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Synthesis of Activated Cyclopropanes by an MIRC Strategy: An Enantioselective Organocatalytic Approach to Spirocyclopropanes[‡]

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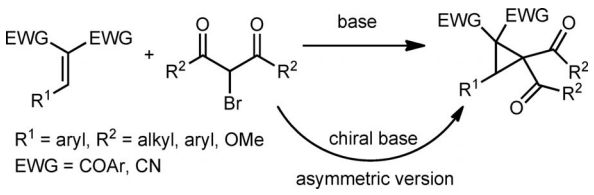
An efficient cyclopropanation, by a Michael-initiated ring-closing (MIRC) reaction of 2-arylidene-1,3-indandiones and 2-arylidene malononitriles, has been developed by using different α-monohalogenated methylene active compounds with triethylamine. The first enantioselective cyclopropanation to spirocyclopropanes derived by the reaction of 2-arylidene-1,3-indandiones and dimethyl bromomalonate with a commercially available α,α-L-diarylprolinol as the organocatalyst and K_2CO_3 as the additive has been accomplished. The spirocyclopropanes were isolated in high yield and up to 85% *ee*. Notably, the asymmetric one-pot sequential approach to spirocyclopropanes proved to be a feasible process.

Introduction

Cyclopropanes are subunits found in many natural products and pharmaceuticals.[1] Moreover, they serve as highly valuable synthetic intermediates amenable to facile ring opening and ring enlargement to give a wide number of functionalized products and complex heterocycles.[2] Therefore, the development of asymmetric methods for their synthesis has attracted considerable attention as attested to by the huge expansion of this area in recent years.[3] Common methodologies for asymmetric cyclopropanation include diastereoselective Simmons–Smith-type processes.[4] Metallocarbenoid reagents are the most investigated and general methods to produce cyclopropanes from alkenes with high stereocontrol.[5] Michael-initiated ring-closing (MIRC) reactions have been successfully applied to obtain cyclopropanes.[6] In this case, conjugate addition to an electron-poor alkene generates an enolate that then undergoes intramolecular ring closure. In a domino process, the final cyclopropanes can be directly obtained. Less conveniently, a two-step procedure is required whenever the cyclization of the first adduct must proceed under different reaction conditions. In this context, elegant asymmetric methods for the cyclopropanation of electron-poor alkenes, such as enals, enones, α,β-unsaturated esters, amides, and nitriles, have been reported, using sulfur and nitrogen ylides, by Aggarwal and co-workers,[7] and more recently organocatalytic versions by the groups of Gaunt,[8] and MacMillan.[9] Chiral nonracemic amines have been reported by the groups of Ley,[10] Cordova,[11] and Wang[12] to be suitable catalysts for the highly stereoselective cyclopropanation of enals and enones by iminium–enamine catalysis using readily available alkyl halides. The feasibility of noncovalent catalysis, by a two-step MIRC strategy, promoted by cinchona-based thioureas was exploited by Connon and co-workers to access functionalized cyclopropanes starting from nitroalkenes and dimethyl chloromalonate.[13a] High diastereocontrol and modest enantiocontrol was achieved in the process (up to 47% *ee*), which was later improved by Yan and co-workers up to 99% *ee*.[13b] We have recently demonstrated that easily available α,α-diarylprolinols are also able to promote this cyclopropanation reaction with high diastereoselectivity and modest enantioselectivity (up to 49% *ee*).[14] With the aim to widen the scope of highly functionalized cyclopropanes accessible by the MIRC strategy, we turned our attention toward the combination of α-halogenated active methylene compounds and poorly investigated alkenes such as 2-arylidene-1,3-indandiones and 2-arylidene malononitriles (Scheme 1).



Scheme 1. MIRC approach to obtain densely functionalized cyclopropanes; EWG = electron-withdrawing group.

Herein, we report an effective and simple domino procedure for their cyclopropanation using triethylamine, which served as a platform to pursue the challenging task of developing an enantioselective catalytic version by ex-

[‡] MIRC = Michael-initiated ring-closing reaction.

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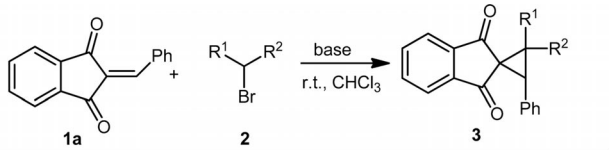
ploiting noncovalent catalysis mediated by commercially available bifunctional organocatalysts.

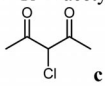
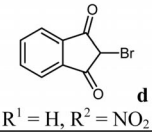
Results and Discussion

A few methods were elaborated for the cyclopropanation of 2-arylidenemalononitriles and 2-arylidene-1,3-indandiones, which generally required special techniques, namely, electrocatalysis,[15] or oxidative addition promoted by molecular iodine and bases under mechanical milling conditions.[16] An organometallic approach using α-dihalogenated methylene active compounds has also been exploited for their synthesis.[17] Monohalomalonates were used with potassium carbonate in THF for the cyclopropanation of different electron-poor alkenes to afford the corresponding cyclopropanes in variable yield.[18] A variety of α-monohalogenated active methylene compounds are commercially available, and thus, we investigated cyclopropanation by reacting them with 2-arylidene-1,3-indandiones and 2-arylidene malononitriles in the presence of common organic bases. Compound **1a** was treated with dimethyl bromomalonate (**2a**) in $CHCl_3$ at room temperature with amines (Table 1).

Table 1. Base-catalyzed cyclopropanation of **1a** with different α-monohalogenated active methylene compounds.[a]



1a 2 3

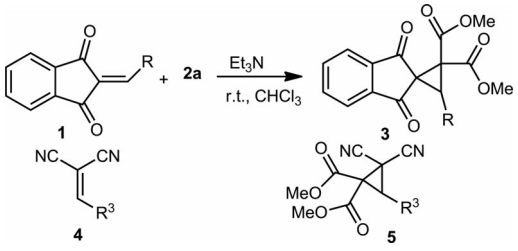
Entry	Base	2	t [h]	Yield 3[%][b]
1	DABCO	$R^1 = R^2 = CO_2Me$ **a**	24	62
2[c]	DBU	$R^1 = R^2 = CO_2Me$ **a**	3	75
3[f]	Et_3N	$R^1 = R^2 = CO_2Me$ **a**	3	92
4[g]	pyrrolidine	$R^1 = R^2 = CO_2Me$ **a**	3	70
5[h]	piperidine	$R^1 = R^2 = CO_2Me$ **a**	3	89
6	Et_3N	$R^1 = R^2 = CN$ **b**	2	99
7	Et_3N	$R^1 = R^2$ = acetyl **c**	2	99
8	Et_3N	 **c**	3	97
9	Et_3N	 **d**	3	99
10	Et_3N	$R^1 = H, R^2 = NO_2$ **e**	24	–

[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.24 mmol), base (0.2 mmol) in $CHCl_3$ (1 mL). [b] Yield of isolated product.

Tertiary and secondary amines of different pK_a afforded cyclopropane **3a** after a short reaction time in good to high yield. Triethylamine proved to be the best base, leading to the cyclopropane in 92% yield (Table 1, entry 3). A variety of α-bromomethylene-active compounds were treated with compound **1a**, employing triethylamine as the base. The corresponding cyclopropanes **3** were obtained in quantitative yields after short reaction times (Table 1, entries 6–9), except when using bromonitromethane. In this case, the formation of the product was not observed (Table 1, entry 10).

The scope of this simple methodology to obtain highly functionalized cyclopropanes was then studied by using **2a** as the alkylating agent (Table 2).

Table 2. Triethylamine-catalyzed cyclopropanation of **1** and **4** with **2a**.[a]



1 4 3 5

Entry	R	3	Yield 3 [%][b]	R^3	5	Yield 5 [%][b]
1	Ph	**3a**	92	Ph	**5a**	99
2	4-*t*BuC$_6$H$_4$	**3f**	88	4-CH$_3$OC$_6$H$_4$	**5b**	99
3	2-CH$_3$C$_6$H$_4$	**3g**	88	4-CF$_3$C$_6$H$_4$	**5c**	99
4	4-MeOC$_6$H$_4$	**3h**	83	2-CH$_3$C$_6$H$_4$	**5d**	93
5	4-BrC$_6$H$_4$	**3i**	98	–		–
6	4-ClC$_6$H$_4$	**3j**	99	–		–
7	2-ClC$_6$H$_4$	**3k**	94	–		–
8	3,5-(*t*Bu)$_2$C$_6$H$_3$	**3l**	94	–		–
9	cyclohexyl	**3m**	–	–		–

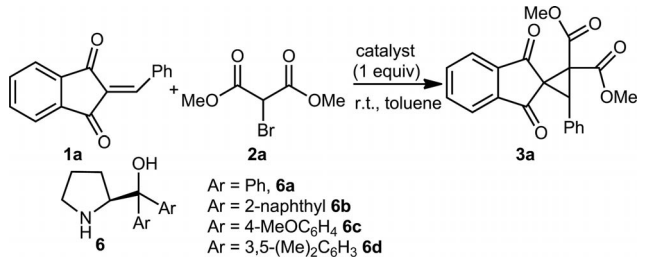
[a] Reaction conditions: **1** (0.2 mmol), **4** (0.2 mmol), **2a** (0.24 mmol), Et_3N (0.2 mmol) in $CHCl_3$ (1 mL). [b] Yield of isolated product.

Spirocyclopropanes **3** were isolated in high yield irrespective of the substitution pattern on the phenyl ring. The cyclopropanation of the aliphatic derivative **1m** did not proceed (Table 2, entry 9). More reactive 2-arylidene malonitriles were converted into cyclopropanes **5** in excellent yields (Table 2, entries 1–4).

We then turned our attention to the development of an asymmetric procedure for the cyclopropanation of these compounds using reagent **2a**. We hypothesized that a bifunctional organocatalyst with a basic and an acidic group would have been able to provide noncovalent activation of the alkene through hydrogen bonding and the pronucleophile through deprotonation. As part of our interest in developing asymmetric processes organocatalyzed by bifunctional promoters, we envisaged easily available cinchona alkaloids and α,α-diarylprolinols as suitable catalysts for cyclopropanation.[19] They were first used under stoichiometric loadings; alkene **1a** and donor **2a** were reacted at room temperature in toluene (Table 3). Although the cyclopropane was easily formed when using cinchona alkaloids, compound **3a** was recovered as a racemic product, except when using cinchonine as the catalyst (Table 3, entries 1–4).

Unexpectedly, cyclopropanation did not proceed under identical conditions when using cinchona-derived thioureas developed by Soòs and co-workers.[20,21] Pleasingly, α,α-diarylprolinols **6** afforded the product in good to high yield with an encouraging level of enantioselectivity (Table 3, entries 5–8). Indeed, commercially available compound **6d**

Table 3. Asymmetric stoichiometric cyclopropanation of **1a** with **2a** using chiral bases.[a]



Entry	Catalyst	*t* [h]	Yield **3a** [%][b]	*ee* **3a** [%][c]
1	quinine	24	93	*rac*
2	quinidine	20	91	5
3	cinchonine	24	86	30
4	cinchonidine	21	95	*rac*
5	**6a**	23	76	32
6	**6b**	23	87	29
7	**6c**	22	87	35
8	**6d**	22	86	45
9[d]	**6d**	24	92	58

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), catalyst (0.2 mmol) in toluene (1 mL). [b] Yield of isolated product. [c] Determined by HPLC on Chiralpak AD-H column. [d] Reaction performed at –20 °C.

gave **3a** in 86% yield and 45% *ee* (Table 3, entry 8). The enantiomeric excess could be improved to 58% when performing the reaction at –20 °C (Table 3, entry 9). The cyclopropanation of compound **4a** with **2a** catalyzed by quinine and catalyst **6a** was also studied under the same conditions, leading in both cases to racemic product **5a**. To reduce the amount of catalyst employed, the cyclopropanation was carried out by adding some basic additives to remove HBr formed during the reaction, thus regenerating the unprotonated catalyst.

The cyclopropanation of **1a** was investigated by using catalyst **6a** (50 mol-%) with an array of bases (1 equiv.) in toluene at room temperature (Table 4). In the absence of any additive, the product was isolated in satisfactory yield, but with reduced *ee* (entry 1 vs. entry 5 in Table 3). The addition of triethylamine as an additive afforded racemic compound **3a** in high yield, which implied the occurrence of a competitive racemic pathway (Table 4, entry 2).[22] Nevertheless, a high conversion to cyclopropane **3a** was achieved together with a variable degree of enantiocontrol when using inorganic bases (Table 4, entries 3–9). We were pleased to observe that potassium carbonate enabled the formation of product **3a** in excellent yield and almost comparable enantioselectivity to that achieved under stoichiometric amounts of catalyst **6a** (Table 4, entry 5 vs. entry 5 in Table 3).[23] An attempt to reduce the catalyst loading to 30 mol-% significantly lowered both the yield and enantioselectivity (Table 4, entry 10). Solvent screening conducted with the most effective catalyst **6d** showed that in aromatic solvents, such as chlorobenzene and *m*-xylene, comparable results to those found in toluene were achieved in terms of conversion and enantioselectivity, whereas halogenated, ethereal, and polar aprotic solvents proved to be unsuitable media.[24] Further optimization of the amount of K_2CO_3, temperature, and dilution was studied by using catalyst **6d**. The best result was attained when working at –30 °C employing 50 mol-% of the basic additive, which enabled the isolation of cyclopropane **3a** in 92% yield and 67% *ee* (Table 4, entry 13).

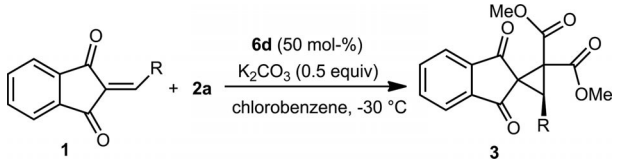
Table 4. Optimization of the asymmetric cyclopropanation of **1a** with **2a** using **6** (50 mol-%) and basic additives.[a]

Entry	Catalyst	Additive (equiv.)	*t* [h]	Yield **3a** [%][b]	*ee* **3a** [%][c]
1	**6a**	–	24	65	18
2	**6a**	Et_3N (1)	19	99	*rac*
3	**6a**	Na_2CO_3 (1)	21	97	12
4	**6a**	$NaHCO_3$ (1)	24	64	18
5	**6a**	K_2CO_3 (1)	23	96	27
6	**6a**	Rb_2CO_3 ()	21	99	7
7	**6a**	$CaCO_3$ (1)	24	68	19
8	**6a**	Cs_2CO_3 (1)	22	80	29
9	**6a**	NaOAc (1)	24	66	10
10[d]	**6a**	K_2CO_3 (0.5)	28	58	21
11[e]	**6d**	K_2CO_3 (1)	60	82	50
12[e]	**6d**	K_2CO_3 (0.5)	22	75	61
13[f]	**6d**	K_2CO_3 (0.5)	26	92	67
14[f,g]	**6d**	K_2CO_3 (0.5)	23	74	49
15[f,h]	**6d**	K_2CO_3 (0.5)	24	60	69

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), **6** (0.1 mmol), additive (*x* mmol) in toluene (1 mL). [b] Isolated yield after flash chromatography. [c] Determined by HPLC on Chiralpak AD-H column. [d] The reaction was carried out with 30 mol-% of catalyst **6a**. [e] Reaction performed at –20 °C. [f] Reaction performed at –30 °C. [g] The reaction was carried out with 30 mol-% of catalyst **6d**. [h] Reaction carried out at C = 0.1 M.

The applicability of this system was then evaluated with a selection of 2-arylidene-1,3-indandiones under optimal reaction conditions (Table 5).[25]

Table 5. Substrate scope of 2-arylidene-1,3-indandiones **1** in the asymmetric cyclopropanation with **2a**.[a]



Entry	R		*t* [h]	Yield **3** [%][b]	*ee* **3** [%][c]
1[d]	Ph	**a**	26	92	67
2[d]	4-*t*BuC_6H_4	**f**	24	73	60
3	2-$CH_3C_6H_4$	**g**	27	85	83
4	4-$CH_3OC_6H_4$	**h**	26	85	63
5	4-ClC_6H_4	**j**	24	96	60
6	2-ClC_6H_4	**k**	24	74	68
7[d]	3,5-(*t*Bu)$_2C_6H_3$	**l**	47	79	60
8	2-$CH_3OC_6H_4$	**n**	48	84	85

[a] Reaction conditions: **1** (0.2 mmol), **2a** (0.24 mmol), **6d** (0.1 mmol), K_2CO_3 (0.1 mmol) in chlorobenzene (1 mL) at –30 °C. [b] Isolated yield after flash chromatography. [c] Determined by HPLC on chiral columns. [d] In toluene as the solvent.

2-Arylidene-1,3-indandiones with electron-donating or -withdrawing substituents in the *para* and *meta* positions afforded the product in high yield and up to 67% *ee* (Table 5, entries 1, 2, 4, 5, and 7). Steric hindrance at the *ortho* position, such as in alkenes **1g**, **1k**, and **1n**, was found to be beneficial in terms of enantiocontrol, leading to cyclopropanes with 83, 68, and 85% *ee*, respectively (Table 5, entries 3, 6, and 8).[26] The absolute configuration of cyclopropanes **3** was assigned to be *S* by analogy to the structure determined by single-crystal X-ray analysis performed on compound **3k** (Figure 1).[27]

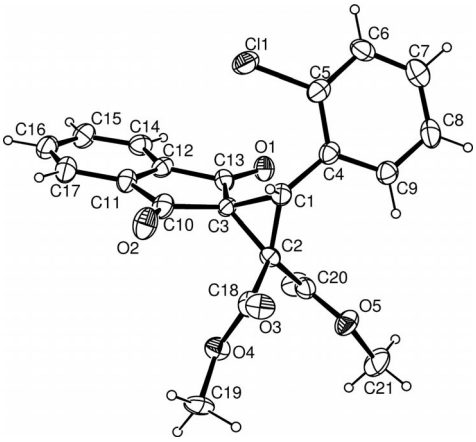
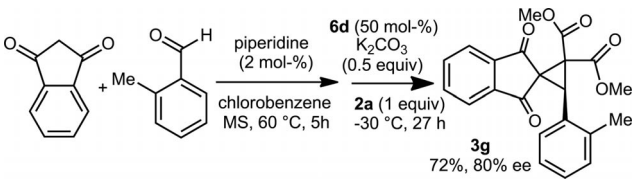


Figure 1. X-ray molecular structure of compound **3k**. Thermal ellipsoids are drawn at the 20% probability level.

The diester moieties in compounds **3** could be eventually manipulated in a few steps to generate cyclopropane amino acids.[28] This class of cyclopropanes is widespread in nature and they generally show interesting biologically activities and find application in peptidomimetics.[29]

Hitherto, few examples of a one-pot sequential domino route to racemic cyclopropanes have been investigated, despite the notable synthetic and economic advantages derived from the one-pot combination of commercially available compounds to produce highly functionalized cyclic products.[30] Hence, the enantioselective one-pot sequential approach to the synthesis of cyclopropanes **3** was investigated (Scheme 2). Typical reaction conditions for the Knoevenagel condensation of representative *ortho*-tolualdehyde and 1,3-indandione were found to be compatible with the enantioselective MIRC route herein developed.



Scheme 2. Enantioselective one-pot domino approach to cyclopropane **3g**.

Cyclopropane **3g** was obtained in good yield and, notably, the level of enantioselectivity illustrated in Table 5 was maintained. To the best of our knowledge, this represents the first example of an enantioselective one-pot sequential domino cyclopropanation.

Conclusions

An efficient and simple synthesis of densely functionalized cyclopropanes has been developed by an MIRC approach by using commercially available α-monohalogenated active methylene compounds and 2-arylidene-1,3-indandiones or 2-arylidene malononitriles in the presence of triethylamine. The first asymmetric route to spirocyclopropanes from 2-arylidene-1,3-indandiones and dimethyl bromomalonate, using a commercially available α,α-L-diarylprolinol as the organocatalyst and K_2CO_3 as additive, has been disclosed. The enantioenriched products were obtained in good yields and with moderate to good enantioselectivity. The present methodology illustrates the potential of noncovalent catalysis, using easily available promoters such as β-amino alcohols, in the enantioselective cyclopropanation of less common, more challenging alkenes. Interestingly, an unprecedented example of an asymmetric one-pot sequential approach to cyclopropanes has been developed.

Experimental Section

General Methods: All reactions requiring dry or inert conditions were conducted in flame-dried glassware under a positive pressure of nitrogen. Reactions were monitored by TLC on silica gel plates (0.25 mm) and visualized by UV light or by phosphomolybdic acid/ethanol spray test. Flash chromatography was performed on silica gel (60, particle size: 0.040–0.063 mm). ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer at room temperature in $CDCl_3$. Chemical shifts for protons are reported by using residual $CHCl_3$ as an internal reference (δ = 7.26 ppm). Carbon spectra were referenced to the shift of the ^{13}C signal of $CDCl_3$ (δ = 77.0 ppm). Optical rotations were performed by using an Na lamp. FTIR spectra were recorded as thin films on KBr plates and absorption maxima are reported in cm^{-1}. ESI mass spectra are reported in the form of *m*/*z*. Elementary analyses were performed by using a CHNS elementary analyzer. Melting points were recorded with a digital Electrothermal 9100 apparatus. Solvents were purified and dried by standard procedures prior to use. Petroleum ether with a boiling range of 60–80 °C was used. Anhydrous *p*-xylene, toluene, chlorobenzene, and CH_3CN were purchased and used as received. 2-Bromomalononitrile and 3-bromopentane-2,4-dione were prepared by using known protocols.[31] Cinchona-derived thioureas and prolinol **6c** were synthesized by following procedures reported in the literature.[32] Alkenes **1** and **4** were prepared by using general procedures reported in the literature.[33] Catalysts **6a**, **6b**, and **6d**, quinine, quinidine, cinchonine, cinchonidine, salts, and all other reagents were purchased from Aldrich and used as received. Cyclopropanes **5a**, **5b**, **3a**, **3d**, **3i** are known compounds.[16,17] Enantiomeric excesses of cyclopropanes **3** were determined by HPLC (UV dual λ absorbance detector) using Daicel Chiralpak AD-H and AS-H columns.

General Procedure for the Cyclopropanation of Compounds 1 and 4 with Triethylamine: In a sample vial, alkenes **1** or **4** (0.20 mmol), appropriate monohalogenated active methylene compound (0.24 mmol), and NEt_3 (28 μL, 0.20 mmol) were dissolved in $CHCl_3$ (1.0 mL). The reaction was stirred at room temperature until completion (monitored by TLC, PE/AcOEt, 7:3 or 1:1). The mixture was directly purified by flash chromatography (eluent pure chloroform) to give products **3** or **5**.

1′,3′-Dioxo-3-phenyl-1′,3′-dihydrospiro(cyclopropane-1,2′-indene)-2,2-dicarbonitrile (3b): White solid; m.p. 222.1–224.9 °C. IR (KBr): $\tilde{\nu}_{max}$ = 3028, 2925, 2250, 1748, 1716, 1591, 1239, 1223, 753, 698 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.16–7.98 (m, 4 H), 7.51–7.28 (m, 5 H), 4.07 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 189.3, 187.5, 142.4, 140.8, 136.9, 136.8, 129.7, 129.4, 129.1, 126.4, 124.2, 124.1, 110.6, 108.8, 44.0, 42.2, 19.4 ppm. MS (ESI): *m/z* (%) = 299.41 (24) [M + H^+], 321.44 (100) [M + Na^+]. $C_{19}H_{10}N_2O_2$ (298.30): *m/z* calcd. C 76.50, H 3.38, N 9.39; found C 76.65, H 3.47, N 9.50.

2,2-Diacetyl-3-phenylspiro(cyclopropane-1,2′-indene)-1′,3′-dione (3c): Yellow solid; m.p. 50.6–54.6 °C. IR (KBr): $\tilde{\nu}_{max}$ = 3027, 2925, 1709, 1595, 1356, 1239, 750, 699 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.99–7.96 (m, 2 H), 7.87–7.85 (m, 2 H), 7.38–7.29 (m, 5 H), 3.94 (s, 1 H), 2.38 (s, 3 H), 2.19 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 198.2, 197.1, 195.4, 193.0, 142.9, 141.1, 135.7, 135.5, 130.6, 130.2, 128.1, 128.0, 123.2, 123.1, 66.2, 47.8, 45.2, 30.8, 28.8 ppm. MS (ESI): *m/z* (%) = 355.37 (100) [M + Na^+], 371.33 (30) [M + K^+]. $C_{21}H_{16}O_4$ (332.36): calcd. C 75.89, H 4.85; found C 76.07, H 3.91.

Dimethyl 2,2-Dicyano-3-[4-(trifluoromethyl)phenyl]cyclopropane-1,1-dicarboxylate (5c): Colorless oil. $\tilde{\nu}_{max}$ (KBr) 3012, 2959, 2925, 2853, 2360, 2253, 1741, 1623, 1438, 1068, 1019, 909, 861, 737, 649 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 6.69 (d, *J* = 8.3 Hz, 2 H), 7.52 (d, *J* = 8.2 Hz, 2 H), 4.00 (s, 1 H), 3.99 (s, 3 H), 3.80 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 163.1, 161.1, 131.9 (q, *J* = 35.1 Hz), 131.0, 129.3, 126.1, 122.1, 111.3, 109.2, 55.1, 54.2, 46.2, 39.4, 16.4 ppm. MS (ESI): *m/z* (%) = 351.45 (100) [M – H^+]. $C_{16}H_{11}F_3N_2O_4$ (352.27): calcd. C 54.55, H 3.15, N 7.95; found C 54.78, H 3.30, N 8.10.

Dimethyl 2,2-Dicyano-3-*o*-tolylcyclopropane-1,1-dicarboxylate (5d): White wax. $\tilde{\nu}_{max}$ (KBr) 3001, 2958, 2924, 2853, 2249, 1747, 1437, 1251, 1205, 1084, 913, 762, 736 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.35–7.28 (m, 3 H), 7.24–7.21 (m, 1 H), 4.01 (s, 3 H), 3.92 (s, 1 H), 3.81 (s, 3 H), 2.44 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 163.6, 161.7, 138.3, 131.1, 129.7, 127.1, 126.4, 125.8, 112.0, 109.7, 54.9, 54.0, 46.2, 39.9, 19.5, 16.4 ppm. MS (ESI): *m/z* (%) = 297.55 (100) [M – H^+]. $C_{16}H_{14}N_2O_4$ (298.30): calcd. C 64.42, H 4.73, N 9.39; found C 64.61, H 4.82, N 9.47.

General Procedure for the Asymmetric Cyclopropanation of Compounds 1: A sample vial charged with a mixture of alkene **1** (0.20 mmol), K_2CO_3 (14 mg, 0.10 mmol), and (*S*)-α-bis(3,5-dimethylphenyl)-2-pyrrolidinemethanol **6d** (31 mg, 0.10 mmol) in anhydrous toluene or chlorobenzene (1.0 mL) was sonicated in a water bath at room temperature. Then, dimethyl 2-bromomalonate (32 μL, 0.24 mmol) was added and the reaction was stirred at –30 °C until completion (monitored by TLC, PE/AcOEt, 7:3). The mixture was directly purified by flash chromatography (eluent: chloroform) to give enantiomerically enriched cyclopropanes **3**. The absolute configuration of compounds **3** was assigned as *S* by analogy to the structure determined by single-crystal X-ray analysis performed on compound **3k**.

(*S*)-Dimethyl 1′,3′-Dioxo-3-phenyl-1′,3′-dihydrospiro(cyclopropane-1,2′-indene)-2,2-dicarboxylate (3a):[17b] $[\alpha]_D^{27}$ = –58.7 (*c* = 0.4, $CHCl_3$), *ee* 67%. HPLC analysis with Chiralpak column AD-H, *n*-hexane/2-propanol (90:10), 1.0 mL min^{-1}, detection at 254 nm; minor enantiomer t_R = 17.9 min, major enantiomer t_R = 22.1 min.

(*S*)-Dimethyl 3-(4-*tert*-Butylphenyl)-1′,3′-dioxo-1′,3′-dihydrospiro-(cyclopropane-1,2′-indene)-2,2-dicarboxylate (3f): White solid; m.p. 79.1–82.3 °C. $[\alpha]_D^{28}$ = –73.3 (*c* = 0.5, $CHCl_3$), *ee* 60%. IR (KBr): $\tilde{\nu}_{max}$ = 2956, 1752, 1713, 1595, 1434, 1244, 1151, 757 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.00–7.98 (m, 1 H), 7.97–7.95 (m, 1 H), 7.86–7.82 (m, 2 H), 7.31 (d, *J* = 8.5 Hz, 2 H), 7.25 (d, *J* = 8.4 Hz, 2 H), 4.09 (s, 1 H), 3.85 (s, 3 H), 3.76 (s, 3 H), 1.29 (s, 9 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 194.8, 191.4, 164.9, 162.9, 143.0, 141.1, 135.6, 135.2, 129.8, 126.9, 124.9, 124.7, 123.2, 123.1, 53.7, 53.2, 51.2, 45.3, 42.8, 34.5, 31.2 ppm. MS (ESI): *m/z* (%) = 443.37 (100) [M + Na^+], 459.21 (8) [M + K^+]. $C_{25}H_{24}O_6$ (420.46): calcd. C 71.41, H 5.75; found C 71.68, H 5.86; HPLC analysis with Chiralpak column AS-H, *n*-hexane/2-propanol (90:10), 1.0 mL min^{-1}, detection at 254 nm; minor enantiomer t_R = 10.3 min, major enantiomer t_R = 13.5 min.

(*S*)-Dimethyl 1′,3′-Dioxo-3-*o*-tolyl-1′,3′-dihydrospiro(cyclopropane-1,2′-indene)-2,2-dicarboxylate (3g): Yellow solid; m.p. 145.1–147.8 °C. $[\alpha]_D^{29}$ = –34.5 (*c* = 0.5, $CHCl_3$), *ee* 83%. IR (KBr): $\tilde{\nu}_{max}$ = 2954, 1754, 1713, 1594, 1435, 1244, 1152, 748 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.03–8.00 (m, 1 H), 7.98–7.96 (m, 1 H), 7.87–7.85 (m, 2 H), 7.21–7.19 (m 2 H), 7.16–7.09 (m, 2 H), 4.03 (s, 1 H), 3.85 (s, 3 H), 3.71 (s, 3 H), 2.18 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 194.7, 191.5, 165.0, 163.0, 142.7, 141.1, 138.3, 135.7, 135.3, 130.0, 129.0, 128.9, 128.0, 125.4, 123.2, 123.1, 53.6, 53.1, 51.3, 45.0, 41.5, 19.9 ppm. MS (ESI$^+$): *m/z* (%) = 379.23 (100) [M + H^+], 401.39 (15) [M + Na^+]. $C_{22}H_{18}O_6$ (378.38): calcd. C 69.83, H 4.79; found C 69.98, H 4.88, HPLC analysis with Chiralpak column AS-H, *n*-hexane/2-propanol (90:10), 1.0 mL min^{-1}, detection at 254 nm; minor enantiomer t_R = 10.7 min, major enantiomer t_R = 13.3 min.

(*S*)-Dimethyl 3-(4-Methoxyphenyl)-1′,3′-dioxo-1′,3′-dihydrospiro-(cyclopropane-1,2′-indene)-2,2-dicarboxylate (3h): Yellow gum. $[\alpha]_D^{27}$ = –59.8 (*c* = 0.4, $CHCl_3$), *ee* 63%. IR (KBr): $\tilde{\nu}_{max}$ = 2954, 2839, 1751, 1712, 1660, 1594, 1516, 1435, 1250, 1181, 1152, 761 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.00–7.98 (m, 1 H), 7.96–7.94 (m, 1 H), 7.86–7.82 (m, 2 H), 7.23 (d, *J* = 8.7 Hz, 2 H), 6.81 (d, *J* = 8.7 Hz, 2 H), 4.09 (s, 1 H), 3.84 (s, 3 H), 3.78 (s, 3 H), 3.74 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 194.8, 191.5, 164.9, 162.9, 159.1, 142.9, 141.2, 135.5, 135.3, 131.3, 123.2, 123.1, 121.8, 113.4, 55.1, 53.7, 53.2, 51.3, 45.3, 42.5 ppm. MS (ESI): *m/z* (%) = 417.26 (100) [M + Na^+]. $C_{22}H_{18}O_7$ (394.38): *m/z* calcd. C 67.00, H 4.60; found C 67.25, H 4.69; HPLC analysis with Chiralpak column AD-H, *n*-hexane/2-propanol (70:30), 1.0 mL min^{-1}, detection at 254 nm; minor enantiomer t_R = 17.1 min, major enantiomer t_R = 19.9 min.

(*S*)-Dimethyl 3-(4-Chlorophenyl)-1′,3′-dioxo-1′,3′-dihydrospiro(cyclopropane-1,2′-indene)-2,2-dicarboxylate (3j): White solid; m.p. 158.8–160.1 °C. $[\alpha]_D^{26}$ = –77.2 (*c* = 0.5, $CHCl_3$), *ee* 60%. IR (KBr): $\tilde{\nu}_{max}$ = 2954, 1752, 1713, 1595, 1496, 1435, 1244, 1151, 759 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.03–7.99 (m, 1 H), 7.98–7.96 (m, 1 H), 7.89–7.85 (m, 2 H), 7.27–7.23 (m, 4 H), 4.09 (s, 1 H), 3.86 (s, 3 H), 3.73 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 194.3, 191.5, 164.5, 162.7, 142.8, 141.2, 135.8, 135.5, 133.9, 131.5, 128.4, 128.1, 123.3, 123.2, 53.8, 53.2, 51.0, 44.9, 41.4 ppm. MS (ESI): *m/z* (%) = 421.37 (100) [M + Na^+], 437.33 (30) [M +K^+]. $C_{21}H_{15}ClO_6$ (398.80): *m/z* calcd. C 63.25, H 3.79; found C 63.41, H 3.84; HPLC analysis with Chiralpak column AD-H, *n*-hexane/2-propanol (90:10), 1.0 mL min^{-1}, detection at 254 nm; minor enantiomer t_R = 26.3 min, major enantiomer t_R = 30.2 min.

(*S*)-Dimethyl 3-(2-Chlorophenyl)-1′,3′-dioxo-1′,3′-dihydrospiro(cyclopropane-1,2′-indene)-2,2-dicarboxylate (3k): White solid; m.p. 155.0–156.2 °C. $[\alpha]_D^{28}$ = –34.3 (*c* = 0.5, $CHCl_3$), *ee* 68%. IR (KBr): $\tilde{\nu}_{max}$ = 2955, 1754, 1714, 1595, 1436, 1336, 1245, 1151, 1047, 754 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.01–7.99 (m, 1 H), 7.92–7.90 (m, 1 H), 7.85–7.79 (m, 3 H), 7.29–7.24 (m, 3 H), 4.04 (s, 1 H), 3.86 (s, 3 H), 3.75 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 194.4, 190.8, 164.7, 163.1, 142.7, 141.3, 135.6, 135.3, 135.1, 131.2, 129.3, 129.1, 126.6, 123.1, 53.8, 53.3, 50.9, 45.1, 39.7 ppm. MS (ESI): *m*/*z* (%) = 421.21 (100) [M + Na^+]. $C_{21}H_{15}ClO_6$ (398.80): *m*/*z* calcd. C 63.25, H 3.79; found C 63.45, H 3.85; HPLC analysis with Chiralpak column AD-H, *n*-hexane/2-propanol (90:10), 1.0 mL min^{-1}, detection at 254 nm; minor enantiomer t_R = 13.8 min, major enantiomer t_R = 15.6 min.

(*S*)-Dimethyl 3-(3,5-Di-*tert*-butylphenyl)-1′,3′-dioxo-1′,3′-dihydrospiro(cyclopropane-1,2′-indene)-2,2-dicarboxylate (3l): White solid; m.p. 191.7–192.4 °C. $[\alpha]_D^{28}$ = –94.7 (*c* = 0.6, $CHCl_3$), *ee* 60%. IR (KBr): $\tilde{\nu}_{max}$ = 2959, 1750, 1712, 1590, 1431, 1248, 1156, 752 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.00–7.98 (m, 1 H), 7.97–7.92 (m, 1 H) 7.85–7.81 (m, 2 H), 7.18 (br. s, 1 H), 7.17 (br. s, 2 H), 4.13 (s, 1 H), 3.86 (s, 3 H), 3.78 (s, 3 H), 1.29 (s, 18 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 195.1, 190.9, 165.0, 162.9, 150.0, 143.1, 140.9, 135.6, 135.1, 128.9, 124.7, 123.0, 121.7, 53.7, 53.2, 51.5, 45.5, 44.1, 34.8, 31.3 ppm. MS (ESI^+): *m*/*z* (%) = 499.32 (100) [M + Na^+]. $C_{29}H_{32}O_6$ (476.57): *m*/*z* calcd. C 73.09, H 6.77; found C 73.27, H 6.89; HPLC analysis with Chiralpak column AD-H, *n*-hexane/2-propanol 90:10, mL min^{-1}, detection at 254 nm; minor enantiomer t_R = 5.1 min, major enantiomer t_R = 6.6 min.

(*S*)-Dimethyl 3-(2-Methoxyphenyl)-1′,3′-dioxo-1′,3′-dihydrospiro-(cyclopropane-1,2′-indene)-2,2-dicarboxylate (3n): White solid; m.p. 164.7–169.2 °C. $[\alpha]_D^{28}$ = –12.5 (*c* = 0.6, $CHCl_3$), *ee* 85%. IR (KBr): $\tilde{\nu}_{max}$ = 2954, 2938, 1752, 1713, 1597, 1436, 1249, 1152, 1027, 755 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 8.03–7.98 (m, 1 H), 7.91–7.87 (m, 1 H), 7.84–7.81 (m, 2 H), 7.74–7.72 (m, 1 H), 7.29–7.25 (m, 1 H), 6.99–6.95 (m, 1 H), 6.71–6.69 (m, 1 H), 3.87 (s, 3 H), 3.80 (s, 1 H), 3.72 (s, 3 H), 3.18 (s, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 195.4, 190.5, 165.1, 163.2, 157.0, 142.9, 141.1, 135.2, 135.0, 134.6, 131.2, 129.3, 122.9, 122.5, 120.3, 118.9, 109.7, 54.5, 53.6, 53.0, 50.5, 44.9, 37.9 ppm. MS (ESI^+): *m*/*z* (%) = 417.26 (100) [M + Na^+]. $C_{22}H_{18}O_7$ (394.38): *m*/*z* calcd. C 67.00, H 4.60; found C 67.30, H 4.67; HPLC analysis with Chiralpak column AD-H, *n*-hexane/2-propanol 70:30, 1.0 mL min^{-1}, detection at 254 nm; minor enantiomer t_R = 6.5 min, major enantiomer t_R = 8.2 min.

X-ray Crystallographic Data of Compound 3k: X-ray diffraction quality single crystals of **3k** were obtained by slow evaporation of a solution of *n*-hexane/ethanol at 25 °C. A suitable crystal of **3k** was selected and glued onto a glass fiber and measured at room temperature with a diffractometer equipped with a CCD detector using Cu-K_α radiation. Data reduction was performed with the crystallographic package CrystalClear.[34] Data have been corrected for Lorentz, polarization, and absorption. The structure was solved by direct methods using the program SIR2002[35] and refined by means of full-matrix least-squares based on F^2 using the program SHELXL97.[36] All non-hydrogen atoms were refined anisotropically; hydrogen atoms were positioned geometrically and included in structure factor calculations but not refined. A total of 253 refinable parameters were finally considered; final disagreement indices are *R*1 = 0.0527 (1903 reflections $F^2 > 2\sigma F^2$), *wR*2 = 0.2065 (all 2183 independent reflections).

Flack parameter is 0.06(4). The ORTEP plot was obtained by means of the program ORTEP32.[37]

Crystal data: $C_{21}H_{15}ClO_6$, monoclinic, space group $P2_1$, Z = 2, a = 8.064(3) Å, b = 12.817(4) Å, c = 9.571(4) Å, β = 109.557(7)°, V = 932.2(6) $Å^3$, D_x = 1.421 g cm^{-3}, $\mu_{calcd.}$ = 2.137 mm^{-1}.

Enantioselective One-Pot Sequential Synthesis of Cyclopropane 3g: In a sample vial, 1,3-indandione (29 mg, 0.20 mmol) and *o*-tolualdehyde (23 μL, 0.20 mmol) were dissolved in chlorobenzene (1 mL) containing piperidine (2 mol-%) and molecular sieves (≈ 80 mg). The reaction was stirred at 60 °C for 5 h [monitored by TLC, PE/AcOEt (7:3) as the eluent]. Catalyst **6d** (31 mg, 0.10 mmol) and K_2CO_3 (14 mg, 0.10 mmol) were subsequently added at room temperature and the mixture was sonicated. Then, dimethyl 2-bromomalonate (32 μL, 0.24 mmol) was added and the reaction was stirred at –30 °C for 27 h. Purification by flash chromatography (eluent: chloroform) gave cyclopropane **3g**.

Supporting Information (see footnote on the first page of this article): ^1H and ^{13}C NMR spectra for new compounds and HPLC traces are presented.

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