Chiral biphenylamide derivative: an efficient organocatalyst for the enantioselective synthesis of α-hydroxy phosphonates†

Jun Jiang, Xiaohong Chen, Jun Wang, Yonghai Hui, Xiaohua Liu, Lili Lin and Xiaoming Feng*

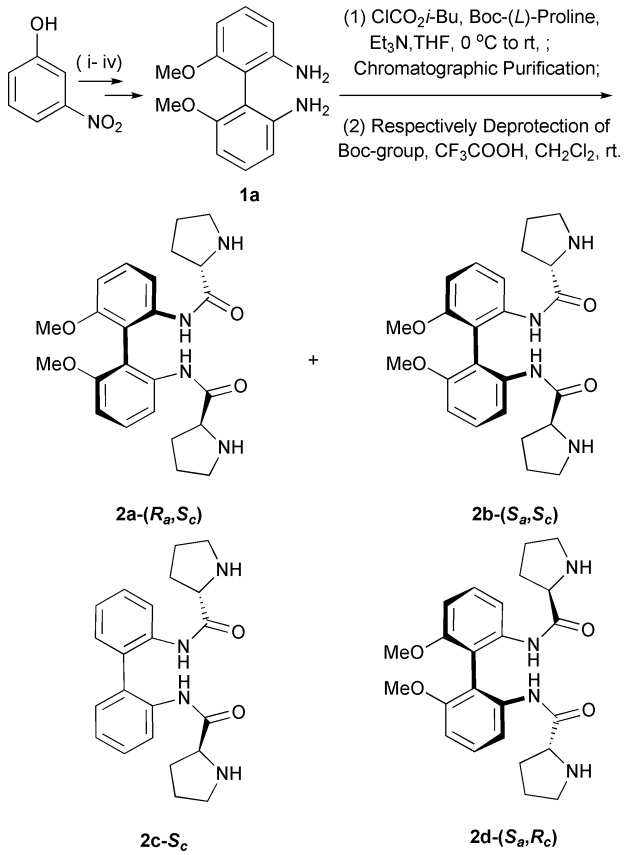
Received 25th August 2009, Accepted 4th September 2009
First published as an Advance Article on the web 17th September 2009
DOI: 10.1039/b917554g

The aldol reactions of α-keto phosphonates and aldehydes were facilitated by an axially chiral biphenylprolinamide under mild conditions, affording the synthetically and pharmaceutically useful products in high yields and excellent enantioselectivities.

Chiral α-hydroxy phosphonic acid derivatives have attracted extensive attention due to their excellent inhibitory bioactivities toward rennin, HIV protease, protein tyrosine kinase and other anticancer activities.[1] Although some asymmetric methods for preparing α-hydroxy phosphonates have been described, including enzymatic[2] and chemical methods,[3] these methods are primarily concentrated on the synthesis of secondary α-hydroxy phosphonates. Since the pioneering work of Zhao using proline as catalyst for the preparation of tertiary α-hydroxy phosphonates,[4] some efficient catalyst systems have been reported by our[5] and other groups.[6] Herein, we describe highly efficient catalysts derived from biphenyldiamine and proline for the asymmetric synthesis of tertiary α-hydroxy phosphonates *via* aldol reaction under mild conditions.

Biphenyl derivatives are versatile building blocks in pharmaceutical and material science.[7] Meanwhile, many chiral biphenyl catalysts were designed and synthesized for synthetic use.[8] However, the reported examples were mainly restricted to diphosphine ligands or cyclic bridged compounds,[9] and there were even a few examples of successful application in asymmetric reactions.[10] Thus, it is interesting to develop some new chiral biphenyl catalysts for the asymmetric catalysis. As shown in Scheme 1, with *m*-NO_2PhOH as the starting material, racemic biphenyldiamine **1a** was synthesized *via* four steps. Then, *rac*-**1a** reacting with Boc-(*L*)-proline afforded the corresponding diamide. Fortunately, the two diastereomers could be easily separated and purified by silica gel chromatography. After deprotection, the diastereomeric **2a** and **2b** were respectively obtained. It should be note that the absolute configuration of the axial chirality of **2a** was identified unambiguously as *R* according to the crystal X-ray diffraction analysis, and the dihedral angle between both phenyl rings is 87.58° (Fig. 1).[11]

With the catalysts in hand, we attempted the reaction of diethyl benzoyl phosphonate **3a** with acetone. To our delight,



Scheme 1 Synthesis of catalysts **2a**-(R_a, S_c)[a] and **2b**, and the structures of catalysts **2c** and **2d**. [a]R_a = axial chirality, S_c = central chirality. (i) $Hg(OAc)_2$, NaOH (aq); KI, I_2; (ii) CH_3I, K_2CO_3, acetone; (iii) Cu, DMF, reflux; (iv) $NH_2NH_2{\cdot}H_2O$, active carbon, $FeCl_3{\cdot}6H_2O$, reflux.

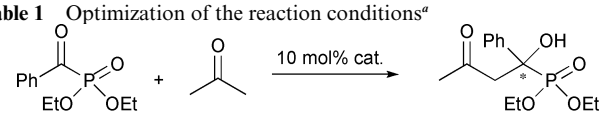
both **2a** and **2b** could effectively activate the model reaction, but with different enantioselectivities, which suggested that the matched chirality of biphenyl was crucial to achieve the good results (Table 1, entries 1-2). To further confirm the role of the axial chirality, axially flexible **2c** without methoxy groups on 6,6′ positions of biphenyl was tested. As expected, somewhat inferior reactivity and enantioselectivity were observed (Table 1, entry 1 *vs* 3). Interestingly, when the configuration of the proline was moiety reversed, catalyst **2d** afforded the product with the opposite absolute configuration, indicating the proline moiety dominated the stereochemistry of the reaction (Table 1, entry 4).

Subsequently, some parameters were considered to obtain higher enantioselectivity. Based on the research of the acidic proton being advantageous to the aldol reaction,[12] **2a** was chosen as the preferable catalyst to screen a series of additives in the

Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, China. E-mail: xmfeng@scu.edu.cn; Fax: +86 28 85418249; Tel: +86 28 85418249

† Electronic supplementary information (ESI) available: Experimental procedures, analytical data (^{1}H NMR, ^{13}C NMR and HRMS) for all new compounds and crystal structure details for **2a**. CCDC reference number 738508. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b917554g

Table 1 Optimization of the reaction conditions[a]



3a **4a**

Entry	Cat.	Yield[b] (%)	Ee[c] (%)
1	**2a**	93	69
2	**2b**	94	35
3	**2c**	49	50
4[d]	**2d**	75	-67
5[e]	**2a**/TFA	95	78
6[e]	**2a**/CH_3COOH	93	65
7[e]	**2a**/PhCOOH	87	58
8[e]	**2a**/TsOH	85	70
9[f]	**2a**/TFA	95	86
10[g]	**2a**/TFA	92	92
11[h]	**2a**/TFA	53	92
12[g,i]	**2a**/TFA	51	91
13[g,j]	**2a**/TFA	89	94

[a] Unless otherwise noted, the reaction was carried out with the diethyl benzoyl phosphonate (0.1 mmol), 0.5 mL of acetone at –20 °C for 2-3 d, using 10 mol% catalyst loading. [b] Isolated yield. [c] Determined by chiral HPLC. [d] The absolute configuration was opposite to entry 1. [e] **2a**/acid = 2/1. [f] **2a**/TFA = 1/1. [g] **2a**/TFA = 1/2. [h] **2a**/TFA = 1/2.5. [i] Using 2.5 mol% catalyst loading. [j] Mixed solvent: ethyl acetate/acetone = 0.3 mL/0.2 mL

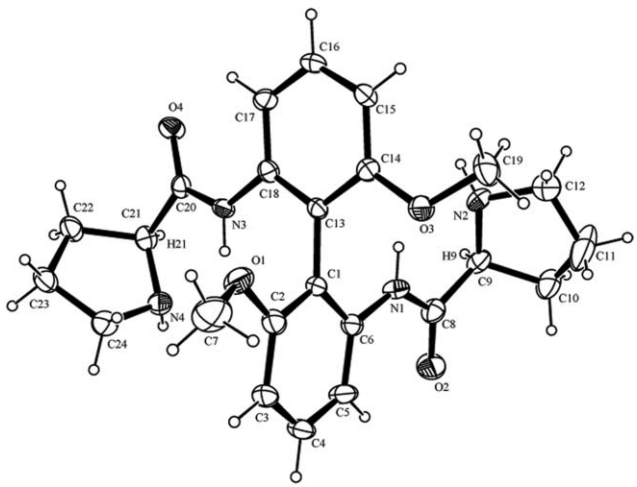
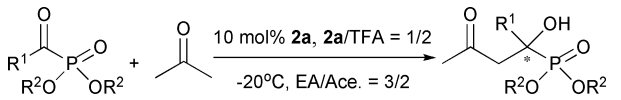


Fig. 1 X-Ray crystal structure of **2a**-(R_a, S_c), showing the 20% probability of the thermal ellipsoids.

following studies. Results revealed that acidity of additives and the ratio with catalyst greatly influenced reaction (Table 1, entries 5-11). Most notably, when TFA was employed with **2a** at the ratio of 2/1, the desired product could be obtained with up to 92% ee and 92% yield (Table 1, entry 10). Other optimization conditions[13] (temperature, solvents, catalyst loading) were investigated for the current catalytic system, however no obvious improvement of enantioselectivity was achieved. Furthermore, the catalyst loading could be reduced to 2.5 mol% without impacting the enantioselectivity (Table 1, entry 12) (prolonging reaction time could obtain comparable yield). When this reaction was carried out in the 0.5 mL mixed solvent of ethyl acetate and acetone at the ratio of 3/2 (V/V), the enantioselectivity was increased slightly (Table 1, entry 13). Extensive screening showed that the optimized conditions were **2a**/TFA = 1/2, 0.1 mmol diethyl benzoyl phosphonate in a 3/2 mixture of ethyl acetate and acetone at –20 °C (89% yield and 94% ee; Table 1, entry 13).

Table 2 Asymmetric aldol reaction of α-keto phosphonate **3**[a]

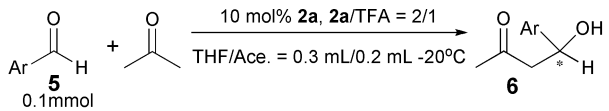


3 **4**

Entry	3	R^1	R^2	4	Time (d)	Yield[b](%)	Ee[c] (%)
1	**3a**	Ph	Et	**4a**	3	89	94
2[d]	**3a**	Ph	Et	**4a**	3	71	–92
3	**3b**	Ph	Me	**4b**	3	91	89
4	**3c**	Ph	*i*-Pr	**4c**	3	74	97
5	**3d**	4-FC_6H_4	Et	**4d**	3	89	93
6	**3e**	4-FC_6H_4	Me	**4e**	3	68	87
7	**3f**	4-FC_6H_4	*i*-Pr	**4f**	3	86	96
8	**3g**	4-ClC_6H_4	Et	**4g**	3	92	91
9	**3h**	4-BrC_6H_4	Et	**4h**	3	86	92
10	**3i**	4-$C(CH_3)_3C_6H_4$	Et	**4i**	5	60	94
11	**3j**	4-MeC_6H_4	Et	**4j**	5	69	94
12	**3k**	3-BrC_6H_4	Et	**4k**	2	87	92
13	**3l**	3-ClC_6H_4	Et	**4l**	2	95	94
14	**3m**	3-MeC_6H_4	Et	**4m**	2	96	96
15	**3n**	3-MeC_6H_4	Me	**4n**	3	75	91

[a] Unless otherwise noted, the reaction was carried out with 0.1 mmol α-keto phosphonates, using 10 mol% catalyst loading at –20 °C, **2a**/TFA= 1/2, solvent: ethyl acetate/acetone = 0.3 mL/0.2 mL. [b] Isolated yield. [c] Determined by chiral HPLC. [d] The absolute configuration was opposite to entry 1 when using catalyst **2d**.

The application scope of the catalytic system was then explored under the optimized conditions. As shown in Table 2, a broad range of α-keto phosphonates were subjected to the aldol reaction, and converted to corresponding tertiary α-hydroxy phosphonates in moderate to high yield with up to 97% ee. Among them, the influence of enantioselectivity was mostly dependent on the size of R^2 group. When the stereohindance of R^2 group was increased from the smaller methyl and ethyl to the bulkier isopropyl, better enantioselectivity turned out (Table 2, entries 1 and 3-7). Regardless of electron withdrawing or the electron donating group on the *para*- or *meta*- position of the aromatic ring, these substrates were underwent smoothly and obtained excellent enantioselectivities (91–97% ee) with moderate to high yields, besides methyl esters (Table 2, entries 3 and 6). Remarkably, when **2d** was employed in this system with the same catalyst loading, diethyl benzoyl phosphonate could be transformed to **4a** with opposite absolute configuration for product (Table 2, entry 2). To our delight, a number of aldehydes were also suitable substrates to give the corresponding products with excellent enantiomeric excess (up to 99%) and high yield (up to 88%), while modifying the conditions slightly (Scheme 2).



5a 3-$NO_2C_6H_4CHO$
5b 4-$CF_3C_6H_4CHO$
5c 3.4-$Cl_2C_6H_3CHO$

6a 88% Yield 97% Ee
6b 86% Yield 99% Ee
6c 87% Yield 97% Ee

Scheme 2 Asymmetric aldol reaction of aldehyde **5**.

In conclusion, we have developed a novel biphenyl-prolinamide as the organocatalyst for the catalytic asymmetric aldol reaction of α-keto phosphonates and aldehydes with good to excellent enantiomeric excess and moderate to high yields. These biphenyl compounds were synthesized conveniently and possessed comparable effect in catalytic reaction, indicating huge potentialities in asymmetric synthesis field. Further application of these catalysts to other reactions are underway.

We are grateful to the National Natural Science Foundation of China (Nos. 20732003 and 20702033) for financial support. We also thank Sichuan University Analytical & Testing Center for NMR analysis and X-ray crystal analysis and the State Key Laboratory of Biotherapy for HRMS analysis.

Notes and references

1 (*a*) R. L. Hilderbrand and T. O. Henderson, *The Role of Phosphonates in Living Systems*, CRC, Boca Raton, FL, 1983; (*b*) J. F. Dellaria Jr,, R. G. Maki, H. H. Stein, J. Cohen, D. Whittern, K. Marsh, D. J. Hoffman, J. J. Plattner and T. J. Perun, *J. Med. Chem.*, 1990, **33**, 534; (*c*) B. Stowasser, K. H. Budt, J. Q. Li, A. Peyman and D. Ruppert, *Tetrahedron Lett.*, 1992, **33**, 6625; (*d*) M. L. Moore and G. B. Dreyer, *Perspect. Drug Discovery Des.*, 1993, **1**, 85; (*e*) B. Z. Leder and H. M. Kronenberg, *Gastroenterology*, 2000, **119**, 866; (*f*) M. L. Peters, M. Leonard and A. A. Licata, *Clev. Clin. J. Med.*, 2001, **68**, 945.

2 (*a*) F. Wuggenig and F. Hammerschmidt, *Monatsh. Chem.*, 1998, **129**, 423; (*b*) P. Kafarski and B. Lecjzak, *J. Mol. Catal. B*, 2004, **29**, 99; (*c*) A. Maly, B. Lejczak and P. Kafarski, *Tetrahedron: Asymmetry*, 2003, **14**, 1019 and references therein.

3 (*a*) T. Arai, M. Bougauchi, H. Sasai and M. Shibasaki, *J. Org. Chem.*, 1996, **61**, 2926; (*b*) D. F. Wiemer, *Tetrahedron*, 1997, **53**, 16609; (*c*) M. J. Burk, T. A. Stammers and J. A. Straub, *Org. Lett.*, 1999, **1**, 387; (*d*) D. M. Cermak, Y. Du and D. F. Wiemer, *J. Org. Chem.*, 1999, **64**, 388; (*e*) H. Gröger and B. Hammer, *Chem.–Eur. J.*, 2000, **6**, 943; (*f*) B. J. Rowe and C. D. Spilling, *Tetrahedron: Asymmetry*, 2001, **12**, 1701; (*g*) A. E. Wróblewski and K. B. Balcerzak, *Tetrahedron: Asymmetry*, 2001, **12**, 427; (*h*) D. Y. Kim and D. F. Wiemer, *Tetrahedron Lett.*, 2003, **44**, 2803; (*i*) D. Skropeta and R. R. Schmidt, *Tetrahedron: Asymmetry*, 2003, **14**, 265; (*j*) O. I. Kolodiazhnyi, *Tetrahedron: Asymmetry*, 2005, **16**, 3295; (*k*) V. Nesterov and O. I. Kolodyazhnyi, *Russ. J. Gen. Chem.*, 2005, **75**, 1161; (*l*) B. Saito and T. Katsuki, *Angew. Chem., Int. Ed.*, 2005, **44**, 4600; (*m*) W. Zhang and M. Shi, *Chem. Commun.*, 2006, 1218; (*n*) O. I. Kolodiazhnyi, *Russ. Chem. Bull.*, 2006, **75**, 227; (*o*) V. D. Pawar, S. Bettigeri, S. S. Weng, J. Q. Kao and C. T. Chen, *J. Am. Chem. Soc.*, 2006, **128**, 6308; (*p*) K. Nakanishi, S. Kotani, M. Sugiura and M. Nakajima, *Tetrahedron*, 2008, **64**, 6415; (*q*) X. Zhou, X. H. Liu, X. Yang, D. J. Shang, J. G. Xin and X. M. Feng, *Angew. Chem., Int. Ed.*, 2008, **47**, 392; (*r*) F. Yang, D. B. Zhao, J. B. Lan, P. H. Xi, L. Yang, S. H. Xiang and J. S. You, *Angew. Chem., Int. Ed.*, 2008, **47**, 5646.

4 S. Samanta and C. G. Zhao, *J. Am. Chem. Soc.*, 2006, **128**, 7442.

5 (*a*) J. Liu, Z. G. Yang, Z. Wang, F. Wang, X. H. Chen, X. H. Liu, X. M. Feng, Z. S. Su and C. W. Hu, *J. Am. Chem. Soc.*, 2008, **130**, 5654; (*b*) J. L. Huang, J. Wang, X. H. Chen, Y. H. Wen, X. H. Liu and X. M. Feng, *Adv. Synth. Catal.*, 2008, **350**, 287; (*c*) X. H. Chen, J. Wang, Y. Zhu, D. J. Shang, B. Gao, X. H. Liu, X. M. Feng, Z. S. Su and C. W. Hu, *Chem.–Eur. J.*, 2008, **14**, 10896.

6 (*a*) T. Mandal, S. Samanta and C. G. Zhao, *Org. Lett.*, 2007, **9**, 943; (*b*) V. B. Gondi, K. Hagihara and V. H. Rawal, *Angew. Chem., Int. Ed.*, 2009, **48**, 776.

7 (*a*) A. A. Patchett and R. P. Nargund, 'Privileged Structures', in *Topics in Drug Design and Discovery*, G. L. Trainor, Ed, *Annu. Rep. Med. Chem. (Section IV)*, 2000, **35**, 289; (*b*) K. C. Nicolaou, C. N. C. Boddy, S. Bräse and N. Winssinger, *Angew. Chem., Int. Ed.*, 1999, **38**, 2096; (*c*) C. S. Hartley, C. Lazar, M. D. Wand and R. P. Lemieux, *J. Am. Chem. Soc.*, 2002, **124**, 13513; (*d*) P. Cyganik and M. Buck, *J. Am. Chem. Soc.*, 2004, **126**, 5960; (*e*) K.-U. Jeong, B. S. Knapp, J. J. Ge, S. Jin, M. J. Graham, F. W. Harris and S. Z. D. Cheng, *Chem. Mater.*, 2006, **18**, 680; (*f*) Y. Yang and A. Sayari, *Chem. Mater.*, 2007, **19**, 4117; (*g*) D. Riedel, M.-L. Bocquet, H. Lesnard, M. Lastapis, N. Lorente, P. Sonnet and G. Dujardin, *J. Am. Chem. Soc.*, 2009, **131**, 7344.

8 (*a*) G. Solladié, P. Hugelé, R. Bartsch and A. Skoulios, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1533; (*b*) K. Aikawa and K. Mikami, *Angew. Chem., Int. Ed.*, 2003, **42**, 5455; (*c*) B. H. Lipshutz, K. Noson, W. Chrisman and A. Lower, *J. Am. Chem. Soc.*, 2003, **125**, 8779; (*d*) R. Holzwarth, R. Bartsch, Z. Cherkaoui and G. Solladié, *Chem.–Eur. J.*, 2004, **10**, 3931; (*e*) G. Bringmann, A. J. P. Mortimer, P. A. Keller, M. J. Gresser, J. Garner and M. Breuning, *Angew. Chem., Int. Ed.*, 2005, **44**, 5384; (*f*) K. Aikawa and K. Mikami, *Chem. Commun.*, 2005, 5799; (*g*) P. J. Montoya-Pelaez, Y. S. Uh, C. Lata, M. P. Thompson, R. P. Lemieux and C. M. Crudden, *J. Org. Chem.*, 2006, **71**, 5921; (*h*) S. Superchi, R. Bisaccia, D. Casarini, A. Laurita and C. Rosini, *J. Am. Chem. Soc.*, 2006, **128**, 6893; (*i*) D. Casarini, L. Lunazzi, M. Mancinelli, A. Mazzanti and C. Rosini, *J. Org. Chem.*, 2007, **72**, 7667; (*j*) C. S. Xie, Y. H. Zhang and Y. Z. Yang, *Chem. Commun.*, 2008, 4810.

9 (*a*) K. Aikawa and K. Mikami, *Angew. Chem., Int. Ed.*, 2003, **42**, 5455; (*b*) B. H. Lipshutz, K. Noson, W. Chrisman and A. Lower, *J. Am. Chem. Soc.*, 2003, **125**, 8779; (*c*) S. Superchi, R. Bisaccia, D. Casarini, A. Laurita and C. Rosini, *J. Am. Chem. Soc.*, 2006, **128**, 6893.

10 (*a*) J. J. Becker, P. S. White and M. R. Gagné, *J. Am. Chem. Soc.*, 2001, **123**, 9478; (*b*) L. Q. Qiu, J. Wu, S. S. Chan, T. T.-L. Au-Yeung, J.-X. Ji, R. W. Guo, C. C. Pai, Z. Y. Zhou, X. S. Li, Q.-H. Fan and A. S. C. Chan, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 5815; (*c*) Y. H. Sun, X. B. Wang, J. P. Wang, Q. H. Meng, H. W. Zhang, L. J. Jiang and Z. G. Zhang, *Org. Lett.*, 2005, **7**, 5425; (*d*) X. B. Wan, Y. H. Sun, Y. F. Luo, D. Li and Z. G. Zhang, *J. Org. Chem.*, 2005, **70**, 1070; (*e*) T. Kano, O. Tokuda and K. Maruoka, *Tetrahedron Lett.*, 2006, **47**, 7423; (*f*) J. Wang, X. L. Hu, J. Jiang, S. H. Gou, X. Huang, X. H. Liu and X. M. Feng, *Angew. Chem., Int. Ed.*, 2007, **46**, 8468; (*g*) Y.-G. Wang, M. Ueda, X. S. Wang, Z. F. Han and K. Maruoka, *Tetrahedron*, 2007, **63**, 6042; (*h*) H. S. Lai, Z. Y. Huang, Q. Wu and Y. Qin, *J. Org. Chem.*, 2009, **74**, 283.

11 Crystal structure data for **2a**-(R_a, S_c): $C_{24}H_{30}N_4O_4$, M =438.52, orthorhombic, space group $P2_12_12_1a$ = 8.771(3), b = 9.743(3), c = 26.204(9) Å, $\alpha = 90$, $\beta = 90$, $\gamma = 90°$, $V = 2239.3(13)$ Å^3, $T = 293(2)$ K, $Z = 4$, 2417 reflections collected, 2391 independent reflections (R_{int} = 0.0070), the final R indices:$R1$ = 0.1969, $wR2$ = 0.1402 (all data). CCDC 738508.

12 (*a*) C. Cheng, J. Sun, C. Wang, Y. Zhang, S. Wei, F. Jiang and Y. D. Wu, *Chem. Commun.*, 2006, 215; (*b*) S. Mukherjee, J. W. Yang, S. Hoffmann and B. List, *Chem. Rev.*, 2007, **107**, 5471; (*c*) C. S. Da, L. P. Che, Q. P. Guo, F. C. Wu, X. Ma and Y. N. Jia, *J. Org. Chem.*, 2009, **74**, 2541.

13 For more details, see the Supporting Information.