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Unexpected stereoselective sodium acetate catalyzed multicomponent cyclization of aryl aldehydes, malononitrile and acetone into *cis*-4-dicyanomethylene-2,6-diarylcyclohexane-1,1-dicarbonitriles

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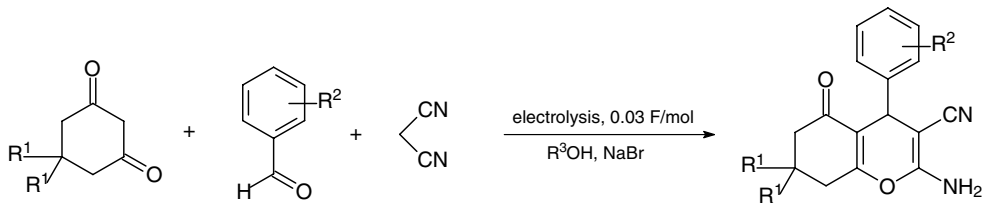
Abstract—A new type of multicomponent reaction is described in which five organic molecules form a cyclohexane ring. Aryl aldehydes, malononitrile and acetone in the presence of a catalytic amount of sodium acetate are stereoselectively cyclized into *cis*-4-dicyanomethylene-2,6-diarylcyclohexane-1,1-dicarbonitriles in 30–60% yields.

Multicomponent reactions (MCRs), an important subclass of tandem reactions,[1] are one-pot processes in which three or four easily accessible components react to form a single product, which incorporates essentially all the carbon atoms of the starting materials.[2] The development of MCRs designed to prepare biologically active compounds has become an important area of research in organic, combinatorial and medicinal chemistry.[3] In times where a premium is put on speed, diversity and efficiency in the drug discovery process, MCR strategies offer significant advantages over conventional linear-type syntheses due to their flexible, convergent and atom efficient nature.[4] The application of high-throughput screening in biomedical studies has dramatically increased the demand for substances, and the search for new drug-like molecules has taken on new urgency.[5] Thus, the success of combinatorial chemistry in drug discovery is dependent considerably on further



Scheme 1.

Keywords: Multicomponent reaction; Stereoselectivity; Catalysis; Aryl aldehydes; Malononitrile; Acetone; Sodium acetate; 2,6-Diarylcyclohexane-1,1-dicarbonitriles.
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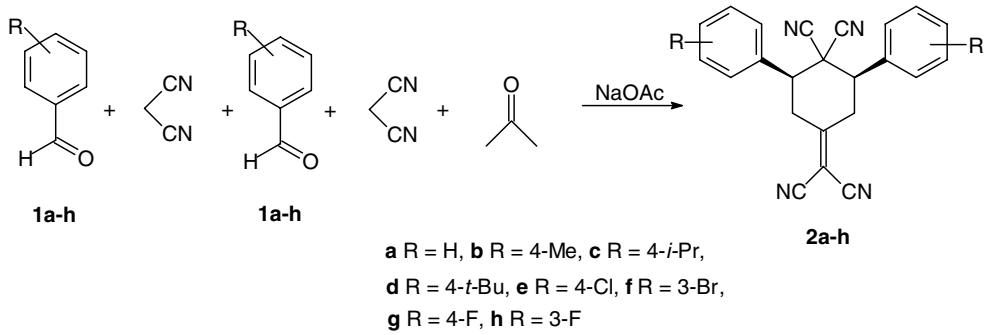


Scheme 2.

Table 1. Stereoselective cyclization of benzaldehyde **1a**, malononitrile and acetone into diarylcyclohexane **2a**[a,b,10]

Ratio aldehyde/malononitrile	Base	Yield[c] (%)
1:2	NaOAc	21
1:1	NaOAc	37
3:2	NaOAc	62
2:1	NaOAc	46
3:2	KOAc	35
3:2	Na_2CO_3	32
3:2	K_2CO_3	25
3:2	KF	50

[a] 5–20 mmol of benzaldehyde **1a**, 10 mmol of malononitrile, 0.01 mmol of base, in 10 ml of acetone, 20 °C, 5 h stirring before isolation of **2a** by filtration.
[b] Melting point 267–268 °C, lit. melting point 269–270 °C.
[c] Isolated yields.

Table 2. Stereoselective cyclization of substituted benzaldehydes **1b–h**, malononitrile and acetone into diarylcyclohexanes **2b–h**[a,10]

Aldehyde	R	Diarylcyclohexane	Yield[b] (%)
1b	4-Me	**2b**	31
1c	4-*i*-Pr	**2c**	29
1d	4-*t*-Bu	**2d**	28
1e	4-Cl	**2e**	33
1f	3-Br	**2f**	36
1g	4-F	**2g**	52
1h	3-F	**2h**	59

[a] 15 mmol of substituted benzaldehyde, 10 mmol of malononitrile, 0.01 mmol of NaOAc, in 10 ml of acetone, 20 °C, 5 h stirring before isolation of **2b–h** by filtration.
[b] Isolated yields.

advances in MCR methodology and, according to current synthetic requirements, effective and environmentally benign multicomponent procedures are particularly welcome.

The Michael reaction of 1,5-diaryl-1,4-pentadiene-3-ones with active methylene compounds has long been employed to prepare highly substituted cyclohexanones, which are of interest in terms of their stereochemistry[6] and as precursors for the synthesis of spiro-pyrimidines[7] with a broad spectrum of chemotherapeutic properties

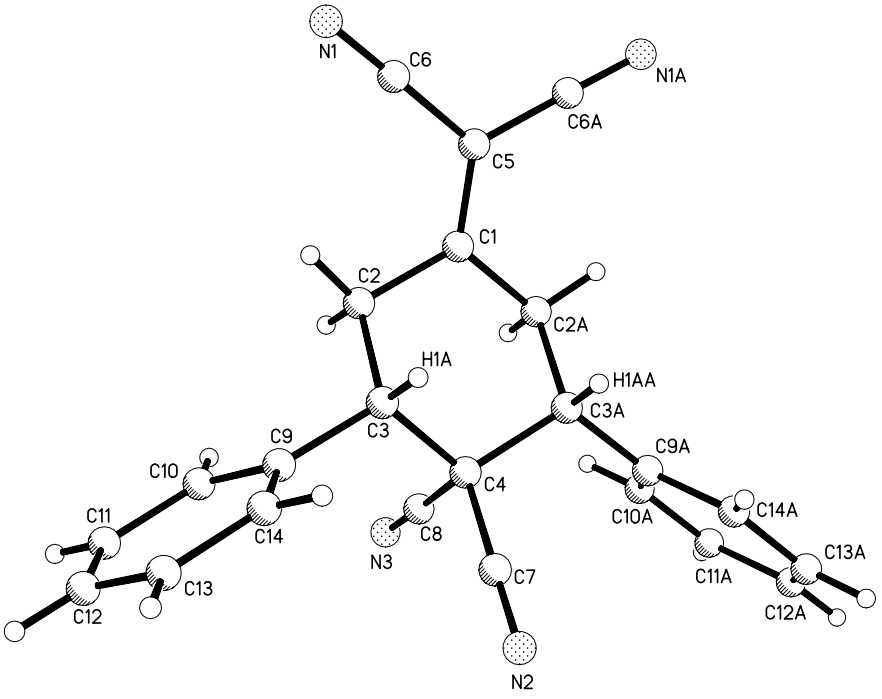
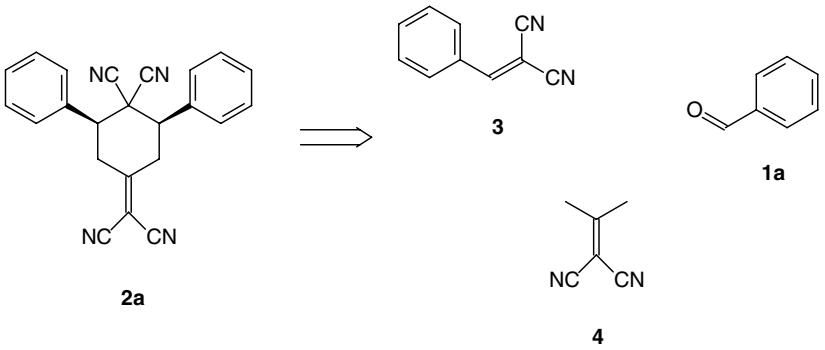


Figure 1. PLUTO view of **2a**.



Scheme 3.

such as hypnotic, antitumour, antiviral, anticonvulsant and analgesic activities.[8]

Recently, we reported new electrocatalytic multicomponent chain transformation of cyclic 1,3-diketones, aryl aldehydes and malononitrile into 2-amino-4-aryl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitriles under mild conditions by electrolysis in an undivided cell in alcohols in the presence of sodium bromide as an electrolyte (Scheme 1).[9]

In the present study, we report our results on a new type of the multicomponent reaction where five molecules react stereoselectively to form a cyclohexane ring. Thus, aromatic aldehydes **1a**–**h**, malononitrile and acetone in the presence of a catalytic amount of sodium acetate were stereoselectively transformed into *cis*-4-dicyanomethylene-2,6-diarylcyclohexane-1,1-dicarbonitriles **2a**–**h** (Tables 1 and 2, Scheme 2).

First, to evaluate the synthetic potential of the proposed procedure and to optimize the reaction conditions, the transformation of benzaldehyde **1a**, malononitrile and acetone in the presence of base into diarylcyclohexane **2a** was studied (Table 1).

Under optimal conditions (ratio aldehyde/malononitrile 3:2, NaOAc as base) the stereoselective cyclization of substituted benzaldehydes **1b**–**h**, malononitrile and acetone was carried out and the results are summarized in Table 2.

The NMR data of diarylcyclohexanes **2a**–**h** clearly show that only one of the two possible stereoisomers was obtained in all cases. The structure of **2a** as the *cis*-isomer was established by single-crystal X-ray diffraction (Fig. 1).[12] Taking into consideration that *cis*-isomers of diarylcyclohexanes of **2a**–**h** are more stable from a thermodynamic point of view,[6c] all the other diarylcyclohexanes **2b**–**h** should have similar structures.

Retro synthesis of **2a** clearly shows three fragments (Scheme 3).

Nevertheless, direct reaction of **1a**, **3** and **4** under the conditions studied resulted in formation of **2a** in only 18% yield. Thus, parallel mechanisms for the formation of **2a** should exist. We have also found that reaction of **4**, 2 equiv of **1a** and malononitrile results in formation of **2a** in 23% yield and the reaction of **4** with 2 equiv of **3** led to diphenylcyclohexane **2a** in 35% yield. Table 1 clearly shows that excess aldehyde was necessary for the optimal formation of **2a**. Taking the above results into account, the following mechanisms for the NaOAc catalyzed stereoselective cyclization of aromatic aldehydes **1a**–**h**, malononitrile and acetone into diarylcyclohexanes **2a**–**h** can be proposed (Scheme 4).

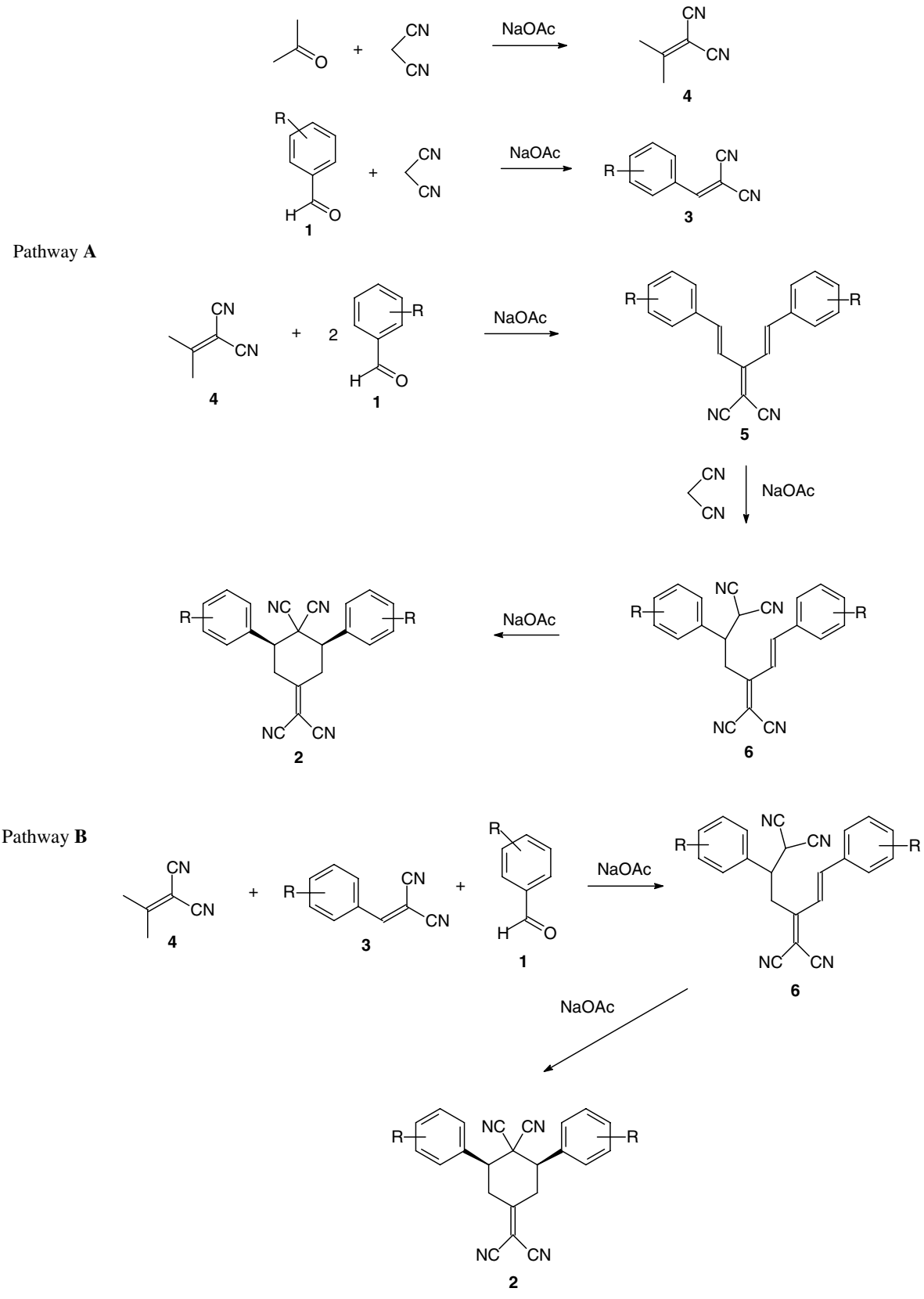
Sodium acetate catalyzes the condensation of acetone and the aldehyde with malononitrile. A similar condensation of carbonyl compounds with malononitrile catalyzed by sodium acetate was reported earlier.[13] Further, at least three reaction pathways could lead to diarylcyclohexanes **2a**–**h**. Pathway **A** involves condensation of *iso*-propylidenemalononitrile **4** and two molecules of aldehyde **1** with the formation of linear substituted triene **5**. Subsequent Michael addition of malononitrile to **5** and cyclization leads to diarylcyclohexanes **2a**–**h**. The final step has earlier been reported as the interaction of 1,5-diphenylpenta-1,4-diene-3-one with malononitrile leading to **2a**.[11]

Pathway **B** involves reaction of *iso*-propylidenemalononitrile **4**, benzylidenemalononitrile **3** and aldehyde **1** giving rise to diaryltetracyanodiene **6**, which is further cyclized into **2**.

In pathway **C**, the consecutive addition of *iso*-propylidenemalononitrile **4** to two molecules of benzylidenemalononitrile **3** leads to diphenylheptane **7**. Then formation of anion **A** takes place, followed by elimination of the anion of malononitrile and then cyclization to give **2**.

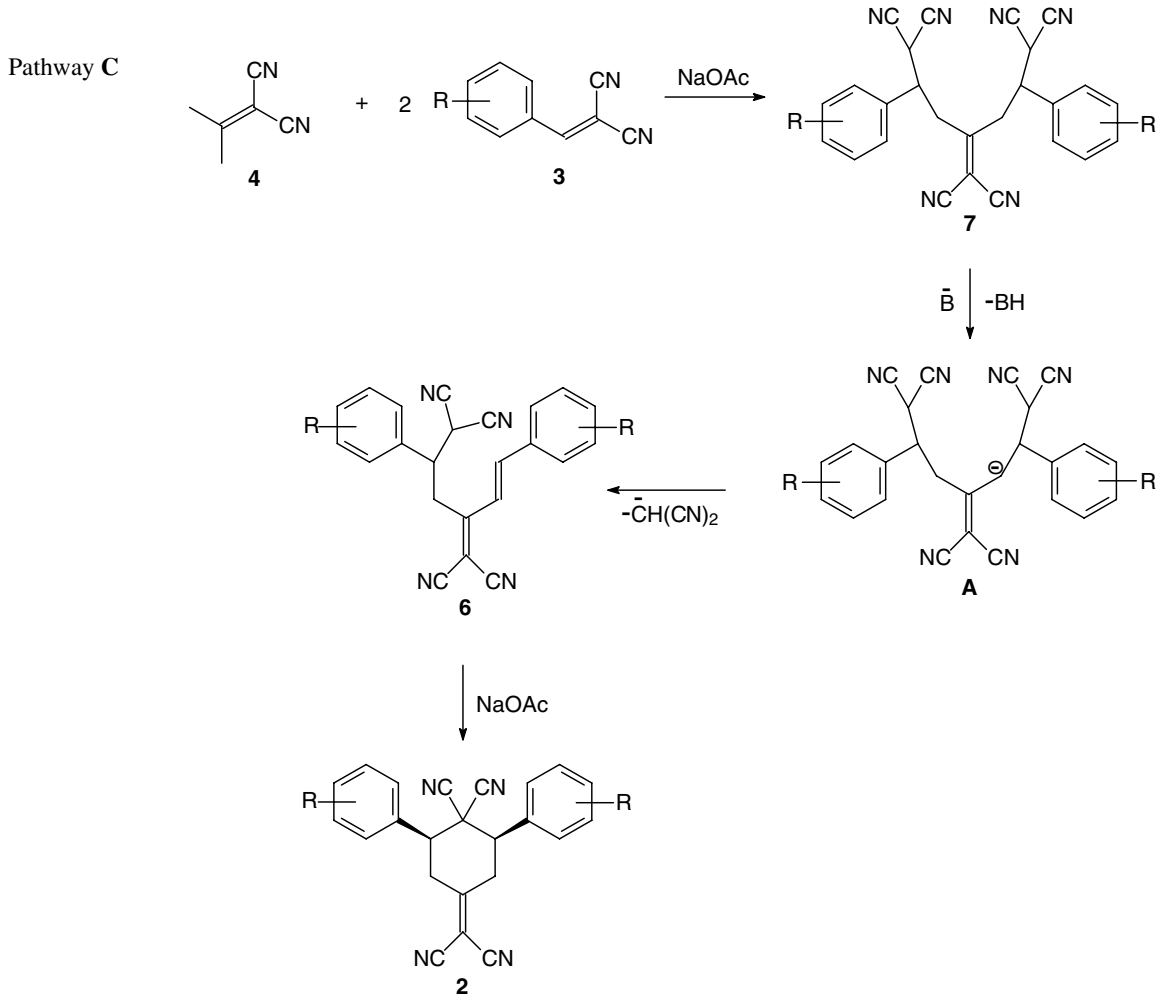
Realization of all these pathways ensures good yields of **2** in the catalytic process.

Thus, the simple catalytic system reported here (sodium acetate in acetone; acetone is both solvent and reagent) affords under mild conditions, a direct multicomponent stereoselective transformation of aryl aldehydes, malononitrile and acetone into *cis*-4-dicyanomethylene-2,6-diarylcyclohexane-1,1-dicarbonitriles. This catalytic process is an efficient and convenient method for the



Scheme 4.

synthesis of 4-dicyanomethylene-2,6-diarylcyclohexane-1,1-dicarbonitriles, the known precursors for the synthesis of spiro-pyrimidines with a broad spectrum of chemotherapeutic activities. The procedure utilizes inexpensive reagents, is easily carried out and the work-up is not complicated.



Scheme 4 *(continued)*

Acknowledgements

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10. *General procedure.* A solution of aromatic aldehyde (15 mmol), malononitrile (10 mmol) and sodium acetate (1 mg, 0.01 mmol) in 10 ml of acetone was stirred at 20 °C for 5 h. The solid phase was filtered and washed with cold acetone to yield pure **2a**–**h**. All compounds (**2a**–**h**) gave

expected NMR and IR spectra. For all new compounds (**2b**–**h**), satisfactory elemental analyses were obtained.

(2*R*,6*S*)* *4-Dicyanomethylene-2,6-diphenylcyclohexane-1,1-dicarbonitrile* **2a**, mp 267–268 °C [lit. mp 269–270 °C];[11] ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 3.09$ (dd, 2H, $J_1 = 3.0$, $J_2 = 15.4$), 3.48 (dd, 2H, $J_1 = 13.6$, $J_2 = 15.4$), 4.05 (dd, 2H, $J_1 = 3.0$, $J_2 = 13.6$), 7.42–7.62 (m, 10H, Ar). ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 34.67$ (CH_2), 47.61 (CH), 47.61 [$C(CN)_2$], 84.90 [$(CN)_2C$=], 111.43 (2CN), 112.21 (CN), 113.52 (CN), 128.32, 128.75, 129.27, 135.58 (all Ar), 176.56 (C=). MS EI (70 eV) *m*/*z* (rel int%): 348 (M^+, 28), 193 (32), 166 (20), 129 (42), 104 (29), 91 (100), 77 (18). IR (KBr): ν_{max} 2240, 1616, 1504, 1440, 768. Anal. Calcd for $C_{23}H_{16}N_4$: C, 79.29; H, 4.63; N, 16.08. Found: C, 79.11; H, 4.55; N, 15.89.

(2*R*,6*S*)* *2,6-Bis(4-methylphenyl)-4-(dicyanomethylene)-cyclohexane-1,1-dicarbonitrile* **2b**, mp 216–217 °C; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 2.34$ (s, 6H, CH_3), 3.06 (dd, 2H, $J_1 = 2.7$, $J_2 = 15.1$ Hz), 3.44 (dd, 2H, $J_1 = 13.9$, $J_2 = 15.1$), 3.98 (dd, 2H, $J_1 = 2.7$, $J_2 = 13.9$), 7.30 (d, 4H, Ar, $J = 7.9$), 7.45 (d, 4H, Ar, $J = 7.9$). ^{13}C NMR (75 MHz, DMSO-d_6): $\delta =$ 20.71 (CH_3), 34.83 (CH_2), 47.39 (CH), 48.05 [$C(CN)_2$], 84.47 [$(CN)_2C$=], 111.60 (2CN), 112.41 (CN), 113.80 (CN), 128.29, 129.42, 132.79, 138.95 (all Ar), 176.56 (C=). MS EI (70 eV) *m*/*z* (rel int%): 376 (M^+, 40), 208 (82), 193 (74), 143 (47), 117 (86), 105 (100), 91 (50). IR (KBr): ν_{max} 2240, 1612, 1516, 1440, 816. Anal. Calcd for $C_{25}H_{20}N_4$: C, 79.76; H, 5.35; N, 14.88. Found: C, 79.63; H, 5.43; N,14.69.

(2*R*,6*S*)* *2,6-Bis(3-bromophenyl)-4-(dicyanomethylene)-cyclohexane-1,1-dicarbonitrile* **2f**, mp 253–254 °C; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 3.15$ (dd, 2H, $J_1 = 3.0$, $J_2 =$ 15.0), 3.49 (dd, 2H, $J_1 = 13.6$, $J_2 = 15.0$), 4.07 (dd, 2H, $J_1 = 3.0$, $J_2 = 13.6$), 7.45–7.60 (m, 4H, Ar), 7.65–7.80 (m, 4H, Ar). ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 34.50$ (CH_2), 47.11 (CH), 47.57 [$C(CN)_2$], 85.20 [$(CN)_2C$=], 111.73 (2CN), 112.25 (CN), 113.59 (CN), 122.22, 127.83, 131.30, 131.74, 132.65, 138.38 (all Ar), 176.19 (C=). MS EI (70 eV) *m*/*z* (rel int%): 508 (M^+, 7), 506 (M^+, 14), 232 (24), 193 (100), 166 (73), 153 (78), 126 (40), 103 (32). IR (KBr): ν_{max} 2240, 1612, 1476, 1436, 792. Anal. Calcd for $C_{23}H_{14}Br_2N_4$: C, 54.57; H, 2.79; Br, 31.57; N, 11.07. Found: C, 54.41; H, 2.76; Br, 31.35; N, 10.93.

(2*R*,6*S*)* *2,6-Bis(4-fluorophenyl)-4-(dicyanomethylene)-cyclohexane-1,1-dicarbonitrile* **2g**, mp 232.5–233 °C; ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 3.08$ (dd, 2H, $J_1 = 2.7$, $J_2 = 14.9$), 3.42 (dd, 2H, $J_1 = 13.4$, $J_2 = 14.9$), 4.05 (dd, 2H, $J_1 = 2.7$, $J_2 = 13.4$), 7.29 (t, 4H, Ar, $J = 8.9$), 7.56 (dd, 4H, Ar, $J_1 = 8.7$, $J_2 = 8.1$). ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 34.65$ (CH_2), 46.73 (CH), 47.90 [$C(CN)_2$], 84.78 [$(CN)_2C$=], 111.50 (2CN), 112.15 (CN), 113.54 (CN), 115.79 (d, $^2J_{CF} = 21.8$), 130.67 (d, $^3J_{CF} = 8.3$), 131.91 (2C), 162.51 (d, $^1J_{CF} = 246.3$) (all Ar), 176.18 (C=). MS EI (70 eV) *m*/*z* (rel int%): 384 (M^+, 16), 212 (49), 211 (36), 172 (31), 147 (74), 122 (100), 109 (79). IR (KBr): ν_{max} 2240, 1616, 1492, 1440, 788. Anal. Calcd for $C_{23}H_{14}F_2N_4$: C, 71.87; H, 3.67; F, 9.89; N, 14.58. Found: C, 71.73; H, 3.71; F, 9.68; N, 14.45.

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12. Crystal data for **2a**: $C_{23}H_{16}N_4$, $M = 343.36$, space group *Pnma*, $a = 12.348(2)$ Å, $b = 20.045(4)$ Å, $c = 7.6244(14)$ Å, $V = 1887.1(6)$ Å^3, $Z = 4$, $D_C = 1.209$ g cm^{-3}. Crystallographic data for **2a** (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication No. CCDC 625181. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 0 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
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