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Stereolabile chiral biphenyl hybrids: crystallization-induced dynamic atropselective resolution involving supramolecular interactions†

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Crystallization-induced dynamic atropselective resolutions of three simple chiral biphenyl hybrids, (1*R*,1′*R*)-1,1′-(biphenyl-2,2′-diyl)diethanol 1, (1*R*,1′*R*)-1,1′-(biphenyl-2,2′-diyl)bis(ethane-1,1-diyl)diacetate 2 and (1*S*,1′*S*)-1,1′-(biphenyl-2,2′-diyl)bis(2,2′-dimethylpropan-1-ol) 3 were achieved. The axial chirality of the biphenyl backbones of 1–3 were found to be determined by (i) the steric bulkiness at the α position of the *ortho*-substituents, and (ii) the intermolecular interactions between the molecules. 1, which possesses the least sterically demanding methyl substituents, was found to form stereoselectively the *S*-atropisomer and gave enantiomerically pure supramolecular right-handed helices through strong and directional intermolecular hydrogen bonds in its crystal.

Axial chirality is a stereogenic element which arises from the hindered rotation of an aryl–aryl single bond.[1] The importance of these chiral elements has been exemplified in both biology[2] and chemistry.[3] A number of natural products are found to contain biaryl components in atropisomerically pure form or in racemates, for example, one atropisomer of michellamine, which contains 3 axial chiral centers, is found to exhibit significant anti-HIV activity *in vitro*.[2a] In chemistry, the axial chiral information encoded in BINAP and BINOL were found to be an excellent element to induce high stereoselectivities in asymmetric catalysis and synthesis. Thus the understanding in controlling the axial chirality of biaryl[4a,b] or polyaryl compounds[4c] is important and it has received increasing attention over the past decades.

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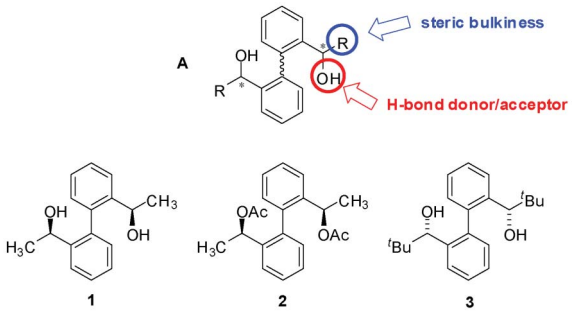
The axial configuration (denoted as R_a and S_a) of chiral biaryls is known to be controlled and stabilized by at least three substituents at the *ortho*-positions.[4] Some *ortho*-disubstituted biaryls were also found to stabilize the axial chirality. For example, Kumadaki had reported a series of fluoro-containing biphenyl carbinols which showed good enantiocontrol in Ti-catalyzed dialkylzinc additions.[5] Other examples containing sterically hindered substituents such as peptides,[6] cyclohexyl,[7] terpenoids[8] and carbinols[9] at the disubstituted *ortho*-positions were also reported. For most cases, the prime factors to control axial chirality are the presence of intramolecular hydrogen bond within the biaryls and the use of sterically bulky substituents.

Due to the importance of axial chirality in biology and chemistry, we intended to use the simplest *ortho*-disubstituted chiral biphenyl hybrids to study the relationship between the steric factors at the α-positions and the role of hydrogen bonds that control the atropisomerization. Surprisingly, our preliminary investigations indicated that the axial configuration was controlled completely by the least sterically demanding methyl substituent at the α-positions of the compound, without any involvement of intramolecular hydrogen bonds which is commonly observed in other studies.[6,8] Instead, its diastereoselectivity is achieved by extensive supramolecular interactions (*e.g.* intermolecular hydrogen bonds or electrostatic interactions) in both solution and solid state. To the best of our knowledge, there are only a few cases that have been reported on the use of supramolecular interactions to control stereolabile biphenyl moieties.[6c,10]

We, herein, report a fundamental study on the atropselectivities of axially chiral biphenyl moieties, which were predetermined by two *ortho*-substituted chiral auxiliaries for steric control and hydrogen bond formation (Scheme 1A). The hydrogen bond connectivities within the biphenyl system play an important role in the formation of an enantiomerically pure supramolecular architecture.

Biphenyl **1** (ESI†) was synthesized through a Ni-mediated homo-coupling reaction. It showed a high control of atropselectivity in solution. In nonpolar solvents such as $CDCl_3$, C_6D_6 and *d*-toluene, prominent high atropisomeric ratios of approximately 9 : 1 were obtained as a result of dynamic resolution (Scheme 2).[11]

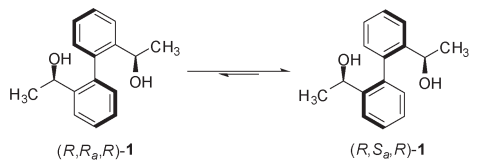


Scheme 1 Structures of biphenyl hybrids with different steric bulkiness and hydrogen bond formation units.

High atropselectivities (~8 : 2 to 7 : 3) were also observed in polar solvents such as CD_3COOD, CD_3OD and *d*-DMSO. However, the high selectivities are in contrast to the small zero-point energy difference (1.38 kcal mol^{-1}) between the two atropisomers (R,R_a,R)-**1** and (R,S_a,R)-**1** as calculated by DFT (Table S1, ESI†).

Further investigation of atropisomerically pure **1** in solution was conducted, and an aggregation of **1** might have occurred. Firstly, the chemical shifts of hydroxyl protons of **1** in concentrated solution were shifted downfield (Fig. S1, ESI†) and it is generally believed to be caused by stronger hydrogen bond formation.[12] In addition, circular dichroism (CD) showed two bands in $CHCl_3$. However the corresponding CD bands were weaker in MeOH (Fig. S2, ESI†). Furthermore, a larger aggregation can be indicated by diffusion-ordered spectroscopy (DOSY) NMR, since the relative diffusion coefficient of **1** decreased with increasing concentration (Fig. S3, ESI†).[13,14]

Recrystallization of **1** from diethyl ether showed a dynamic atropselective resolution of two diastereomers. This observation can be described as a phenomenon of an asymmetric transformation of second kind.[15] The molecule crystallized in a monoclinic non-centrosymmetric space group $P2_1$ with $Z = 4$. The molecular structure of **1** in Fig. 1a showed a stereogenic aryl–aryl center as S_a configuration and all molecules possess the same sense axial chirality. Two hydroxyl groups of **1** are directed to the same orientation, and forcing the two methyl groups to point outward to minimize the steric hindrance between molecules. The molecular structure is mainly stabilized by strong intermolecular hydrogen bonds (OH···O distance of 1.74–1.87 Å), leading to a single-stranded enantiomerically pure infinite helix along the *c*-axis (Fig. 1b). The pitch of the helix is *ca.* 9.28 Å. It is of interest to note that the strand further interacts with its nearby strand by forming additional short intermolecular (sp^2)C–H···π interactions (C43–H43A···Cg1 distance of 2.79 Å).[16,17] Overall, the *P* helicity is



Scheme 2 Atropisomerization of (R,R_a,R)-**1** and (R,S_a,R)-**1**.

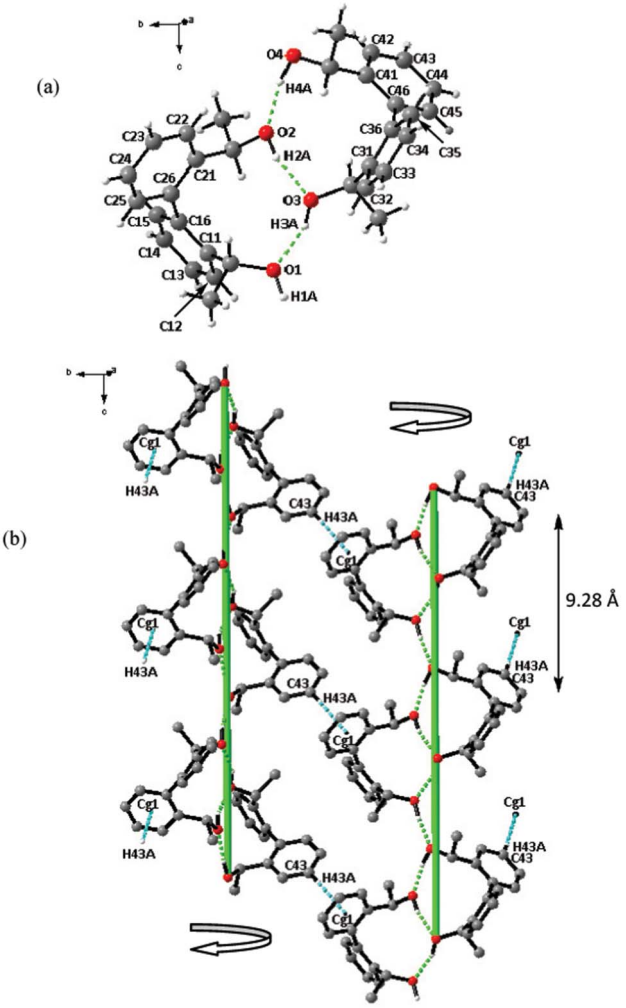


Fig. 1 (a) Single crystal X-ray structure of **1** with a partial labelling scheme showing strong intermolecular hydrogen bonds (torsion angles of biphenyl rings of 82.81(27)–87.83(27)° and axial configuration of S_a). (b) Crystal packing of **1** showing two strands of supramolecular right-handed helixes and inter-strands (sp^2)C–H···π interaction (C43–H43A···Cg1) (hydrogens that are not involved in interactions are omitted for clarity).

imposed by the predefined S_a stereochemistry of the biphenyl moiety.[18] It is interesting that no intramolecular hydrogen bond is observed within the molecule structure of **1**. Such phenomenon is in contrast to all other reported chiral *ortho*-substituted biphenyl systems, in which the intramolecular hydrogen bondings is the main force in stabilizing the absolute configuration of the biphenyl rings.[6c,8] Instead, the axial conformation of the biphenyl **1** is fixed in a cooperative way through strong and uni-directional intermolecular hydrogen bonding. A summary of hydrogen bondings and other interactions are listed in Table 1.

The effect of supramolecular interaction to the axial chirality of biphenyl hybrids was further studied with biphenyl **2**, with the hydroxyl units of **1** replaced by acetyl groups. The axial configuration of **2** is unstable in solution (chloroform), and it equilibrated rapidly to obtain an atropisomer ratio of 6 : 4 after dissolution for a few hours. The low stereoselectivities might be

Table 1 Selected structural parameters for biphenyl **1–3** and ***rac*-1**

Biphenyl	D–H···A	Distance of (H···A) (Å)	Distance of (D···A) (Å)	Angle of (D–H–A) (°)
1	O1–H1A···O4	1.79	2.783(9)	171
	O3–H3A···O1	1.87	2.823(1)	158
	O2–H2A···O3	1.81	2.775(10)	159
	O4–H4A···O2	1.74	2.700(7)	165
	C43–H43A···Cg1[a]	2.79	3.715(15)	177
2	C10–H10C···O1	2.61	3.470(2)	149
	C2–H2A···O2	2.52	3.331(2)	146
	C10–H10B···O2	2.86	3.770(3)	160
	C8–H8C···Cg2[b]	2.85	3.753(2)	157
3	O1–H11···O2	1.96	2.874(2)	170
	O2–H21···O2	1.89	2.792(2)	179
	O2–H22···O1	2.07	2.874(2)	144
***rac*-1**	O1–H1···O6	2.09	2.865(5)	153
	O6–H6···O8	1.95	2.790(5)	177
	O8–H8···O3	1.91	2.755(4)	172
	O3–H3···O5	2.15	2.934(5)	158
	O5–H5···O4	1.96	2.704(5)	150
	O4–H4···O2	2.01	2.819(4)	171
	O2–H2···O7	1.94	2.739(4)	155
	O7–H7···O1	2.14	2.912(5)	150
	C35–H35A···Cg3[c]	2.79	3.618(3)	149

[a] Cg1 is the centroid of aryl ring C21–C26 of **1**. [b] Cg2 is the centroid of aryl ring C1–C6 of **2**. [c] Cg3 is the centroid of aryl ring C81–C86 of ***rac*-1**.

due to a small energy difference (2.32 kcal mol^{-1}) in DFT calculations between (*R*,R_a,*R*)-**2** and (*R*,S_a,*R*)-**2** (Table S2, ESI†).

However, dynamic atropselective resolution of two diastereomers was observed upon crystallization of **2**. The crystal structure of the more thermodynamically stable isomer exhibits an R_a absolute configuration of the biphenyl rings (Fig. 2), unlike biphenyl **1**. The molecule crystallizes in an orthorhombic $P2_12_12$ space group. Only weak electrostatic intermolecular interactions were observed between the molecules in this crystal structure (Table 1). The interactions formed between (i) O=C(O) of acetyl groups and CH of the methyl substituents at the α-positions, having C10H10C···O1 distances of 2.61 Å, (ii) (sp^2)C–H···O of C2H2A···O2 with distance of 2.52 Å. In the packed structure, along the *ab* plane, a total of six intermolecular interactions are found in one molecule, which extended to give an enantiopure two-dimensional sheet (Fig. 2a). The layers are also stacked in close proximity by four weak electrostatic interactions of which two of them are H10B···O2 of 2.86 Å and two are (sp^3)C–H···π interactions with C8H8C···Cg2 of 2.85 Å (Fig. 2b), giving an enantiopure supramolecular network.

The effect of steric hindrance at the *ortho*-substituents to the atropselectivity of biphenyls was also investigated. Biphenyl **3** (ESI†) showed complete diastereoselectivity in both solution and solid state. The molecule **3** crystallizes in a tetragonal $P4_32_12$ space group with $Z = 8$. The crystal structure of **3** presented a dimer with a configuration of (*S*,R_a,*S*) (Fig. 3). The dimer is mainly held strongly by only three intermolecular hydrogen bonds (1.89–2.07 Å, Table 1).[17] This is very different from a dimeric racemate of ***rac*-3**,[19] which exhibits four intermolecular hydrogen bonds (2.04–2.09 Å) forming a distorted square hydrogen bonds unit. Moreover, the torsional angle of **3** is smaller than that of ***rac*-3** (*S*,R_a,*S* = 76.56(71)° and *R*,S_a,*R* = −74.53(77)°). For the enantiomerically pure **3**, the *t*-butyl groups are in close proximity to the

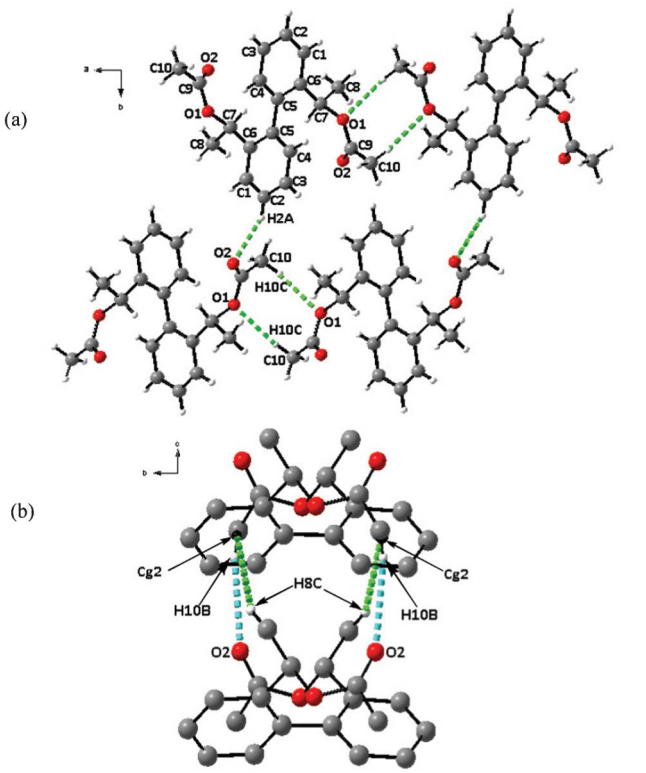


Fig. 2 (a) Single crystal X-ray structure of **2** with a partial labelling scheme showing multiple electrostatic interactions (torsion angles of biphenyl rings of 94.35(15)° and axial configuration of R_a). Symmetry equivalent atoms were generated with symmetry operation −*x*, −*y*, −*z*. (b) Crystal packing of **2** (along the *a*-axis) showing electrostatic interactions (H10B···O2: 2.86 Å) and (sp^3)C–H···π interaction (C8H8C···Cg2: 2.85 Å) between 2 layers. (Hydrogens that are not involved in interactions are omitted for clarity.)

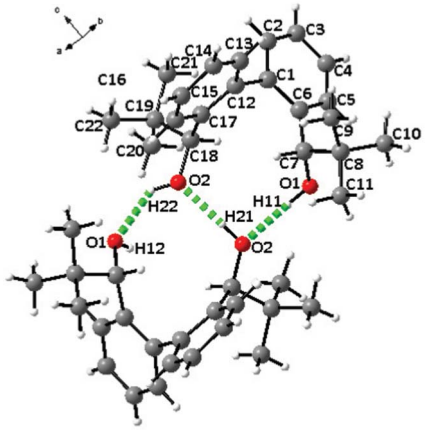


Fig. 3 Molecular structure and single crystal X-ray structure of dimer of **3**, with a partial labelling scheme, showing intermolecular hydrogen bonds (torsion angles of biphenyl rings of 71.10(28)° and axial configuration of R_a).

hydroxyl groups of the ligands, making the hydroxyl groups difficult to form extensive intermolecular hydrogen bonds as observed in the case of **1**. In solution, the helical chirality of **3** is maintained in all solvents. DFT calculations on the diastereomers of **3** show a good agreement to the excellent diastereoselectivity (Table S3, ESI†).

Apart from polymeric structure, the axial chirality of stereolabile biphenyl **1** can also be maintained by forming a different supramolecular structure. Opposite diastereomers of biphenyl **1**, (R,S_a,R)-**1** and (S,R_a,S)-**1**, were mixed in a ratio of 1 : 1 in solution. Interestingly, the crystal structure (Fig. 4) shows that the molecules self-assembled into a hetero-tetrameric unit containing two diastereomeric pairs *via* a chiral self-discrimination process. Self-assembly of tetramers such as tetrameric square with a rigid biphenyl backbone is known.[20] Examples of tetrameric assemblies that are based on a conformationally flexible biphenyl moiety are exceptional.

The molecule ***rac*-1** crystallizes in a monoclinic $P2_1/n$ space group. In our structure, the four molecules are principally held together by a total of eight intermolecular hydrogen bonds (1.91–2.14 Å) which are longer than that of the helical structure of (R,S_a,R)-**1** (Table 1). Moreover, the tetrameric unit is further maintained by an additional (sp^2)C–H···π interaction with a short distance of 2.79 Å.[17] In order to facilitate the formation of a 2 : 2 tetramer, which is supposed to be more sterically congested, the conformation of each molecule has to be adjusted independently as revealed by the difference in torsional angles between the two phenyl rings (varied from 74.40(46)° to 95.44(40)°) and intramolecular O···O distances (varied from 4.120(5) Å to 4.433(4) Å) (Fig. 4). The whole supramolecular structure is asymmetric as observed in the hydrogen bond networks. This slight variation is believed to be originated from the flexibility of the molecule and makes this tetramer unique.

The key factors for controlling the atropselectivities of biphenyl hybrids are (i) the steric bulkiness of the *ortho*-substituents; and (ii) the intermolecular interactions formed within or between biphenyl compound(s). Previous studies indicate that the steric

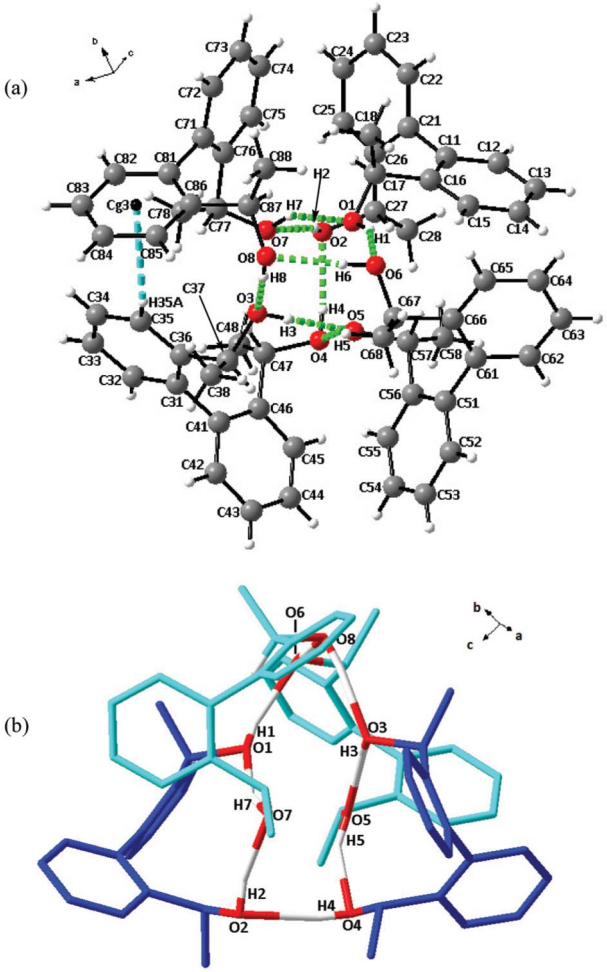


Fig. 4 (a) Single crystal X-ray structure of ***rac*-1**, with a partial labelling scheme, showing the network of hydrogen bonds and a (sp^2)C–H···π interaction (C35–H35A···Cg3). (Torsion angles of biphenyl rings and intramolecular O···O distances: (R,S_a,R)-**1**, 74.40(46)°, 4.120(5) Å and 94.85(40)°, 4.681(5) Å, (S,R_a,S)-**1**, 83.73(42)°, 4.328(6) Å and 95.44(40)°, 4.433(4) Å). (b) Wire model of ***rac*-1** showing relative positions of (R,S_a,R)-**1** (pale blue) and (S,R_a,S)-**1** (blue) and the network of hydrogen bonds (hydrogens that are not involved in interactions are omitted for clarity).

factor is the dominant effect to induce high atropselectivity of biaryl compounds, as observed from the DFT calculations.[8a] In theory, biphenyl **1** should not be able to induce high atropselectivity of the biphenyl rings, since it possesses the least sterically demanding methyl groups, however, this was not the case in our study. This is because the dominant factor of **1** is its extensive intermolecular interactions, which overrule its steric effects. Moreover, such supramolecular interactions lead biphenyl **2** to have complete atropselectivity in the solid state.

This study shows some distinct examples of using supramolecular interactions to control the atropselectivities in which they are seldom observed in other similar biphenyl carbinols systems.[6c,10] In most cases, complete atropselectivity of biphenyl compounds were achieved. We believe this facile and effective strategy in the synthesis of configurationally well-defined axially chiral systems can be applied in the construction of various chiral

functional units such as chiral supramolecular materials and chiral catalysts. Works in catalytic activities of these enantiopure biphenyl hybrids in asymmetric catalysis are currently being studied.

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References

1 (*a*) R. Adams and H. C. Yuan, *Chem. Rev.*, 1933, **12**, 261; (*b*) G. H. Christie and J. Kenner, *J. Chem. Soc. Trans.*, 1922, **121**, 614.
2 (*a*) K. P. Manfredi, J. W. Blunt, J. H. II. Cardellina, J. B. McMahon, L. L. Pannell, G. M. Cragg and M. R. Boyd, *J. Med. Chem.*, 1991, **34**, 3402; (*b*) H.-C. Chiang, D.-P. Wu, I.-W. Cherng and C.-H. Ueng, *Phytochemistry*, 1995, **39**, 613; (*c*) B. K. Hubbard and C. T. Walsh, *Angew. Chem., Int. Ed.*, 2003, **42**, 730.
3 (*a*) A. Miyashita, A. Yasuda, H. Takaya, K. Toriumi, T. Ito, T. Souchi and R. Noyori, *J. Am. Chem. Soc.*, 1980, **102**, 7932; (*b*) J. G. Strong, *PharmChem.*, 2003, **2**, 20; (*c*) K.-C. Sham, C.-S. Lee, K.-Y. Chan, S.-M. Yiu, W.-T. Wong and H.-L. Kwong, *Polyhedron*, 2011, **30**, 1149.
4 (*a*) G. Bringmann, A. J. R. Mortimer, P. A. Keller, M. J. Gresser, J. Garner and M. Breuning, *Angew. Chem., Int. Ed.*, 2005, **44**, 5384; (*b*) G. Bringmann, T. Gulder, T. A. M. Gulder and M. Breuning, *Chem. Rev.*, 2011, **111**, 563; (*c*) R. Katoono, H. Kawai, K. Fujiwara and T. Suzuki, *Chem. Commun.*, 2008, 4906.
5 M. Omote, K. Sato, A. Ando and I. Kumadaki, *Curr. Org. Synth.*, 2007, **4**, 137 and reference therein.
6 (*a*) V. Brandmeier, M. Feigel and M. Bremer, *Angew. Chem., Int. Ed. Engl.*, 1989, **28**, 486; (*b*) C. Weigand, M. Feigel and C. Landrafe, *Chem. Commun.*, 1998, 679; (*c*) B. Herradón, A. Montero, E. Mann and M. A. Maestro, *CrystEngComm*, 2004, **6**, 512.
7 M. Nieger, H. Hupfer and M. Bolte, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.*, 1998, **54**, 656.
8 (*a*) B. Goldfuss and F. Rominger, *Tetrahedron*, 2000, **56**, 881; (*b*) Y. Alphagut, B. Goldfuss and J. M. Neudörfl, *Beilstein J. Org. Chem.*, 2008, **4**, 25.
9 D. Casarini, L. Lunazzi, M. Mancinelli, A. Mazzanti and C. Rosini, *J. Org. Chem.*, 2007, **72**, 7667.
10 H. Degenbeck, A.-S. Felten, J. Etxebarria, E. C. Escudero-Adán, J. Benet-Buchholz and A. Vidal-Ferran, *Cryst. Growth Des.*, 2012, **12**, 2719.
11 Ratios of atropisomers were obtained by dissolving atropisomeric pure **1** in different solvents (0.01 M): $CDCl_3$ (90 : 10), C_6D_6 (91 : 9), d-toluene (88 : 12), CD_3NO_2 (83 : 17), CD_3COOD (82 : 18), CD_3OD (74 : 26) and d-DMSO (68 :32).
12 M. A. Wendt, J. Meiler, F. Weinhold and T. C. Farrar, *Mol. Phys.*, 1998, **93**, 145.
13 (*a*) B. J. B. Folmer, R. P. Sijbesma and E. W. Meijer, *J. Am. Chem. Soc.*, 2001, **123**, 2093; (*b*) S.-L. Li, T. Xiao, W. Xia, X. Ding, Y. Yu, J. Jiang and L. Wang, *Chem.–Eur. J.*, 2011, **17**, 10716.
14 A. T. ten Cate, P. Y. W. Dankers, H. Kooijman, A. L. Spek, R. P. Sijbesma and E. W. Meijer, *J. Am. Chem. Soc.*, 2003, **125**, 6860.
15 (*a*) R. J. Arthur, M. P. Coogan, M. Casadesus, R. Haigh, D. A. Headspith, M. G. Francesconi and R. H. Laye, *CrystEngComm*, 2009, **11**, 610; (*b*) K. M. J. Brands and A. J. Davies, *Chem. Rev.*, 2006, **106**, 2711.
16 (*a*) H. Suazawa, T. Yoshida, M. Hirota, H. Takahashi, Y. Umezawa, K. Honda, S. Tsuboyma and M. Nishio, *J. Chem. Soc., Perkin Trans. 1*, 2001, 2053; (*b*) S. N. Nayak, R. Sathishkumar and T. N. G. Row, *CrystEngComm*, 2010, **12**, 3112.
17 Other longer C–H···π distances are shown in Table S5, ESI.†.
18 I. Hisaki, T. Sasaki, N. Tohnai and M. Miyata, *Chem.–Eur. J.*, 2012, **18**, 10066.
19 V. J. Lillo, C. Gómez and M. Yus, *Tetrahedron Lett.*, 2009, **50**, 2266.
20 M. Tichý, T. Kraus, J. Závada, I. Císařová and J. Podlaha, *Tetrahedron: Asymmetry*, 1999, **10**, 3277.

