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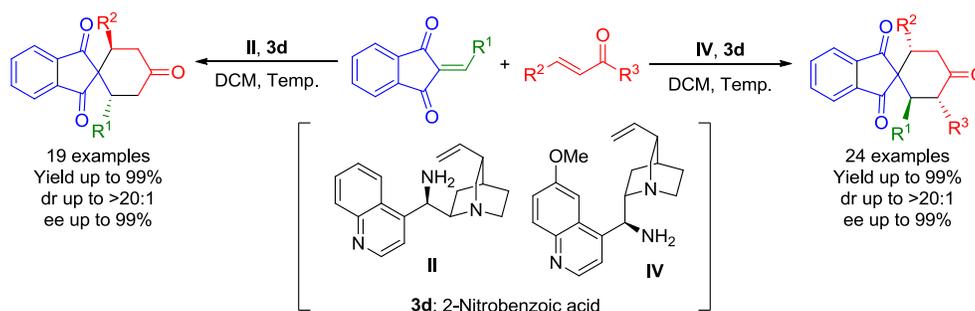
# Expanding the scope of primary amine catalysis: Stereoselective synthesis of indanedione-fused 2,6-disubstituted *trans*-spirocyclohexanones

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**ABSTRACT:** A cinchona-alkaloid-derived chiral primary amine-catalyzed enantioselective method for the synthesis of the thermodynamically less stable indanedione-fused 2,6-*trans*-disubstituted spiro cyclohexanones is demonstrated. Both the enantiomeric forms of the *trans* isomer are obtained in excellent yields and enantioselectivities. Furthermore, one of the enantiopure *trans* spiranes bearing an additional  $\alpha$ -substitution on the cyclohexanone ring was then epimerized into its thermodynamically stable *cis* counterpart, with little loss of enantioselectivity to demonstrate the feasibility of such transformation. Mechanistic investigations revealed two competing pathways, a concerted Diels-Alder reaction and a step-wise Michael addition for the formation of corresponding products.

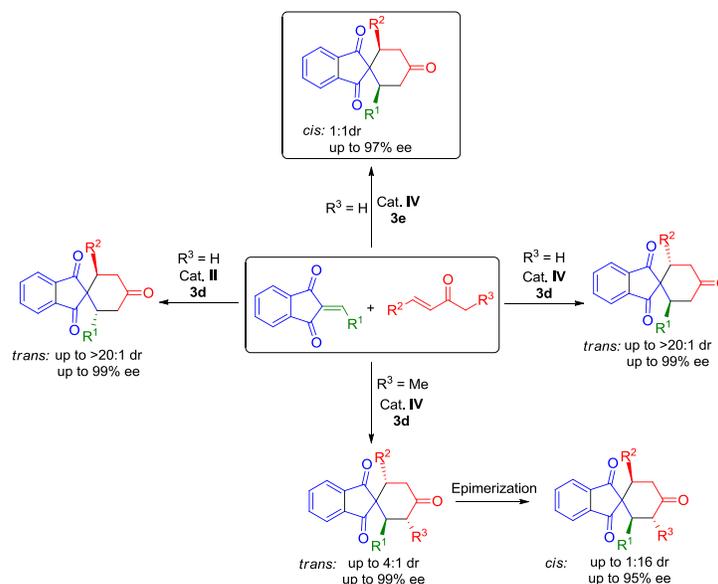
## INTRODUCTION

Over the years, asymmetric aminocatalysis has been widely used for the functionalization of carbonyl compounds, which happens to be one of the most classical organic transformations, in an enantioselective fashion. However, for a substantially long period, the potential of primary amines<sup>1</sup> as chiral inducers for such aminocatalysis has been overshadowed by the chiral cyclic secondary amines such as *L*-proline and its derivatives accompanied by phenylalanine-derived imidazolidinones.<sup>2,3</sup> The latter have been considered to be far superior organocatalysts for aminocatalysis of the sterically non-demanding carbonyl compounds. But the task of asymmetric induction becomes quite challenging in case of sterically hindered and less reactive substrates, where neither the classical secondary amine catalysis nor the metal-based approaches could prove to be successful. In such context, primary amines could prove to be more efficient and could broaden the scope of the substrates for aminocatalysis to a large extent *via* their diverse modes of activation.<sup>4a</sup>

Among all the classes of primary amine organocatalysts, those derived from cinchona alkaloids have attracted much attention of the researchers working on asymmetric aminocatalysis as they could be easily synthesized and are readily tunable. Moreover, these conformationally unique catalytic systems could activate both the electrophiles and the nucleophiles simultaneously, and have the ability to catalyze the reaction either *via* the base-catalyzed or the enamine/iminium activation pathway. Melchiorre et. al. have illustrated the potential of cinchona alkaloid derived primary amines as organocatalysts to replace the conventional cyclic secondary amines for the activation of  $\alpha,\beta$ -unsaturated ketones to furnish the formal Diels-Alder products with far superior enantioselectivities, *via* an alternative double Michael reaction pathway.<sup>5,6</sup> Since then,

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3 considerable efforts have been made towards the development of asymmetric aminocatalysis  
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5 using cinchona alkaloid derived primary amines.<sup>4,7</sup>  
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10 In an attempt to expand the scope of such primary amine catalysis, our group has been recently  
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12 evaluating the cases where the results of aminocatalysis with cyclic secondary amines were not  
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14 convincing. In such context, we encountered the *L*-proline-catalyzed domino Knoevenagel/Diels-  
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16 Alder/epimerization sequence for the synthesis of indanedione-fused *cis*-spirocyclohexanones  
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18 reported by Barbas et. al.,<sup>8</sup> where the chiral secondary amine could not induce any considerable  
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20 enantioselectivity. It has been more than a decade, but till date, there have been no substantial  
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22 efforts to develop an enantioselective format of this transformation resulting in indanedione-  
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24 fused spirocyclohexanones.<sup>9-16</sup> However, there have been a few methods reported for the  
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26 synthesis of spirocyclohexanones fused to other ring systems.<sup>17</sup> So we decided to evaluate the  
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28 ability of cinchona alkaloid-derived primary amines to stereoselectively catalyze the reaction  
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30 leading to indanedione-fused spirocyclohexanones and then were keen to investigate the  
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32 corresponding reaction mechanism (Scheme 1). The resulting adducts represent the potential  
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34 leads for the development of anti-cancer agents which have a well-defined activity on apoptosis  
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36 and cell differentiation.<sup>18</sup>  
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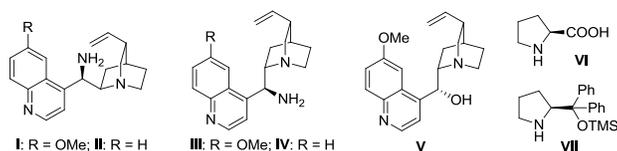


**Scheme 1. Domino reaction for formation of 2,6-disubstituted cyclohexanones from 2-arylidene-1,3-indanediones and 4-substituted-3-buten-2-ones.**

## RESULTS AND DISCUSSION

Initially, we carried out the reaction of *trans*-4-phenyl-3-buten-2-one (**2a**) with 2-arylidene indanedione (**1c**) using 10 mol% each of **I** and 2-fluoro benzoic acid (**3a**) (Table 1, entry 1). The spirocyclohexanone product **4ca** was obtained in 80% yield (dr = 1.4:1). From the X-ray crystallographic analysis of the product **4ca**, it was quite unexpected to see the formation of thermodynamically less stable *trans* spirane (*exo* product) in excess as against the earlier results,<sup>8</sup> where *cis* spirane (*endo* product) was exclusively formed in most cases. This indicated a competing two-step enamine/iminium activation pathway for the formation of *trans*-**4ca** as against the concerted Diels-Alder mechanism which results in *cis*-**4ca** as reported earlier. The ee of *cis* and *trans* diastereomers was found to be 77% and 98% respectively, which was promising when compared to the same reaction being catalyzed by *L*-proline (**VI**) or Jørgensen's catalyst **VII** (entries 6 and 7). From the previous reports, it could be evaluated that the synthesis of

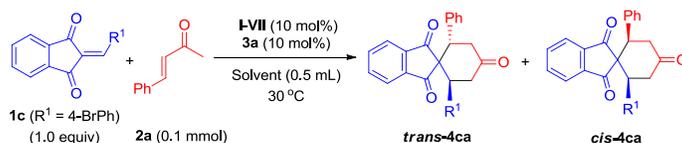
indanedione-fused *trans* spirocyclohexanones (cyclohexanone fused to a 5-membered ring) is difficult to accomplish as compared to the *trans* isomers of spirocyclohexanones that are fused to other ring systems.<sup>17</sup> Encouraged by this, we initially focused on the stereoselective synthesis of thermodynamically less stable *trans* spiranes **4**.



**Figure 1.** Catalysts screened during optimization.

We screened other cinchona alkaloid-derived catalysts **II-V** (Table 1, entries 2-5) and found that catalyst **IV** gave the best results (97% yield, 3.6:1 dr and 99% ee; entry 3). Following this, an extensive screening of different solvents was carried out using **IV** (Table 2, entries 1-11). The *ee* of *trans* diastereomer remained unaffected in most cases, while that of *cis* isomer varied over a wide range. Although the mixed solvent system of DCM:Toluene (Table 2, entry 11) initially appeared to give better results in terms of diastereoselectivity, it was found later during the screening of additives, catalyst loading and reaction temperatures that the use of single solvent system was beneficial.

**Table 1. Optimization of reaction conditions.<sup>a</sup>**



Entry	Cat.	Solvent	T (d)	Yield (%) <sup>b</sup>	dr <sup>b</sup>	ee (%) <sup>c</sup>
1	<b>I</b>	Toluene	6	80	1.4:1	98/77 <sup>d</sup>
2	<b>II</b>	Toluene	1	95	1.6:1	99/70 <sup>d</sup>
3	<b>III</b>	Toluene	2	97	2:1	98/84

4	<b>IV</b>	Toluene	1	97	3.6:1	99/85
5	<b>V</b>	Toluene	10	Trace	--	--
6	<b>VI</b>	Toluene	6	75	1:2.6	11/13
7	<b>VII</b>	Toluene	11	0	--	--

<sup>a</sup> **3a** (2-Fluorobenzoic acid, 10 mol%). <sup>b</sup> Yield of **4ca** (*cis* + *trans*) as determined by <sup>1</sup>H NMR analysis of the crude reaction mixture using Ph<sub>3</sub>CH as an internal standard. <sup>c</sup> ee of *trans/cis* products as determined by HPLC analysis on a chiral stationary phase. <sup>d</sup> ee of *ent-trans-4ca/ent-cis-4ca*.

**Table 2: Solvent screening for the domino double Michael addition of 2a to 1c.<sup>a</sup>**

Entry	Cat.	Solvent	T (d)	Yield (%) <sup>b</sup>	dr <sup>b</sup>	ee (%) <sup>c</sup>
1	<b>IV</b>	DCM	1	84	3.7:1	98/47
2	<b>IV</b>	THF	8.5	47	4.2:1	90/28
3	<b>IV</b>	EA	9.5	66	2.9:1	98/36
4	<b>IV</b>	MeOH	9.5	44	1:7	-/36
5	<b>IV</b>	CHCl <sub>3</sub>	10	71	1.6:1	98/25
6	<b>IV</b>	Xylenes	6	94	1.2:1	97/82
7	<b>IV</b>	Et <sub>2</sub> O	1	96	1:1.2	98/36
8	<b>IV</b>	1,4-Dioxane	2	81	1:1.1	96/43
9	<b>IV</b>	BrPh	1	98	2.6:1	99/59
10	<b>IV</b>	1,2-DCE	5	>99	1.2:1	99/26
11	<b>IV</b>	DCM:Toluene (1:4)	1	>99	4.3:1	98/84
12 <sup>d</sup>	<b>IV</b>	DCM	4	85	>20:1	98/97
13 <sup>d</sup>	<b>II</b>	DCM	5	81	14:1	98/97 <sup>e</sup>
14 <sup>f</sup>	<b>IV</b>	Toluene	1	96	1:1	98/97

<sup>a</sup> **3a** (2-Fluorobenzoic acid, 10 mol%). <sup>b</sup> Yield of **4ca** (*cis* + *trans*) as determined by <sup>1</sup>H NMR analysis of the crude reaction mixture using Ph<sub>3</sub>CH as an internal standard. <sup>c</sup> ee of *trans/cis* products as determined by HPLC analysis on a chiral stationary phase. <sup>d</sup> **1c** (1.2 equiv), **IV** or **II** (5 mol%) and **3d** (2-nitrobenzoic acid, 20 mol%) in DCM (0.25 mL) at 10 °C. <sup>e</sup> ee of *ent-trans-4ca/ent-cis-4ca*. <sup>f</sup> **IV** (5 mol%) and **3e** (2,6-dihydroxybenzoic acid, 10 mol%) in toluene (0.5mL) at 60 °C (to obtain *cis* isomer).

A rigorous screening of catalyst loadings, additives, temperature and concentrations was then carried out (see SI for detailed screening of reaction conditions). It is clear that an enhanced reaction rate resulted in the formation of the kinetically favoured *trans* spirane, while the prolonged reaction time increased the formation of thermodynamically more stable *cis* spirane. After a careful study of different reaction parameters, the optimal conditions were established as in table 2, entry 12. Additionally, under these optimized conditions, *ent-trans-4ca* could also be obtained in good yields and selectivities using the pseudo-enantiomer **II** (entry 13). To our surprise, when the additive **3e** was used, the thermodynamic endo product (*cis-4ca*) could also be acquired with good enantioselectivity under slightly modified reaction conditions (entry 14).

**Table 3. Substrate scope for the domino Michael addition using different substituted **1** and **2** for the synthesis of *trans-4*.**



Entry	R <sup>1</sup>	R <sup>2</sup>	T [d]	Yield [%] <sup>a</sup>	dr <sup>b</sup>	ee [%] <sup>c</sup>
1	Ph ( <b>1a</b> )	Ph ( <b>2a</b> )	5	75 ( <b>4aa</b> )	13:1	96
2	4-ClPh ( <b>1b</b> )	Ph ( <b>2a</b> )	5	80( <b>4ba</b> )	17:1	98
3	4-BrPh ( <b>1c</b> )	Ph ( <b>2a</b> )	4	85 ( <b>4ca</b> )	>20:1	98
4	4-CNPh ( <b>1d</b> )	Ph ( <b>2a</b> )	4	90 ( <b>4da</b> )	>20:1	98
5	4-NO <sub>2</sub> Ph ( <b>1e</b> )	Ph ( <b>2a</b> )	10	96 ( <b>4ea</b> )	14:1	97
6	2-BrPh ( <b>1f</b> )	Ph ( <b>2a</b> )	3.5	91 ( <b>4fa</b> )	12:1	82
7	4-MePh ( <b>1g</b> )	Ph ( <b>2a</b> )	11	80 ( <b>4ga</b> )	10:1	97
8	4-OMePh ( <b>1h</b> )	Ph ( <b>2a</b> )	10	71 ( <b>4ha</b> )	7:1	99
9	2-OMePh ( <b>1i</b> )	Ph ( <b>2a</b> )	4	66 ( <b>4ia</b> )	>20:1	91
10 <sup>d</sup>	2-Thienyl ( <b>1j</b> )	Ph ( <b>2a</b> )	4	82 ( <b>4ja</b> )	1:1	97
11	4-BrPh ( <b>1c</b> )	4-ClPh ( <b>2b</b> )	5	74 ( <b>4cb</b> )	>20:1	98
12	4-BrPh ( <b>1c</b> )	4-BrPh ( <b>2c</b> )	5	77 ( <b>4cc</b> )	>20:1	98

13	4-BrPh ( <b>1c</b> )	4-CNPh ( <b>2d</b> )	4	89 ( <b>4cd</b> )	15:1	97
14	4-BrPh ( <b>1c</b> )	4-NO <sub>2</sub> Ph ( <b>2e</b> )	10	73 ( <b>4ce</b> )	8:1	97
15	4-BrPh ( <b>1c</b> )	2-BrPh ( <b>2f</b> )	5	70 ( <b>4cf</b> )	18:1	98
16	4-BrPh ( <b>1c</b> )	4-OMePh ( <b>2g</b> )	4	76 ( <b>4cg</b> )	11:1	98
17	4-BrPh ( <b>1c</b> )	2-OMePh ( <b>2h</b> )	6	89 ( <b>4ch</b> )	>20:1	97
18	4-BrPh ( <b>1c</b> )	2-Thienyl ( <b>2i</b> )	8	75 ( <b>4ci</b> )	10:1	98

<sup>a</sup> Isolated yield of **4**. <sup>b</sup> Diastereomeric ratio of *trans*:*cis* as determined by <sup>1</sup>H NMR analysis of the crude reaction mixture using Ph<sub>3</sub>CH as an internal standard. <sup>c</sup> ee of *trans*-**4** as determined by HPLC analysis on a chiral stationary phase. <sup>d</sup> Reaction temperature: 30 °C.

With the optimal conditions in hand, we then studied the scope of this domino Michael addition reaction for the synthesis of *trans* spiranes with varying R<sup>1</sup> and R<sup>2</sup> substituents. The excellent results with a wide range of the substrates are presented in table 3. Likewise, using the pseudo-enantiomer **II**, we also demonstrated the synthesis of *ent-trans*-**4** and the results are summarized in table 4. It could be seen that the results with catalyst **II** followed the similar trend as seen with catalyst **IV**, and the excellent outcome of the reaction could be reiterated.

**Table 4.** Substrate scope for the domino Michael addition using different substituted **1** and **2** for the synthesis of *ent-trans*-**4**.

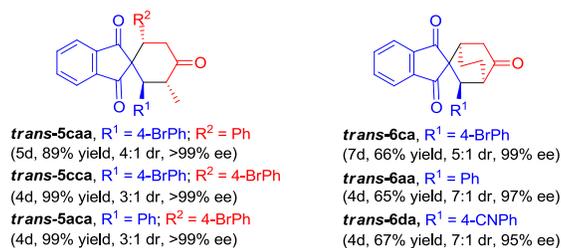


Entry	R <sup>1</sup>	R <sup>2</sup>	T [d]	Yield [%] <sup>a</sup>	dr <sup>b</sup>	ee [%] <sup>c</sup>
1	Ph ( <b>1a</b> )	Ph ( <b>2a</b> )	5	73 ( <b>4aa</b> )	13:1	97
2	4-ClPh ( <b>1b</b> )	Ph ( <b>2a</b> )	5	85 ( <b>4ba</b> )	17:1	97
3	4-BrPh ( <b>1c</b> )	Ph ( <b>2a</b> )	5	81 ( <b>4ca</b> )	14:1	98
4	4-CNPh ( <b>1d</b> )	Ph ( <b>2a</b> )	4	99 ( <b>4da</b> )	>20:1	98
5	4-NO <sub>2</sub> Ph ( <b>1e</b> )	Ph ( <b>2a</b> )	10	95 ( <b>4ea</b> )	17:1	99
6	2-BrPh ( <b>1f</b> )	Ph ( <b>2a</b> )	7	78 ( <b>4fa</b> )	10:1	68

7	4-MePh ( <b>1g</b> )	Ph ( <b>2a</b> )	11	75 ( <b>4ga</b> )	13:1	98
8	4-OMePh ( <b>1h</b> )	Ph ( <b>2a</b> )	10	61 ( <b>4ha</b> )	9:1	93
9	2-OMePh ( <b>1i</b> )	Ph ( <b>2a</b> )	10	62 ( <b>4ia</b> )	>20:1	78
10 <sup>d</sup>	2-Thienyl ( <b>1j</b> )	Ph ( <b>2a</b> )	4	80 ( <b>4ja</b> )	1:1	96
11	4-BrPh ( <b>1c</b> )	4-ClPh ( <b>2b</b> )	5	82 ( <b>4cb</b> )	>20:1	97
12	4-BrPh ( <b>1c</b> )	4-BrPh ( <b>2c</b> )	5	70 ( <b>4cc</b> )	>20:1	98
13	4-BrPh ( <b>1c</b> )	4-CNPh ( <b>2d</b> )	4	73 ( <b>4cd</b> )	18:1	97
14	4-BrPh ( <b>1c</b> )	4-NO <sub>2</sub> Ph ( <b>2e</b> )	10	79 ( <b>4ce</b> )	9:1	97
15	4-BrPh ( <b>1c</b> )	2-BrPh ( <b>2f</b> )	5	65 ( <b>4cf</b> )	>20:1	97
16	4-BrPh ( <b>1c</b> )	4-OMePh ( <b>2g</b> )	4	88 ( <b>4cg</b> )	10:1	94
17	4-BrPh ( <b>1c</b> )	2-OMePh ( <b>2h</b> )	6	81 ( <b>4ch</b> )	>20:1	97
18	4-BrPh ( <b>1c</b> )	2-Thienyl ( <b>2i</b> )	8	70 ( <b>4ci</b> )	12:1	98

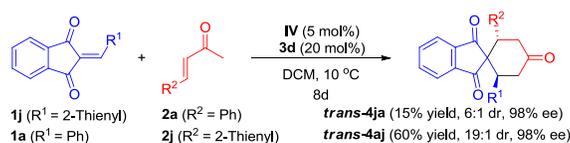
<sup>a</sup> Isolated yield of *ent*-**4**. <sup>b</sup> Diastereomeric ratio of *trans*:*cis* as determined by <sup>1</sup>H NMR analysis of the crude reaction mixture using Ph<sub>3</sub>CH as an internal standard. <sup>c</sup> ee of *ent*-*trans*-**4** as determined by HPLC analysis on a chiral stationary phase. <sup>d</sup> Reaction temperature: 30 °C.

We then extended the scope of the reaction using ethyl vinyl ketones and 2-cyclohexenone as pronucleophiles, which would result in an additional stereocenter in the corresponding products **5** and **6** (Scheme 2). Since the reactivity of the substrates was lower, the reactions had to be carried out at room temperature resulting in a lower diastereoselectivities while the excellent enantioselectivities were still retained.



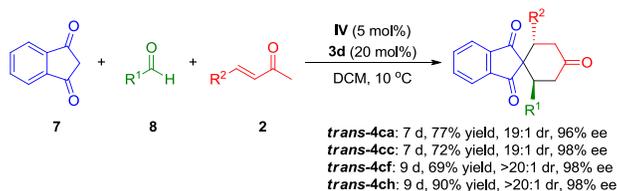
**Scheme 2.** Asymmetric synthesis of **5** and **6** with an additional stereocenter.

Later on, we were keen to take the advantage of the fact that  $R^1$  and  $R^2$  groups in substrates could be exchanged, that would still result in the same product. This gave us the flexibility to tune the reactivity of the substrates accordingly. To demonstrate this, we chose the substrates **1j** and **2a** which displayed poor reactivity at 10 °C (Table 3, entry 10). When the reaction was carried out with the substrates having  $R^1$  and  $R^2$  groups exchanged (**1a** and **2j**), both the reactivity and the selectivity improved drastically (Scheme 3). This result showed that it was possible to synthesize an array of spiranes with excellent results by interchanging the substituents on the substrates.



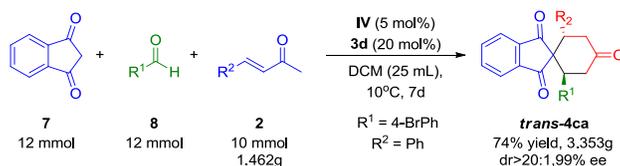
**Scheme 3. Scope of the reaction by interchanging the  $R^1$  and  $R^2$  substituents.**

We then attempted the one-pot operation for the synthesis of the *trans* spiranes starting from 1,3-indanedione (**7**), aldehyde **8** and **2** (Scheme 4). The results were equally promising and the products could be obtained in almost similar yields and stereoselectivities as compared to the two-step process.



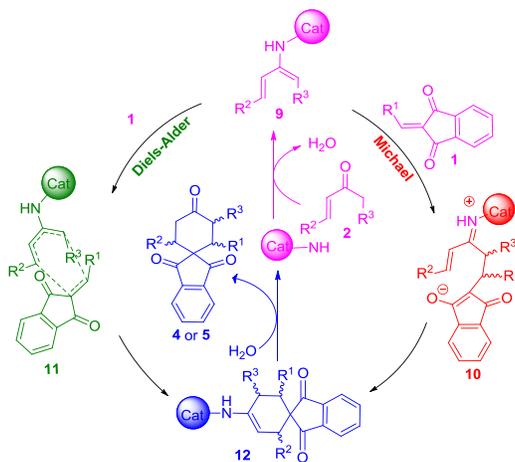
**Scheme 4. One-pot reaction for the synthesis of *trans*-4.**

To establish the viability of this protocol, we also carried out a gram-scale reaction (10 mmol scale) for the synthesis of *trans*-4ca from **7**, **8** and **2**, which furnished the product in 74% yield (>20:1 dr; 99% ee) under the similar reaction conditions (Scheme 5).



Scheme 5. Gram-scale reaction for the synthesis of *trans*-4ca.

The absolute configurations of *trans*-4ca, *trans*-5cca, *cis*-4ca (from its acetal derivative, *cis*-15ca) and *cis*-5aca (from its acetal derivative, *cis*-16aca) were established by X-ray crystallography.<sup>19</sup> Mechanistically, this reaction could proceed either *via* the Diels-Alder pathway or the double Michael addition pathway (Scheme 6).

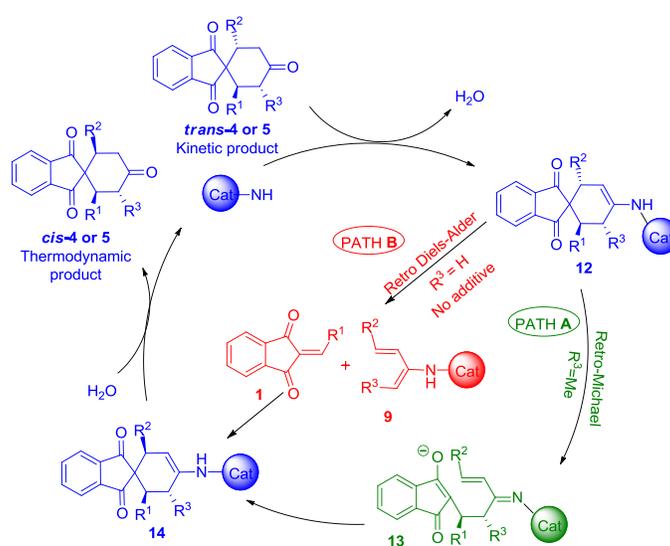


Scheme 6. Possible reaction pathways.

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3 One of our vital objectives was to transform the kinetic *trans* spiranes into the  
4 thermodynamically stable *cis* congeners so as to demonstrate the generality of this method for  
5 the synthesis of all four stereoisomeric forms of the product. We envisioned that, based on the  
6 retro-Michael/Michael mechanism for epimerization proposed earlier,<sup>8,20</sup> when the *trans* spirane  
7 is treated with an amine in a polar protic solvent, only one of the two stereocenters would be  
8 rearranged and hence the enantioselectivity would be retained by the resulting *cis* products  
9 (Scheme 7, path **A**).<sup>21</sup> But the results were rather unlike. In all the cases, irrespective of the  
10 catalyst (**IV**, cyclohexylamine or pyrrolidine) and the solvent used, we could observe complete  
11 conversion of the *trans* isomer **4ca** into *cis*-**4ca**, but only as racemic mixture (Scheme 8, eqn.  
12 a).<sup>22</sup> We initially attributed this result to the lack of regioselectivity during the formation of the  
13 initial enamine intermediate, which would subsequently result in the formation of both the  
14 enantiomers in almost equal amounts (Scheme 9, case 1).  
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34 In an attempt to confirm this, enantiopure *cis*-**4ca** was treated with amine in DCM under similar  
35 conditions (Scheme 8, eqn. b). It was envisioned that regioselectivity during enamine formation  
36 would have no role to play in this case, and both the regioisomeric enamines would go through  
37 the retro-Michael/Michael pathway and result in the regeneration of starting material *cis*-**4ca**,  
38 with complete retention of enantioselectivity (Scheme 9, case 2). But, to our surprise, the  
39 enantiopure *cis*-**4ca** completely racemized even in this case (eqn. b).<sup>23</sup> This clearly indicated that  
40 the epimerization may not be taking place solely *via* the retro-Michael/Michael pathway as  
41 proposed earlier. We assume that it follows a competing retro-Diels-Alder/Diels-Alder pathway,  
42 where both the stereocenters would be rearranged (Scheme 7, path **B**), and result in the racemic  
43 products in presence of an achiral amine. However, during the epimerization of *trans*-**4ca**, the  
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3 use of acidic additive or performing the reaction at 10°C resulted in *cis*-**4ca** with slight ee (23-  
4 25%) (Scheme 8, eqn c).<sup>22</sup> This result demonstrates that the retro-Diels-Alder pathway is  
5 decelerated in presence of additive or at lower temperature, thereby allowing the retro-  
6 Michael/Michael pathway to takeover. Moreover, the epimerization of the products by either of  
7 these pathways is slowed down to a large extent when **IV** was used as the catalyst (Scheme 8,  
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Scheme 7. Mechanistic possibilities for epimerization.



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3 These results also explain the formation of kinetic *trans* spiranes with excellent diastereo- and  
4 enantioselectivities (Tables 3 and 4), as the reactions are carried out using **II** or **IV** at lower  
5 temperatures and in presence of additive which would suppress the subsequent epimerization of  
6 the *trans* products. Furthermore, it could be ascertained that the formation of *cis*-**4ca** in entry 14  
7 of table 2 is indeed taking place *via* the domino Michael addition pathway and not by the  
8 epimerization of the initially formed *trans*-**4ca**, which if took place, would have resulted in the  
9 loss of enantioselectivity of *cis*-**4ca**. It has been a general perception that it is very difficult to  
10 ascertain the mechanistic pathway followed by a reaction when it has more than one possibilities  
11 that could result in quite similar transition states or intermediates, thereby yielding similar  
12 products. But in this case, using the enantiopure substrates for epimerization under different  
13 conditions, we were able to understand and ascertain the reaction pathway.  
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32 We then carried out the epimerization of substrate *trans*-**5cca** which has an additional methyl  
33 substitution that would direct the regioselective formation of less substituted enamine **12**  
34 (Scheme 8, eqn. d). This should result in the inversion of R<sup>2</sup> stereocenter after ring  
35 opening/closing and lead to the formation of *cis*-**5cca**, without any loss of enantioselectivity. As  
36 expected, the *trans* spirane could be successfully epimerized into its *cis* counterpart with 95% ee  
37 using 3 eq of pyrrolidine.<sup>23</sup> This result substantiated that the retro-Michael/Michael pathway was  
38 predominantly followed during epimerization resulting in retention of enantioselectivity by the  
39 *cis* products. These results were helpful to prove that the additional substitution on the  
40 cyclohexanone ring of *trans* spiranes prevented the racemisation by retro-Diels-Alder pathway  
41 and allowed the stereoselective synthesis of corresponding *cis* products. As a consequence, the  
42 long-standing problem of obtaining both the *cis* and *trans* isomers of indanedione-fused spiro  
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3 cyclohexanones with good enantioselectivities was solved. The *cis* spiranes without the methyl  
4 substitution could be preferably synthesized following the conditions as in Table 2, entry 14,  
5  
6 resulting in the products with excellent enantioselectivity.  
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## 10 11 12 13 **CONCLUSIONS:**

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16 In summary, we have developed an efficient cinchona alkaloid-derived primary amine catalysis  
17 for an unprecedented enantioselective synthesis of 1,3-indanedione-fused *trans* spiro  
18 cyclohexanones. This method happens to be the first one to be reported for the enantioselective  
19 synthesis of the kinetically controlled *trans* congeners of such spiranes. We then conclusively  
20 demonstrated an alternative retro-Diels-Alder/Diels-Alder pathway for the epimerization of *trans*  
21 spiranes into the corresponding *cis* congeners, which could be prevented by incorporating an  
22 additional substitution on the cyclohexanone ring, resulting in the generation of *cis* spiranes with  
23 good selectivities *via* retro-Michael/Michael pathway.  
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## 39 **EXPERIMENTAL SECTION:**

### 40 41 42 **General experimental methods:**

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44 All solvents and reagents were used as purchased from commercial suppliers without further  
45 purification. Starting materials and catalysts which were not commercially available were  
46 synthesized by the previously reported methods. Analytical thin layer chromatography (TLC)  
47 was performed on precoated alumina-backed silica gel plates (0.2 mm thickness) which were  
48 developed using UV fluorescence and iodine. Flash-chromatography was performed on silica gel  
49 (230-400 mesh). Melting points were measured on a standard melting point apparatus and are  
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3 uncorrected.  $^1\text{H}$  NMR spectra were recorded on a 400 MHz spectrometer, while  $^{13}\text{C}$  NMR  
4  
5 spectra were recorded on a 100 MHz instrument. Chemical shifts are reported in  $\delta$  ppm  
6  
7 referenced to an internal TMS standard for  $^1\text{H}$  NMR and chloroform-d ( $\delta = 77.0$  ppm) for  $^{13}\text{C}$   
8  
9 NMR. HRMS spectra were recorded using MALDI (TOF analyzer), ESI (TOF analyzer) and EI  
10  
11 (Magnetic sector analyzer). The X-ray diffraction measurements were carried out at 298 K on a  
12  
13 CCD area detector system equipped with a graphite monochromator and a Mo-K $\alpha$  fine-focus  
14  
15 sealed tube ( $k = 0.71073$  Å). Optical rotations were measured in  $\text{CHCl}_3$  on a polarimeter with a  
16  
17 50 mm cell ( $c$  given in g/100mL) operating at  $\lambda = 589$  nm, corresponding to the sodium D line, at  
18  
19 the indicated temperatures. The enantiomeric excess of compounds whose racemic samples  
20  
21 could not be synthesized was analyzed by comparing the retention times in the HPLC  
22  
23 chromatograms of the corresponding enantiomers.  
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30 **a) General procedure A for the synthesis of *trans-4* or *ent-trans-4* from **1** and **2**:**

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33 To a glass vial equipped with a magnetic stir bar was charged **2** (0.1 mmol), **1** (1.2 eq), **IV** (5  
34  
35 mol%), **3d** (20 mol%) and DCM (0.25 mL) and stirred at 10 °C for the time specified. Then the  
36  
37 reaction was quenched by the addition of 0.1M HCl (0.25 mL) and the aqueous layer was  
38  
39 extracted with DCM (2 x 0.25 mL). The combined organic layers were concentrated *in vacuo*  
40  
41 and the crude reaction mass was purified by flash column chromatography over silica gel to give  
42  
43 the pure compound *trans-4*.  
44  
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48 **b) General procedure B for the synthesis of *trans-4* or *ent-trans-4* from **1** and **2**:**

49  
50  
51 To a glass vial equipped with a magnetic stir bar was charged **2** (0.1 mmol), **1** (1.2 eq), **II** (5  
52  
53 mol%), **3d** (20 mol%) and DCM (0.25 mL) and stirred at 10 °C for the time specified. Then the  
54  
55 reaction was quenched by the addition of 0.1M HCl (0.25 mL) and the aqueous layer was  
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3 extracted with DCM (2 x 0.25 mL). The combined organic layers were concentrated *in vacuo*  
4 and the crude reaction mass was purified by flash column chromatography over silica gel to give  
5  
6 the pure compound *ent-trans-4*.  
7  
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11 **c) General procedure C for the one-pot synthesis of *trans-4* from **7**, **8** and **2**:**  
12

13  
14 To a glass vial equipped with a magnetic stir bar was charged **2** (0.1 mmol), **7** (1.2 eq), **8** (1.2 eq),  
15  
16 **IV** (5 mol%), **3d** (20 mol%) and DCM (0.25 mL) and stirred at 10 °C for the time specified.  
17  
18 Then the reaction was quenched by the addition of 0.1M HCl (0.25 mL) and the aqueous layer  
19  
20 was extracted with DCM (2 x 0.25 mL). The combined organic layers were concentrated *in*  
21  
22 *vacuo* and the crude reaction mass was purified by flash column chromatography over silica gel  
23  
24 to give the pure compound *trans-4*.  
25  
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29 **d) General procedure D for the synthesis of *trans-5*:**  
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32 To a glass vial equipped with a magnetic stir bar was charged ethyl vinyl ketone (0.1 mmol), **1**  
33  
34 (1.2 eq), **IV** (5 mol%), **3d** (10 mol%) and DCM (0.25 mL) and stirred at 30 °C for the time  
35  
36 specified. Then the reaction was quenched by the addition of 0.1 M HCl (0.25 mL) and the  
37  
38 aqueous layer was extracted with DCM (2 x 0.25 mL). The combined organic layers were  
39  
40 concentrated *in vacuo* and the crude reaction mass was purified by flash column chromatography  
41  
42 over silica gel to give pure compound *trans-5*.  
43  
44  
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47 **e) General procedure E for the synthesis of *trans-6*:**  
48

49  
50 To a glass vial equipped with a magnetic stir bar was charged **1** (0.1 mmol), 2-cyclohexenone (5  
51  
52 eq), **IV** (5 mol%), **3d** (20 mol%) and Toluene (0.25 mL) and stirred at 30 °C for the time  
53  
54 specified. Then the reaction was quenched by the addition of 0.1 M HCl (0.25 mL) and the  
55  
56 aqueous layer was extracted with DCM (2 x 0.25 mL). The combined organic layers were  
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3 concentrated *in vacuo* and the crude reaction mass was purified by flash column chromatography  
4  
5 over silica gel to give the pure compound *trans-6*.  
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9 **f) General procedure F for the epimerization of enantiopure *trans-4* to *cis-4*:**

10  
11 To a glass vial equipped with a magnetic stir bar was charged *trans-4* (0.1 mmol), pyrrolidine,  
12  
13 **IV**, cyclohexylamine or **VI** (20 mol%) and appropriate solvent (0.25 mL) and stirred at room  
14  
15 temperature. Then the reaction was quenched by the addition of 0.1M HCl (0.25 mL) and the  
16  
17 aqueous layer was extracted with DCM (2 x 0.25 mL). The combined organic layers were  
18  
19 concentrated *in vacuo* and the crude reaction mass was purified by flash column chromatography  
20  
21 over silica gel to give pure *cis-4*.  
22  
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27 **g) General procedure G for the epimerization of enantiopure *trans-5* to *cis-5*:**

28  
29 To a glass vial equipped with a magnetic stir bar was charged *trans-5* (0.1 mmol), pyrrolidine (3  
30  
31 eq), **3d** (3 eq) and MeOH:DCM (1:2, 0.25 mL) and stirred at 50°C for 7 days. Then the reaction  
32  
33 was quenched by the addition of 0.1M HCl (0.25 mL) and the aqueous layer was extracted with  
34  
35 DCM (2 x 0.25 mL). The combined organic layers were concentrated *in vacuo* and the crude  
36  
37 reaction mass was purified by flash column chromatography over silica gel to give pure *cis-5*.  
38  
39  
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41  
42 **h) General procedure H for the synthesis of *cis-15ca* and *cis-17aca*:**

43  
44 To a glass vial equipped with a magnetic stir bar was charged *cis-4ca* or *cis-5aca* (0.1 mmol),  
45  
46 ethylene glycol (1.2 eq), *p*-TSA (10 mol%) and DCM (0.5 mL) and stirred under reflux for 12h.  
47  
48 Then the crude reaction mass was directly purified by flash column chromatography over silica  
49  
50 gel to give pure *cis-15ca* or *cis-17aca* as a colorless solid.  
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**6. Characterization data for all compounds:**

**(2*S*, 6*S*)-2,6-diphenylspiro[cyclohexane-1,2'-indene]-1',3',4-trione (*trans*-4aa):** Following the general procedure A, **4aa** was obtained in 75% yield (28.5 mg, *trans:cis* = 13:1) as a yellow solid (mp.: 205.1-209.1 °C). HPLC analysis (Chiralpak IB column, Hexane-IPA = 90:10, flow rate = 1.0 mL min<sup>-1</sup>, λ = 227 nm; T<sub>R</sub> = 15.97 min (major), 24.09 min (minor)): 96% ee, [α]<sub>D</sub><sup>30</sup> = -166.1 (c = 0.5 in CH<sub>2</sub>Cl<sub>2</sub>); R<sub>f</sub> 0.25 (EA/hexanes: 1/5); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ/ppm, 7.59-7.52 (m, 4H), 7.07-6.99 (m, 6H), 6.96-6.93 (m, 4H), 3.98 (dd, *J* = 13.5, 3.2 Hz, 2H), 3.62 (dd, *J* = 16.7, 13.5 Hz, 2H), 2.78 (dd, *J* = 16.8, 3.3 Hz, 2H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ/ppm, 210.0, 202.9, 142.1, 137.3, 135.4, 128.4, 128.2, 127.4, 122.5, 61.7, 43.5, 41.6. IR (KBr): 3036, 2923, 1739, 1593, 1409, 1242, 758, 698 cm<sup>-1</sup>. HRMS (ESI) for C<sub>26</sub>H<sub>21</sub>O<sub>3</sub> [M+H]<sup>+</sup> (381.1491) found: 381.1492.

**(2*R*, 6*R*)-2,6-diphenylspiro[cyclohexane-1,2'-indene]-1',3',4-trione (*ent-trans*-4aa):**

Following the general procedure B, *ent*-**4aa** was obtained in 73% yield (27.7 mg, *trans:cis* = 13:1) as a yellow solid (mp.: 205.1-209.1 °C). [α]<sub>D</sub><sup>30</sup> = +166.5 (c = 0.5 in CH<sub>2</sub>Cl<sub>2</sub>). HPLC analysis (Chiralpak IB column, Hexane-IPA = 90:10, flow rate = 1.0 mL min<sup>-1</sup>, λ = 227 nm; T<sub>R</sub> = 16.73 min (major), 24.27 min (minor)): 97% ee

**(2*S*,6*S*)-2-(4-chlorophenyl)-6-phenylspiro[cyclohexane-1,2'-indene]-1',3',4-trione (*trans*-**

**4ba)** : Following the general procedure A, **4ba** was obtained in 80% yield (33.2 mg, *trans:cis* = 17:1) as a white solid (mp.: 177.4-178.2 °C). HPLC analysis (Chiralpak IB column (Hexane-IPA = 90:10, flow rate = 1.0 mL min<sup>-1</sup>, λ = 227 nm): T<sub>R</sub> = 17.91 min (major), 27.54 min (minor)): 98% ee, [α]<sub>D</sub><sup>30</sup> = -140.2 (c = 0.5 in CH<sub>2</sub>Cl<sub>2</sub>); R<sub>f</sub> 0.28 (EA/hexanes: 1/5); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ/ppm, 7.64-7.57 (m, 4H), 7.07-7.00 (m, 5H), 6.94-6.90 (m, 4H), 3.95 (td, *J* = 13.3, 3.2

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2  
3 Hz, 2H), 3.60 (dd,  $J = 13.8, 7.1$  Hz, 1H), 3.57 (dd,  $J = 13.2, 6.7$  Hz, 1H), 2.81-2.72 (m, 2H).  $^{13}\text{C}$   
4  
5 NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ /ppm, 209.5, 202.8, 202.6, 142.0, 141.9, 137.0, 135.9, 135.63, 135.62,  
6  
7 133.2, 129.7, 128.4, 128.3, 128.2, 127.5, 122.62, 122.56, 61.5, 43.9, 42.5, 41.59, 41.56. IR (KBr):  
8  
9 1794, 1721, 1644, 1610, 1489, 1104, 758  $\text{cm}^{-1}$ . HRMS (ESI) for  $\text{C}_{26}\text{H}_{20}\text{O}_3\text{Cl}$   $[\text{M}+\text{H}]^+$  (415.1101)  
10  
11 found: 415.1109.  
12  
13

14  
15  
16 **(2*R*,6*R*)-2-(4-chlorophenyl)-6-phenylspiro[cyclohexane-1,2'-indene]-1',3',4-trione** (*ent*-  
17  
18 ***trans*-4ba**) : Following the general procedure B, *ent*- **4ba** was obtained in 85% yield (35.3 mg,  
19  
20 *trans:cis* = 17:1) as a white solid (mp.: 177.4-178.2 °C).  $[\alpha]_{\text{D}}^{30} = +141.6$ . HPLC analysis:  
21  
22 Chiralpak IB column (Hexane-IPA = 90:10, flow rate = 1.0  $\text{mL min}^{-1}$ ,  $\lambda = 227$  nm):  $T_{\text{R}} = 19.32$   
23  
24 min (minor), 31.16 min (major), 97% ee.  
25  
26

27  
28 **(2*S*,6*S*)-2-(4-bromophenyl)-6-phenylspiro[cyclohexane-1,2'-indene]-1',3',4-trione** (*trans*-  
29  
30 **4ca**) : Following the general procedure A, **4ca** was obtained in 85% yield (39.0 mg) as a white  
31  
32 solid (mp.: 143.0-144.1 °C). HPLC analysis (Chiralpak IB column (Hexane-IPA = 90:10, flow  
33  
34 rate = 1.0  $\text{mL min}^{-1}$ ,  $\lambda = 227$  nm):  $T_{\text{R}} = 18.53$  min (major), 32.43 min (minor)): 98% ee,  $[\alpha]_{\text{D}}^{30} =$   
35  
36  $-178.5$  ( $c = 0.5$  in  $\text{CH}_2\text{Cl}_2$ );  $R_f$  0.25 (EA/hexanes: 1/5);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ /ppm, 7.64-  
37  
38 7.57 (m, 4H), 7.18 (d, 2H,  $J = 8.3$  Hz), 7.07-7.00 (m, 3H), 6.93-6.91 (m, 2H), 6.87-6.83 (m, 2H),  
39  
40 3.95 (dd, 1H,  $J = 10.1, 3.3$  Hz), 3.92 (dd, 1H,  $J = 9.9, 3.3$  Hz), 3.60 (dd, 1H,  $J = 13.6, 8.0$  Hz),  
41  
42 3.56 (dd, 1H,  $J = 13.1, 7.7$  Hz), 2.78 (td, 2H,  $J = 3.4, 15.8$  Hz).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  
43  
44  $\delta$ /ppm, 209.4, 202.7, 202.5, 142.0, 141.9, 137.0, 136.5, 135.63, 135.61, 131.4, 130.1, 128.3,  
45  
46 128.2, 127.5, 122.64, 122.57, 121.4, 61.4, 44.0, 42.6, 41.57, 41.56. IR (KBr): 3062, 2957, 2921,  
47  
48 1704, 1594, 1490, 1255, 763, 736, 700  $\text{cm}^{-1}$ . HRMS (ESI) for  $\text{C}_{26}\text{H}_{20}\text{O}_3\text{Br}$   $[\text{M}+\text{H}]^+$  (459.0596)  
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50 found: 459.0606.  
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**(2R,6R)-2-(4-bromophenyl)-6-phenylspiro[cyclohexane-1,2'-indene]-1',3',4-trione** (*ent-*

*trans-4ca*): Following the general procedure B, *ent-4ca* was obtained in 81% yield (37.2 mg, *trans:cis* = 14:1) as a white solid (mp.: 143.0-144.1 °C).  $[\alpha]_D^{30} = +180.6$  (c = 0.5 in CH<sub>2</sub>Cl<sub>2</sub>). HPLC analysis: Chiralpak IB column (Hexane-IPA = 90:10, flow rate = 1.0 mL min<sup>-1</sup>, λ = 227 nm): T<sub>R</sub> = 19.61 min (minor), 32.70 min (major), 98% ee.

**(2S,6S)-2-(4-bromophenyl)-6-phenylspiro[cyclohexane-1,2'-indene]-1',3',4-trione** (*cis-4ca*) :

To a glass vial equipped with a magnetic stir bar was charged **2** (0.1 mmol), **1** (1.2 eq), **IV** (5 mol%), **3e** (10 mol%) and toluene (0.5 mL) and stirred at 60 °C for 24h. Then the reaction was quenched by the addition of 0.1M HCl (0.25 mL) and the aqueous layer was extracted with DCM (2 x 0.25 mL). The combined organic layers were concentrated *in vacuo* and the crude reaction mass was purified by flash column chromatography over silica gel to give the pure compound **4ca**. in 96% yield (44.1 mg, *trans:cis* = 1:1) as a colorless solid (mp.: 93.2-94.4 °C). HPLC analysis (Chiralpak AD-H column (Hexane-IPA = 90:10, flow rate = 1.0 mL min<sup>-1</sup>, λ = 227 nm): T<sub>R</sub> = 39.13 min (major), 51.80 min (minor)): 97% ee,  $[\alpha]_D^{29} = +1.8$  (c = 0.5 in CH<sub>2</sub>Cl<sub>2</sub>); R<sub>f</sub> 0.30 (EA/hexanes: 1/5); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ/ppm: 7.66 (d, J = 7.6 Hz, 1H), 7.53 (td, J = 6.7, 1.7 Hz, 1H), 7.50-7.41 (m, 2H), 7.15 (d, J = 8.6 Hz, 2H), 7.03-6.88 (m, 7H), 3.86-3.70 (m, 4H), 2.71-2.56 (m, 2H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ/ppm: 207.8, 203.2, 201.6, 142.6, 141.9, 137.1, 136.6, 135.54, 135.5, 131.5, 129.8, 128.4, 127.9, 127.7, 122.5, 122.1, 131.6, 61.8, 49.0, 47.9, 43.3, 43.27. IR (KBr): 3062, 2957, 2921, 1704, 1594, 1490, 1255, 763, 736, 700 cm<sup>-1</sup>. HRMS (ESI) for C<sub>26</sub>H<sub>20</sub>O<sub>3</sub>Br [M+H]<sup>+</sup> (459.0596) found: 459.0596.

**4-((2S,6S)-1',3',4-trioxo-2-phenyl-1',3'-dihydrospiro[cyclohexane-1,2'-inden]-6-**

**yl)benzotrile** (*trans-4da*) : Following the general procedure A, **4da** was obtained in 90% yield (36.5 mg) as a yellow solid (mp.: 158.5-159.2 °C). HPLC analysis (Chiralpak IB column

(Hexane-IPA = 90:10, flow rate = 1.0 mL min<sup>-1</sup>, λ = 227 nm): T<sub>R</sub> = 48.15 min (major), 68.52 min (minor): 98% ee, [α]<sub>D</sub><sup>30</sup> = -203.5 (c = 0.5 in CH<sub>2</sub>Cl<sub>2</sub>); R<sub>f</sub> 0.09 (EA/hexanes: 1/5); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ/ppm: 7.62-7.58 (m, 4H), 7.38 (d, J = 8.3 Hz, 2H), 7.10 (d, J = 8.3 Hz, 2H), 7.05-7.01 (m, 3H), 6.92-6.90 (m, 2H), 4.04 (dd, J = 13.5, 3.2 Hz, 1H), 3.94 (dd, J = 13.2, 3.2 Hz, 1H), 3.68-3.54 (m, 2H), 2.82 (dd, J = 10.5, 3.2 Hz, 1H), 2.77 (dd, J = 10.4, 3.3 Hz, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ/ppm: 208.8, 202.4, 202.2, 143.0, 141.9, 141.8, 136.7, 135.9, 135.9, 132.1, 129.3, 128.3, 127.7, 122.72, 122.70, 118.2, 111.5, 61.4, 44.2, 43.0, 41.6, 41.1. IR (KBr): 3063, 2915, 1702, 1597, 1499, 1254, 163, 735, 699 cm<sup>-1</sup>. HRMS (ESI) for C<sub>27</sub>H<sub>20</sub>NO<sub>3</sub> [M+H]<sup>+</sup> (406.1443) found: 406.1451.

**4-((2*R*,6*R*)-1',3',4-trioxo-2-phenyl-1',3'-dihydrospiro[cyclohexane-1,2'-inden]-6-**

**yl)benzotrile (*ent-trans-4da*)** : Following the general procedure B, *ent-4da* was obtained in 99% yield (40.1 mg) as a yellow solid (mp.: 158.5-159.2 °C). [α]<sub>D</sub><sup>30</sup> = +200.2 (c = 0.5 in CH<sub>2</sub>Cl<sub>2</sub>). HPLC analysis: Chiralpak IB column (Hexane-IPA = 90:10, flow rate = 1.0 mL min<sup>-1</sup>, λ = 227 nm): T<sub>R</sub> = 55.43 min (minor), 73.71 min (major), 98% ee.

**(2*S*,6*S*)-2-(4-nitrophenyl)-6-phenylspiro[cyclohexane-1,2'-indene]-1',3',4-trione (*trans-4ea*)** :

Following the general procedure A, *4ea* was obtained in 96% yield (40.8 mg, *trans:cis* = 14:1) as a white solid (mp.: 141.3-141.8 °C). HPLC analysis (Chiralpak IB column (Hexane-IPA = 90:10, flow rate = 1.0 mL min<sup>-1</sup>, λ = 229 nm): T<sub>R</sub> = 45.65 min (major), 55.84 min (minor)): 97% ee, [α]<sub>D</sub><sup>30</sup> = -182.9 (c = 0.5 in CH<sub>2</sub>Cl<sub>2</sub>); R<sub>f</sub> 0.13(EA/hexanes: 1/5); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ/ppm: 7.94 (d, J = 8.6 Hz, 2H), 7.63-7.59 (m, 4H), 7.17 (d, J = 8.7 Hz, 2H), 7.08-7.03 (m, 3H), 6.93-6.91 (m, 2H), 4.11 (dd, J = 13.5, 3.4 Hz, 1H), 3.94 (dd, J = 13.1, 3.4 Hz, 1H), 3.65 (dd, J = 16.6, 13.5 Hz, 1H), 3.58 (dd, J = 16.9, 13.1 Hz, 1H), 2.82 (td, J = 16.9, 4.4 Hz, 2H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ/ppm: 208.6, 202.4, 202.1, 147.1, 145.1, 141.9, 141.8, 136.7, 136.0, 135.9,

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3 129.5, 128.3, 127.7, 123.4, 122.8, 122.7, 61.3, 44.4, 42.6, 41.6, 41.2. IR (KBr): 3061, 2925, 1702,  
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5 1604, 1512, 1255, 761, 736, 701  $\text{cm}^{-1}$ . HRMS (ESI) for  $\text{C}_{26}\text{H}_{20}\text{NO}_5$   $[\text{M}+\text{H}]^+$  (426.1341) found:  
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7 426.1351.  
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11 **(2R,6R)-2-(4-nitrophenyl)-6-phenylspiro[cyclohexane-1,2'-indene]-1',3',4-trione** (*ent-trans-*  
12  
13 **4ea**) : Following the general procedure B, *ent-4ea* was obtained in 95% yield (40.4 mg, *trans:cis*  
14 = 17:1) as a white solid (mp.: 158.5-159.2 °C).  $[\alpha]_{\text{D}}^{30} = +200.2$  (c = 0.5 in  $\text{CH}_2\text{Cl}_2$ ). HPLC  
15 analysis: Chiralpak IB column (Hexane-IPA = 90:10, flow rate = 1.0  $\text{mL min}^{-1}$ ,  $\lambda = 227$  nm):  $T_{\text{R}}$   
16 = 46.79 min (minor), 54.54 min (major), 99% ee.  
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24 **(2R,6S)-2-(2-bromophenyl)-6-phenylspiro[cyclohexane-1,2'-indene]-1',3',4-trione** (*trans-*  
25  
26 **4fa**): Following the general procedure A, **4fa** was obtained in 91% yield (41.8 mg, *trans:cis* =  
27 12:1) as a white solid (mp.: 163.6-164.9 °C). HPLC analysis (Chiralpak IB column (Hexane-IPA  
28 = 90:10, flow rate = 1.0  $\text{mL min}^{-1}$ ,  $\lambda = 227$  nm):  $T_{\text{R}} = 14.39$  min (major), 42.78 min (minor)):  
29 82% ee,  $[\alpha]_{\text{D}}^{30} = +3.5$  (c = 0.5 in  $\text{CH}_2\text{Cl}_2$ );  $R_f$  0.25 (EA/hexanes: 1/5);  $^1\text{H}$  NMR (400 MHz,  
30  $\text{CDCl}_3$ )  $\delta$ /ppm: 7.84 (d,  $J = 7.6$  Hz, 1H), 7.71-7.59 (m, 3H), 7.41 (dd,  $J = 0.9, 7.9$  Hz, 1H), 7.33  
31 (td,  $J = 1.3, 7.6$  Hz, 1H), 7.28 (dd,  $J = 1.8, 8.0$  Hz, 1H), 7.10 (td,  $J = 1.7, 7.9$  Hz, 1H), 7.06-6.95  
32 (m, 5H), 4.30 (t,  $J = 6.1$  Hz, 1H), 3.94 (dd,  $J = 3.9, 13.8$  Hz, 1H), 3.76 (dd,  $J = 14.0, 15.9$  Hz,  
33 1H), 3.28 (dd,  $J = 6.3, 16.0$  Hz, 1H), 2.98 (dd,  $J = 6.0, 16.0$  Hz, 1H), 2.79 (dd,  $J = 3.9, 16.0$  Hz,  
34 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ /ppm: 209.8, 202.5, 199.9, 142.4, 141.0, 138.8, 137.3, 135.7,  
35 135.4, 132.8, 129.8, 129.0, 128.7, 128.2, 127.7, 127.5, 125.9, 123.0, 122.8, 59.4, 43.4, 43.3, 43.1,  
36 42.9. IR (KBr): 2924, 1701, 1595, 1458, 1257, 1024, 758, 701  $\text{cm}^{-1}$ . HRMS (ESI) for  
37  $\text{C}_{26}\text{H}_{20}\text{O}_3\text{Br}$   $[\text{M}+\text{H}]^+$  (459.0596) found: 459.0604.  
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55 **(2S,6R)-2-(2-bromophenyl)-6-phenylspiro[cyclohexane-1,2'-indene]-1',3',4-trione** (*ent-*  
56  
57 *trans-4fa*): Following the general procedure B, *ent-4fa* was obtained in 78% yield (35.8 mg,  
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3 *trans:cis* = 10:1) as a white solid. HPLC analysis: Chiralpak IB column (Hexane-IPA = 90:10,  
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5 flow rate = 1.0 mL min<sup>-1</sup>,  $\lambda$  = 227 nm): T<sub>R</sub> = 14.43 min (minor), 41.42 min (major), 68%.  
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9 **(2*S*,6*S*)-2-(4-methylphenyl)-6-phenylspiro[cyclohexane-1,2'-indene]-1',3',4-trione** (*trans*-

10 **4ga**) : Following the general procedure A, **4ga** was obtained in 80% yield (31.6 mg, *trans:cis* =  
11  
12 10:1) as a yellow solid (mp.: 135.8-136.2 °C). HPLC analysis (Chiralpak IB column (Hexane-  
13  
14 IPA = 90:10, flow rate = 1.0 mL min<sup>-1</sup>,  $\lambda$  = 226 nm): T<sub>R</sub> = 13.59 min (major), 20.55 min (minor));  
15  
16 97% ee,  $[\alpha]_D^{30} = -157.0$  (c = 0.5 in CH<sub>2</sub>Cl<sub>2</sub>); R<sub>f</sub> 0.28 (EA/hexanes: 1/5); <sup>1</sup>H NMR (400 MHz,  
17  
18 CDCl<sub>3</sub>)  $\delta$ /ppm: 7.60-7.53 (m, 4H), 7.06-6.99 (m, 3H), 6.95-6.93 (m, 2H), 6.87-6.82 (m, 4H),  
19  
20 3.96 (dd, *J* = 6.1, 3.4 Hz, 1H), 3.93 (dd, *J* = 6.1, 3.4 Hz, 1H), 3.61 (dd, *J* = 16.8, 9.6 Hz, 1H),  
21  
22 3.57 (dd, *J* = 16.8, 9.4 Hz, 1H), 2.77 (dd, *J* = 16.8, 3.4 Hz, 2H), 2.14 (s, 3H). <sup>13</sup>C NMR (100  
23  
24 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm: 210.2, 203.0, 202.9, 142.2, 142.1, 137.4, 137.0, 135.3, 134.4, 128.9, 128.4,  
25  
26 128.3, 128.2, 127.4, 122.6, 122.5, 61.7, 43.7, 43.1, 41.9, 41.7, 20.9. IR (KBr): 3032, 2920, 1703,  
27  
28 1595, 1254, 761, 699 cm<sup>-1</sup>. HRMS (ESI) for C<sub>27</sub>H<sub>23</sub>O<sub>3</sub> [M+H]<sup>+</sup> (395.1647) found: 395.1645.  
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35 **(2*R*,6*R*)-2-(4-methylphenyl)-6-phenylspiro[cyclohexane-1,2'-indene]-1',3',4-trione** (*ent*-

36 *trans*-**4ga**) : Following the general procedure B, *ent*-**4ga** was obtained in 75% yield (29.6 mg,  
37  
38 *trans:cis* = 13:1) as a yellow solid (mp.: 135.8-136.2 °C).  $[\alpha]_D^{30} = +156.0$  (c = 0.5 in CH<sub>2</sub>Cl<sub>2</sub>).  
39  
40 HPLC analysis: Chiralpak IB column (Hexane-IPA = 90:10, flow rate = 1.0 mL min<sup>-1</sup>,  $\lambda$  = 226  
41  
42 nm): T<sub>R</sub> = 13.79 min (minor), 20.34 min (major), 98% ee.  
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48 **(2*S*,6*S*)-2-(4-methoxyphenyl)-6-phenylspiro[cyclohexane-1,2'-indene]-1',3',4-trione** (*trans*-

49 **4ha**) : Following the general procedure A, **4ha** was obtained in 71% yield (29.1 mg, *trans:cis* =  
50  
51 7:1) as a yellow solid (mp.: 120.2-121.0 °C). HPLC analysis (Chiralpak IB column (Hexane-IPA  
52  
53 = 90:10, flow rate = 1.0 mL min<sup>-1</sup>,  $\lambda$  = 226 nm): T<sub>R</sub> = 21.64 min (major), 33.58 min (minor));  
54  
55 99% ee,  $[\alpha]_D^{30} = -155.3$  (c = 0.5 in CH<sub>2</sub>Cl<sub>2</sub>); R<sub>f</sub> 0.16 (EA/hexanes: 1/5); <sup>1</sup>H NMR (400 MHz,  
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CDCl<sub>3</sub>)  $\delta$ /ppm: 7.61-7.54 (m, 4H), 7.07-7.00 (m, 3H), 6.95-6.93 (m, 2H), 6.87 (d,  $J = 8.7$  Hz, 2H), 6.58 (d,  $J = 8.7$ , 2H), 3.94 (dt,  $J = 13.4, 3.7$ , 2H), 3.64-3.55 (m, 5H), 2.78 (dd,  $J = 9.2, 3.3$  Hz, 1H), 2.73 (dd,  $J = 9.2, 3.3$  Hz, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm: 210.2, 203.1, 203.0, 158.6, 142.2, 137.4, 135.38, 135.36, 129.5, 129.4, 128.4, 128.2, 127.4, 122.54, 122.49, 113.6, 61.8, 55.0, 43.6, 42.8, 42.0, 41.7. IR (KBr): 3068, 2918, 1702, 1598, 1522, 1348, 1255, 761, 698 cm<sup>-1</sup>. HRMS (ESI) for C<sub>27</sub>H<sub>23</sub>O<sub>4</sub> [M+H]<sup>+</sup> (411.1596) found: 411.1600.

**(2R,6R)-2-(4-methoxyphenyl)-6-phenylspiro[cyclohexane-1,2'-indene]-1',3',4-trione** (*ent-trans-4ha*) : Following the general procedure B, *ent-4ha* was obtained in 61% yield (25.0 mg, *trans:cis* = 9:1) as a yellow solid (mp.: 120.2-121.0 °C). [ $\alpha$ ]<sub>D</sub><sup>30</sup> = +154.2 (c = 0.5 in CH<sub>2</sub>Cl<sub>2</sub>). HPLC analysis: Chiralpak IB column (Hexane-IPA = 90:10, flow rate = 1.0 mL min<sup>-1</sup>,  $\lambda = 226$  nm): T<sub>R</sub> = 22.62 min (minor), 32.23 min (major), 93% ee.

**(2S,6S)-2-(2-methoxyphenyl)-6-phenylspiro[cyclohexane-1,2'-indene]-1',3',4-trione** (*trans-4ia*) : Following the general procedure A, **4ia** was obtained in 66% yield (27.1 mg) as a yellow solid (mp.: 133.5-134.1 °C). HPLC analysis (Chiralpak IB column (Hexane-IPA = 90:10, flow rate = 1.0 mL min<sup>-1</sup>,  $\lambda = 227$  nm): T<sub>R</sub> = 14.79 min (major), 18.57 min (minor)): 91% ee, [ $\alpha$ ]<sub>D</sub><sup>30</sup> = -35.4 (c = 0.5 in CH<sub>2</sub>Cl<sub>2</sub>); R<sub>f</sub> 0.14 (EA/hexanes: 1/5); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm: 7.78 (d,  $J = 7.6$  Hz, 1H), 7.64-7.50 (m, 3H), 7.17-7.13 (m, 2H), 7.00-6.93 (m, 6H), 6.52 (d,  $J = 8.1$  Hz, 1H), 4.14 (dd,  $J = 8.9, 5.2$  Hz, 1H), 3.93 (dd,  $J = 14.4, 3.0$  Hz, 1H), 3.81 (dd,  $J = 16.4, 14.5$  Hz, 1H), 3.27 (s, 3H), 3.22 (dd,  $J = 16.2, 9.0$  Hz, 1H), 3.01 (dd,  $J = 16.1, 5.2$  Hz, 1H), 2.70 (dd,  $J = 16.4, 3.1$  Hz, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm: 210.6, 202.5, 200.5, 155.9, 141.8, 141.6, 137.7, 135.0, 134.9, 128.7, 128.6, 128.5, 128.1, 127.2, 122.4, 122.1, 120.7, 109.5, 60.0, 53.8, 42.7, 42.2, 41.9, 37.2. IR (KBr): 3063, 2958, 1704, 1597, 1493, 1461, 1249, 755, 700 cm<sup>-1</sup>. HRMS (ESI) for C<sub>27</sub>H<sub>23</sub>O<sub>4</sub> [M+H]<sup>+</sup> (411.1596) found: 411.1597.

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4 **(2R,6R)-2-(2-methoxyphenyl)-6-phenylspiro[cyclohexane-1,2'-indene]-1',3',4-trione** (*ent-*  
5  
6 *trans-4ia*) : Following the general procedure B, *ent-4ia* was obtained in 62% yield (25.4 mg) as a  
7  
8 yellow solid (mp.: 133.5-134.1 °C).  $[\alpha]_D^{30} = +25.8$  (c = 0.5 in CH<sub>2</sub>Cl<sub>2</sub>); HPLC analysis:  
9  
10 Chiralpak IB column (Hexane-IPA = 90:10, flow rate = 1.0 mL min<sup>-1</sup>, λ = 227 nm): T<sub>R</sub> = 14.99  
11  
12 min (minor), 17.51 min (major), 78% ee.

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16 **(2S,6R)-2-phenyl-6-(thiophen-2-yl)spiro[cyclohexane-1,2'-indene]-1',3',4-trione** (*trans-4ja*) :  
17  
18 Following the general procedure A, **4ja** was obtained in 82% yield (31.7 mg, *trans:cis* = 1:1) as a  
19  
20 yellow solid (mp.: 195.8-196.5 °C). HPLC analysis (Chiralpak IB column (Hexane-IPA = 90:10,  
21  
22 flow rate = 1.0 mL min<sup>-1</sup>, λ = 226 nm): T<sub>R</sub> = 18.03 min (major), 20.02 min (minor)): 97% ee,  
23  
24  $[\alpha]_D^{30} = -134.6$  (c = 0.5 in CH<sub>2</sub>Cl<sub>2</sub>); R<sub>f</sub> 0.23(EA/hexanes: 1/5); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  
25  
26 δ/ppm: 7.72-7.69 (m, 1H), 7.66-7.60 (m, 3H), 7.09-7.02 (m, 3H), 6.97-6.93 (m, 3H), 6.72 (dd, *J*  
27  
28 = 3.7, 5.0 Hz, 1H), 6.66 (d, *J* = 3.5 Hz, 1H), 4.27 (dd, *J* = 12.8, 3.8 Hz, 1H), 3.93 (dd, *J* = 12.7,  
29  
30 3.6 Hz, 1H), 3.55 (dd, *J* = 12.8, 7.9 Hz, 1H), 3.52 (dd, *J* = 12.7, 7.5 Hz, 1H), 2.96 (dd, *J* = 16.8,  
31  
32 3.9 Hz, 1H), 2.82 (dd, *J* = 16.5, 3.7 Hz, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ/ppm: 208.9, 202.3,  
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34 202.2, 142.2, 142.1, 140.2, 137.4, 135.5, 128.4, 128.3, 127.5, 126.6, 126.5, 124.5, 122.7, 61.4,  
35  
36 44.1, 43.1, 41.9, 38.9. IR (KBr): 3071, 2956, 2922, 1724, 1701, 1593, 1349, 1254, 765, 705 cm<sup>-1</sup>.  
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41  
42 HRMS (ESI) for C<sub>24</sub>H<sub>19</sub>O<sub>3</sub>S [M+H]<sup>+</sup> (387.1055) found: 387.1055.

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44  
45 **(2R,6S)-2-phenyl-6-(thiophen-2-yl)spiro[cyclohexane-1,2'-indene]-1',3',4-trione** (*ent-trans-*  
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47 **4ja**) : Following the general procedure B, *ent-4ja* was obtained in 80% yield (30.9 mg, *trans:cis*  
48  
49 = 1:1) as a yellow solid (mp.: 195.3-196.3 °C).  $[\alpha]_D^{30} = +135.5$  (c = 0.5 in CH<sub>2</sub>Cl<sub>2</sub>). HPLC  
50  
51 analysis: Chiralpak IB column (Hexane-IPA = 90:10, flow rate = 1.0 mL min<sup>-1</sup>, λ = 226 nm): T<sub>R</sub>  
52  
53 = 18.24 min (minor), 19.90 min (major), 96% ee.  
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**(2*S*,6*S*)-2-(4-bromophenyl)-6-(4-chlorophenyl)spiro[cyclohexane-1,2'-indene]-1',3',4-trione**

**(*trans*-4cb)** : Following the general procedure A, **4cb** was obtained in 74% yield (36.5 mg) as a yellow solid (mp.: 193.7-194.8 °C). HPLC analysis (Chiralpak IB column (Hexane-IPA = 90:10, flow rate = 1.0 mL min<sup>-1</sup>, λ = 226 nm): T<sub>R</sub> = 19.32 min (major), 30.19 min (minor)): 98% ee, [α]<sub>D</sub><sup>30</sup> = -152.4 (c = 0.5 in CH<sub>2</sub>Cl<sub>2</sub>); R<sub>f</sub> 0.29 (EA/hexanes: 1/5); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ/ppm: 7.62 (s, 4H), 7.18 (d, *J* = 8.5 Hz, 2H), 7.03 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 6.83 (d, *J* = 8.5 Hz, 2H), 3.92 (dt, *J* = 13.3, 3.5 Hz, 2H), 3.55 (dd, *J* = 16.8, 13.4 Hz, 2H), 2.75 (dd, *J* = 16.6, 3.4 Hz, 2H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ/ppm: 208.8, 202.3, 141.8, 136.2, 135.8, 135.7, 133.3, 131.3, 130.0, 129.7, 128.4, 122.7, 121.5, 61.1, 42.93, 42.90, 41.51, 41.4. IR (KBr): 3065, 2920, 1703, 1593, 1490, 1253, 824, 735, 700 cm<sup>-1</sup>. HRMS (EI) for C<sub>26</sub>H<sub>18</sub>O<sub>3</sub>ClBr [M]<sup>+</sup> (492.0128) found: 492.0125.

**(2*R*,6*R*)-2-(4-bromophenyl)-6-(4-chlorophenyl)spiro[cyclohexane-1,2'-indene]-1',3',4-trione**

**(*ent-trans*-4cb)** : Following the general procedure B, **ent-4cb** was obtained in 82% yield (40.4 mg) as a yellow solid (mp.: 193.7-194.8 °C). [α]<sub>D</sub><sup>30</sup> = +151.6 (c = 0.5 in CH<sub>2</sub>Cl<sub>2</sub>). HPLC analysis: Chiralpak IB column (Hexane-IPA = 90:10, flow rate = 1.0 mL min<sup>-1</sup>, λ = 226 nm): T<sub>R</sub> = 19.62 min (minor), 29.98 min (major), 97% ee.

**(2*S*,6*S*)-2,6-bis(4-bromophenyl)spiro[cyclohexane-1,2'-indene]-1',3',4-trione (*trans*-4cc) :**

Following the general procedure A, **4cc** was obtained in 77% yield (41.4 mg) as a yellow solid (mp.: 203.9-204.5 °C). HPLC analysis (Chiralpak IB column (Hexane-IPA = 90:10, flow rate = 1.0 mL min<sup>-1</sup>, λ = 226 nm): T<sub>R</sub> = 20.50 min (major), 34.79 min (minor)): 98% ee, [α]<sub>D</sub><sup>30</sup> = -157.2 (c = 0.5 in CH<sub>2</sub>Cl<sub>2</sub>); R<sub>f</sub> 0.29 (EA/hexanes: 1/5); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ/ppm: 7.62 (s, 4H), 7.18 (d, *J* = 8.5 Hz, 4H), 6.83 (d, *J* = 8.5 Hz, 4H), 3.91 (dd, *J* = 13.2, 3.3 Hz, 2H), 3.54 (dd, *J* = 16.7, 13.3 Hz, 2H), 2.75 (dd, *J* = 16.7, 3.4 Hz, 2H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ/ppm: 208.8,

202.3, 141.8, 136.2, 135.9, 131.4, 130.0, 122.7, 121.5, 61.1, 43.0, 41.5. IR (KBr): 3062, 2919, 1703, 1593, 1488, 1254, 822, 735, 698  $\text{cm}^{-1}$ . HRMS (MALDI) for  $\text{C}_{26}\text{H}_{18}\text{O}_3\text{Br}_2\text{Na}$   $[\text{M}+\text{Na}]^+$  (558.9515) found: 558.9535.

**(2R,6R)-2,6-bis(4-bromophenyl)spiro[cyclohexane-1,2'-indene]-1',3',4-trione** (*ent-trans-4cc*) : Following the general procedure B, *ent-4cc* was obtained in 70% yield (37.7 mg) as a yellow solid (mp.: 203.9-204.5 °C).  $[\alpha]_{\text{D}}^{30} = +157.8$  (c = 0.5 in  $\text{CH}_2\text{Cl}_2$ ). HPLC analysis: Chiralpak IB column (Hexane-IPA = 90:10, flow rate = 1.0  $\text{mL min}^{-1}$ ,  $\lambda = 226$  nm):  $T_{\text{R}} = 20.75$  min (minor), 34.48 min (major), 98% ee.

**(2S,6S)-4-(2-(4-bromophenyl)-1',3',4-trioxo-1',3'-dihydrospiro[cyclohexane-1,2'-inden]-6-yl)benzotrile** (*trans-4cd*) : Following the general procedure A, **4cd** was obtained in 89% yield (43.1 mg, *trans:cis* = 15:1) as a yellow solid (mp.: 189.8-190.3 °C). HPLC analysis (Chiralpak IB column (Hexane-IPA = 85:15, flow rate = 1.0  $\text{mL min}^{-1}$ ,  $\lambda = 226$  nm):  $T_{\text{R}} = 36.58$  min (major), 48.26 min (minor)): 97% ee,  $[\alpha]_{\text{D}}^{30} = -180.7$  (c = 0.5 in  $\text{CH}_2\text{Cl}_2$ );  $R_{\text{f}}$  0.09 (EA/hexanes: 1/5);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ /ppm: 7.67-7.60 (m, 4H), 7.37 (d,  $J = 8.2$  Hz, 2H), 7.19 (d,  $J = 8.6$  Hz, 2H), 7.08 (d,  $J = 8.3$  Hz, 2H), 6.81 (d,  $J = 8.3$  Hz, 2H), 3.99 (dd,  $J = 13.2, 3.4$  Hz, 1H), 3.91 (dd,  $J = 13.3, 3.4$  Hz, 1H), 3.58 (dd,  $J = 16.7, 8.8$  Hz, 1H), 3.54 (dd,  $J = 13.3, 9.0$  Hz, 1H), 2.80 (dd,  $J = 4.5, 3.8$  Hz, 1H), 2.76 (dd,  $J = 4.7, 3.7$  Hz, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ /ppm: 208.2, 202.1, 202.0, 142.7, 141.75, 141.66, 136.21, 136.19, 135.9, 132.1, 131.5, 130.0, 129.2, 122.9, 122.8, 121.8, 118.2, 111.6, 61.0, 43.4, 43.2, 41.5, 41.1. IR (KBr): 2922, 1702, 1598, 1489, 1412, 1255, 735, 700  $\text{cm}^{-1}$ . HRMS (ESI) for  $\text{C}_{27}\text{H}_{19}\text{NO}_3\text{Br}$   $[\text{M}+\text{H}]^+$  (484.0548) found: 484.0553.

**(2R,6R)-4-(2-(4-bromophenyl)-1',3',4-trioxo-1',3'-dihydrospiro[cyclohexane-1,2'-inden]-6-yl)benzotrile** (*ent-trans-4cd*) : Following the general procedure B, *ent-4cd* was obtained in 73% yield (35.3 mg, *trans:cis* = 18:1) as a yellow solid (mp.: 189.8-190.3 °C).  $[\alpha]_{\text{D}}^{30} = +181.7$  (c

= 0.5 in CH<sub>2</sub>Cl<sub>2</sub>). HPLC analysis: Chiralpak IB column (Hexane-IPA = 85:15, flow rate = 1.0 mL min<sup>-1</sup>, λ = 226 nm): T<sub>R</sub> = 37.50 min (minor), 46.86 min (major), 97% ee.

**(2*S*,6*S*)-2-(4-bromophenyl)-6-(4-nitrophenyl)spiro[cyclohexane-1,2'-indene]-1',3',4-trione**

**(*trans*-4ce)** : Following the general procedure A, **4ce** was obtained in 73% yield (36.8 mg, *trans:cis* = 8:1) as a yellow solid (mp.: 197.2-197.9 °C). HPLC analysis (Chiralpak IB column (Hexane-IPA = 90:10, flow rate = 1.0 mL min<sup>-1</sup>, λ = 227 nm): T<sub>R</sub> = 53.82 min (major), 75.37 min (minor)): 97% ee, [α]<sub>D</sub><sup>30</sup> = -179.6 (c = 0.5 in CH<sub>2</sub>Cl<sub>2</sub>); R<sub>f</sub> 0.11 (EA/hexanes: 1/5); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ/ppm: 7.94 (d, *J* = 8.7 Hz, 2H), 7.66-7.63 (m, 4H), 7.20 (d, *J* = 8.5 Hz, 2H), 7.15 (d, *J* = 8.9 Hz, 2H), 6.82 (d, *J* = 8.4 Hz, 2H), 4.06 (dd, *J* = 13.3, 3.4 Hz, 1H), 3.92 (dd, *J* = 13.1, 3.2 Hz, 1H), 3.60 (dd, *J* = 20.6, 13.3 Hz, 1H), 3.56 (dd, *J* = 20.7, 13.3 Hz, 1H), 2.82 (dd, *J* = 10.0, 3.6 Hz, 1H), 2.78 (dd, *J* = 10.0, 3.4 Hz, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ/ppm: 208.1, 202.1, 201.9, 147.1, 144.8, 141.7, 141.6, 136.3, 136.2, 135.8, 131.5, 130.0, 129.4, 123.5, 122.94, 122.85, 121.8, 61.0, 43.4, 43.0, 41.5, 41.2. IR (KBr): 3078, 2923, 1703, 1598, 1522, 1348, 1255, 735, 697 cm<sup>-1</sup>. HRMS (ESI) for C<sub>26</sub>H<sub>17</sub>NO<sub>5</sub>Br [M-H]<sup>+</sup> (502.0290) found: 502.0282.

**(2*R*,6*R*)-2-(4-bromophenyl)-6-(4-nitrophenyl)spiro[cyclohexane-1,2'-indene]-1',3',4-trione**

**(*ent-trans*-4ce)** : Following the general procedure B, **ent-4ce** was obtained in 79% yield (39.8 mg, *trans:cis* = 9:1) as a yellow solid (mp.: 197.2-197.9 °C). [α]<sub>D</sub><sup>30</sup> = +179.0 (c = 0.5 in CH<sub>2</sub>Cl<sub>2</sub>). HPLC analysis: Chiralpak IB column (Hexane-IPA = 90:10, flow rate = 1.0 mL min<sup>-1</sup>, λ = 227 nm): T<sub>R</sub> = 56.00 min (minor), 73.43 min (major), 97% ee.

**(2*R*,6*S*)-2-(2-bromophenyl)-6-(4-bromophenyl)spiro[cyclohexane-1,2'-indene]-1',3',4-trione**

**(*trans*-4cf)**: Following the general procedure A, **4cf** was obtained in 70% yield (37.7 mg, *trans:cis* = 18:1) as a white solid (mp.: 202.0-204.4 °C). HPLC analysis (Chiralpak IB column (Hexane-IPA = 90:10, flow rate = 1.0 mL min<sup>-1</sup>, λ = 226 nm): T<sub>R</sub> = 14.87 min (major), 37.13 min

(minor): 98% ee,  $[\alpha]_{\text{D}}^{30} = -9.8$  ( $c = 0.5$  in  $\text{CH}_2\text{Cl}_2$ );  $R_f$  0.26 (EA/hexanes: 1/5);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta/\text{ppm}$ : 7.90-7.83 (m, 1H), 7.75-7.60 (m, 3H), 7.44-7.37 (m, 1H), 7.36-7.28 (m, 1H), 7.24 (d,  $J = 7.9$  Hz, 1H), 7.15 (dd,  $J = 2.7, 8.4$  Hz, 2H), 7.12-7.05 (m, 1H), 6.87 (dd,  $J = 1.0, 8.5$  Hz, 2H), 4.29 (t,  $J = 6.1$  Hz, 1H), 3.92 (dd,  $J = 4.0, 13.8$  Hz, 1H), 3.73 (t,  $J = 15.5$  Hz, 1H), 3.26 (ddd,  $J = 1.4, 6.1, 16.0$  Hz, 1H), 2.95 (dd,  $J = 5.7, 16.0$  Hz, 1H), 2.76 (dd,  $J = 4.0, 16.0$  Hz, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta/\text{ppm}$ : 209.2, 202.2, 199.6, 142.3, 140.8, 138.4, 136.4, 136.0, 135.6, 132.9, 131.4, 130.4, 129.7, 127.7, 125.9, 123.1, 122.9, 121.5, 59.2, 43.4, 42.9, 42.7, 42.1. IR (KBr): 3066, 2854, 2924, 1701, 1592, 1490, 1469, 1412, 1352, 1260, 1011, 869, 799, 758, 736, 696  $\text{cm}^{-1}$ . HRMS (ESI) for  $\text{C}_{26}\text{H}_{19}\text{O}_3\text{Br}_2$   $[\text{M}+\text{H}]^+$  (536.9701) found: 536.9709.

**(2*S*,6*R*)-2-(2-bromophenyl)-6-(4-bromophenyl)spiro[cyclohexane-1,2'-indene]-1',3',4-trione (ent-trans-4cf)**: Following the general procedure B, **ent-4cf** was obtained in 65% yield (35.0 mg) as a white solid. HPLC analysis: Chiralpak IB column (Hexane-IPA = 90:10, flow rate = 1.0 mL  $\text{min}^{-1}$ ,  $\lambda = 226$  nm):  $T_R = 15.45$  min (minor), 36.02 min (major), 97%.

**(2*S*,6*S*)-2-(4-bromophenyl)-6-(4-methoxyphenyl)spiro[cyclohexane-1,2'-indene]-1',3',4-trione (trans-4cg)**: Following the general procedure A, **4cg** was obtained in 76% yield (37.2 mg, *trans:cis* = 11:1) as a yellow solid (mp.: 102.8-103.2 °C). HPLC analysis (Chiralpak IB column (Hexane-IPA = 90:10, flow rate = 1.0 mL  $\text{min}^{-1}$ ,  $\lambda = 226$  nm):  $T_R = 24.78$  min (major), 41.05 min (minor): 98% ee,  $[\alpha]_{\text{D}}^{30} = -172.7$  ( $c = 0.5$  in  $\text{CH}_2\text{Cl}_2$ );  $R_f$  0.14 (EA/hexanes: 1/5);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta/\text{ppm}$ : 7.63-7.57 (m, 4H), 7.18 (d,  $J = 8.4$  Hz, 2H), 6.84 (d,  $J = 8.6$  Hz, 4H), 6.57 (d,  $J = 8.7$  Hz, 2H), 3.91 (td,  $J = 14.0, 3.2$  Hz, 2H), 3.62 (s, 3H), 3.60-3.50 (m, 2H), 2.76 (dd,  $J = 5.7, 3.4$  Hz, 1H), 2.72 (dd,  $J = 5.7, 3.4$  Hz, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta/\text{ppm}$ : 209.5, 202.8, 202.6, 158.6, 142.0, 141.9, 136.6, 135.6, 135.56, 131.3, 130.0, 129.4, 129.0, 128.6, 122.59, 122.56, 121.3, 113.5, 61.4, 55.0, 43.1, 42.6, 41.9, 41.5. IR (KBr): 3062, 2957, 1704, 1607, 1513,

1  
2  
3 1489, 1412, 1255, 1182, 826, 736  $\text{cm}^{-1}$ . HRMS (MALDI) for  $\text{C}_{27}\text{H}_{21}\text{O}_4\text{BrNa}$   $[\text{M}+\text{Na}]^+$  (511.0515)  
4  
5 found: 511.0520.  
6  
7

8  
9 **(2*R*,6*R*)-2-(4-bromophenyl)-6-(4-methoxyphenyl)spiro[cyclohexane-1,2'-indene]-1',3',4-**

10 **trione (*ent-trans*-4cg)** : Following the general procedure B, *ent*-4cg was obtained in 88% yield  
11  
12 (43.0 mg, *trans:cis* = 10:1) as a yellow solid (mp.: 102.8-103.2 °C).  $[\alpha]_{\text{D}}^{30} = +179.0$  (c = 0.5 in  
13  
14  $\text{CH}_2\text{Cl}_2$ ). HPLC analysis: Chiralpak IB column (Hexane-IPA = 90:10, flow rate = 1.0  $\text{mL min}^{-1}$ ,  
15  
16  $\lambda = 226$  nm):  $T_{\text{R}} = 26.02$  min (minor), 39.70 min (major), 94% ee.  
17  
18  
19

20  
21 **(2*S*,6*S*)-2-(4-bromophenyl)-6-(2-methoxyphenyl)spiro[cyclohexane-1,2'-indene]-1',3',4-**

22 **trione (*trans*-4ch)** : Following the general procedure A, 4ch was obtained in 89% yield (43.6 mg)  
23  
24 as a white solid (mp.: 98.5-99.8 °C). HPLC analysis (Chiralpak IB column (Hexane-IPA = 90:10,  
25  
26 flow rate = 1.0  $\text{mL min}^{-1}$ ,  $\lambda = 227$  nm):  $T_{\text{R}} = 17.81$  min (major), 23.02 min (minor)): 97% ee,  
27  
28  $[\alpha]_{\text{D}}^{30} = -36.2$  (c = 0.5 in  $\text{CH}_2\text{Cl}_2$ );  $R_{\text{f}}$  0.14 (EA/hexanes: 1/5);  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  
29  
30  $\delta/\text{ppm}$ : 7.82 (d,  $J = 7.5$  Hz, 1H), 7.68 (t,  $J = 7.3$  Hz, 1H), 7.62 (t,  $J = 7.3$  Hz, 1H), 7.54 (d,  $J = 7.5$   
31  
32 Hz, 1H), 7.18-7.13 (m, 4H), 6.95 (t,  $J = 7.5$  Hz, 1H), 6.89 (d,  $J = 8.5$  Hz, 2H), 6.54 (d,  $J = 8.2$  Hz,  
33  
34 1H), 4.11 (dd,  $J = 8.3, 5.4$  Hz, 1H), 3.90-3.73 (m, 2H), 3.30 (s, 3H), 3.17 (dd,  $J = 16.2, 8.2$  Hz,  
35  
36 1H), 3.03 (dd,  $J = 16.2, 5.5$  Hz, 1H), 2.67 (dd,  $J = 16.2, 3.0$  Hz, 1H).  $^{13}\text{C NMR}$  (100 MHz,  
37  
38  $\text{CDCl}_3$ )  $\delta/\text{ppm}$ : 210.1, 202.4, 200.2, 155.9, 141.8, 141.4, 137.0, 135.4, 135.1, 131.3, 130.5, 128.8,  
39  
40 128.7, 127.0, 122.6, 122.3, 121.2, 120.7, 109.5, 59.9, 53.9, 42.2, 41.9, 37.5. IR (KBr): 2960,  
41  
42 1702, 1639, 1490, 1463, 1252, 752, 697  $\text{cm}^{-1}$ . HRMS (ESI) for  $\text{C}_{27}\text{H}_{21}\text{O}_4\text{Br}$   $[\text{M}+\text{H}]^+$  (489.0701)  
43  
44 found: 489.0706.  
45  
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52 **(2*R*,6*R*)-2-(4-bromophenyl)-6-(2-methoxyphenyl)spiro[cyclohexane-1,2'-indene]-1',3',4-**

53 **trione (*ent-trans*-4ch)** : Following the general procedure B, *ent*-4ch was obtained in 81% yield  
54  
55 (39.6 mg) as a white solid (mp.: 98.5-99.8 °C).  $[\alpha]_{\text{D}}^{30} = +34.9$  (c = 0.5 in  $\text{CH}_2\text{Cl}_2$ ). HPLC  
56  
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60

analysis: Chiralpak IB column (Hexane-IPA = 90:10, flow rate = 1.0 mL min<sup>-1</sup>, λ = 227 nm): T<sub>R</sub> = 18.21 min (minor), 22.35 min (major), 97% ee.

**(2*S*,6*R*)-2-(4-bromophenyl)-6-(thiophen-2-yl)spiro[cyclohexane-1,2'-indene]-1',3',4-trione**

**(*trans*-4*ci*)** : Following the general procedure A, **4*ci*** was obtained in 75% yield (34.9 mg, *trans*:*cis* = 10:1) as a white solid (mp.: 101.7-102.5 °C). HPLC analysis (Chiralpak IB column (Hexane-IPA = 90:10, flow rate = 1.0 mL min<sup>-1</sup>, λ = 226 nm): T<sub>R</sub> = 21.74 min (major), 32.40 min (minor)): 98% ee, [α]<sub>D</sub><sup>30</sup> = -133.3 (c = 0.5 in CH<sub>2</sub>Cl<sub>2</sub>); R<sub>f</sub> 0.23(EA/hexanes: 1/5); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ/ppm: 7.72-7.65 (m, 4H), 7.20 (d, *J* = 8.5 Hz, 2H), 6.95 (d, *J* = 5.2 Hz, 1H), 6.83 (d, *J* = 8.5 Hz, 2H), 6.71 (dd, *J* = 5.0, 3.6 Hz, 1H), 6.63 (d, *J* = 3.4 Hz, 1H), 4.20 (dd, *J* = 12.3, 3.9 Hz, 1H), 3.91 (dd, *J* = 12.6, 3.7 Hz, 1H), 3.52-3.43 (m, 2H), 2.95 (dd, *J* = 16.8, 3.9 Hz, 1H), 2.77 (dd, *J* = 16.4, 3.7 Hz, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ/ppm: 208.3, 202.1, 201.9, 142.0, 141.9, 139.9, 136.5, 135.83, 135.81, 131.5, 130.1, 126.61, 126.57, 124.6, 122.91, 122.87, 121.6, 61.1, 43.2, 43.1, 41.9, 39.3. IR (KBr): 3071, 2924, 1703, 1593, 1488, 1411, 1255, 734, 702 cm<sup>-1</sup>. HRMS (ESI) for C<sub>24</sub>H<sub>18</sub>O<sub>3</sub>SBr [M+H]<sup>+</sup> (465.0160) found: 465.0165.

**(2*R*,6*S*)-2-(4-bromophenyl)-6-(thiophen-2-yl)spiro[cyclohexane-1,2'-indene]-1',3',4-trione**

**(*ent-trans*-4*ci*)** : Following the general procedure B, ***ent*-4*ci*** was obtained in 70% yield (32.6 mg, *trans*:*cis* = 12:1) as a white solid (mp.: 101.7-102.5 °C). [α]<sub>D</sub><sup>30</sup> = +132.2 (c = 0.5 in CH<sub>2</sub>Cl<sub>2</sub>). HPLC analysis: Chiralpak IB column (Hexane-IPA = 90:10, flow rate = 1.0 mL min<sup>-1</sup>, λ = 226 nm): T<sub>R</sub> = 22.58 min (minor), 31.60 min (major), 98% ee.

**(2*S*,3*R*,6*S*)-2-(4-bromophenyl)-3-methyl-6-phenylspiro[cyclohexane-1,2'-indene]-1',3',4-**

**trione (*trans*-5*caa*)** : Following the general procedure D, **5*caa*** was obtained in 89% yield (42.1 mg, *trans*:*cis* = 4:1) as a white solid (mp.: 84.6-85.5 °C). HPLC analysis (Chiralpak IB column (Hexane-IPA = 98:2, flow rate = 1.0 mL min<sup>-1</sup>, λ = 227 nm): T<sub>R</sub> = 20.07 min (major), 22.86 min

(minor): >99% ee,  $[\alpha]_D^{30} = -119.1$  (c = 0.5 in  $\text{CH}_2\text{Cl}_2$ );  $R_f$  0.30 (EA/hexanes: 1/5);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ /ppm: 7.73-7.66 (m, 1H), 7.65-7.51 (m, 3H), 7.23-7.04 (m, 5H), 6.98-6.72 (m, 4H), 3.87 (dd,  $J = 10.9, 4.1$  Hz, 1H), 3.65 (d, 2H), 3.40 (dd,  $J = 16.5, 11.0$  Hz, 1H), 2.98 (dd,  $J = 16.5, 4.2$  Hz, 1H), 1.01-0.96 (m, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ /ppm: 211.2, 203.3, 201.7, 141.8, 141.6, 137.7, 135.7, 135.6, 131.3, 128.5, 128.3, 127.5, 122.8, 122.7, 121.2, 62.5, 49.0, 44.0, 43.3, 41.4, 12.5. IR (KBr): 2922, 1702, 1593, 1489, 1249, 763, 701  $\text{cm}^{-1}$ . HRMS (ESI) for  $\text{C}_{27}\text{H}_{22}\text{O}_3\text{Br}$   $[\text{M}+\text{H}]^+$  (473.0752) found: 473.0746.

**(2*S*,3*R*,6*S*)-2,6-bis(4-bromophenyl)-3-methylspiro[cyclohexane-1,2'-indene]-1',3',4-trione**

**(*trans*-5cca)** : Following the general procedure D, **5cca** was obtained in 99% yield (54.7 mg, *trans*:*cis* = 3:1) as a white solid (mp.: 119.1-120.0 °C). HPLC analysis (Chiralpak IA column (Hexane-IPA = 80:20, flow rate = 1.0 mL min<sup>-1</sup>,  $\lambda = 226$  nm):  $T_R = 15.63$  min (major), 20.92 min (minor)) : >99% ee,  $[\alpha]_D^{30} = -166.1$  (c = 0.5 in  $\text{CH}_2\text{Cl}_2$ );  $R_f$  0.31 (EA/hexanes: 1/5);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ /ppm: 7.72-7.55 (m, 4H), 7.23 (d,  $J = 8.5$  Hz, 2H), 7.15 (br, 2H), 7.01-6.58 (m, 4H), 3.85 (dd,  $J = 11.0, 4.1$  Hz, 1H), 3.68-3.55 (m, 2H), 3.37 (dd,  $J = 16.4, 11.0$  Hz, 1H), 2.95 (dd,  $J = 16.4, 4.2$  Hz, 1H), 0.97 (d,  $J = 6.0$  Hz, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ /ppm: 210.8, 203.0, 201.6, 141.7, 141.6, 136.8, 135.95, 135.87, 135.3, 131.44, 131.35, 130.1, 122.9, 122.8, 121.6, 121.4, 62.2, 49.3, 43.3, 43.1, 41.2, 12.4. IR (KBr): 2922, 1701, 1592, 1488, 1254, 821, 735, 697  $\text{cm}^{-1}$ . HRMS (EI) for  $\text{C}_{27}\text{H}_{20}\text{O}_3\text{Br}_2$   $[\text{M}]^+$  (549.9779) found: 549.9776.

**(2*S*,3*R*,6*R*)-2,6-bis(4-bromophenyl)-3-methylspiro[cyclohexane-1,2'-indene]-1',3',4-trione**

**(*cis*-5cca)** : Following the general procedure G, **cis-5cca** was obtained from **trans-5cca** in 94% yield (51.9 mg) as a white solid (mp.: 106.6-107.8 °C). HPLC analysis (Chiralpak IA column (Hexane-IPA = 80:20, flow rate = 1.0 mL min<sup>-1</sup>,  $\lambda = 226$  nm):  $T_R = 12.61$  min (minor), 15.25 min (major)): 95% ee,  $[\alpha]_D^{29} = +12.1$  (c = 0.5 in  $\text{CH}_2\text{Cl}_2$ );  $R_f$  0.40 (EA/hexanes: 1/5);  $^1\text{H}$  NMR

(400 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm: 7.66 (d,  $J$  = 7.4 Hz, 1H), 7.56 (td,  $J$  = 7.4, 1.3 Hz, 1H), 7.50 (td,  $J$  = 7.4, 1.3 Hz, 1H), 7.45 (d,  $J$  = 7.4 Hz, 1H), 7.13 (dd,  $J$  = 8.8, 2.7 Hz, 4H), 6.87 (d,  $J$  = 8.8 Hz, 4H), 3.86 (dd,  $J$  = 14.0, 27.9 Hz, 1H), 3.83-3.74 (m, 1H), 3.69 (dd,  $J$  = 3.6, 14.6 Hz, 1H), 3.34 (d,  $J$  = 12.7 Hz, 1H), 2.64 (dd,  $J$  = 3.6, 13.6 Hz, 1H), 0.87 (d,  $J$  = 6.6 Hz, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm: 208.8, 203.2, 201.4, 142.5, 141.6, 136.3, 135.8, 135.7, 131.5, 131.46, 129.6, 122.6, 122.2, 121.7, 121.4, 62.5, 54.9, 48.1, 44.5, 43.0, 11.9. IR (KBr): 2922, 1701, 1592, 1488, 1254, 821, 735, 697 cm<sup>-1</sup>. HRMS (EI) for C<sub>27</sub>H<sub>21</sub>O<sub>3</sub>Br<sub>2</sub> [M+H]<sup>+</sup> (550.9857) found: 550.9841.

**(2*S*,3*R*,6*S*)-6-(4-bromophenyl)-3-methyl-2-phenylspiro[cyclohexane-1,2'-indene]-1',3',4-**

**trione (*trans*-5*aca*):** Following the general procedure D, **5aca** was obtained in 99% yield (46.8 mg, *trans*:*cis* = 3:1) as a white solid (mp.: 85.5-87.0 °C). HPLC analysis (Chiralpak IB column (Hexane-IPA = 98:02, flow rate = 1.0 mL min<sup>-1</sup>,  $\lambda$  = 226 nm): T<sub>R</sub> = 18.74 min (major), 25.34 min (minor)) : >99% ee; [ $\alpha$ ]<sub>D</sub><sup>24</sup> = -157.6 (c = 0.5 in CH<sub>2</sub>Cl<sub>2</sub>); R<sub>f</sub> 0.14 (EA/hexanes: 1/5); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm: 7.64-7.51 (m, 4H), 7.22 (d,  $J$  = 8.4 Hz, 2H), 7.08-6.85 (m, 5H), 6.83 (d,  $J$  = 8.4 Hz, 2H), 3.91 (dd,  $J$  = 11.9, 3.9 Hz, 1H), 3.70-3.58 (m, 2H), 3.44 (dd,  $J$  = 16.8, 11.9 Hz, 1H), 2.92 (dd,  $J$  = 16.8, 3.9 Hz, 1H), 0.99 (d,  $J$  = 6.1 Hz, 3H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm: 211.4, 203.2, 202.0, 141.8, 137.0, 135.9, 135.6, 135.5, 131.4, 130.2, 128.1, 127.3, 122.64, 122.60, 121.4, 62.4, 50.3, 43.2, 42.5, 41.2, 12.4. IR (KBr): 2926, 1736, 1701, 1591, 1490, 1255, 1076, 1011, 822, 737 cm<sup>-1</sup>. HRMS (ESI) for C<sub>27</sub>H<sub>21</sub>O<sub>3</sub>Br [M]<sup>+</sup> (472.0674) found: 472.0673.

**(2*S*,3*R*,6*R*)-6-(4-bromophenyl)-3-methyl-2-phenylspiro[cyclohexane-1,2'-indene]-1',3',4-**

**trione (*cis*-5*aca*):** Obtained as a minor diastereomer in the above reaction as a white solid (mp.: 82.5-83.5 °C). HPLC analysis (Chiralpak IB column (Hexane-IPA = 98:02, flow rate = 1.0 mL min<sup>-1</sup>,  $\lambda$  = 226 nm): T<sub>R</sub> = 14.51 min (minor), 16.24 min (major)) : 94% ee; [ $\alpha$ ]<sub>D</sub><sup>24</sup> = +20.9 (c = 0.5 in CH<sub>2</sub>Cl<sub>2</sub>); R<sub>f</sub> 0.18 (EA/hexanes: 1/5); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm: 7.64 (d,  $J$  = 7.6 Hz,

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3 1H), 7.53-7.45 (m, 1H), 7.45-7.38 (m, 2H), 7.12 (d,  $J = 8.0$  Hz, 2H), 6.97 (d,  $J = 4.3$  Hz, 4H),  
4  
5 6.91 (d,  $J = 8.4$  Hz, 3H), 3.99-3.78 (m, 2H), 3.74 (dd,  $J = 14.1, 4.0$  Hz, 1H), 3.38 (d,  $J = 12.8$  Hz,  
6  
7 1H), 2.64 (dd,  $J = 3.9, 13.6$  Hz, 1H), 0.89 (d,  $J = 6.6$  Hz, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  
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9  $\delta/\text{ppm}$ : 209.3, 203.4, 201.5, 142.6, 141.6, 136.6, 136.4, 135.4, 131.4, 129.7, 128.2, 127.4, 122.4,  
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11 122.0, 121.5, 62.7, 55.8, 47.8, 44.5, 43.1, 11.9. IR (KBr): 2922, 1735, 1700, 1594, 1485, 1250,  
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13 1076, 820, 733  $\text{cm}^{-1}$ .  
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18 **(1R,3S,4R)-3-(4-bromophenyl)spiro[bicyclo[2.2.2]octane-2,2'-indene]-1',3',5-trione** (*trans-*  
19  
20 **6ca**) : Following the general procedure E, *trans-6ca* was obtained in 66% yield (27.0 mg,  
21  
22 *trans:cis* = 5:1) as a white solid (mp.: 83.2-83.8 °C). HPLC analysis (Chiralpak IA column  
23  
24 (Hexane-IPA = 90:10, flow rate = 1.0 mL  $\text{min}^{-1}$ ,  $\lambda = 226$  nm):  $T_R = 21.10$  min (major), 32.53 min  
25  
26 (minor)): 99% ee,  $[\alpha]_D^{30} = -112.3$  (c = 0.5 in  $\text{CH}_2\text{Cl}_2$ );  $R_f$  0.09 (EA/hexanes: 1/5);  $^1\text{H}$  NMR (400  
27  
28 MHz,  $\text{CDCl}_3$ )  $\delta/\text{ppm}$ : 8.03 (d,  $J = 7.6$  Hz, 1H), 7.85 (t,  $J = 7.3$  Hz, 1H), 7.78 (t,  $J = 7.4$  Hz, 1H),  
29  
30 7.72 (d,  $J = 7.4$  Hz, 1H), 7.21 (d,  $J = 7.6$  Hz, 2H), 6.86 (d,  $J = 8.4$  Hz, 2H), 4.03 (s, 1H), 2.91 (td,  
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32  $J = 18.9, 3.1$  Hz, 1H), 2.87-2.82 (m, 1H), 2.56-2.43 (m, 1H), 2.34-2.20 (m, 3H), 2.02-1.90 (m,  
33  
34 1H), 1.72-1.61 (m, 1H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta/\text{ppm}$ : 213.9, 201.7, 198.6, 141.2, 140.6,  
35  
36 139.0, 136.1, 135.8, 131.3, 129.0, 123.62, 123.56, 120.6, 60.2, 46.2, 45.5, 40.5, 35.6, 24.2, 20.0.  
37  
38 IR (KBr): 3059, 2923, 1728, 1703, 1593, 1489, 1266, 779, 734, 698  $\text{cm}^{-1}$ . HRMS (ESI) for  
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40  $\text{C}_{22}\text{H}_{18}\text{O}_3\text{Br}$   $[\text{M}+\text{H}]^+$  (409.0439) found: 409.0440.  
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47 **(1R,3S,4R)-3-phenylspiro[bicyclo[2.2.2]octane-2,2'-indene]-1',3',5-trione** (*trans-6aa*):  
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50 Following the general procedure E, *trans-6aa* was obtained in 65% yield (21.5 mg, *trans:cis* =  
51  
52 7:1) as a white solid (mp.: 176.2-177.9 °C). HPLC analysis (Chiralpak IA column (Hexane-IPA  
53  
54 = 90:10, flow rate = 1.0 mL  $\text{min}^{-1}$ ,  $\lambda = 226$  nm):  $T_R = 17.56$  min (major), 22.36 min (minor)):  
55  
56 97% ee,  $[\alpha]_D^{30} = -132.5$  (c = 0.5 in  $\text{CH}_2\text{Cl}_2$ );  $R_f$  0.11 (EA/hexanes: 1/5);  $^1\text{H}$  NMR (400 MHz,  
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CDCl<sub>3</sub>)  $\delta$ /ppm: 8.03 (d,  $J = 7.6$  Hz, 1H), 7.83 (td,  $J = 1.2, 7.7$  Hz, 1H), 7.75 (td,  $J = 0.8, 7.4$  Hz, 1H), 7.69 (d,  $J = 7.6$  Hz, 1H), 7.14-7.02 (m, 3H), 7.02-6.94 (m, 2H), 4.09 (s, 1H), 3.00-2.89 (m, 2H), 2.58-2.46 (m, 1H), 2.36-2.19 (m, 3H), 2.03-1.90 (m, 1H), 1.72-1.61 (m, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm: 214.4, 202.1, 198.7, 141.4, 140.7, 140.1, 135.9, 135.6, 128.3, 127.2, 126.7, 123.6, 123.5, 60.3, 46.3, 46.2, 40.6, 35.6, 24.4, 20.1. IR (KBr): 2923, 1702, 1594, 1266, 780, 700 cm<sup>-1</sup>. HRMS (ESI) for C<sub>22</sub>H<sub>19</sub>O<sub>3</sub> [M+H]<sup>+</sup> (331.1334) found: 331.1336.

**4-((1R,3S,4R)-1',3',5-trioxo-1',3'-dihydrospiro[bicyclo[2.2.2]octane-2,2'-inden]-3-**

**yl)benzotrile (*trans*-6da):** Following the general procedure E, *trans*-6da was obtained in 67% yield (23.8 mg, *trans*:*cis* = 7:1) as a pale yellow solid (mp.: 101.2-103.3 °C). HPLC analysis (Chiralpak IA column (Hexane-IPA = 90:10, flow rate = 1.0 mL min<sup>-1</sup>,  $\lambda = 226$  nm): T<sub>R</sub> = 50.11 min (major), 60.39 min (minor)) : 95% ee,  $[\alpha]_D^{30} = -152.7$  ( $c = 0.5$  in CH<sub>2</sub>Cl<sub>2</sub>); R<sub>f</sub> 0.04 (EA/hexanes: 1/5); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm: 8.05 (d,  $J = 7.5$  Hz, 1H), 7.87 (td,  $J = 1.4, 7.5$  Hz, 1H), 7.80 (td,  $J = 1.0, 7.5$  Hz, 1H), 7.72 (d,  $J = 7.5$  Hz, 1H), 7.40 (d,  $J = 8.3$  Hz, 2H), 7.11 (d,  $J = 8.4$  Hz, 2H), 4.12 (s, 1H), 2.92-2.82 (m, 2H), 2.55-2.43 (m, 1H), 2.36-2.22 (m, 3H), 2.04-1.92 (m, 1H), 1.76-1.65 (m, 1H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm: 213.5, 201.1, 198.4, 145.6, 141.1, 140.5, 136.2, 136.0, 132.1, 128.0, 123.8, 123.6, 118.6, 110.7, 60.4, 45.8, 45.6, 40.5, 24.0, 19.9. IR (KBr): 2923, 2228, 1728, 1702, 1594, 1269, 1107, 843, 877, 779, 736, 709 cm<sup>-1</sup>. HRMS (ESI) for C<sub>23</sub>H<sub>18</sub>NO<sub>3</sub> [M+H]<sup>+</sup> (356.1287) found: 356.1288.

**(*cis*-15ca):** Following the general procedure H, *cis*-15ca was obtained from *cis*-4ca in quantitative yield (50.3 mg) as a white solid (mp.: 155.5-157.0 °C). HPLC analysis (Chiralpak IB column (Hexane-IPA = 95:05, flow rate = 1.0 mL min<sup>-1</sup>,  $\lambda = 227$  nm): T<sub>R</sub> = 10.48 min (major), 11.62 min (minor)): 98% ee,  $[\alpha]_D^{29} = +5.5$  ( $c = 0.5$  in CH<sub>2</sub>Cl<sub>2</sub>); R<sub>f</sub> 0.35 (EA/hexanes: 1/5); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm, 7.55 (d,  $J = 7.2$  Hz, 1H), 7.37-7.48 (m, 3H), 7.10 (d,  $J = 8.5$  Hz,

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3 2H), 6.86-7.02 (m, 7H), 4.05 (s, 4H), 3.74 (dt,  $J = 13.7, 3.1$  Hz, 2H), 3.04 (dt,  $J = 13.7, 7.2$  Hz,  
4  
5 2H), 1.86-1.98 (m, 2H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ /ppm, 203.2, 203.1, 142.6, 141.9, 138.7,  
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7 138.2, 135.1, 135.0, 131.2, 130.2, 128.3, 128.1, 127.1, 122.2, 121.9, 121.0, 108.4, 64.7, 64.6,  
8  
9 62.3, 47.0, 45.8, 36.4, 36.2. IR (KBr): 2882, 1739, 1699, 1594, 1488, 1334, 1254, 1148, 1075,  
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11 1010, 880, 763, 700, 527  $\text{cm}^{-1}$ .

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16 (**cis-16aca**): Following the general procedure H, **cis-16aca** was obtained from **cis-5aca** in  
17  
18 quantitative yield (51.7 mg) as a white solid (mp.: 253.5-255.0 °C). HPLC analysis (Chiralpak  
19  
20 IA column (Hexane-EtOH = 90:10, flow rate = 1.0 mL  $\text{min}^{-1}$ ,  $\lambda = 254$  nm):  $T_R = 23.05$  min  
21  
22 (minor), 35.09 min (major)): 94% ee;  $[\alpha]_D^{24} = +19.5$  (c = 1.0 in  $\text{CH}_2\text{Cl}_2$ );  $R_f$  0.22 (EA/hexanes:  
23  
24 1/5);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ /ppm, 7.53 (d,  $J = 7.4$  Hz, 1H), 7.46-7.34 (m, 3H), 7.09 (d,  $J$   
25  
26 = 8.4 Hz, 2H), 7.01-6.81 (m, 7H), 4.11-4.01 (m, 4H), 3.70 (dd,  $J = 13.6, 3.4$  Hz, 1H), 3.42 (d,  $J =$   
27  
28 12.3 Hz, 1H), 3.27-3.16 (m, 1H), 3.04 (t,  $J = 13.6$  Hz, 1H), 1.92 (dd,  $J = 13.1, 3.5$  Hz, 1H), 0.71  
29  
30 (d,  $J = 6.6$  Hz, 3H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ /ppm, 203.5, 203.0, 142.7, 141.7, 138.3,  
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32 137.8, 135.0, 134.9, 131.5, 131.1, 130.2, 128.1, 127.9, 126.8, 126.5, 122.1, 121.8, 120.9, 110.1,  
33  
34 65.5, 65.2, 63.0, 53.2, 45.3, 38.4, 36.3, 11.1. IR (KBr): 2890, 1742, 1703, 1590, 1481, 1332,  
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36 1256, 1146, 1075, 887, 765, 702, 525  $\text{cm}^{-1}$ .

## 37 38 39 40 41 42 ASSOCIATED CONTENT

### 43 44 45 Supporting Information

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48 The supporting information is available free of charge via the Internet at <http://pubs.acs.org>.

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51 Copies of  $^1\text{H}$ ,  $^{13}\text{C}$  NMR spectra for all compounds and HPLC chromatograms for  
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53 appropriate compounds (PDF).

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56 X-ray crystallographic data for compound **trans-4ca** (CIF)

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3 X-ray crystallographic data for compound *cis-15ca* (CIF)  
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6 X-ray crystallographic data for compound *trans-5cca* (CIF)  
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9 X-ray crystallographic data for compound *cis-16aca* (CIF)  
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### 18 19 **Author Contributions**

20  
21 †(G.M.R., C.-T.K) These authors made equal contribution to this work.  
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### 24 25 **Notes**

26  
27 The authors declare no competing financial interest.  
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3 (19) The absolute configurations of *trans-4ca*, *cis-15ca* and *trans-5cca*, *cis-16aca* were  
4 established by X-ray crystallography (CCDC Nos. 1021314, 1429053, 1402038 and 1431465  
5 respectively), and more information is provided in supporting information.  
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17 (21) We tried to carry out the epimerization under exactly the same conditions as the actual  
18 optimized conditions in table 3 (10 °C, 5 mol % **IV**, 20 mol % **3d**). But the transformation was  
19 very slow and could not furnish isolable amount of *cis* isomer. Hence we tried for the  
20 epimerization under different modified conditions.  
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27 (22) See the supporting information for the additional results of the control experiments.  
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30 (23) This is the first time that the optically pure *trans* spiranes **4ca** and **5ca** have been  
31 transformed into the *cis* spiranes, which gave a clear insight into the mechanism of epimerization.  
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33 However, the racemic *trans* spiranes have been earlier epimerized into *cis* spiranes, where the  
34 results could not conclusively elucidate the mechanism.  
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