is observed.

The introduction of OTf groups results in separation of not only $(OTf)_1P5$ and $(OTf)_2P5$ but also two different regioisomers of $(OTf)_2P5$. In principle, $(OTf)_2P5$ can exist (Figure S1) as five possible regioisomers,[16] namely, **A1/A2**, **A1/B2**, **A1/B1**, **A1/C2**, and **A1/C1**. In the mixture of $(OTf)_2P5$, one regioisomer with an R_f value of 0.70 on thin layer chromatography (SiO_2:CH_2Cl_2/hexanes = 1/1) can be isolated in 2% yield by column chromatography on silica gel and further recrystallization from CH_2Cl_2/hexanes (Table 1, entry 6). The ^1H NMR spectrum (Figure 1a) of this isomer shows ten aromatic, five methylene,[20] and eight methoxyl protons resonances, indicating a lack of symmetry in the molecule, pointing to either **A1/B1** or **A1/C1** as the two possible regioisomers. Since it was far from straightforward to assign the constitution to this regioisomer by either 1D or 2D NMR spectroscopy, crystals of it, suitable for single X-ray diffraction, were obtained by slow vapor diffusion of hexanes into a CH_2Cl_2 solution at room temperature. The solid-state structure (Figure S27) reveals that the constitution of this regioisomer is **A1/B1**. The cavity size of **A1/B1** is very similar to that[5a] of **DMP5**, rendering **A1/B1** a potential host molecule. One *n*-hexane molecule is included inside the cavity of the **P5** core and stabilized by C−H···π interactions with distances of 2.76−2.91 Å between the hydrogens of the *n*-hexane and the aromatic planes of the **P5** core, thus forming a [2]-

DOI: 10.1021/acs.orglett.5b01418
Org. Lett. 2015, 17, 3260−3263

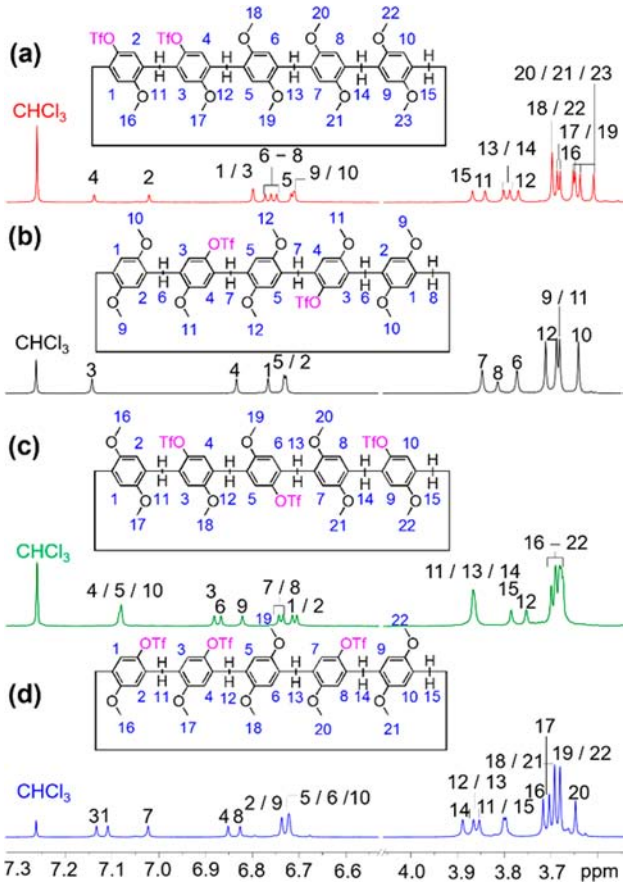


Figure 1. ^{1}H NMR spectra (500 MHz) of (a) **A1/B1**, (b) **A1/C2**, (c) **A1/B2/D1**, and (d) **A1/B1/D1** in $CDCl_3$ at 298 K.

pseudorotaxane in the solid state while suggesting that **A1/B1** may potentially serve as a host for long-chain hydrocarbons.

Fractional crystallization of the mixture of other isomers (R_f = 0.78) of $(\mathbf{OTf})_2$**P5** in CH_2Cl_2/hexanes affords yet another regioisomer in 6% yield (Table 1, entry 6) with the **A1/C2** constitution, as revealed by its solid-state structure (Figure 2a–b). On account of the C_2 symmetry of **A1/C2**, there are five sets of aromatic protons (H1–H5, δ 7.12–6.70 in Figure 1b), three sets of methylene protons (H6–H8, δ 3.83–3.75 in Figure 1b), and four sets of methoxyl protons (H9–H12, δ 3.69–3.62 in Figure 1b) observed in the ^{1}H NMR spectrum. It is noteworthy that **A1/C2** is the major regioisomer of the disubstituted $(\mathbf{OTf})_2$**P5** after de-*O*-methylation and triflation, indicating the possible existence of a steric effect during the second de-*O*-methylation step. BBr_3 first forms a B–O bond on one aromatic unit of **DMP5**, while the second de-*O*-methylation prefers to take place at the nonadjacent aromatic ring.

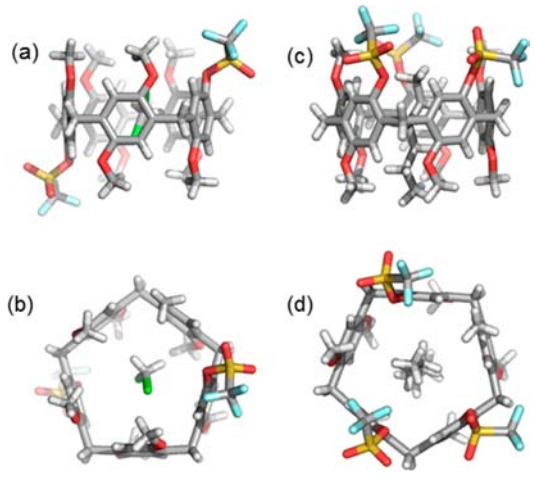


Figure 2. Side-on and plan views of the X-ray crystal superstructures of **A1/C2**⊃CH_2Cl_2 (a,b) and **A1/B1/D1**⊃*n*-hexane (c,d).

A third regioisomer was also obtained from fractional crystallization of the mixture (R_f = 0.78) of $(\mathbf{OTf})_2$**P5**. Its constitution is revealed (Figure S26) to be **A1/B2** from its solid-state structure. The ^{1}H NMR spectrum of this fraction indicates a mixture of **A1/B2** and a small amount of other unidentified isomers.

Following a similar strategy, two tritriflated $(\mathbf{OTf})_3$**P5** regioisomers (Table 1, entry 7) were also isolated by silica gel column chromatography. $(\mathbf{OTf})_3$**P5** can exist (Figure S2) as 10 regioisomers,[15b] namely **A1/B1/C1**, **A1/B1/D1**, **A1/B1/C2**, **A1/B1/D2**, **A1/A2/B1**, **A1/A2/B2**, **A1/A2/C1**, **A1/A2/C2**, **A1/B2/C1**, and **A1/B2/D1**. Since all of these regioisomers lack symmetry, their protons should give rise to ten aromatic, five methylene, and seven methoxyl resonances in the ^{1}H NMR spectra (Figure 1c and 1d); however, these resonances are far from easy to assign.

The constitutions of the two isolated regioisomers of $(\mathbf{OTf})_3$**P5** are revealed by their solid-state structures. Slow vapor diffusion of hexanes into CH_2Cl_2 solutions of the isolated isomers at room temperature afforded single crystals of both regioisomers, which are identified as the **A1/B1/D1** and **A1/B2/D1** isomers. In the solid state, **A1/B1/D1** (Figure 2c–d) and **A1/B2/D1** (Figure S27c–d) have similar cavity sizes that are comparable with the disubstituted derivatives **A1/B1** and **A1/B2**, with one *n*-hexane molecule included in their cavities in each case. The host–guest complexes are stabilized by C–H···π interactions with distances of 2.48–2.83 Å between the hydrogens of the *n*-hexane and the aromatic planes of the pillar[5]arene core. The fact that **A1/B2/D1** populate up to 43% of all $(\mathbf{OTf})_3$**P5** isomers (Table 1, entry 7) lends further support to the hypothesis that the stepwise de-*O*-methylation occurs under steric control, as this isomer has the least steric strain among the 10 possible isomers.

Although we have isolated several regioisomers in the case of the di- and trifunctionized **P5** derivatives, the full chromatographic resolution of di-, tri-, and even higher-order functionalized regioisomers of **P5** remains elusive. When it comes to characterizing the multifunctionalized **P5** isomers, however, the corresponding ^{1}H NMR spectra quickly become complicated to the extent that, with limited information, assigning constitutions becomes challenging. Assignment of the proton resonances (Figure 1) of the four isolated regioisomers is aided by observation of their solid-state structures. Nonetheless, this deprotection-followed-by-activation strategy could still provide a large variety of oligo-substituted regioisomers of pillar[*n*]arenes in reasonable yields.

In summary, a series of regioselective di- and trifunctionalized pillar[5]arene derivatives have been synthesized by a deprotection-followed-by-activation strategy and their constitutions have been established as a result of having access to their solid-state structures. It has been discovered that de-*O*-methylation occurs in a stepwise manner at low reaction temperatures under kinetic control, affording the desired oligo-substituted **P5** derivatives. Furthermore, the regioisomers of the

DOI: 10.1021/acs.orglett.5b01418
Org. Lett. 2015, 17, 3260–3263

oligo-functionalized **P5** derivatives can be isolated by installing triflate groups on the free hydroxyl groups. The deprotection-followed-by-activation strategy opens up a new avenue toward the separation and isolation of different regioisomers of higher-order functionalized pillararenes. The triflate groups on the **P5** derivatives could be used as active intermediates in the synthesis of **P5**-based functional compounds.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, ^{1}H, ^{13}C, and $^{1}H - {}^{1}H$ NOESY NMR spectra, high resolution mass spectra, and crystallographic information (CIF) for all new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01418.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: stoddart@northwestern.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research is part (Project-34-943) of the Joint Center of Excellence in Integrated Nanosystems (JCIN) at the King Abdulaziz City for Science and Technology (KACST) and Northwestern University (NU). The authors would like to thank both KACST and NU for their continued support of this research. J.H. thanks the National Natural Science Foundation of China (No. 21272130) for financial support. X.H. acknowledges the award of a Ryan Fellowship from Northwestern University.

■ REFERENCES

(1) (a) Szejtli, J. *Chem. Rev.* **1998**, *98*, 1743−1754. (b) Uekama, K.; Hirayama, F.; Irie, T. *Chem. Rev.* **1998**, *98*, 2045−2076. (c) Crini, G. *Chem. Rev.* **2014**, *114*, 10940−10975.

(2) (a) Pedersen, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 2495−2496. (b) Dietrich, B.; Lehn, J.-M.; Sauvage, J.-P. *Tetrahedron Lett.* **1969**, *10*, 2885−2888. (c) Cram, D. J. *Angew. Chem., Int. Ed.* **1988**, *27*, 1009−1020. (d) Sun, J.; Frasconi, M.; Liu, Z.; Barnes, J. C.; Wang, Y.; Chen, D.; Stern, C. L.; Stoddart, J. F. *Chem. Commun.* **2015**, *51*, 1432−1435.

(3) (a) Freeman, W. A.; Mock, W. L.; Shih, N. Y. *J. Am. Chem. Soc.* **1981**, *103*, 7367−7368. (b) Lee, J. W.; Samal, S.; Selvapalam, N.; Kim, H.-J.; Kim, K. *Acc. Chem. Res.* **2003**, *36*, 621−630. (c) Lagona, J.; Mukhopadhyay, P.; Chakrabarti, S.; Isaacs, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 4844−4870.

(4) (a) Gutsche, C. D.; Dhawan, B.; No, K. H.; Muthukrishnan, R. *J. Am. Chem. Soc.* **1981**, *103*, 3782−3792. (b) Sessler, J. L.; Kim, S. K.; Gross, D. E.; Lee, C.-H.; Kim, J. S.; Lynch, V. M. *J. Am. Chem. Soc.* **2008**, *130*, 13162−13166. (c) Wang, M.-X. *Chem. Commun.* **2008**, 4541−4551. (d) Guo, D.-S.; Liu, Y. *Chem. Soc. Rev.* **2012**, *41*, 5907−5921. (e) Ajami, D., Jr.; Rebek, J. *Acc. Chem. Res.* **2013**, *46*, 990−999.

(5) (a) Ogoshi, T.; Kanai, S.; Fujinami, S.; Yamagishi, T.; Nakamoto, Y. *J. Am. Chem. Soc.* **2008**, *130*, 5022−5023. (b) Xue, M.; Yang, Y.; Chi, X.; Zhang, Z.; Huang, F. *Acc. Chem. Res.* **2012**, *45*, 1294−1308. (c) Strutt, N. L.; Zhang, H.; Schneebeli, S. T.; Stoddart, J. F. *Acc. Chem. Res.* **2014**, *47*, 2631−2642.

(6) (a) Molad, A.; Goldberg, I.; Vigalok, A. *J. Am. Chem. Soc.* **2012**, *134*, 7290−7292. (b) Kim, S. K.; Lynch, V. M.; Young, N. J.; Hay, B. P.; Lee, C.-H.; Kim, J. S.; Moyer, B. A.; Sessler, J. L. *J. Am. Chem. Soc.* **2012**, *134*, 20837−20843.

(7) Pease, A. R.; Jeppesen, J. O.; Stoddart, J. F.; Luo, Y.; Collier, C. P.; Heath, J. R. *Acc. Chem. Res.* **2001**, *34*, 433−444.

(8) Ambrogio, M. W.; Thomas, C. R.; Zhao, Y.-L.; Zink, J. I.; Stoddart, J. F. *Acc. Chem. Res.* **2011**, *44*, 903−913.

(9) (a) Cao, D.; Kou, Y.; Liang, J.; Chen, Z.; Wang, L.; Meier, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 9721−9723. (b) Ogoshi, T.; Demachi, K.; Kitajima, K.; Yamagishi, T.-A *Chem. Commun.* **2011**, *47*, 7164−7166. (c) Ogoshi, T.; Aoki, T.; Kitajima, K.; Fujinami, S.; Yamagishi, T.-A.; Nakamoto, Y. *J. Org. Chem.* **2011**, *76*, 328−331.

(10) (a) Ogoshi, T.; Kitajima, K.; Aoki, T.; Fujinami, S.; Yamagishi, T.-A.; Nakamoto, Y. *J. Org. Chem.* **2010**, *75*, 3268−3273. (b) Zhang, Z.; Xia, B.; Han, C.; Yu, Y.; Huang, F. *Org. Lett.* **2010**, *12*, 3285−3287. (c) Ma, Y.; Zhang, Z.; Ji, X.; Han, C.; He, J.; Abliz, Z.; Chen, W.; Huang, F. *Eur. J. Org. Chem.* **2011**, 5331−5335.

(11) (a) Li, C.; Xu, Q.; Li, J.; Yao, F.; Jia, X. *Org. Biomol. Chem.* **2010**, *8*, 1568−1576. (b) Strutt, N. L.; Forgan, R. S.; Spruell, J. M.; Botros, Y. Y.; Stoddart, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 5668−5671. (c) Ogoshi, T.; Yamafuji, D.; Aoki, T.; Kitajima, K.; Yamagishi, T.-A.; Hayashi, Y.; Kwauchi, S. *Chem.—Eur. J.* **2012**, *18*, 7493−7500. (d) Strutt, N. L.; Zhang, H.; Giesener, M. A.; Lei, J.; Stoddart, J. F. *Chem. Commun.* **2012**, *48*, 1647−1649. (e) Guan, Y.; Ni, M.; Hu, X.; Xiao, T.; Xiong, S.; Lin, C.; Wang, L. *Chem. Commun.* **2012**, *48*, 8529−8531.

(12) (a) Liu, L.; Cao, D.; Jin, Y.; Tao, H.; Kou, Y.; Meier, H. *Org. Biomol. Chem.* **2011**, *9*, 7007−7010. (b) Ogoshi, T.; Demachi, K.; Kitajima, K.; Yamagishi, T.-A. *Chem. Commun.* **2011**, *47*, 10290−10292. (c) Ogoshi, T.; Ueshima, N.; Yamagishi, T.-A.; Toyota, Y.; Matsumi, N. *Chem. Commun.* **2012**, *48*, 3536−3538. (d) Hu, X.-B.; Chen, Z.; Chen, L.; Zhang, L.; Hou, J.-L.; Li, Z.-T. *Chem. Commun.* **2012**, *48*, 10999−11001. (e) Han, K.; Zhang, Y.; Li, J.; Yu, Y.; Jia, X.; Li, C. *Eur. J. Org. Chem.* **2013**, 2057−2060.

(13) (a) Strutt, N. L.; Fairen-Jimenez, D.; Iehl, J.; Lalonde, M. B.; Snurr, R. Q.; Farha, O. K.; Hupp, J. T.; Stoddart, J. F. *J. Am. Chem. Soc.* **2012**, *134*, 17436−17439. (b) 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*, 8577−8589. (c) Ogoshi, T.; Iizuka, R.; Kotera, D.; Yamagishi, T.-A. *Org. Lett.* **2015**, *17*, 350−353. (d) Zhou, Q.; Zhang, B.; Han, D.; Chen, R.; Qiu, F.; Wu, J.; Jiang, H. *Chem. Commun.* **2015**, *51*, 3124−3126.

(14) Chen, Y.; He, M.; Li, B.; Wang, L.; Meier, H.; Cao, D. *RSC Adv.* **2013**, *3*, 21405−21408.

(15) (a) Han, C.; Zhang, Z.; Yu, G.; Huang, F. *Chem. Commun.* **2012**, *48*, 9876−9878. (b) Ogoshi, T.; Yamafuji, D.; Kotera, D.; Aoki, T.; Fujinami, S.; Yamagishi, T.-A. *J. Org. Chem.* **2012**, *77*, 11146−11152. (c) Pan, M.; Xue, M. *Eur. J. Org. Chem.* **2013**, 4787−4793.

(16) Ogoshi, T.; Kitajima, K.; Fujinami, S.; Yamagishi, T.-A. *Chem. Commun.* **2011**, *47*, 10106−10108.

(17) (a) Murai, N.; Yonaga, M.; Tanaka, K. *Org. Lett.* **2012**, *14*, 1278−1281. (b) Vinogradova, E. V.; Park, N. H.; Fors, B. F.; Buchwald, S. L. *Org. Lett.* **2013**, *15*, 1394−1397. (c) Hale, K. J.; Hough, L.; Manaviazar, S.; Calabrese, A. *Org. Lett.* **2014**, *16*, 4838−4841. (d) Tanaka, S.; Umetsu, T.; Nebuya, S.; Marohashi, N.; Hattori, T. *J. Org. Chem.* **2015**, *80*, 1070−1081.

(18) (a) Sase, S.; Jaric, M.; Metzger, A.; Malakhov, V.; Knochel, P. *J. Org. Chem.* **2008**, *73*, 7380−7382. (b) Gooβen, J.; Lange, P. P.; Rodríguez, N.; Linder, C. *Chem.—Eur. J.* **2010**, *16*, 3906−3909. (c) Shang, R.; Xu, Q.; Jiang, Y.-Y.; Wang, Y.; Liu, L. *Org. Lett.* **2010**, *12*, 1000−1003. (d) Joshi-Pangu, A.; Wang, C.-Y.; Biscoe, M. R. *J. Am. Chem. Soc.* **2011**, *133*, 8478−8481. (e) Yang, Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2013**, *135*, 10642−10645.

(19) In principle, increasing the reaction time should increase the production of deprotected derivatives of **P5**. In our experiments, we noticed that increasing the amount of deprotecting agent can also lead to an increase in the yields of products in shorter reaction times.

(20) The methylene protons in the labeled structures for the NMR spectra in Figure 1 are diastereotopic, but they are grouped together with one label. They are most likely exchanging rapidly on the NMR time scale; however, they are not equivalent as suggested by the label.

DOI: 10.1021/acs.orglett.5b01418
Org. Lett. 2015, 17, 3260−3263