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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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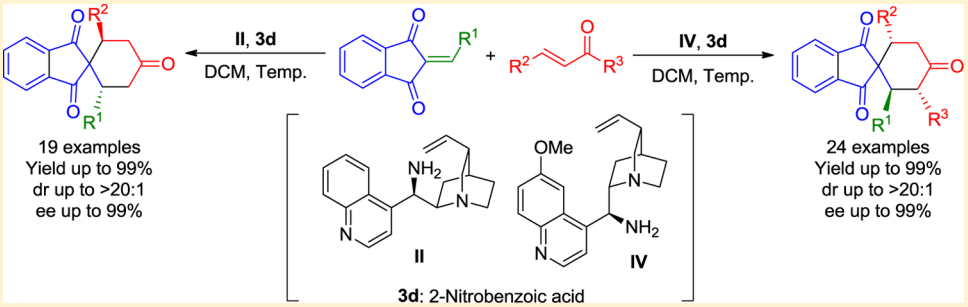
Supporting Information



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 spirocyclohexanones 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 α-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 a transformation. Mechanistic investigations revealed two competing pathways, a concerted Diels−Alder reaction and a stepwise 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[1] 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.[2,3] The latter have been considered to be far superior organocatalysts for aminocatalysis of the sterically nondemanding carbonyl compounds. However, the task of asymmetric induction becomes quite challenging in the 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.[4a]

Among all classes of primary amine organocatalysts, those derived from cinchona alkaloids have attracted much attention of 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 α,β-unsaturated ketones to furnish the formal Diels−Alder products with far superior enantioselectivities, via an alternative double Michael reaction pathway.[5,6] Since then, considerable efforts have been made toward the development of asymmetric aminocatalysis using cinchona alkaloid derived primary amines.[4,7]

In an attempt to expand the scope of such primary amine catalysis, our group has been recently evaluating the cases where the results of aminocatalysis with cyclic secondary amines were not convincing. In such context, we encountered the L-proline-catalyzed domino Knoevenagel/Diels−Alder/epimerization sequence for the synthesis of indanedione-fused *cis*-spirocyclohexanones reported by Barbas et al.,[8] where the chiral secondary amine could not induce any considerable enantioselectivity. It has been more than a decade, but to date, there have been no substantial efforts to develop an enantioselective format of this transformation, resulting in indanedione-fused spirocyclohexanones.[9−16] However, there have been a few methods reported for the synthesis of

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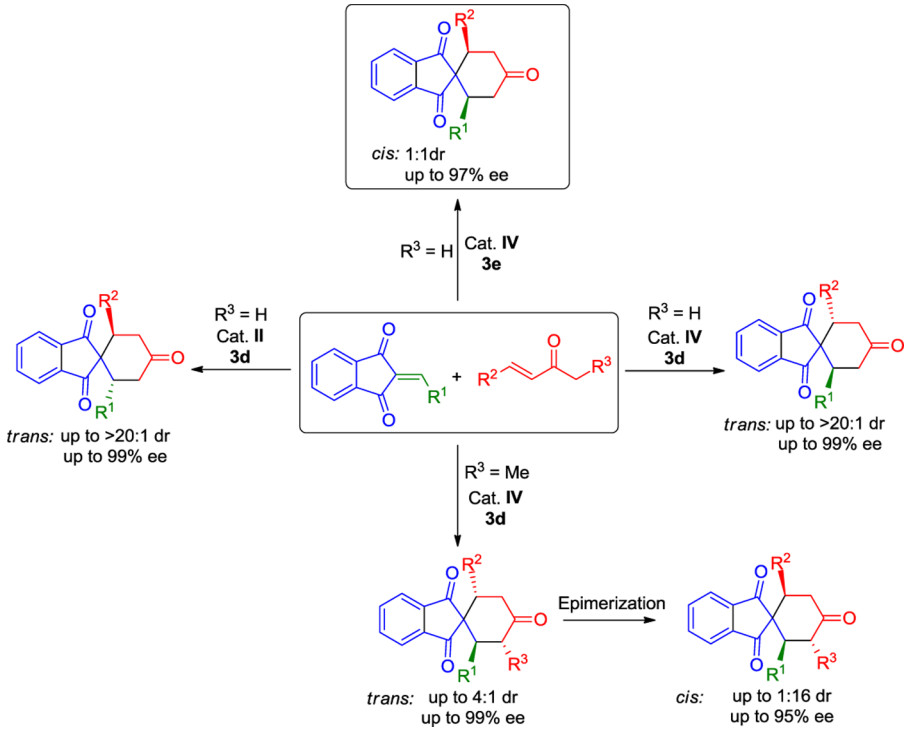
Scheme 1. Domino Reaction for the Formation of 2,6-Disubstituted Cyclohexanones from 2-Arylidene-1,3-indanediones and 4-Substituted 3-Buten-2-ones



spirocyclohexanones fused to other ring systems.[17] So we decided to evaluate the ability of cinchona-alkaloid-derived primary amines to stereoselectively catalyze the reaction leading to indanedione-fused spirocyclohexanones and then were keen to investigate the corresponding reaction mechanism (Scheme 1). The resulting adducts represent the potential leads for the development of anticancer agents which have a well-defined activity on apoptosis and cell differentiation.[18]

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-fluorobenzoic acid (**3a**) (Figure 1 and Table 1, entry 1). The spirocyclohexanone product **4ca** was obtained in 80% yield (dr = 1.4:1). From the X-ray crystallographic analysis of product **4ca**, it was quite unexpected to see the formation of thermodynamically less stable *trans*-spirane (*exo* product) in excess compared to the earlier results,[8] 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 five-membered ring) is difficult to accomplish as compared to the *trans* isomers of spirocyclohexanones that are fused to other ring systems.[17] Encouraged by this, we initially focused on the stereoselective synthesis of thermodynamically less stable *trans*-spiranes **4**.

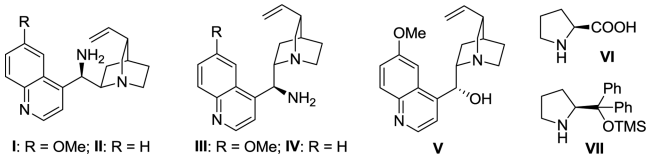


Figure 1. Catalysts screened during optimization.

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 4). 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 the *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.

A rigorous screening of catalyst loadings, additives, temperature, and concentrations was then carried out (see Supporting Information for detailed screening of reaction conditions). It is clear that an enhanced reaction rate resulted in the formation of the kinetically favored *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 pseudoenantioner **II** (entry 13). To our surprise, when the additive **3e** was used, the thermodynamic *endo* product (*cis*-**4ca**) could also be acquired with good

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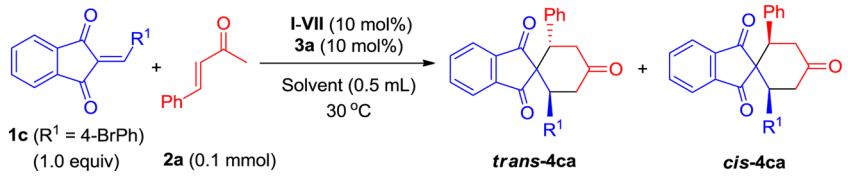
Table 1. Optimization of Reaction Conditions[a]



entry	cat.	solvent	time (days)	yield (%)[b]	dr[b]	ee (%)[c]
1	**I**	toluene	6	80	1.4:1	98/77[d]
2	**II**	toluene	1	95	1.6:1	99/70[d]
3	**III**	toluene	2	97	2:1	98/84
4	**IV**	toluene	1	97	3.6:1	99/85
5	**V**	toluene	10	trace		
6	**VI**	toluene	6	75	1:2.6	11/13
7	**VII**	toluene	11	0		

[a]2-Fluorobenzoic acid (**3a**, 10 mol %). [b]Yield of **4ca** (*cis* + *trans*) as determined by ^{1}H NMR analysis of the crude reaction mixture using Ph_3CH as an internal standard. [c]Enantioselectivity of *trans*/*cis* products as determined by HPLC analysis on a chiral stationary phase. [d]Enantioselectivity of *ent-trans*-**4ca**/*ent-cis*-**4ca**.

Table 2. Solvent Screening for the Domino Double Michael Addition of 2a to 1c[a]

entry	cat.	solvent	time (days)	yield (%)[b]	dr[b]	ee (%)[c]
1	**IV**	DCM	1	84	3.7:1	98/47
2	**IV**	THF	8.5	47	4.2:1	90/28
3	**IV**	EA	9.5	66	2.9:1	98/36
4	**IV**	MeOH	9.5	44	1:7	−/36
5	**IV**	$CHCl_3$	10	71	1.6:1	98/25
6	**IV**	xylene	6	94	1.2:1	97/82
7	**IV**	Et_2O	1	96	1:1.2	98/36
8	**IV**	1,4-dioxane	2	81	1:1.1	96/43
9	**IV**	BrPh	1	98	2.6:1	99/59
10	**IV**	1,2-DCE	5	>99	1.2:1	99/26
11	**IV**	DCM/toluene (1:4)	1	>99	4.3:1	98/84
12[d]	**IV**	DCM	4	85	>20:1	98/97
13[d]	**II**	DCM	5	81	14:1	98/97[e]
14[f]	**IV**	toluene	1	96	1:1	98/97

[a]2-Fluorobenzoic acid (**3a**, 10 mol %). [b]Yield of **4ca** (*cis* + *trans*) as determined by ^{1}H NMR analysis of the crude reaction mixture using Ph_3CH as an internal standard. [c]Enantioselectivity of *trans*/*cis* products as determined by HPLC analysis on a chiral stationary phase. [d]**1c** (1.2 equiv), **IV** or **II** (5 mol %), and **3d** (2-nitrobenzoic acid, 20 mol %) in DCM (0.25 mL) at 10 °C. [e]Enantioselectivity of *ent-trans*-**4ca**/*ent-cis*-**4ca**. [f]**IV** (5 mol %) and **3e** (2,6-dihydroxybenzoic acid, 10 mol %) in toluene (0.5 mL) at 60 °C (to obtain *cis* isomer).

enantioselectivity under slightly modified reaction conditions (entry 14).

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^1 and R^2 substituents. The excellent results with a wide range of the substrates are presented in Table 3. Likewise, using the pseudoenantiomer **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.

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 lower diastereoselectivities, while the excellent enantioselectivities were still retained.

Later, we were keen to take the advantage of the fact that R^1 and R^2 groups in substrates could be exchanged, which 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.

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 yields and stereoselectivities almost similar to those of the two-step process.

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).

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.[19] Mechanistically, this reaction could proceed either via the Diels−Alder pathway or via the double Michael addition pathway (Scheme 6).

One of our vital objectives was to transform the kinetic *trans*-spiranes into the thermodynamically stable *cis* congeners to demonstrate the generality of this method for the synthesis of all four stereoisomeric forms of the product. We envisioned that, based on the retro-Michael/Michael mechanism for epimerization proposed earlier,[8,20] when the *trans*-spirane is treated with an amine in a polar protic solvent, only one of the two stereocenters would be rearranged and hence the enantioselectivity would be retained by the resulting *cis* products (Scheme 7, path A).[21] However, the results were

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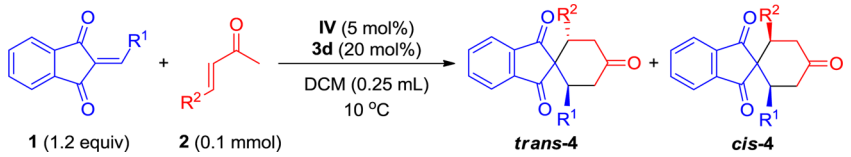
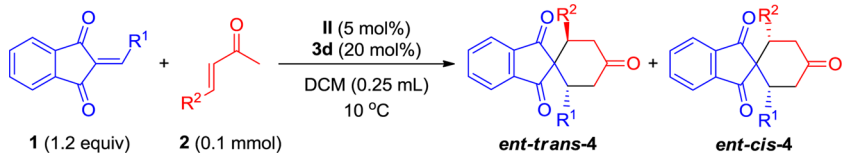
Table 3. Substrate Scope for the Domino Michael Addition Using Different Substituted 1 and 2 for the Synthesis of *trans*-4



entry	R^1	R^2	time (days)	yield (%)[a]	dr[b]	ee (%)[c]
1	Ph (**1a**)	Ph (**2a**)	5	75 (**4aa**)	13:1	96
2	4-ClPh (**1b**)	Ph (**2a**)	5	80 (**4ba**)	17:1	98
3	4-BrPh (**1c**)	Ph (**2a**)	4	85 (**4ca**)	>20:1	98
4	4-CNPh (**1d**)	Ph (**2a**)	4	90 (**4da**)	>20:1	98
5	4-NO_2Ph (**1e**)	Ph (**2a**)	10	96 (**4ea**)	14:1	97
6	2-BrPh (**1f**)	Ph (**2a**)	3.5	91 (**4fa**)	12:1	82
7	4-MePh (**1g**)	Ph (**2a**)	11	80 (**4ga**)	10:1	97
8	4-OMePh (**1h**)	Ph (**2a**)	10	71 (**4ha**)	7:1	99
9	2-OMePh (**1i**)	Ph (**2a**)	4	66 (**4ia**)	>20:1	91
10[d]	2-thienyl (**1j**)	Ph (**2a**)	4	82 (**4ja**)	1:1	97
11	4-BrPh (**1c**)	4-ClPh (**2b**)	5	74 (**4cb**)	>20:1	98
12	4-BrPh (**1c**)	4-BrPh (**2c**)	5	77 (**4cc**)	>20:1	98
13	4-BrPh (**1c**)	4-CNPh (**2d**)	4	89 (**4cd**)	15:1	97
14	4-BrPh (**1c**)	4-NO_2Ph (**2e**)	10	73 (**4ce**)	8:1	97
15	4-BrPh (**1c**)	2-BrPh (**2f**)	5	70 (**4cf**)	18:1	98
16	4-BrPh (**1c**)	4-OMePh (**2g**)	4	76 (**4cg**)	11:1	98
17	4-BrPh (**1c**)	2-OMePh (**2h**)	6	89 (**4ch**)	>20:1	97
18	4-BrPh (**1c**)	2-thienyl (**2i**)	8	75 (**4ci**)	10:1	98

[a]Isolated yield of **4**. [b]Diastereomeric ratio of *trans*/*cis* as determined by ^{1}H NMR analysis of the crude reaction mixture using Ph_3CH as an internal standard. [c]Enantioselectivity of *trans*-**4** as determined by HPLC analysis on a chiral stationary phase. [d]Reaction temperature = 30 °C.

Table 4. Substrate Scope for the Domino Michael Addition Using Different Substituted 1 and 2 for the Synthesis of *ent-trans*-4



entry	R^1	R^2	time (days	yield (%)[a]	dr[b]	ee (%)[c]
1	Ph (**1a**)	Ph (**2a**)	5	73 (**4aa**)	13:1	97
2	4-ClPh (**1b**)	Ph (**2a**)	5	85 (**4ba**)	17:1	97
3	4-BrPh (**1c**)	Ph (**2a**)	5	81 (**4ca**)	14:1	98
4	4-CNPh (**1d**)	Ph (**2a**)	4	99 (**4da**)	>20:1	98
5	4-NO_2Ph (**1e**)	Ph (**2a**)	10	95 (**4ea**)	17:1	99
6	2-BrPh (**1f**)	Ph (**2a**)	7	78 (**4fa**)	10:1	68
7	4-MePh (**1g**)	Ph (**2a**)	11	75 (**4ga**)	13:1	98
8	4-OMePh (**1h**)	Ph (**2a**)	10	61 (**4ha**)	9:1	93
9	2-OMePh (**1i**)	Ph (**2a**)	10	62 (**4ia**)	>20:1	78
10[d]	2-thienyl (**1j**)	Ph (**2a**)	4	80 (**4ja**)	1:1	96
11	4-BrPh (**1c**)	4-ClPh (**2b**)	5	82 (**4cb**)	>20:1	97
12	4-BrPh (**1c**)	4-BrPh (**2c**)	5	70 (**4cc**)	>20:1	98
13	4-BrPh (**1c**)	4-CNPh (**2d**)	4	73 (**4cd**)	18:1	97
14	4-BrPh (**1c**)	4-NO_2Ph (**2e**)	10	79 (**4ce**)	9:1	97
15	4-BrPh (**1c**)	2-BrPh (**2f**)	5	65 (**4cf**)	>20:1	97
16	4-BrPh (**1c**)	4-OMePh (**2g**)	4	88 (**4cg**)	10:1	94
17	4-BrPh (**1c**)	2-OMePh (**2h**)	6	81 (**4ch**)	>20:1	97
18	4-BrPh (**1c**)	2-thienyl (**2i**)	8	70 (**4ci**)	12:1	98

[a]Isolated yield of *ent*-**4**. [b]Diastereomeric ratio of *trans*/*cis* as determined by ^{1}H NMR analysis of the crude reaction mixture using Ph_3CH as an internal standard. [c]Enantioselectivity of *ent-trans*-**4** as determined by HPLC analysis on a chiral stationary phase. [d]Reaction temperature = 30 °C.

rather different. In all cases, irrespective of the catalyst (**IV**, cyclohexylamine, or pyrrolidine) and the solvent used, we could observe complete conversion of the *trans* isomer **4ca** into *cis*-**4ca** but only as a racemic mixture (Scheme 8, eq a).[22] We initially attributed this result to the lack of regioselectivity during the formation of the initial enamine intermediate, which would subsequently result in the formation of both the enantiomers in almost equal amounts (Scheme 9, case 1).

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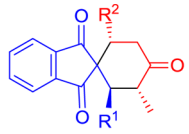
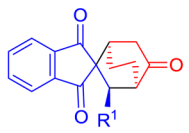
Scheme 2. Asymmetric Synthesis of 5 and 6 with an Additional Stereocenter

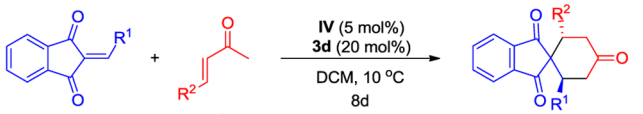


***trans*-5caa**, R^1 = 4-BrPh; R^2 = Ph
(5d, 89% yield, 4:1 dr, >99% ee)
***trans*-5cca**, R^1 = 4-BrPh; R^2 = 4-BrPh
(4d, 99% yield, 3:1 dr, >99% ee)
***trans*-5aca**, R^1 = Ph; R^2 = 4-BrPh
(4d, 99% yield, 3:1 dr, >99% ee)



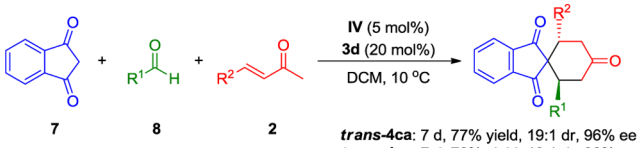
***trans*-6ca**, R^1 = 4-BrPh
(7d, 66% yield, 5:1 dr, 99% ee)
***trans*-6aa**, R^1 = Ph
(4d, 65% yield, 7:1 dr, 97% ee)
***trans*-6da**, R^1 = 4-CNPh
(4d, 67% yield, 7:1 dr, 95% ee)

Scheme 3. Scope of the Reaction by Interchanging the R^1 and R^2 Substituents



1j (R^1 = 2-Thienyl)
1a (R^1 = Ph)
2a (R^2 = Ph)
2j (R^2 = 2-Thienyl)
***trans*-4ja** (15% yield, 6:1 dr, 98% ee)
***trans*-4aj** (60% yield, 19:1 dr, 98% ee)

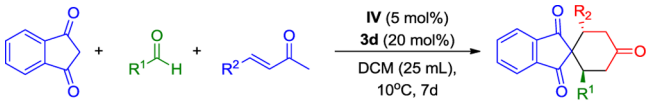
Scheme 4. One-Pot Reaction for the Synthesis of *trans*-4



7 **8** **2**

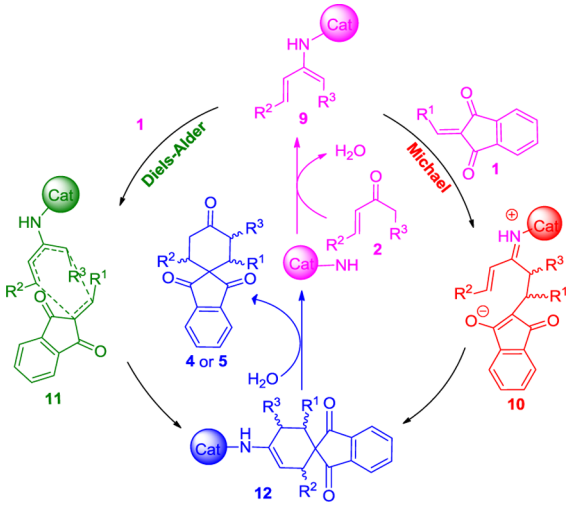
***trans*-4ca**: 7 d, 77% yield, 19:1 dr, 96% ee
***trans*-4cc**: 7 d, 72% yield, 19:1 dr, 98% ee
***trans*-4cf**: 9 d, 69% yield, >20:1 dr, 98% ee
***trans*-4ch**: 9 d, 90% yield, >20:1 dr, 98% ee

Scheme 5. Gram-Scale Reaction for the Synthesis of *trans*-4ca



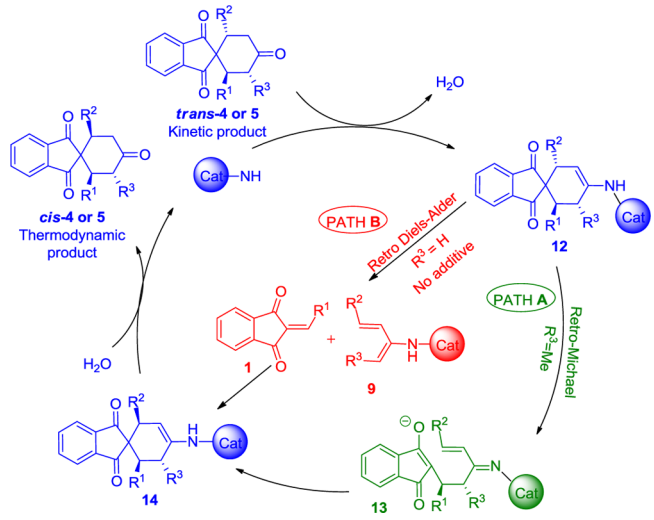
7 12 mmol
8 12 mmol
2 10 mmol 1.462g
R^1 = 4-BrPh
R^2 = Ph
***trans*-4ca** 74% yield, 3.353g dr>20:1,99% ee

Scheme 6. Possible Reaction Pathways

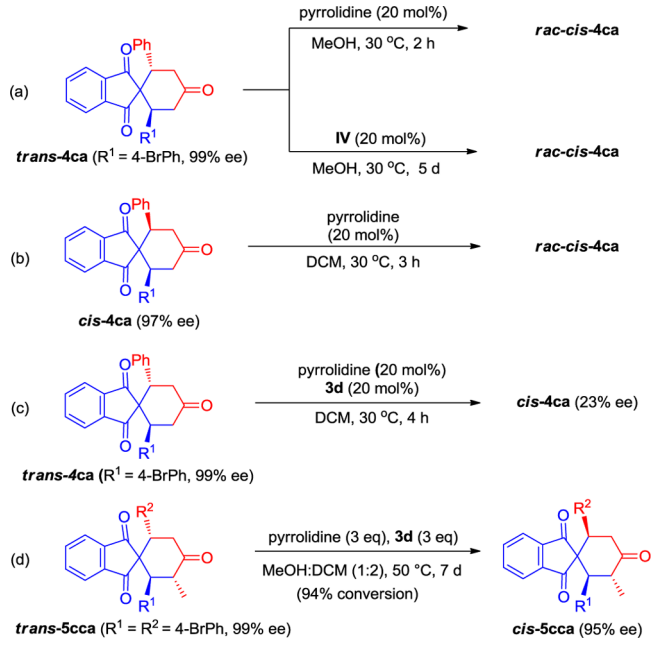


In an attempt to confirm this, enantiopure *cis*-**4ca** was treated with amine in DCM under similar conditions (Scheme 8, eq b).

Scheme 7. Mechanistic Possibilities for Epimerization



Scheme 8. Control Experiments To Elucidate the Mechanism of Epimerization



It was envisioned that regioselectivity during enamine formation would have no role to play in this case, and both the regioisomeric enamines would go through the retro-Michael/Michael pathway and result in the regeneration of starting material *cis*-**4ca**, with complete retention of enantioselectivity (Scheme 9, case 2). To our surprise, the enantiopure *cis*-**4ca** completely racemized even in this case (eq b).[23] This clearly indicated that the epimerization may not be taking place solely via the retro-Michael/Michael pathway as proposed earlier. We assume that it follows a competing retro-Diels–Alder/Diels–Alder pathway, where both the stereocenters would be rearranged (Scheme 7, path B) and result in the racemic products in the presence of an achiral amine. However, during the epimerization of *trans*-**4ca**, the use of acidic additive or performing the reaction at 10 °C resulted in *cis*-**4ca** with slight ee (23–25%) (Scheme 8, eq c).[22] This result demonstrates that the retro-Diels–Alder pathway is decelerated

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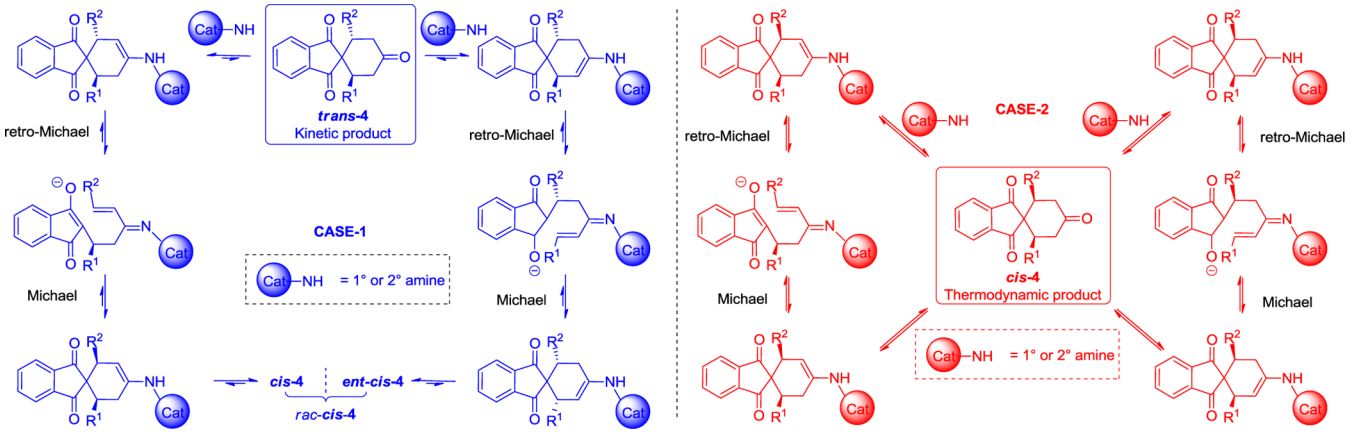
Scheme 9[a]



[a]Retro-Michael/Michael pathway for epimerization of *trans*-**4** results in *rac-cis*-**4** due to lack of regioselectivity during enamine formation (case 1). Similar transformation of *cis*-**4** would be expected to result in retention of enantioselectivity (case 2, which is not observed during our study, thereby ascertaining the retro-Diels–Alder/Diels–Alder pathway for epimerization).

in the presence of additive or at lower temperature, thereby allowing the retro-Michael/Michael pathway to takeover. Moreover, the epimerization of the products by either of these pathways is slowed down to a large extent when **IV** was used as the catalyst (Scheme 8, eq a).[22]

These results also explain the formation of kinetic *trans*-spiranes with excellent diastereo- and enantioselectivities (Tables 3 and 4), as the reactions are carried out using **II** or **IV** at lower temperatures and in the presence of additive, which would suppress the subsequent epimerization of the *trans* products. Furthermore, it could be ascertained that the formation of *cis*-**4ca** in entry 14 of Table 2 is indeed taking place via the domino Michael addition pathway and not by the epimerization of the initially formed *trans*-**4ca**, which if it had taken place would have resulted in the loss of enantioselectivity of *cis*-**4ca**. It has been a general perception that it is very difficult to ascertain the mechanistic pathway followed by a reaction when it has more than one possibility that could result in quite similar transition states or intermediates, thereby yielding similar products. In this case, using the enantiopure substrates for epimerization under different conditions, we were able to understand and ascertain the reaction pathway.

We then carried out the epimerization of substrate *trans*-**5cca**, which has an additional methyl substitution that would direct the regioselective formation of less substituted enamine **12** (Scheme 8, eq d). This should result in the inversion of the R^2 stereocenter after ring opening/closing and lead to the formation of *cis*-**5cca**, without any loss of enantioselectivity. As expected, the *trans*-spirane could be successfully epimerized into its *cis* counterpart with 95% ee using 3 equiv of pyrrolidine.[23] This result substantiated that the retro-Michael/Michael pathway was predominantly followed during epimerization, resulting in retention of enantioselectivity by the *cis* products. These results were helpful to prove that the additional substitution on the cyclohexanone ring of *trans*-spiranes prevented the racemization by the retro-Diels–Alder pathway and allowed the stereoselective synthesis of corresponding *cis* products. As a consequence, the long-standing problem of obtaining both the *cis* and the *trans* isomers of indanedione-fused spirocyclohexanones with good enantioselectivities was solved. The *cis*-spiranes without the methyl substitution could be preferably synthesized following the conditions as in Table 2, entry 14, resulting in the products with excellent enantioselectivity.

CONCLUSIONS

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

EXPERIMENTAL SECTION

General Experimental Methods. All solvents and reagents were used as purchased from commercial suppliers without further purification. Starting materials and catalysts which were not commercially available were synthesized by the previously reported methods. Analytical thin-layer chromatography was performed on precoated alumina-backed silica gel plates (0.2 mm thickness), which were developed using UV fluorescence and iodine. Flash chromatography was performed on silica gel (230–400 mesh). Melting points were measured on a standard melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a 400 MHz spectrometer, while ^{13}C NMR spectra were recorded on a 100 MHz instrument. Chemical shifts are reported in δ parts per million referenced to an internal tetramethylsilane standard for ^{1}H NMR and chloroform-*d* (δ = 77.0 ppm) for ^{13}C NMR. HRMS spectra were recorded using MALDI (TOF analyzer), ESI (TOF analyzer), and EI (magnetic sector analyzer). The X-ray diffraction measurements were carried out at 298 K on a CCD area detector system equipped with a graphite monochromator and a Mo Kα fine-focus sealed tube (k = 0.71073 Å). Optical rotations were measured in $CHCl_3$ on a polarimeter with a 50 mm cell (c given in g/100 mL) operating at λ = 589 nm, corresponding to the sodium D line, at the indicated temperatures. The enantiomeric excess of compounds whose racemic samples could not be synthesized was analyzed by comparing the retention times in the HPLC chromatograms of the corresponding enantiomers.

General Procedure A for the Synthesis of *trans*-4 or *ent-trans*-4 from 1 and 2. To a glass vial equipped with a magnetic stir

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bar were charged **2** (0.1 mmol), **1** (1.2 equiv), **IV** (5 mol %), **3d** (20 mol %), and DCM (0.25 mL) and stirred at 10 °C for the time specified. Then the reaction was quenched by the addition of 0.1 M HCl (0.25 mL), and the aqueous layer was extracted with DCM (2 × 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 *trans*-**4**.

General Procedure B for the Synthesis of *trans*-4 or *ent-trans*-4 from 1 and 2. To a glass vial equipped with a magnetic stir bar were charged **2** (0.1 mmol), **1** (1.2 equiv), **II** (5 mol %), **3d** (20 mol %), and DCM (0.25 mL) and stirred at 10 °C for the time specified. Then the reaction was quenched by the addition of 0.1 M HCl (0.25 mL), and the aqueous layer was extracted with DCM (2 × 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 *ent-trans*-**4**.

General Procedure C for the One-Pot Synthesis of *trans*-4 from 7, 8, and 2. To a glass vial equipped with a magnetic stir bar were charged **2** (0.1 mmol), **7** (1.2 equiv), **8** (1.2 equiv), **IV** (5 mol %), **3d** (20 mol %), and DCM (0.25 mL) and stirred at 10 °C for the time specified. Then the reaction was quenched by the addition of 0.1 M HCl (0.25 mL), and the aqueous layer was extracted with DCM (2 × 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 *trans*-**4**.

General Procedure D for the Synthesis of *trans*-5. To a glass vial equipped with a magnetic stir bar were charged ethyl vinyl ketone (0.1 mmol), **1** (1.2 equiv), **IV** (5 mol %), **3d** (10 mol %), and DCM (0.25 mL) and stirred at 30 °C for the time specified. Then the reaction was quenched by the addition of 0.1 M HCl (0.25 mL), and the aqueous layer was extracted with DCM (2 × 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 pure compound *trans*-**5**.

General Procedure E for the Synthesis of *trans*-6. To a glass vial equipped with a magnetic stir bar were charged **1** (0.1 mmol), 2-cyclohexenone (5 equiv), **IV** (5 mol %), **3d** (20 mol %), and toluene (0.25 mL) and stirred at 30 °C for the time specified. Then the reaction was quenched by the addition of 0.1 M HCl (0.25 mL), and the aqueous layer was extracted with DCM (2 × 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 *trans*-**6**.

General Procedure F for the Epimerization of Enantiopure *trans*-4 to *cis*-4. To a glass vial equipped with a magnetic stir bar were charged *trans*-**4** (0.1 mmol), pyrrolidine, **IV**, cyclohexylamine or **VI** (20 mol %), and appropriate solvent (0.25 mL) and stirred at room temperature. Then the reaction was quenched by the addition of 0.1 M HCl (0.25 mL), and the aqueous layer was extracted with DCM (2 × 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 pure *cis*-**4**.

General Procedure G for the Epimerization of Enantiopure *trans*-5 to *cis*-5. To a glass vial equipped with a magnetic stir bar were charged *trans*-**5** (0.1 mmol), pyrrolidine (3 equiv), **3d** (3 equiv), and MeOH/DCM (1:2, 0.25 mL) and stirred at 50 °C for 7 days. Then the reaction was quenched by the addition of 0.1 M HCl (0.25 mL), and the aqueous layer was extracted with DCM (2 × 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 pure *cis*-**5**.

General Procedure H for the Synthesis of *cis*-15ca and *cis*-17aca. To a glass vial equipped with a magnetic stir bar were charged *cis*-**4ca** or *cis*-**5aca** (0.1 mmol), ethylene glycol (1.2 equiv), *p*-TSA (10 mol %), and DCM (0.5 mL) and stirred under reflux for 12 h. Then the crude reaction mass was directly purified by flash column chromatography over silica gel to give pure *cis*-**15ca** or *cis*-**17aca** as a colorless solid.

Characterization Data for All Compounds. *(2S,6S)-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^{-1}, λ = 227 nm; T_R = 15.97 min (major), 24.09 min (minor)) 96% ee; $[\alpha]_D^{30}$ = −166.1 (*c* = 0.5 in CH_2Cl_2); R_f 0.25 (EA/hexanes = 1/5); ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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^{-1}; HRMS (ESI) for $C_{26}H_{21}O_3$ $[M + H]^+$ (381.1491), found 381.1492.

*(2R,6R)-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): $[\alpha]_D^{30}$ = +166.5 (*c* = 0.5 in CH_2Cl_2); HPLC analysis (Chiralpak IB column, hexane/IPA = 90:10, flow rate = 1.0 mL min^{-1}, λ = 227 nm; T_R = 16.73 min (major), 24.27 min (minor)) 97% ee.

*(2S,6S)-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^{-1}, λ = 227 nm; T_R = 17.91 min (major), 27.54 min (minor)) 98% ee; $[\alpha]_D^{30}$ = −140.2 (*c* = 0.5 in CH_2Cl_2); R_f 0.28 (EA/hexanes = 1/5); ^{1}H NMR (400 MHz, $CDCl_3$) 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 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}C NMR (100 MHz, $CDCl_3$) δ/ppm, 209.5, 202.8, 202.6, 142.0, 141.9, 137.0, 135.9, 135.63, 135.62, 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) 1794, 1721, 1644, 1610, 1489, 1104, 758 cm^{-1}; HRMS (ESI) for $C_{26}H_{20}O_3Cl$ $[M + H]^+$ (415.1101), found 415.1109.

*(2R,6R)-2-(4-Chlorophenyl)-6-phenylspiro[cyclohexane-1,2′-indene]-1′,3′,4-trione (ent-trans-**4ba**).* Following the general procedure B, *ent*-**4ba** was obtained in 85% yield (35.3 mg, *trans*/*cis* = 17:1) as a white solid (mp 177.4−178.2 °C): $[\alpha]_D^{30}$ = +141.6; HPLC analysis (Chiralpak IB column, hexane/IPA = 90:10, flow rate = 1.0 mL min^{-1}, λ = 227 nm; T_R = 19.32 min (minor), 31.16 min (major)) 97% ee.

*(2S,6S)-2-(4-Bromophenyl)-6-phenylspiro[cyclohexane-1,2′-indene]-1′,3′,4-trione (trans-**4ca**).* Following the general procedure A, **4ca** was obtained in 85% yield (39.0 mg) as a white solid (mp 143.0−144.1 °C): HPLC analysis (Chiralpak IB column, hexane/IPA = 90:10, flow rate = 1.0 mL min^{-1}, λ = 227 nm; T_R = 18.53 min (major), 32.43 min (minor)) 98% ee; $[\alpha]_D^{30}$ = −178.5 (*c* = 0.5 in CH_2Cl_2); R_f 0.25 (EA/hexanes = 1/5); ^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm, 7.64−7.57 (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), 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), 3.56 (dd, 1H, *J* = 13.1, 7.7 Hz), 2.78 (td, 2H, *J* = 3.4, 15.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ/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, 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, 1704, 1594, 1490, 1255, 763, 736, 700 cm^{-1}; HRMS (ESI) for $C_{26}H_{20}O_3Br$ $[M + H]^+$ (459.0596), found 459.0606.

*(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_2Cl_2); HPLC analysis (Chiralpak IB column, hexane/IPA = 90:10, flow rate = 1.0 mL min^{-1}, λ = 227 nm; T_R = 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 were charged **2** (0.1 mmol), **1** (1.2 equiv), **IV** (5 mol %), **3e** (10 mol %), and toluene (0.5 mL) and stirred at 60 °C for 24 h. Then the reaction was quenched by the addition of 0.1 M HCl (0.25 mL), and the aqueous layer was extracted with DCM (2 × 0.25 mL). The combined organic layers were concentrated in vacuo, and

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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^{-1}, λ = 227 nm; T_R = 39.13 min (major), 51.80 min (minor)) 97% ee; $[\alpha]_D^{29}$ = +1.8 (*c* = 0.5 in CH_2Cl_2); R_f 0.30 (EA/hexanes = 1/5); ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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^{-1}; HRMS (ESI) for $C_{26}H_{20}O_3Br$ $[M + H]^+$ (459.0596), found 459.0596.

*4-((2S,6S)-1′,3′,4-Trioxo-2-phenyl-1′,3′-dihydrospiro-[cyclohexane-1,2′-inden]-6-yl)benzonitrile (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^{-1}, λ = 227 nm; T_R = 48.15 min (major), 68.52 min (minor)) 98% ee; $[\alpha]_D^{30}$ = −203.5 (*c* = 0.5 in CH_2Cl_2); R_f 0.09 (EA/hexanes = 1/5); ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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^{-1}; HRMS (ESI) for $C_{27}H_{20}NO_3$ $[M + H]^+$ (406.1443), found 406.1451.

*4-((2R,6R)-1′,3′,4-Trioxo-2-phenyl-1′,3′-dihydrospiro-[cyclohexane-1,2′-inden]-6-yl)benzonitrile (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): $[\alpha]_D^{30}$ = +200.2 (*c* = 0.5 in CH_2Cl_2); HPLC analysis (Chiralpak IB column, hexane/IPA = 90:10, flow rate = 1.0 mL min^{-1}, λ = 227 nm; T_R = 55.43 min (minor), 73.71 min (major)) 98% ee.

*(2S,6S)-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^{-1}, λ = 229 nm; T_R = 45.65 min (major), 55.84 min (minor)) 97% ee; $[\alpha]_D^{30}$ = −182.9 (*c* = 0.5 in CH_2Cl_2); R_f 0.13 (EA/hexanes = 1/5); ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm, 208.6, 202.4, 202.1, 147.1, 145.1, 141.9, 141.8, 136.7, 136.0, 135.9, 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, 1604, 1512, 1255, 761, 736, 701 cm^{-1}; HRMS (ESI) for $C_{26}H_{20}NO_5$ $[M + H]^+$ (426.1341), found 426.1351.

*(2R,6R)-2-(4-Nitrophenyl)-6-phenylspiro[cyclohexane-1,2′-indene]-1′,3′,4-trione (ent-trans-**4ea**).* Following the general procedure B, *ent*-**4ea** was obtained in 95% yield (40.4 mg, *trans*/*cis* = 17:1) as a white solid (mp 158.5−159.2 °C): $[\alpha]_D^{30}$ = +200.2 (*c* = 0.5 in CH_2Cl_2); HPLC analysis (Chiralpak IB column, hexane/IPA = 90:10, flow rate = 1.0 mL min^{-1}, λ = 227 nm; T_R = 46.79 min (minor), 54.54 min (major)) 99% ee.

*(2R,6S)-2-(2-Bromophenyl)-6-phenylspiro[cyclohexane-1,2′-indene]-1′,3′,4-trione (trans-**4fa**).* Following the general procedure A, **4fa** was obtained in 91% yield (41.8 mg, *trans*/*cis* = 12:1) as a white solid (mp 163.6−164.9 °C): HPLC analysis (Chiralpak IB column, hexane/IPA = 90:10, flow rate = 1.0 mL min^{-1}, λ = 227 nm; T_R = 14.39 min (major), 42.78 min (minor)) 82% ee; $[\alpha]_D^{30}$ = +3.5 (*c* = 0.5 in CH_2Cl_2); R_f 0.25 (EA/hexanes = 1/5); ^{1}H NMR (400 MHz, $CDCl_3$) δ/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 (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 (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, 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, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm, 209.8, 202.5, 199.9, 142.4, 141.0, 138.8, 137.3, 135.7, 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, 42.9; IR (KBr) 2924, 1701, 1595, 1458, 1257, 1024, 758, 701 cm^{-1}; HRMS (ESI) for $C_{26}H_{20}O_3Br$ $[M + H]^+$ (459.0596), found 459.0604.

*(2S,6R)-2-(2-Bromophenyl)-6-phenylspiro[cyclohexane-1,2′-indene]-1′,3′,4-trione (ent-trans-**4fa**).* Following the general procedure B, *ent*-**4fa** was obtained in 78% yield (35.8 mg, *trans*/*cis* = 10:1) as a white solid: HPLC analysis (Chiralpak IB column, hexane/IPA = 90:10, flow rate = 1.0 mL min^{-1}, λ = 227 nm; T_R = 14.43 min (minor), 41.42 min (major)) 68% ee.

*(2S,6S)-2-(4-Methylphenyl)-6-phenylspiro[cyclohexane-1,2′-indene]-1′,3′,4-trione (trans-**4ga**).* Following the general procedure A, **4ga** was obtained in 80% yield (31.6 mg, *trans*/*cis* = 10:1) as a yellow solid (mp 135.8−136.2 °C): HPLC analysis (Chiralpak IB column, hexane/IPA = 90:10, flow rate = 1.0 mL min^{-1}, λ = 226 nm; T_R = 13.59 min (major), 20.55 min (minor)) 97% ee; $[\alpha]_D^{30}$ = −157.0 (*c* = 0.5 in CH_2Cl_2); R_f 0.28 (EA/hexanes = 1/5); ^{1}H NMR (400 MHz, $CDCl_3$) δ/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), 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), 3.57 (dd, *J* = 16.8, 9.4 Hz, 1H), 2.77 (dd, *J* = 16.8, 3.4 Hz, 2H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm, 210.2, 203.0, 202.9, 142.2, 142.1, 137.4, 137.0, 135.3, 134.4, 128.9, 128.4, 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, 1595, 1254, 761, 699 cm^{-1}; HRMS (ESI) for $C_{27}H_{23}O_3$ $[M + H]^+$ (395.1647), found 395.1645.

*(2R,6R)-2-(4-Methylphenyl)-6-phenylspiro[cyclohexane-1,2′-indene]-1′,3′,4-trione (ent-trans-**4ga**).* Following the general procedure B, *ent*-**4ga** was obtained in 75% yield (29.6 mg, *trans*/*cis* = 13:1) as a yellow solid (mp 135.8−136.2 °C): $[\alpha]_D^{30}$ = +156.0 (*c* = 0.5 in CH_2Cl_2); HPLC analysis (Chiralpak IB column, hexane/IPA = 90:10, flow rate = 1.0 mL min^{-1}, λ = 226 nm; T_R = 13.79 min (minor), 20.34 min (major)) 98% ee.

*(2S,6S)-2-(4-Methoxyphenyl)-6-phenylspiro[cyclohexane-1,2′-indene]-1′,3′,4-trione (trans-**4ha**).* Following the general procedure A, **4ha** was obtained in 71% yield (29.1 mg, *trans*/*cis* = 7:1) as a yellow solid (mp 120.2−121.0 °C): HPLC analysis (Chiralpak IB column, hexane/IPA = 90:10, flow rate = 1.0 mL min^{-1}, λ = 226 nm; T_R = 21.64 min (major), 33.58 min (minor)) 99% ee; $[\alpha]_D^{30}$ = −155.3 (*c* = 0.5 in CH_2Cl_2); R_f 0.16 (EA/hexanes = 1/5); ^{1}H NMR (400 MHz, $CDCl_3$) δ/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); ^{13}C NMR (100 MHz, $CDCl_3$) δ/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^{-1}; HRMS (ESI) for $C_{27}H_{23}O_4$ $[M + H]^+$ (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): $[\alpha]_D^{30}$ = +154.2 (*c* = 0.5 in CH_2Cl_2); HPLC analysis (Chiralpak IB column, hexane/IPA = 90:10, flow rate = 1.0 mL min^{-1}, λ = 226 nm; T_R = 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^{-1}, λ = 227 nm; T_R = 14.79 min (major), 18.57 min (minor)) 91% ee; $[\alpha]_D^{30}$ = −35.4 (*c* = 0.5 in CH_2Cl_2); R_f 0.14 (EA/hexanes = 1/5); ^{1}H NMR (400 MHz, $CDCl_3$) δ/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

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(dd, J = 16.4, 3.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ/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^{-1}; HRMS (ESI) for $C_{27}H_{23}O_4$ $[M + H]^+$ (411.1596), found 411.1597.

*(2R,6R)-2-(2-Methoxyphenyl)-6-phenylspiro[cyclohexane-1,2′-indene]-1′,3′,4-trione (ent-trans-**4ia**).* Following the general procedure B, *ent*-**4ia** was obtained in 62% yield (25.4 mg) as a yellow solid (mp 133.5−134.1 °C): $[\alpha]_D^{30}$ = +25.8 (c = 0.5 in CH_2Cl_2); HPLC analysis (Chiralpak IB column, hexane/IPA = 90:10, flow rate = 1.0 mL min^{-1}, λ = 227 nm; T_R = 14.99 min (minor), 17.51 min (major)) 78% ee.

*(2S,6R)-2-Phenyl-6-(thiophen-2-yl)spiro[cyclohexane-1,2′-indene]-1′,3′,4-trione (trans-**4ja**).* Following the general procedure A, **4ja** was obtained in 82% yield (31.7 mg, *trans*/*cis* = 1:1) as a yellow solid (mp 195.8−196.5 °C): HPLC analysis (Chiralpak IB column, hexane/IPA = 90:10, flow rate = 1.0 mL min^{-1}, λ = 226 nm; T_R = 18.03 min (major), 20.02 min (minor)) 97% ee; $[\alpha]_D^{30}$ = −134.6 (c = 0.5 in CH_2Cl_2); R_f 0.23(EA/hexanes = 1/5); ^{1}H NMR (400 MHz, $CDCl_3$) 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 = 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, 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, 3.9 Hz, 1H), 2.82 (dd, J = 16.5, 3.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm, 208.9, 202.3, 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, 44.1, 43.1, 41.9, 38.9; IR (KBr) 3071, 2956, 2922, 1724, 1701, 1593, 1349, 1254, 765, 705 cm^{-1}; HRMS (ESI) for $C_{24}H_{19}O_3S$ $[M + H]^+$ (387.1055), found 387.1055.

*(2R,6S)-2-Phenyl-6-(thiophen-2-yl)spiro[cyclohexane-1,2′-indene]-1′,3′,4-trione (ent-trans-**4ja**).* Following the general procedure B, *ent*-**4ja** was obtained in 80% yield (30.9 mg, *trans*/*cis* = 1:1) as a yellow solid (mp 195.3−196.3 °C): $[\alpha]_D^{30}$ = +135.5 (c = 0.5 in CH_2Cl_2); HPLC analysis (Chiralpak IB column, hexane/IPA = 90:10, flow rate = 1.0 mL min^{-1}, λ = 226 nm; T_R = 18.24 min (minor), 19.90 min (major)) 96% ee.

*(2S,6S)-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^{-1}, λ = 226 nm; T_R = 19.32 min (major), 30.19 min (minor)) 98% ee; $[\alpha]_D^{30}$ = −152.4 (c = 0.5 in CH_2Cl_2); R_f 0.29 (EA/hexanes = 1/5); ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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^{-1}; HRMS (EI) for $C_{26}H_{18}O_3ClBr$ $[M]^+$ (492.0128), found 492.0125.

*(2R,6R)-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): $[\alpha]_D^{30}$ = +151.6 (c = 0.5 in CH_2Cl_2); HPLC analysis (Chiralpak IB column, hexane/IPA = 90:10, flow rate = 1.0 mL min^{-1}, λ = 226 nm; T_R = 19.62 min (minor), 29.98 min (major)) 97% ee.

*(2S,6S)-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^{-1}, λ = 226 nm; T_R = 20.50 min (major), 34.79 min (minor)) 98% ee; $[\alpha]_D^{30}$ = −157.2 (c = 0.5 in CH_2Cl_2); R_f 0.29 (EA/hexanes = 1/5); ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 cm^{-1}; HRMS (MALDI) for $C_{26}H_{18}O_3Br_2Na$ $[M + Na]^+$ (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): $[\alpha]_D^{30}$ = +157.8 (c = 0.5 in CH_2Cl_2); HPLC analysis (Chiralpak IB column, hexane/IPA = 90:10, flow rate = 1.0 mL min^{-1}, λ = 226 nm; T_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)benzonitrile (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 mL min^{-1}, λ = 226 nm; T_R = 36.58 min (major), 48.26 min (minor)) 97% ee; $[\alpha]_D^{30}$ = −180.7 (c = 0.5 in CH_2Cl_2); R_f 0.09 (EA/hexanes = 1/5); ^{1}H NMR (400 MHz, $CDCl_3$) δ/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}C NMR (100 MHz, $CDCl_3$) δ/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 cm^{-1}; HRMS (ESI) for $C_{27}H_{19}NO_3Br$ $[M + H]^+$ (484.0548), found 484.0553.

*(2R,6R)-4-(2-(4-Bromophenyl)-1′,3′,4-trioxo-1′,3′-dihydrospiro[cyclohexane-1,2′-inden]-6-yl)benzonitrile (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): $[\alpha]_D^{30}$ = +181.7 (c = 0.5 in CH_2Cl_2); HPLC analysis (Chiralpak IB column, hexane/IPA = 85:15, flow rate = 1.0 mL min^{-1}, λ = 226 nm; T_R = 37.50 min (minor), 46.86 min (major)) 97% ee.

*(2S,6S)-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^{-1}, λ = 227 nm; T_R = 53.82 min (major), 75.37 min (minor)) 97% ee; $[\alpha]_D^{30}$ = −179.6 (c = 0.5 in CH_2Cl_2); R_f 0.11 (EA/hexanes = 1/5); ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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^{-1}; HRMS (ESI) for $C_{26}H_{17}NO_5Br$ $[M - H]^+$ (502.0290), found 502.0282.

*(2R,6R)-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): $[\alpha]_D^{30}$ = +179.0 (c = 0.5 in CH_2Cl_2); HPLC analysis (Chiralpak IB column, hexane/IPA = 90:10, flow rate = 1.0 mL min^{-1}, λ = 227 nm; T_R = 56.00 min (minor), 73.43 min (major)) 97% ee.

*(2R,6S)-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^{-1}, λ = 226 nm; T_R = 14.87 min (major), 37.13 min (minor)) 98% ee; $[\alpha]_D^{30}$ = −9.8 (c = 0.5 in CH_2Cl_2); R_f 0.26 (EA/hexanes = 1/5); ^{1}H NMR (400 MHz, $CDCl_3$) δ/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}C NMR (100 MHz, $CDCl_3$) δ/ppm, 209.2, 202.2, 199.6, 142.3, 140.8,

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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 cm^{-1}; HRMS (ESI) for $C_{26}H_{19}O_3Br_2$ $[M + H]^+$ (536.9701), found 536.9709.

*(2S,6R)-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 min^{-1}, λ = 226 nm; T_R = 15.45 min (minor), 36.02 min (major)) 97% ee.

*(2S,6S)-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 min^{-1}, λ = 226 nm; T_R = 24.78 min (major), 41.05 min (minor)) 98% ee; $[\alpha]_D^{30}$ = −172.7 (*c* = 0.5 in CH_2Cl_2); R_f 0.14 (EA/hexanes = 1/5); ^1H NMR (400 MHz, $CDCl_3$) δ/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}C NMR (100 MHz, $CDCl_3$) δ/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, 1489, 1412, 1255, 1182, 826, 736 cm^{-1}; HRMS (MALDI) for $C_{27}H_{21}O_4BrNa$ $[M + Na]^+$ (511.0515), found 511.0520.

*(2R,6R)-2-(4-Bromophenyl)-6-(4-methoxyphenyl)spiro-[cyclohexane-1,2′-indene]-1′,3′,4-trione (ent-trans-**4cg**).* Following the general procedure B, *ent*-**4cg** was obtained in 88% yield (43.0 mg, *trans*/*cis* = 10:1) as a yellow solid (mp 102.8−103.2 °C): $[\alpha]_D^{30}$ = +179.0 (*c* = 0.5 in CH_2Cl_2); HPLC analysis (Chiralpak IB column, hexane/IPA = 90:10, flow rate = 1.0 mL min^{-1}, λ = 226 nm; T_R = 26.02 min (minor), 39.70 min (major)) 94% ee.

*(2S,6S)-2-(4-Bromophenyl)-6-(2-methoxyphenyl)spiro-[cyclohexane-1,2′-indene]-1′,3′,4-trione (trans-**4ch**).* Following the general procedure A, **4ch** was obtained in 89% yield (43.6 mg) as a white solid (mp 98.5−99.8 °C): HPLC analysis (Chiralpak IB column, hexane/IPA = 90:10, flow rate = 1.0 mL min^{-1}, λ = 227 nm; T_R = 17.81 min (major), 23.02 min (minor)) 97% ee; $[\alpha]_D^{30}$ = −36.2 (*c* = 0.5 in CH_2Cl_2); R_f 0.14 (EA/hexanes = 1/5); ^1H NMR (400 MHz, $CDCl_3$) δ/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 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, 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, 1H), 3.03 (dd, *J* = 16.2, 5.5 Hz, 1H), 2.67 (dd, *J* = 16.2, 3.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ/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, 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, 1702, 1639, 1490, 1463, 1252, 752, 697 cm^{-1}; HRMS (ESI) for $C_{27}H_{21}O_4Br$ $[M + H]^+$ (489.0701), found 489.0706.

*(2R,6R)-2-(4-Bromophenyl)-6-(2-methoxyphenyl)spiro-[cyclohexane-1,2′-indene]-1′,3′,4-trione (ent-trans-**4ch**).* Following the general procedure B, *ent*-**4ch** was obtained in 81% yield (39.6 mg) as a white solid (mp 98.5−99.8 °C): $[\alpha]_D^{30}$ = +34.9 (*c* = 0.5 in CH_2Cl_2); HPLC analysis (Chiralpak IB column, hexane/IPA = 90:10, flow rate = 1.0 mL min^{-1}, λ = 227 nm; T_R = 18.21 min (minor), 22.35 min (major)) 97% ee.

*(2S,6R)-2-(4-Bromophenyl)-6-(thiophen-2-yl)spiro[cyclohexane-1,2′-indene]-1′,3′,4-trione (trans-**4ci**).* Following the general procedure A, **4ci** 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^{-1}, λ = 226 nm; T_R = 21.74 min (major), 32.40 min (minor)) 98% ee; $[\alpha]_D^{30}$ = −133.3 (*c* = 0.5 in CH_2Cl_2); R_f 0.23(EA/hexanes = 1/5); ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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^{-1}; HRMS (ESI) for $C_{24}H_{18}O_3SBr$ $[M + H]^+$ (465.0160), found 465.0165.

*(2R,6S)-2-(4-Bromophenyl)-6-(thiophen-2-yl)spiro[cyclohexane-1,2′-indene]-1′,3′,4-trione (ent-trans-**4ci**).* Following the general procedure B, *ent*-**4ci** was obtained in 70% yield (32.6 mg, *trans*/*cis* = 12:1) as a white solid (mp 101.7−102.5 °C): $[\alpha]_D^{30}$ = +132.2 (*c* = 0.5 in CH_2Cl_2); HPLC analysis (Chiralpak IB column, hexane/IPA = 90:10, flow rate = 1.0 mL min^{-1}, λ = 226 nm; T_R = 22.58 min (minor), 31.60 min (major)) 98% ee.

*(2S,3R,6S)-2-(4-Bromophenyl)-3-methyl-6-phenylspiro-[cyclohexane-1,2′-indene]-1′,3′,4-trione (trans-**5caa**).* Following the general procedure D, **5caa** 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^{-1}, λ = 227 nm; T_R = 20.07 min (major), 22.86 min (minor)) >99% ee; $[\alpha]_D^{30}$ = −119.1 (*c* = 0.5 in CH_2Cl_2); R_f 0.30 (EA/hexanes = 1/5); ^1H NMR (400 MHz, $CDCl_3$) δ/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}C NMR (100 MHz, $CDCl_3$) δ/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 cm^{-1}; HRMS (ESI) for $C_{27}H_{22}O_3Br$ $[M + H]^+$ (473.0752), found 473.0746.

*(2S,3R,6S)-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^{-1}, λ = 226 nm; T_R = 15.63 min (major), 20.92 min (minor)) >99% ee; $[\alpha]_D^{30}$ = −166.1 (*c* = 0.5 in CH_2Cl_2); R_f 0.31 (EA/hexanes = 1/5); ^1H NMR (400 MHz, $CDCl_3$) δ/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}C NMR (100 MHz, $CDCl_3$) δ/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 cm^{-1}; HRMS (EI) for $C_{27}H_{20}O_3Br_2$ $[M]^+$ (549.9779), found 549.9776.

*(2S,3R,6R)-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^{-1}, λ = 226 nm; T_R = 12.61 min (minor), 15.25 min (major)) 95% ee; $[\alpha]_D^{29}$ = +12.1 (*c* = 0.5 in CH_2Cl_2); R_f 0.40 (EA/hexanes = 1/5); ^1H NMR (400 MHz, $CDCl_3$) δ/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, 2 = 12.7 Hz, 1H), 2.64 (dd, *J* = 3.6, 13.6 Hz, 1H), 0.87 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ/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^{-1}; HRMS (EI) for $C_{27}H_{21}O_3Br_2$ $[M + H]^+$ (550.9857), found 550.9841.

*(2S,3R,6S)-6-(4-Bromophenyl)-3-methyl-2-phenylspiro-[cyclohexane-1,2′-indene]-1′,3′,4-trione (trans-**5aca**).* 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^{-1}, λ = 226 nm; T_R = 18.74 min (major), 25.34 min (minor)) >99% ee; $[\alpha]_D^{24}$ = −157.6 (*c* = 0.5 in CH_2Cl_2); R_f 0.14 (EA/hexanes = 1/5); ^1H NMR (400 MHz, $CDCl_3$) δ/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* =

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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); ^{13}C NMR (100 MHz, $CDCl_3$) δ/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^{-1}; HRMS (ESI) for $C_{27}H_{21}O_3Br$ $[M]^+$ (472.0674), found 472.0673.

*(2S,3R,6R)-6-(4-Bromophenyl)-3-methyl-2-phenylspiro-[cyclohexane-1,2′-indene]-1′,3′,4-trione (cis-**5aca**).* Product was 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^{-1}, λ = 226 nm; T_R = 14.51 min (minor), 16.24 min (major)) 94% ee; $[\alpha]_D^{24}$ = +20.9 (c = 0.5 in CH_2Cl_2); R_f 0.18 (EA/hexanes = 1/5); ^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm, 7.64 (d, J = 7.6 Hz, 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), 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, 1H), 2.64 (dd, J = 3.9, 13.6 Hz, 1H), 0.89 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ/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, 122.0, 121.5, 62.7, 55.8, 47.8, 44.5, 43.1, 11.9; IR (KBr) 2922, 1735, 1700, 1594, 1485, 1250, 1076, 820, 733 cm^{-1}.

*(1R,3S,4R)-3-(4-Bromophenyl)spiro[bicyclo[2.2.2]octane-2,2′-indene]-1′,3′,5-trione (trans-**6ca**).* Following the general procedure E, *trans*-**6ca** was obtained in 66% yield (27.0 mg, *trans*/*cis* = 5:1) as a white solid (mp 83.2−83.8 °C): HPLC analysis (Chiralpak IA column, hexane/IPA = 90:10, flow rate = 1.0 mL min^{-1}, λ = 226 nm; T_R = 21.10 min (major), 32.53 min (minor)) 99% ee; $[\alpha]_D^{30}$ = −112.3 (c = 0.5 in CH_2Cl_2); R_f 0.09 (EA/hexanes = 1/5); ^{1}H NMR (400 MHz, $CDCl_3$) δ/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), 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, 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, 1H), 1.72−1.61 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm, 213.9, 201.7, 198.6, 141.2, 140.6, 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; IR (KBr) 3059, 2923, 1728, 1703, 1593, 1489, 1266, 779, 734, 698 cm^{-1}; HRMS (ESI) for $C_{22}H_{18}O_3Br$ $[M + H]^+$ (409.0439), found 409.0440.

*(1R,3S,4R)-3-Phenylspiro[bicyclo[2.2.2]octane-2,2′-indene]-1′,3′,5-trione (trans-**6aa**).* Following the general procedure E, *trans*-**6aa** was obtained in 65% yield (21.5 mg, *trans*/*cis* = 7:1) as a white solid (mp 176.2−177.9 °C): HPLC analysis (Chiralpak IA column, hexane/IPA = 90:10, flow rate = 1.0 mL min^{-1}, λ = 226 nm; T_R = 17.56 min (major), 22.36 min (minor)) 97% ee; $[\alpha]_D^{30}$ = −132.5 (c = 0.5 in CH_2Cl_2); R_f 0.11 (EA/hexanes = 1/5); ^{1}H NMR (400 MHz, $CDCl_3$) δ/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); ^{13}C NMR (100 MHz, $CDCl_3$) δ/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^{-1}; HRMS (ESI) for $C_{22}H_{19}O_3$ $[M + H]^+$ (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)benzonitrile (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^{-1}, λ = 226 nm; T_R = 50.11 min (major), 60.39 min (minor)) 95% ee; $[\alpha]_D^{30}$ = −152.7 (c = 0.5 in CH_2Cl_2); R_f 0.04 (EA/hexanes = 1/5); ^{1}H NMR (400 MHz, $CDCl_3$) δ/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); ^{13}C NMR (100 MHz, $CDCl_3$) δ/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^{-1}; HRMS (ESI) for $C_{23}H_{18}NO_3$ $[M + H]^+$ (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^{-1}, λ = 227 nm; T_R = 10.48 min (major), 11.62 min (minor)) 98% ee; $[\alpha]_D^{29}$ = +5.5 (c = 0.5 in CH_2Cl_2); R_f 0.35 (EA/hexanes = 1/5); ^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm, 7.55 (d, J = 7.2 Hz, 1H), 7.37−7.48 (m, 3H), 7.10 (d, J = 8.5 Hz, 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, 2H), 1.86−1.98 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm, 203.2, 203.1, 142.6, 141.9, 138.7, 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, 62.3, 47.0, 45.8, 36.4, 36.2; IR (KBr) 2882, 1739, 1699, 1594, 1488, 1334, 1254, 1148, 1075, 1010, 880, 763, 700, 527 cm^{-1}.

*cis-**16aca**.* Following the general procedure H, *cis*-**16aca** was obtained from *cis*-**5aca** in quantitative yield (51.7 mg) as a white solid (mp 253.5−255.0 °C): HPLC analysis (Chiralpak IA column, hexane/EtOH = 90:10, flow rate = 1.0 mL min^{-1}, λ = 254 nm; T_R = 23.05 min (minor), 35.09 min (major)) 94% ee; $[\alpha]_D^{24}$ = +19.5 (c = 1.0 in CH_2Cl_2); R_f 0.22 (EA/hexanes = 1/5); ^{1}H NMR (400 MHz, $CDCl_3$) δ/ppm, 7.53 (d, J = 7.4 Hz, 1H), 7.46−7.34 (m, 3H), 7.09 (d, J = 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 = 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 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ/ppm, 203.5, 203.0, 142.7, 141.7, 138.3, 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, 65.5, 65.2, 63.0, 53.2, 45.3, 38.4, 36.3, 11.1; IR (KBr) 2890, 1742, 1703, 1590, 1481, 1332, 1256, 1146, 1075, 887, 765, 702, 525 cm^{-1}.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02921.

Copies of ^{1}H and ^{13}C NMR spectra for all compounds and HPLC chromatograms for appropriate compounds (PDF)

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

X-ray crystallographic data for compound *cis*-**15ca** (CIF)

X-ray crystallographic data for compound *trans*-**5cca** (CIF)

X-ray crystallographic data for compound *cis*-**16aca** (CIF)

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Notes

The authors declare no competing financial interest.

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(22) See the Supporting Information for the additional results of the control experiments.
(23) This is the first time that the optically pure *trans*-spiranes **4ca** and **5ca** have been transformed into the *cis*-spiranes, which gave a clear insight into the mechanism of epimerization. However, the racemic *trans*-spiranes were already epimerized into *cis*-spiranes, where the results could not conclusively elucidate the mechanism.

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