Organic LETTERS

Letter

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# Control of a Chiral Property of a Calix[3]aramide: The Racemization Suppressed by Intramolecular Cyclic Hydrogen Bonds and DMSO−$H_2O$ System-Induced Spontaneous Resolution

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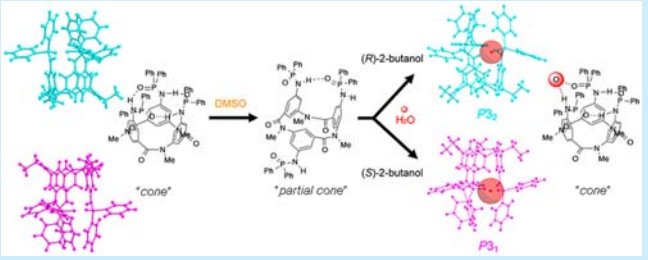
Supporting Information

**ABSTRACT:** A calix[3]aramide has been synthesized bearing three triphenylphosphinic amide moieties, which formed intramolecular cyclic hydrogen bonds that suppressed its *cone*/*partial cone* inversion. The intramolecular cyclic hydrogen bonds were disrupted by DMSO, and the insertion of $H_2O$ into the hydrogen bonds triggered the spontaneous resolution of the calix[3]aramide. Within a chiral environment, such as that afforded by the presence of optically active 2-butanol, the calix[3]aramide underwent a symmetry breaking crystallization process.




Helical,[1] axial,[2] and planar chiralities[3] are interesting not only from a structural perspective but also in terms of their potential application for expanding the scope of chiral molecular devices. In particular, planar-chiral molecules have been investigated in detail in terms of their unique three-dimensional structures and potential applications as auxiliaries and catalysts in asymmetric synthesis and chiral sensors. Planar-chiral molecules such as substituted [2,2]paracyclophanes,[4] metallocenes,[5] and *o*-substituted paracyclophane-type cyclic amide[6] have generally been developed on the basis of design concepts aimed at suppressing the rotation of their prochiral planar skeletons, which can be desymmetrized by the attachment of different substituents. In contrast, the inherent chirality of concave molecules[7] such as calixarenes,[8] resorcinarenes,[9] or cavitands[10] derives from suppressing the inversion of the curvature via hydrogen bonds. In this context, we have reported that calix[3]aramides, which are cyclic trimers consisting of benzamide units, have a planar chirality based on the direction of the amide bond.[11] The racemization of calix[3]aramides requires the flipping of their phenyl rings, and the inversion of the conformation of these compounds is generally fast in the solution phase, where it occurs with an energy barrier of 13.5 kcal/mol.[11a] Rapid ring inversion can be efficiently blocked by cupping with trimesic acid, leading to the formation of chiral spherical capsules.[12] Tubular-type molecules have been prepared to suppress the flipping of the phenyl rings in calix[3]aramides, where three bithiophene groups were covalently connected through twin calix[3]aramides.[13] We also succeeded in the formation of capsule-like chiral dimeric structures via intermolecular hydrogen bonds of a calix[3]aramide bearing carbamoyl groups in the crystal.[14] In this Letter, we report a novel calix[3]aramide bearing three triphenylphosphinic amide moieties, the flipping of the phenyl rings of which, that is, a racemization was suppressed by the formation of "intra"-molecular cyclic hydrogen bonds. In a DMSO−$H_2O$ system, the DMSO molecules led to the disruption of the hydrogen bonds, and water was inserted into the existing intramolecular cyclic hydrogen boning network, which led to the chiral crystallization of the calix[3]aramide.

The synthesis of calix[3]aramide with triphenylphosphinic amide **1** is shown in Scheme 1. Compound **1** was characterized by NMR, FTIR, FAB-MS, and single crystal X-ray diffraction. The $^1$H NMR spectrum of **1** in $CDCl_3$ revealed that the signal belonging to the N−H proton had been shifted downfield to 8.98 ppm, which indicated that there were intramolecular hydrogen bonds between the oxygen atoms of the P═O moieties and N−H groups. In contrast, the N−H proton of *N*,*P*,*P*-triphenylphosphinic amide (**3**) was detected at 5.29 ppm. Because the hydrogen bonding interactions in **1** restricted the motion of calix[3]aramide, the methylene protons of the *N*-ethyl groups

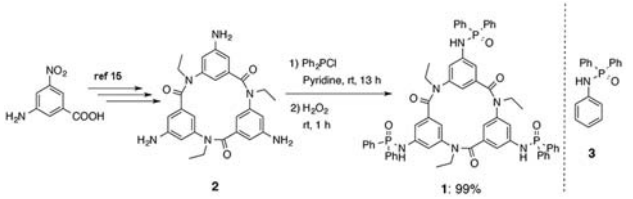
**Received:** May 19, 2015
**Published:** July 17, 2015





DOI: 10.1021/acs.orglett.5b01455
*Org. Lett.* 2015, 17, 3650−3653

**Scheme 1. Preparation of Tris(*N,P,P*-triphenylphosphinic amide)-calix[3]aramide**




were detected at 4.07 and 3.02 ppm with diastereotopic splitting. The $^1$H NMR spectrum of **1** in methanol-$d_4$ was similar to the spectrum recorded in $CDCl_3$. Variable-temperature (VT) dynamic NMR studies in $CDCl_3$ and methanol-$d_4$ showed that the rates of the flipping of the phenyl rings in **1** were also slow in solution. In contrast, two different types of methylene protons were observed for the *N*-ethyl groups of calix[3]aramide **1** in DMSO-$d_6$, which indicated that **1** existed in its *partial cone* conformation in DMSO. These peaks coalesced to form a singlet at 363 K, which was attributed to the facile flipping of the phenyl groups at a higher temperature ($\Delta G$ = 16.2 kcal/mol, Figures S11 and S12). Taken together, these observations indicated that the intramolecular cyclic hydrogen bonds were responsible for fixing the chirality of calix[3]aramide **1** in $CDCl_3$ and methanol-$d_4$, and that the intramolecular cyclic hydrogen bonds were disconnected in DMSO.

The recrystallization of compound **1** from $CHCl_3$ yielded colorless crystals suitable for X-ray crystallographic analysis (**1a**). As shown in Figure 1, the intramolecular cyclic hydrogen bonds

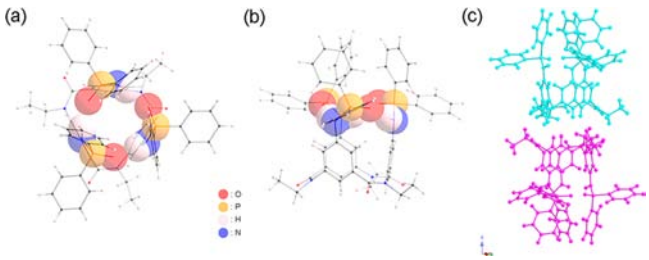



**Figure 1.** Crystal structure of the $CHCl_3$ solvate **1a** as a stick model. Part of the intramolecular network of cyclic hydrogen bonds has been drawn as a surface model. The chloroform molecules have been omitted for clarity: (a) top view and (b) side view. Ball and stick models of the enantiomeric pair found in **1a**: (c) the magenta- and cyan-colored molecules are enantiomeric conformers of each other.

were observed in the X-ray crystal structure. The crystal structure of the $CHCl_3$ solvate **1a** also revealed that both enantiomeric conformers of compound **1** were alternately connected to form racemic crystals through CH−O hydrogen bonding interactions (Figure 1c).

Pleasingly, the recrystallization of compound **1** from EtOAc or acetonitrile provided single crystals suitable for X-ray crystallographic analysis. Both of the crystal structures were solved in the triclinic $P\bar{1}$ space group and were also found to possess the same shape. The three different crystals (i.e., **1a**, **1b**, and **1c**) were determined to be solvatomorphs because the packing of compound **1** within all three crystals was found to be quite different, even though the compositions of the different crystals were the same (Figure S19−S24). Alcohols are known to form hydrogen bonding interactions with the oxygen atoms of carbonyl, sulfonyl, sulfoxide, and phosphine oxide groups and could potentially form adducts with **1**, which could promote its *cone/partial cone* inversion. Although the results of VT-NMR experiments in methanol-$d_4$ suggested that the rate of inversion of **1** was slow, the O−H functional group of 2-propanol inserted into the cyclic hydrogen bonds of compound **1** in the solid state to give the corresponding adduct **1d** (Figure S25). The vapor diffusion of water into a DMSO solution of compound **1** led to the formation of a mixture of single crystals of the $H_2O$ adducts and DMSO solvates of **1** (i.e., **1e** and **1f**, respectively), which were formed as block crystals and plate crystals, respectively. The crystals of the $H_2O$ adduct **1e** were found to belong to the noncentrosymmetric space group $P3_1$ (or $P3_2$). The conformation of **1e** was found to be similar to that of the 2-propanol adduct **1d**, in that the water molecules had inserted themselves into the intramolecular cyclic hydrogen bonds, with the unit cell containing only single enantiomers (Figure 2).

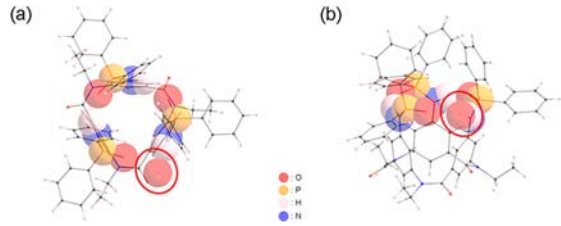



**Figure 2.** Crystal structure of the $H_2O$ adduct **1e**, which belongs to the $P3_1$ space group, as a stick model. Part of the cyclic intramolecular hydrogen bond network has been drawn as a surface model. The water molecule that inserted into the intramolecular cyclic hydrogen bond network has been highlighted with a red ellipse. Free water molecules have been omitted for clarity: (a) top view and (b) side view.

The chirality of **1** was spontaneously resolved within the individual single crystals. The solid-state circular dichroism (CD) spectra of several crystals of **1e** were measured as KBr pellets to confirm the optical activity of the material. The spectrum of an enantiopure crystal of **1e** with space group $P3_1$ showed positive and negative "Cotton effect" bands with peaks at 270, 315 and 230, 215 nm, respectively (Figure 3, magenta line). In contrast,

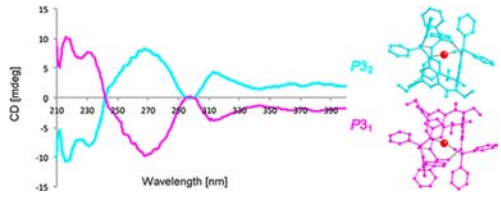



**Figure 3.** Solid-state CD spectra of enantiopure crystals of **1e** with space groups $P3_1$ (magenta-colored line) and $P3_2$ (cyan-colored line) in KBr.

the CD spectrum of an enantiopure crystal of **1e** with space group $P3_2$ was the complete opposite (Figure 3, cyan line). The crystal structure of the DMSO adduct **1f** was similar to those of **1b** and **1c**, which existed as a triclinic system with space group $P\bar{1}$ (Figures S25 and S26). Interestingly, the vapor diffusion of water into $CHCl_3$, EtOAc, and $CH_3CN$ solutions of **1** did not result in the insertion of $H_2O$ into the intramolecular hydrogen bonds of **1**. The 2-propanol solvate **1d** was obtained as racemic crystals following the vapor diffusion of 2-propanol into a DMSO solution of **1**. Taken together, these results suggest that the presence of DMSO and the insertion of water are both important factors governing the spontaneous resolution of **1**.



DOI: 10.1021/acs.orglett.5b01455
*Org. Lett.* 2015, 17, 3650−3653

Density functional theory (DFT) calculations were conducted at the B3LYP/6-31G* level to elucidate the mechanism for the inversion of calix[3]aramide **1**.[16] The initial structure EQ1 was selected as a simplified model of **1** (Figures 4 and S31).

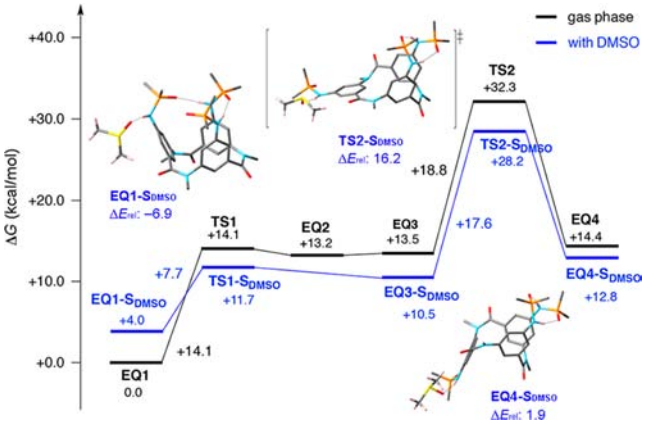
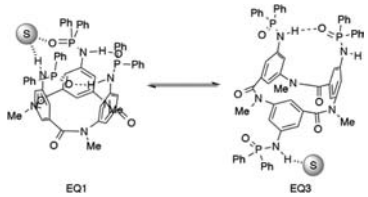



**Figure 4.** Comparison of the energy profiles and structures involved in the inversion of **1** both with and without DMSO (Δ*G*, kcal/mol).

Disconnection of the intramolecular cyclic hydrogen bonds (1.90 Å) of EQ1 gave intermediate EQ2 with an activation energy of 14.1 kcal/mol. EQ2 was then easily converted to conformer EQ3 over a much smaller energy barrier. The formation of the *partial cone*-conformation EQ4 from EQ3 occurred by the rotation of the amide bonds. This rotation step was calculated to be the rate-determining step, with an activation energy of 18.8 kcal/mol to TS2. In contrast, calculations for the inversion of **1** using DMSO as a solvent revealed that the addition of DMSO led to the distinct weakening of the intramolecular cyclic hydrogen bonding network. The coordination of DMSO to the hydrogen of the N−H bond in EQ1 led to the cleavage of the hydrogen bond (4.48 Å, EQ1-$S_{DMSO}$). This interruption to the hydrogen bonding network promoted the inversion from *cone* (EQ1-$S_{DMSO}$) to *partial cone* (EQ4-$S_{DMSO}$) through two transition states (TSs), TS1-$S_{DMSO}$ and TS2-$S_{DMSO}$, which had much lower activation energies of 7.7 and 17.7 kcal/mol, respectively.

The effects of various solvents on the mechanism of the insertion into the cyclic intramolecular hydrogen bonding network was also studied using DFT calculations (Table 1). The insertion of $H_2O$ into the cyclic intramolecular hydrogen bonding network was determined to contribute to the stabilization of the *cone*-conformer (EQ1-$S_{H2O}$) with a small energy gain (4.0 kcal/mol). Methanol and 2-propanol were also determined to be suitable for obtaining the corresponding alcohol adducts of **1**, which were similar to that of **1e**, whereas the structure of the DMSO adduct was calculated to be less stable than that of **1** without solvent. In contrast, the optimized structure of the *partial cone*-conformer containing DMSO (EQ3-$S_{DMSO}$) was lower in energy than that of the corresponding EQ3 structures containing an alcohol or $H_2O$. This result suggested that the addition of DMSO led to the disconnection of the intramolecular cyclic hydrogen bonding network and promoted the *cone*/*partial cone* inversion of the calix[3]aramide. These results are in good agreement with the NMR and crystallography data for the different solvents (**1d**−**f**).

**Table 1. Solvent Effects for the Conformational Flipping of Calix[3]aramides, As Determined by DFT Calculations**




| | | Δ*G* [kcal/mol] | | |
|---|---|---|---|---|
| *S* | | EQ1 | EQ3 | EQ3 − EQ1 |
| none | | 0.0 | +14.4 | +14.4 |
| $H_2O$ | $S_{H2O}$ | −4.0 | +14.3 | +18.3 |
| MeOH | $S_{MeOH}$ | −3.2 | +16.3 | +19.5 |
| IPA | $S_{IPA}$ | −1.9 | +15.9 | +17.8 |
| DMSO | $S_{DMSO}$ | +3.8 | +12.8 | +9.0 |

Within a chiral environment, such as in the presence of 2-butanol, we observed the breaking of the symmetry associated with the crystallization process. The vapor diffusion of $H_2O$ into a DMSO solution of **1** containing 1 equiv of (*R*)-2-butanol resulted in the crystallization of a mixture of the optically active $H_2O$ adduct **1e**, which was formed in the $P3_2$ space group, and the achiral DMSO solvate **1f**. In contrast, the use of (*S*)-2-butanol under the same conditions afforded crystals of the $H_2O$ adduct **1e** in the $P3_1$ space group. The role of 2-butanol can therefore be regarded as providing a chiral environment for the spontaneous resolution of **1** because the insertion of the O−H functional group of this alcohol into the cyclic intramolecular hydrogen bonding network was not observed.

In conclusion, we have succeeded in fixing the chirality of calix[3]aramide via the formation of intramolecular cyclic hydrogen bonds between the oxygen and nitrogen atoms of its triphenylphosphinic amide moiety. The results of a series of NMR studies, crystallographic analyses, and theoretical calculations suggested that the addition of DMSO led to the disconnection of all of the intramolecular cyclic hydrogen bonds and promoted the *cone*/*partial cone* inversion of calix[3]aramide. The addition of $H_2O$ vapor into a DMSO solution of calix[3]aramide containing triphenylphosphinic amide triggered the spontaneous resolution, and the presence of optically active 2-butanol provided a chiral environment capable of breaking the symmetry of the system.

## ■ ASSOCIATED CONTENT

### Supporting Information

Detailed experimental procedures for synthesis and $^1$H NMR, $^{13}$C NMR, $^{31}$P NMR, VT-NMR, IR data of **1**, CD spectra of **1e** and **1f**, and X-ray diffraction data of **1a**−**f** in the form of single crystal X-ray crystallographic information files (CIF). The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01455.

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

This work was supported in part by Senryaku, 2008−2012, from the Ministry of Education, Culture, Sports, Science and



DOI: 10.1021/acs.orglett.5b01455
*Org. Lett.* 2015, 17, 3650−3653

Technology of Japan. The calculations were performed on the RIKEN Integrated Cluster of Clusters (RICC) facility, Japan.

## REFERENCES

(1) For reviews, see (a) Zhang, D.-W.; Zhao, X.; Li, Z.-T. *Acc. Chem. Res.* **2014**, *47*, 1961−1970. (b) Saraogi, I.; Hamilton, A. D. *Chem. Soc. Rev.* **2009**, *38*, 1726−1743. (c) Yashima, E.; Maeda, K.; Furusho, Y. *Acc. Chem. Res.* **2008**, *41*, 1166−1180. (d) Huc, I. *Eur. J. Org. Chem.* **2004**, *2004*, 17−29.

(2) For reviews, see (a) Wallace, T. W. *Org. Biomol. Chem.* **2006**, *4*, 3197−3210. (b) Brunel, J. M. *Chem. Rev.* **2005**, *105*, 857−897. (c) Kocovsky, P.; Vyskocil, S.; Smrcina, M. *Chem. Rev.* **2003**, *103*, 3213−3245. (d) Chen, Y.; Yekta, S.; Yudin, A. K. *Chem. Rev.* **2003**, *103*, 3155−3211.

(3) For reviews, see (a) Goto, H.; Sudoh, M.; Kawamoto, K.; Sugimoto, H.; Inoue, S. *Chirality* **2012**, *24*, 867−878. (b) Bolm, C.; Muniz, K. *Chem. Soc. Rev.* **1999**, *28*, 51−59. (c) Schlögl, K. *Top. Curr. Chem.* **1984**, *125*, 27−62.

(4) (a) Gon, M.; Morisaki, Y.; Chujo, Y. *J. Mater. Chem. C* **2015**, *3*, 521−529. (b) Morisaki, Y.; Gon, M.; Sasamori, T.; Tokitoh, N.; Chujo, Y. *J. Am. Chem. Soc.* **2014**, *136*, 3350−3353.

(5) (a) Schaarschmidt, D.; Lang, H. *Organometallics* **2013**, *32*, 5668−5704. (b) Kinbara, K.; Muraoka, T.; Aida, T. *Org. Biomol. Chem.* **2008**, *6*, 1871−1876. (c) Taylor, C. J.; Motevalli, M.; Richards, C. J. *Organometallics* **2006**, *25*, 2899−2902. (d) Jekki, L.; Pala, C.; Calmuschi, B.; Ganter, C. *Eur. J. Inorg. Chem.* **2005**, *2005*, 745−750. (e) Paley, R. S. *Chem. Rev.* **2002**, *102*, 1493−1523. (f) Togni, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1475−1477. (g) Erker, G.; Aulbach, M.; Knickmeier, M.; Wingbermuehle, D.; Krueger, C.; Nolte, M.; Werner, S. *J. Am. Chem. Soc.* **1993**, *115*, 4590−4601.

(6) Katagiri, K.; Ikeda, T.; Muranaka, A.; Uchiyama, M.; Tominaga, M.; Azumaya, I. *Tetrahedron: Asymmetry* **2009**, *20*, 2646−2650.

(7) Szumna, A. *Chem. Soc. Rev.* **2010**, *39*, 4274−4285.

(8) (a) Luo, J.; Zheng, Y.-S. *Curr. Org. Chem.* **2012**, *16*, 483−506. (b) Li, S.-Y.; Xu, Y.-W.; Liu, J.-M.; Su, C.-Y. *Int. J. Mol. Sci.* **2011**, *12*, 429−455. (c) Xu, Z.-X.; Huang, Z.-T.; Chen, C.-F. *Tetrahedron Lett.* **2009**, *50*, 5430−5433. (d) Okada, Y.; Mizutani, M.; Ishii, F.; Nishimura, J. *Tetrahedron Lett.* **1997**, *38*, 9013−9016. (e) Böhmer, V.; Kraft, D.; Tabatabai, M. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1994**, *19*, 17−39.

(9) (a) Arnecke, R.; Böhmer, V.; Paulus, E. F.; Vogt, W. *J. Am. Chem. Soc.* **1995**, *117*, 3286−3287. (b) Schmidt, C.; Paulus, E. F.; Böhmer, V.; Vogt, W. *New J. Chem.* **2000**, *24*, 123−125. (c) McIldowie, M. J.; Mocerino, M.; Ogden, M. I. *Supramol. Chem.* **2010**, *22*, 13−39.

(10) (a) Shivanyuk, A.; Rissanen, K.; Korner, S. K.; Rudkevich, D. A.; Rebek, J. *Helv. Chim. Acta* **2000**, *83*, 1778−1790. (b) Saito, S.; Nuckolls, C.; Rebek, J. *J. Am. Chem. Soc.* **2000**, *122*, 9628−9630.

(11) (a) Kakuta, H.; Azumaya, I.; Masu, H.; Matsumura, M.; Yamaguchi, K.; Kagechika, H.; Tanatani, A. *Tetrahedron* **2010**, *66*, 8254−8260. (b) Azumaya, I.; Kagechika, H.; Yamaguchi, K.; Shudo, K. *Tetrahedron Lett.* **1996**, *37*, 5003−5006.

(12) Masu, H.; Katagiri, K.; Kato, T.; Kagechika, H.; Tominaga, M.; Azumaya, I. *J. Org. Chem.* **2008**, *73*, 5143−5146.

(13) Yamakado, R.; Mikami, K.; Takagi, K.; Azumaya, I.; Sugimoto, S.; Matsuoka, S.; Suzuki, M.; Katagiri, K.; Uchiyama, M.; Muranaka, A. *Chem. - Eur. J.* **2013**, *19*, 11853−11857.

(14) Fujimoto, N.; Matsumura, M.; Azumaya, I.; Nishiyama, S.; Masu, H.; Kagechika, H.; Tanatani, A. *Chem. Commun.* **2012**, *48*, 4809−4811.

(15) Imabeppu, F.; Katagiri, K.; Masu, H.; Kato, T.; Tominaga, M.; Therrien, B.; Takayanagi, H.; Kaji, E.; Yamaguchi, K.; Kagechika, H.; Azumaya, I. *Tetrahedron Lett.* **2006**, *47*, 413−416.

(16) The DFT calculations were performed by using the Gaussian 09 program: Frisch, M. J.; et al. *Gaussian 09*, revision D.01; Gaussian, Inc.: Wallingford, CT, 2013. The full citation and details of calculations are given in the Supporting Information.



DOI: 10.1021/acs.orglett.5b01455
*Org. Lett.* 2015, 17, 3650−3653