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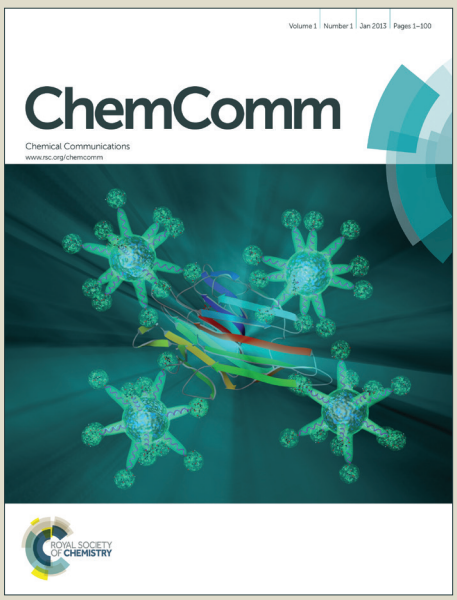





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ARTICLE TYPE

# Asymmetric Synthesis of Heteroaryl Atropisomers via a Gold-Catalyzed Cycloisomerization/Amination Cascade Reaction

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**The chiral gold (I) complex enables an enantioselective cycloisomerization/amination of boronic acids and diazenes in high yields. A wide scope of substrates bearing various functional groups was tolerated to generate structurally different hydrazide derivatives as a new type of atropisomers.**

Atropisomers, resulting from highly steric hindered rotation of one single bond (i.e. chiral axis), have received great interest from chemists for their widespread appearance in naturally occurring biologically active compounds and artificial chiral ligands for asymmetric catalysis.[1] However, the sensitivity of steric strain barrier to different conditions, such as temperature, solvent and light, would lead to axial rotation, which basically causes racemization.[2] This feature actually makes the enantioselective synthesis of atropisomers remain a big challenge in organic chemistry. Since Christie and Kenner reported the atropisomerism in resolution of 6,6'-dinitro-2,2'-diphenic acid in 1922,[3] the chemical resolution and derivatization from appropriate precursors were historically dominating in the preparation of optically pure atropisomers,[4] while catalytic asymmetric approaches have recently been much more fashionable.[5]

The atropisomers formed by catalytic synthesis so far are constituted of two types of different core structures as defined on the basis of the number of aromatic moieties at either end of the chiral axis. One type of atropisomers possessing a chiral axis connecting two aromatic moieties have been named as biaryl atropisomers (Fig. 1, a). The catalytic enantioselective construction of biaryl atropisomers have been intensively investigated and could be accessed by asymmetric oxidative coupling, cross-coupling and other methods.[5, 6] The other type of atropisomers are called non-biaryl atropisomers because they have a typical chiral axis connecting an aryl substituent and the nitrogen-related hindrance (Fig. 1, b). They can also been accessed by a variety of asymmetric catalytic transformation.[7-10] However, at least one traditional aryl was involved in both of the two types of atropisomers. Herein, we will demonstrate that a novel type of heteroaryl atropisomers which can be accessed by asymmetric catalysis. As a typical example, compounds **I** represent a completely new type of chiral molecules.

Nowadays, chiral gold catalysts have arisen as excellent promoters in various organic transformations[11] and therefore, have received a great deal of research interest. As a continuous interest in the gold-catalyzed asymmetric cascade reaction,[12] we initially probed a reaction between 2-(alkynyl)phenyl boronic acid **1** and a diazene-1,2-dicarboxylate **2** catalyzed by a chiral gold complex. Hopefully, the reaction will undergo a sequential intramolecular boryloxylation and [4+2]-type cyclization reaction with an azodicarboxylate (Scheme 1). As indicated by Sheppard,[13] this cascade reaction would be more reasonable to proceed than other pathways.

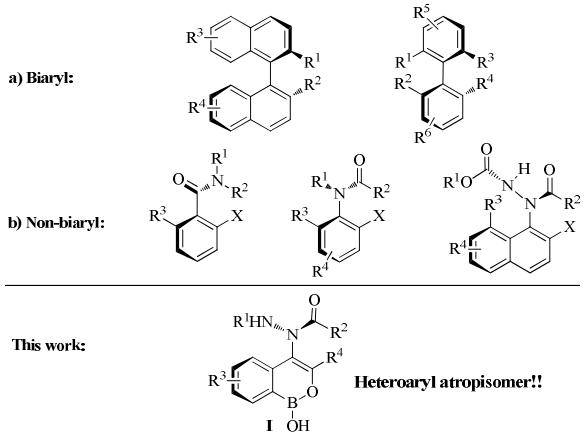
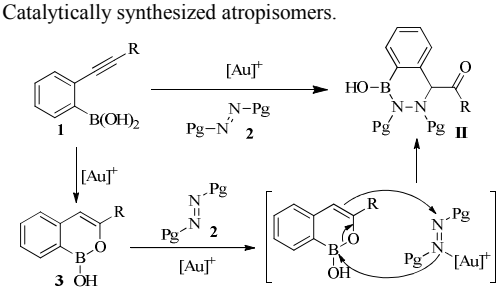



**Fig. 1** Catalytically synthesized atropisomers.

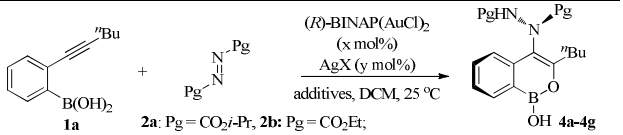



**Scheme 1** The initially planned gold-catalyzed cascade reaction.

However, the reaction of **1a** and **2a** *exclusively generated* an unpredicted product **4a** in 89% yield under the promotion of 6 mol% of (*R*)-BINAP $(AuCl)_2$ and 5 mol% of $AgSbF_6$ (Table 1, entry 1). More surprisingly, the compound **4a** is a chiral molecule with 36% ee. The unusual results encouraged us to carefully optimize the reaction conditions. BINAP showed the highest levels of enantioselectivity.[14] The ratio of gold complex to $AgSbF_6$ turned out to have a remarkable effect on the enantioselectivity (entries 1-2).[15] Obviously, the addition of molecular sieves dramatically enhanced the enantioselectivity (entries 3-5) and 4Å molecular sieves was convinced to be the best additive, capable of giving 73% yield and 70% ee (entry 4). The reaction proceeded comparably slower at 0 °C, but gave a higher stereoselectivity (entry 6). A variety of counterions of salt were then examined and the addition of $AgNTf_2$ provided the highest level of enantioselectivity (entries 6-9). Both the yield and enantioselectivity could be improved by using 10 mol% of chiral gold catalyst (entry 10, 83% yield and 82% ee). The influence of the protecting group on nitrogen of diazene-1,2-

dicarboxylates was next evaluated (entries 11-16). Indeed, the substituents exerted a remarkable impact on both the conversion and the stereoselection. Basically, the employment of sterically bulky di-*tert*-butyl diazene-1,2-dicarboxylate **2g** gave the corresponding hydrazide adduct **4g** with the highest level of enantioselectivity (85% ee, entry 16). The stereoselectivity was able to be further improved to 89% ee by conducting the reaction at the diluted concentration (entry 17).

**Table 1** Screening of chiral gold catalysts and optimization of conditions for the cascade asymmetric cycloisomerization/amination of 2-(hexynyl)phenylboronic acid **1a** with different azodicarboxylate esters **2**[a].



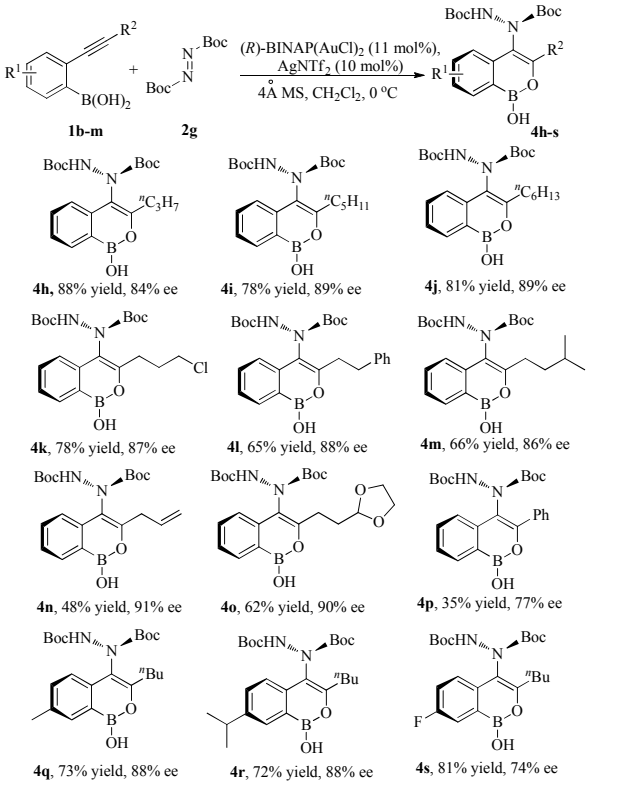

**2a**: Pg = $CO_2$*i*-Pr, **2b:** Pg = $CO_2$Et; **2c:** Pg = Cbz; **2d:** Pg = $CO_2$(cyclopentyl); **2e:** Pg = $CO_2CH_2$Bu-*t*; **2f:** Pg = Troc; **2g:** Pg = Boc.

| Entry | x:y | AgX (mol %) | Additives | Pg | Product | Yield (%)[b] | Ee (%)[c] |
|---|---|---|---|---|---|---|---|
| 1 | 1.2 | $AgSbF_6$ (5) | None | $CO_2$Pr-*i* | **4a** | 89 | 36 |
| 2 | 0.5 | $AgSbF_6$ (10) | None | $CO_2$Pr-*i* | **4a** | 88 | 17 |
| 3 | 1.2 | $AgSbF_6$ (5) | 3Å MS | $CO_2$Pr-*i* | **4a** | 66 | 67 |
| 4 | 1.2 | $AgSbF_6$ (5) | 4Å MS | $CO_2$Pr-*i* | **4a** | 73 | 70 |
| 5 | 1.2 | $AgSbF_6$ (5) | 5Å MS | $CO_2$Pr-*i* | **4a** | 75 | 65 |
| 6[d] | 1.2 | $AgSbF_6$ (5) | 4Å MS | $CO_2$Pr-*i* | **4a** | 43 | 77 |
| 7[d] | 1.2 | $AgPF_6$ (5) | 4Å MS | $CO_2$Pr-*i* | **4a** | 36 | 77 |
| 8[d] | 1.2 | $AgBF_4$ (5) | 4Å MS | $CO_2$Pr-*i* | **4a** | 46 | 72 |
| 9[d] | 1.2 | $AgNTf_2$ (5) | 4Å MS | $CO_2$Pr-*i* | **4a** | 48 | 79 |
| 10[d] | 1.1 | $AgNTf_2$ (10) | 4Å MS | $CO_2$Pr-*i* | **4a** | 83 | 82 |
| 11[d] | 1.1 | $AgNTf_2$ (10) | 4Å MS | $CO_2$Et | **4b** | 92 | 62 |
| 12[d] | 1.1 | $AgNTf_2$ (10) | 4Å MS | Cbz | **4c** | 60 | 59 |
| 13[d] | 1.1 | $AgNTf_2$ (10) | 4Å MS | $CO_2$(cyclopentyl) | **4d** | 61 | 77 |
| 14[d] | 1.1 | $AgNTf_2$ (10) | 4Å MS | $CO_2CH_2$Bu-*t* | **4e** | 79 | 81 |
| 15[d] | 1.1 | $AgNTf_2$ (10) | 4Å MS | Troc | **4f** | 82 | 80 |
| 16[d] | 1.1 | $AgNTf_2$ (10) | 4Å MS | Boc | **4g** | 72 | 85 |
| **17**[d,e] | **1.1** | **$AgNTf_2$ (10)** | **4Å MS** | **Boc** | **4g** | **70** | **89** |

[a] To a mixture of **2a** (0.4 mmol), catalysts and additives were added DCM (1 mL) and a solution of **1a** (0.2 mmol) in DCM (1 mL) and the reaction was performed for 12 h. [b] Isolated yields. [c] Determined by HPLC. [d] The reaction was run at 0 °C. [e] The concentration of **1a** was 0.025M in DCM (2 mL) and reaction time was 24 h.

With the optimized reaction conditions in hand, the generality of the protocol for various 2-alkynylphenyl boronic acid substrates was investigated (Scheme 1). The alkynylphenylboronic acids bearing linear alkyl substituents bonded to the carbon-carbon triple bond underwent a clean reaction to afford the corresponding products **4h-4k** in good yields and with high levels of enantioselectivity (84%-89% ee). The presence of either of branched alkyl, aryl substituents or functional groups at the alkynylboronic acid was allowed to undergo the cascade reaction, giving **4l-4o** in good yields and with high enantioselectivities. However, the introduction of a phenyl group led to significant erosion of yield and enantioselectivity (**4p**). As shown in **4q** and **4r**, the installation of an alkyl substituent at the benzene ring was also allowed to participate in the reaction in high yields and high stereoselectivities, while the electron-withdrawing group to some degree was deleterious to stereochemical control (**4s**).

The structure of **4** was determined by comparing with the analogous adduct **4t** through X-ray crystallographic analysis (Fig. 2).[16] Unfortunately, the single crystal of optically pure **4t** was unable to be obtained although a great deal of effort was




**Scheme 1** The generality of the cascade reaction with boronic acids.

directed toward optimizing conditions. Moreover, optical purity of the compounds was very sensitive to some reaction conditions and therefore, the derivatization of them into crystalline molecules always led to racemization. Consequently, the absolute configuration of the product was hard to be determined by commonly used methods.

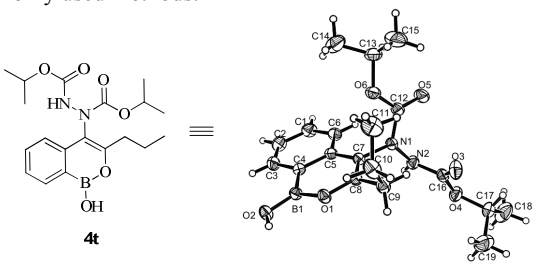



**Fig. 2** ORTEP representation of Racemic-**4t**.

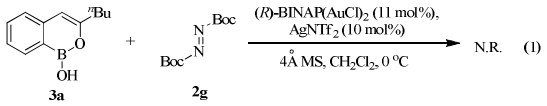
The VCD (Vibrational Circular Dichroism) technology has been accepted as a reliable new method to determine the configuration of chiral molecules.[17] Thus, a VCD study was performed on **4t** obtained in 80% ee from the cascade reaction (Fig. S1, ESI†). It is found that the two VCD curves matched well and therefore, the absolute configuration of **4t** was detemined to be *S* (Fig. S2, ESI†).

**Table 2** Barriers to racemization of **4g.**

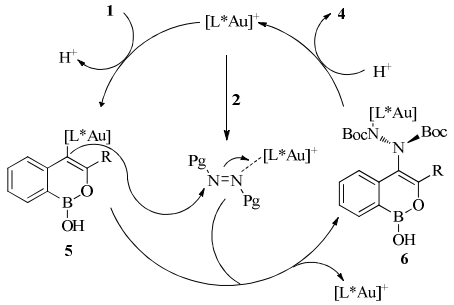
| Entry | Temp (°C) | Half-life (h) | $k$ ($10^{-6}$ $s^{-1}$) | $\Delta G^{\ddagger}_{temp}$ (kcal/mol) |
|---|---|---|---|---|
| 1 | 40 | 163.8 | 1.17 | 112.6 |
| 2 | 60 | 17.3 | 11.1 | 32.9 |
| 3 | 80 | 5.0 | 38.4 | 20.8 |

To understand the stability of this axial chirality, barriers to racemization of compound **4g** (89% ee, entry 17, Table 1) at different temperatures were measured. As shown in Table 3, the racemization was the first-order and the half-lives ranged from 5

h at 80 °C to 164 h at 40 °C (Table 2). Obviously, the lower temperature leads to a higher barrier to racemization.




To learn more details of the cascade reaction, a controlled reaction of boron enolate **3a**, generated from the gold-catalyzed cyclization, with **2g** was conducted under the optimized conditions. However, no product was observed with both **3a** and **2g** recycled, indicating that the more reactive species might be involved in the reaction (eqn (1)). Presumably, the Au (I) complex firstly coordinates to the carbon-carbon triple bond of **1**, enabling the formation of vinylgold intermediate **5**, which might stereoselectively attack the diazene **2** simultaneously activated by chiral gold complex via δ-coordination to the nitrogen.[12] After proton transfer, the final product **4** would be generated and the Au (I) complex was regenerated for the next catalytic cycle.




**Scheme 2** Proposed mechanism (L* = (*R*)-BINAP).

In summary, a family of unprecedented chiral molecules, heteroaryl atropisomers, has been accessed in high yields and fairly good enantioselectivity by using a chiral complex-catalyzed cascade cycloadditon/amination cascade reaction. The chirality of such atropisomers is relatively stable at room temperature, but undergoes racemization at the elevated temperature. The configuration of the novel chiral C-N axis was tentatively assigned by VCD calculation.

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## Notes and references

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†Electronic Supplementary Information (ESI) available: Experimental procedures, characterization data, copies of $^1$H NMR, $^{13}$C NMR and HPLC spectra, crystal data and structure refinement by VCD. See DOI: 10.1039/b000000x/

1 (a) E. L. Eliel, S. H. Wilen and M. P. Doyle, *Basic Organic Stereochemistry*, Wiley: New York, **2001**, 608; (b) *Chem. Soc. Rev.*, 2013, **42**, 8434.

2 (a) S. R. LaPlante, L. D. Fader, K. R. Fandrick, D. R. Fandrick, O. Hucke, R. Kemper, S. P. F. Miller and P. J. Edwards, *J. Med. Chem.* 2011, **54**, 7005; (b) N. Z. Burns, I. N. Krylova, R. N. Hannoush and P. S. Baran, *J. Am. Chem. Soc.*, 2009, **131**, 9172; (c) G. Bringmann, A. J. P. Mortimer, P. A. Keller, M. J. Gresser, J. Garner and M. Breuning, *Angew. Chem. Int. Ed.*, 2005, **44**, 5384; (d) J. Clayden, W. J. Moran, P. J. Edwards and S. R. LaPlante, *Angew. Chem. Int. Ed.*, 2009, **48**, 6398.

3 G. H. Christie and J. Kenner, *J. Chem. Soc., Trans.*, 1922, **121**, 614.

4 (a) A. Latorre, A. Urbano and M. C. Carreño, *Chem. Commun.*, 2009, 6652; (b) J. Clayden, J. Senior and M. Helliwell, *Angew. Chem. Int. Ed.*, 2009, **48**, 6270; (c) H. Takahashi, S. Wakamatsu, H. Tabata, T. Oshitari, A. Harada, K. Inoue and H. Natsugari, *Org. Lett.*, 2011, **13**, 760; (d) R. Rios, C. Jimeno, P. J. Carroll and P. J. Walsh, *J. Am. Chem. Soc.*, 2002, **124**, 10272; (e) W.-M. Dai and Y. Zhang, *Tetrahedron: Asymmetry*, 2004, **15**, 525.

5 (a) K. Tanaka, G. Nishida, A. Wada and K. Noguchi, *Angew. Chem. Int. Ed.* 2004, **43**, 6510; (b) V. Chan, J. G. Kim, C. Jimeno, P. J. Carroll and P. J. Walsh, *Org. Lett.*, 2004, **6**, 2051; (c) K. T. Barrett and S. J. Miller, *J. Am. Chem. Soc.*, 2013, **135**, 2963; (d) J. L. Gustafson, D. Lim and S. J. Miller, *Science,* 2010, **328**, 1251; (e) S. Shirakawa, K. Liu and K. Maruoka, *J. Am. Chem. Soc.*, 2012, **134**, 916; (f) O. Kitagawa, M. Yoshikawa, H. Tanabe, T. Morita, M. Takahashi, Y. Dobashi and T. Taguchi, *J. Am. Chem. Soc.*, 2006, **128**, 12923.

6 (a) Z.-B. Luo, Q.-Z. Liu, L.-Z. Gong, X. Cui, A.-Q. Mi and Y.-Z. Jiang, *Chem. Commun.,* 2002, 914; (b) Z.-B. Luo, Q.-Z. Liu, L.-Z. Gong, X. Cui, A.-Q. Mi and Y.-Z. Jiang, *Angew. Chem. Int. Ed.*, 2002, **41**, 4532; (c) N. B. Barhate and C.-T. Chen, *Org. Lett.*, 2002, **4**, 2529; (d) C. A. Mulrooney, X.-L. Li, E. S. DiVirgilio and M. C. Kozlowski, *J. Am. Chem. Soc.*, 2003, **125**, 6856; (e) T. Hayashi, K. Hayashizaki, T. Kiyoi and Y. Ito, *J. Am. Chem. Soc.*, 1988, **110**, 8153; (f) A. N. Cammidge and K. V. L. Crépy, *Chem. Commun.*, 2000, 1723; (g) J.-J. Yin and S. L. Buchwald, *J. Am. Chem. Soc.*, 2000, **122**, 12051; (h) K. Tanaka, G. Nishida, M. Ogino, M. Hirano and K. Noguchi, *Org. Lett.*, 2005, **7**, 3119; (i) K. Tanaka, *Chem. Asian J.*, 2009, **4**, 508.

7 D. P. Curran, H. Qi, S. J. Geib and N. C. DeMello, *J. Am. Chem. Soc.*, 1994, **116**, 3131.

8 (a) O.Kitagawa, M. Takahashi, M.Yoshikawa and T.Taguchi, *J. Am. Chem. Soc.*, 2005, **127**, 3676; (b) O. Kitagawa, M. Kohriyama and T. Taguchi, *J. Org. Chem.,* 2002, **67**, 8682; (c) J. Terauchi and D. P. Curran, *Tetrahedron: Asymmetry*, 2003, **14**, 587; (d) W.-L. Duan, Y. Imazaki, R. Shintani and T. Hayashi, *Tetrahedron*, 2007, **63**, 8529.

9 (a) K. Tanaka, K. Takeishi and K. Noguchi, *J. Am. Chem. Soc.*, 2006, **128**, 4586. (b) K.Tanaka and K Takeishi, *Synthesis,* 2007, **18**, 2920; (c) K.Tanaka, Y. Takahashi, T. Suda and M. Hirano, *Synlett*, 2008, **11**, 1724.

10 (a) S. Brandes, M. Bella, A. Kjærsgaard and K. A. Jørgensen, *Angew. Chem. Int. Ed.*, 2006, **45**, 1147; (b) S. Brandes, B. Niess, M. Bella, A. Prieto, J. Overgaard and K. A. Jørgensen, *Chem. Eur. J.*, 2006, **12**, 6039.

11 (a) F. López and J. L. Mascareñas, *Beilstein J. Org. Chem.*, 2013, **9**, 2250; (b) D. Garayalde and C. Nevado, *ACS Catal.*, 2012, **2**, 1462; (c) M. Rudolph and A. S. K. Hashmi, *Chem. Soc. Rev.*, 2012, **41**, 2448; (d) F. López and J. L. Mascareñas, *Beilstein J. Org. Chem.*, 2011, **7**, 1075; (e) A. Pradal, P. Y. Toullec and V. Michelet, *Synthesis*, 2011, **10**, 1501; (f) M. Bandini and A. Eichholzer, *Angew. Chem. Int. Ed.*, 2009, **49**, 9533; (g) M. J. Campbella and F. D. Toste, *Chem. Sci.*, 2011, **2**, 1369; (h) G.-H. Zhou, F. Liu and J.-L. Zhang, *Chem. Eur. J.*, 2011, **17**, 3101; (i) I. Alonso, B. Trillo, F. López, S. Montserrat, G. Ujaque, L. Castedo, A. Lledós, and J. L. Mascareñas, *J. Am. Chem. Soc.*, 2009, **131**, 13020; (j) W.-D. Rao, M.-J. Koh, P. Kothandaraman, and P. W. H. Chan, *J. Am. Chem. Soc.*, 2012, **134**, 10811; (k) W.-D. Rao, M.-J. Koh, D. Li, H. Hirao, and P. W. H. Chan, *J. Am. Chem. Soc.*, 2013, **135**, 7926.

12 B. Liu, K.-N. Li, S.-W. Luo, J.-Z. Huang, H. Pang and L.-Z. Gong, *J. Am. Chem. Soc.*, 2013, **135**, 3323.

13 C. Körner, P. Starkov and T. D. Sheppard, *J. Am. Chem. Soc.*, 2010, **132**, 5968.

14 See Table S1 in the ESI† for details

15 M. P. Muñoz, J. Adrio, J. C. Carretero and A. M. Echavarren, *Organometallics*, 2005, **24**, 1293.

16 CCDC970847. See the ESI† for details.

17 (a) T. B. Freedman, X.-L. Cao, R. K. Dukor and L. A. Nafie, *Chirality*, 2003, **15**, 743; (b) Y.-N. He, W. Bo, R. K. Dukor and L. A. Nafie, *Applied Spectroscopy*, 2011, **65**, 699.