Organocatalytic Enantioselective Approach to Spirocyclic $\Delta^{\beta,\gamma}$-Butenolides

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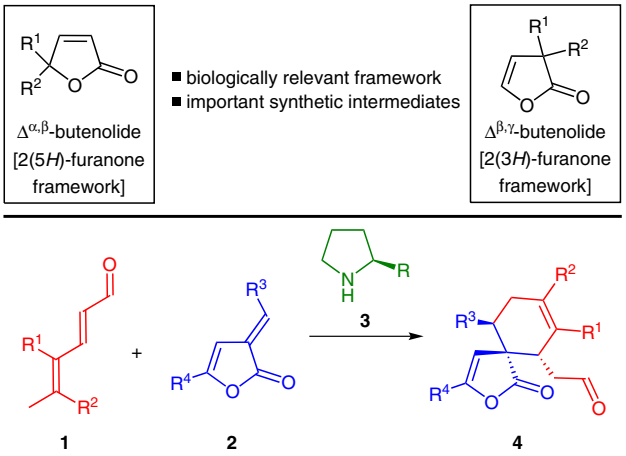
Abstract: A novel method for the preparation of the spirocyclic $\Delta^{\beta,\gamma}$-butenolides is presented. The developed strategy is based on a trienamine-mediated [4+2]-cycloaddition between (*E*)-3-alkylidene-5-arylfuran-2(3*H*)-ones and 2,4-dienals. Target products containing three contiguous centres including one quaternary are efficiently formed in a highly enantiomerically enriched form in the presence of the silyl-protected diphenylprolinol aminocatalyst.

Key words: asymmetric synthesis, aminocatalysis, trienamines, $\Delta^{\beta,\gamma}$-butenolides, quaternary stereogenic center

Asymmetric aminocatalysis[1] where chiral primary or secondary amines are employed as catalysts of various chemical transformations constitute an interesting field of research that has been developing intensively since its rediscovery in 2000.[1a,b] The application of enamines and iminium-ions as reactive catalytic intermediates has been widely studied establishing these two activation modes among the most reliable tools in the asymmetric catalysis.[1c–e] Recently, the aminocatalytic principles have been extended allowing for the introduction of new stereogenic centres up to seven bonds away from the chirality of the catalyst.[2] Such a remote functionalization strategies proceeding via the intermediacy of dienamines or trienamines as reactive intermediates are receiving an increasing attention from the chemical community and reveal a potential of aminocatalysts to control not only stereoselectivity but also site-selectivity of promoted reactions.

Δ-Butenolides constitute a group of unsaturated γ-lactones that is widely distributed in nature (Scheme 1, top).[3] Their biological activity is well recognized and many members of that family has found application in the life-science industry. Furthermore, Δ-butenolides are useful intermediates in the target-oriented organic synthesis.[4] Although the synthetic routes for the preparation of $\Delta^{\alpha,\beta}$-butenolides are well established,[5] the general methods for the synthesis of their $\Delta^{\beta,\gamma}$-counterparts are much less common.[6]

Taking into account the importance and interesting biological activity of the $\Delta^{\beta,\gamma}$-butenolide framework and the limited availability of methods for their preparation, in particular in an enantioselective fashion, we undertook studies on the development of a facile and stereoselective approach to this group of compounds. We envisioned that a direct and facile approach to Δ-butenolides **4** might rely on a trienamine-mediated reaction between 2,4-dienals **1** and (*E*)-3-alkylidene-5-substituted furan-2(3*H*)-ones **2** (Scheme 1, bottom). The reaction was expected to operate via the C-4-C-5-*s*-*cis*-configured trienamine intermediate. Furthermore, due to the bulkiness of the substituent present at the C-2 atom of the catalyst a formal [4+2]-cycloaddition should proceed in a highly stereoselective manner from the side opposite to the steric bulk of the aminocatalyst **3**. Herein, we report our results on a novel and enantioselective approach to spirocyclic $\Delta^{\beta,\gamma}$-butenolides based on a trienamine activation strategy.



Scheme 1 The importance of a Δ-butenolide structural motif and an enantioselective strategy for the preparation of spirocyclic $\Delta^{\beta,\gamma}$-butenolides

We initiated our studies with the goal of finding the optimal reaction conditions for the devised synthetic strategy (Table 1). The commercially available 2,4-hexadienal (**1a**) and (*E*)-3-benzylidene-5-phenylfuran-2(3*H*)-one (**2a**) were chosen as model substrates. Among solvents tested (Table 1, entries 1–7) chlorinated solvents (Table 1, entries 1–3) gave the best results with dichloromethane being the most optimal (Table 1, entry 2). Increasing the reaction temperature resulted in no improvement of the conversion with the diastereoselectivity of the reaction being decreased (Table 1, entry 8). Among aminocatalysts **3a–d** tested, the TES-protected diphenylprolinol **3b** proved the best in terms of reactivity ensuring good level of diastereoselectivity and excellent enantioselectivity at the same time. Finally, employing three-fold excess of **1a** enabled us to achieve full conversion within 24 hours.

Having optimized the reaction conditions, the studies on the scope of the developed methodology were undertaken.

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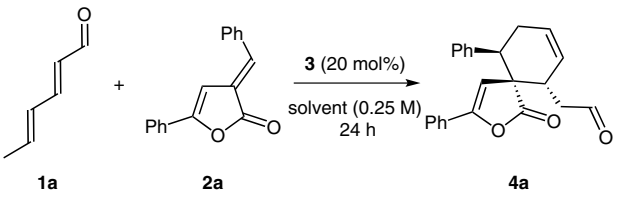
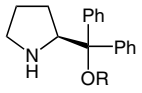
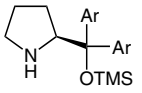
Table 1 Enantioselective Synthesis of Spirocyclic $\Delta^{\beta,\gamma}$-Butenolides: Optimization Studies[a]



1a 2a 4a



3a: R = TMS
3b: R = TES
3c: R = TBS



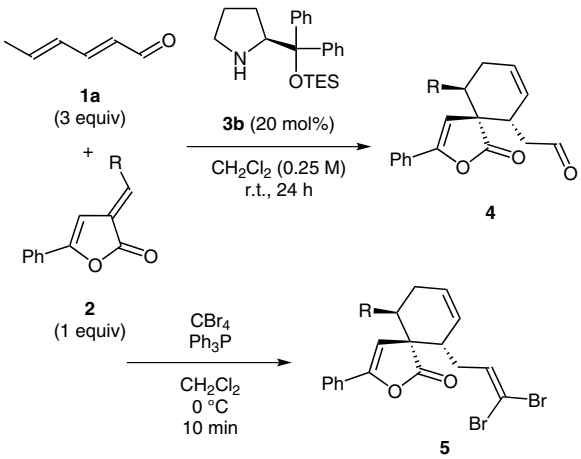
3d: Ar = 3,5-$(CF_3)_2C_6H_3$

Entry	Solvent	Cat.	Temp	Conv. [yield (%)][b]	dr[c]	ee (%)[d]
1	$CHCl_3$	**3a**	r.t.	54	2:1	nd
2	CH_2Cl_2	**3a**	r.t.	72 (45)	2:1	98
3	CCl_4	**3a**	r.t.	29	1:1	nd
4	MeCN	**3a**	r.t.	29	1:1	nd
5	toluene	**3a**	r.t.	21	1:1	nd
6	Et_2O	**3a**	r.t.	22	1:1	nd
7	*i*-PrOH	**3a**	r.t.	18	1:1	nd
8	CH_2Cl_2	**3a**	40 °C	70	1:1	nd
9	CH_2Cl_2	**3b**	r.t.	88 (52)	3.5:1	99
10	CH_2Cl_2	**3c**	r.t.	78	4:1	97
11	CH_2Cl_2	**3d**	r.t.	10	>20:1	nd
12[e]	CH_2Cl_2	**3b**	r.t.	>95 (65)	3.5:1	98

[a] Reactions were performed on a 0.1 mmol scale.
[b] Conversion as determined by ^{1}H NMR of a crude reaction mixture. Given in parentheses are the isolated yields after the Ramirez olefination of the initial cycloadduct **4a**.
[c] Determined by ^{1}H NMR of a crude reaction mixture.
[d] Enantiomeric excess of the major diastereoisomer as determined by a chiral stationary phase HPLC on a Ramirez olefination product **5a**.
[e] Three equivalents of **1a** were used.

Initially the usefulness of different olefinic butenolides **2** in the developed cycloaddition was investigated. For the isolation purposes and to be able to directly determine enantioselectivity of the trienamine-mediated reaction, crude [4+2]-cycloadducts **4** were directly subjected to the Ramirez olefination affording dibromo derivatives **5** as the final products. Importantly, in all of the cases the major diastereoisomer of the product **5** could be easily separated by flash chromatography. In the first part of the scope studies the possibility to introduce various aromatic substituents on the alkylidene moiety of dienophiles **2** was investigated (Table 2). It was found that the reaction proceeded efficiently for a wide variety of butenolides **2**. In terms of stereoselectivity both electron-withdrawing (Table 2, entries 2–7) and electron-donating substituents (Table 2, entries 8 and 9) were well tolerated with lower yields being observed for the latter. Importantly, excellent enantioselectivities were obtained for most of the cases. Furthermore, the position of the substituent had no major influence on the reaction outcome (Table 2, compare entries 2–5).

Table 2 Enantioselective Synthesis of Spirocyclic $\Delta^{\beta,\gamma}$-Butenolides: (*E*)-3-Alkylidene-5-phenylfuran-2(3*H*)-one Scope[a]



Entry	R	Yield (%)[b]	dr[c]	ee (%)[d]
1	Ph (**5a**)	65	3.5:1	98
2	2-FC_6H_4 (**5b**)	52	2:1	98
3	3-FC_6H_4 (**5c**)	54	1.5:1	89
4	3-ClC_6H_4 (**5d**)	62	1.5:1	92
5	4-BrC_6H_4 (**5e**)	28	1:1	>99
6	4-$F_3CC_6H_4$ (**5f**)	44	2:1	>99
7	4-NCC_6H_4 (**5g**)	26	1:1	98
8	4-MeC_6H_4 (**5h**)	48	2:1	98
9	4-$MeOC_6H_4$ (**5i**)	33	3:1	98

[a] Reactions were performed on 0.2 mmol scale.[7]
[b] Isolated yields over two steps.
[c] Determined by ^{1}H NMR of the crude reaction mixture.
[d] Enantiomeric excess of the major diastereoisomer as determined by a chiral stationary phase HPLC.

In the course of the further studies the possibility to introduce various substituents at the C-5 position of the butenolide framework was investigated (Scheme 2). Importantly, it was found that the reaction was unbiased towards the electronic properties of the aromatic ring in this position and both electron-poor and electron-rich aromatic rings could be present as demonstrated in the synthesis of **5j** and **5k**.

In the final part of the studies various 2,4-dienals **1** were evaluated (Scheme 3). The possibility to introduce substit-

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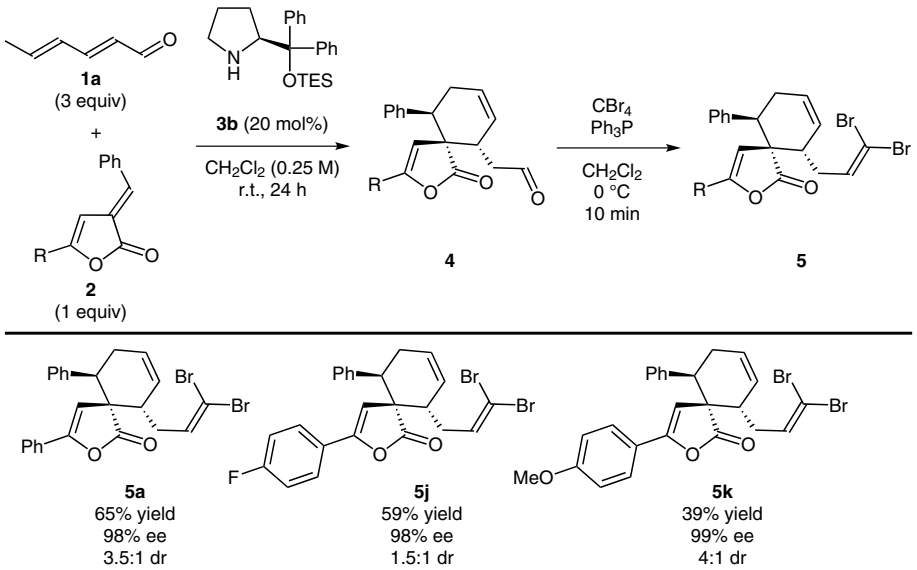
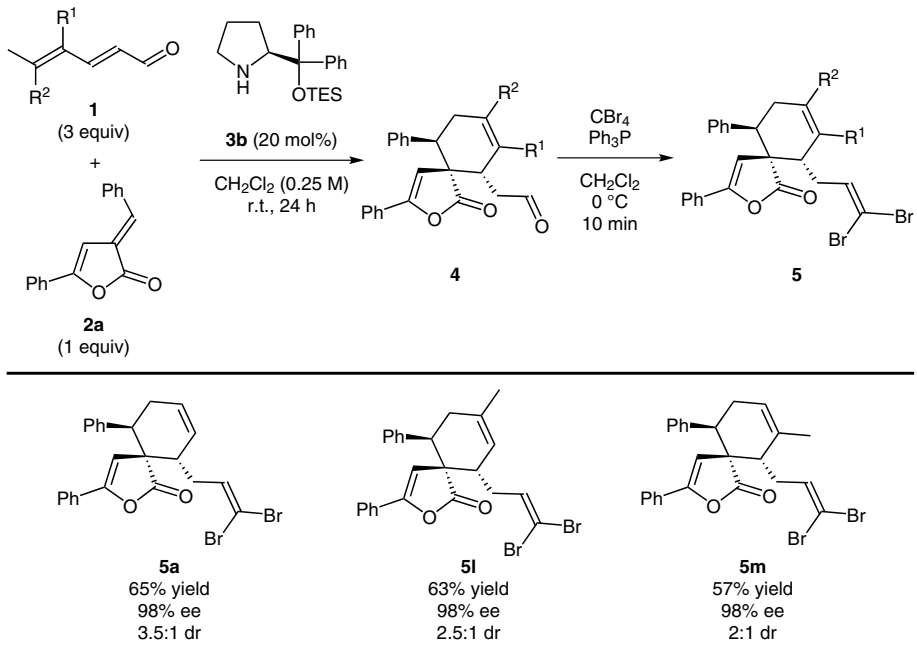


Scheme 2 Enantioselective synthesis of spirocyclic $\Delta^{\beta,\gamma}$-butenolides **5**: (*E*)-5-aryl-3-benzylidenefuran-2(3*H*)-one scope

uents at the 4- and 5-position of 2,4-dienals **1** was investigated. In both cases similar good results were obtained.

Absolute configuration of the major diastereoisomer of the final products was unambiguously assigned by a single crystal X-ray analysis of the compound **5d** as 5*S*,6*S*,10*R* (Scheme 4, top).[8] The absolute configuration of other major products **5a**–**c**,**e**–**m** was assigned by analogy. This configurational assignment allowed us to propose a plausible reaction mechanism of the reaction accounting for the observed stereochemistry (Scheme 4, bottom). Initial condensation of a dienal **1** with the aminocatalyst **3b** followed by a deprotonation from the ε-position and isomerisation affords a trienamine intermediate **7** which reacts in a s-*cis* conformation. The *endo* approach of the dienophile **2** is favoured. Taking into account previous studies on the trienamine-mediated reactions[9] a stepwise mechanism for the cycloaddition step is postulated. Initial 1,4-addition from the ε-position of the trienamine intermediate **7** yields adduct **8** bearing an aromatic furan moiety. Subsequent intramolecular 1,4-addition involving the iminium-ion-activated Michael acceptor furnishes the cyclohexene framework in **9**. The catalytic cycle is accomplished via an enamine protonation and subsequent hydrolytic cleavage of the catalyst to afford the target spirocyclic $\Delta^{\beta,\gamma}$-butenolide **4**.



Scheme 3 Enantioselective synthesis of spirocyclic $\Delta^{\beta,\gamma}$-butenolides **5**: scope of 2,4-dienals **1**

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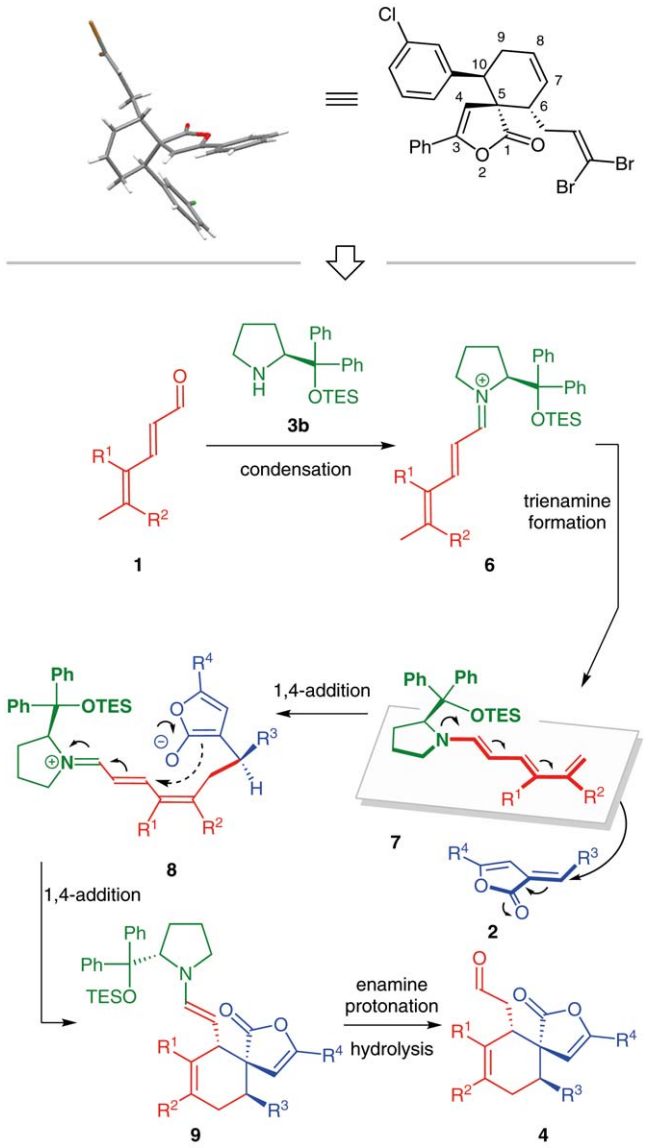
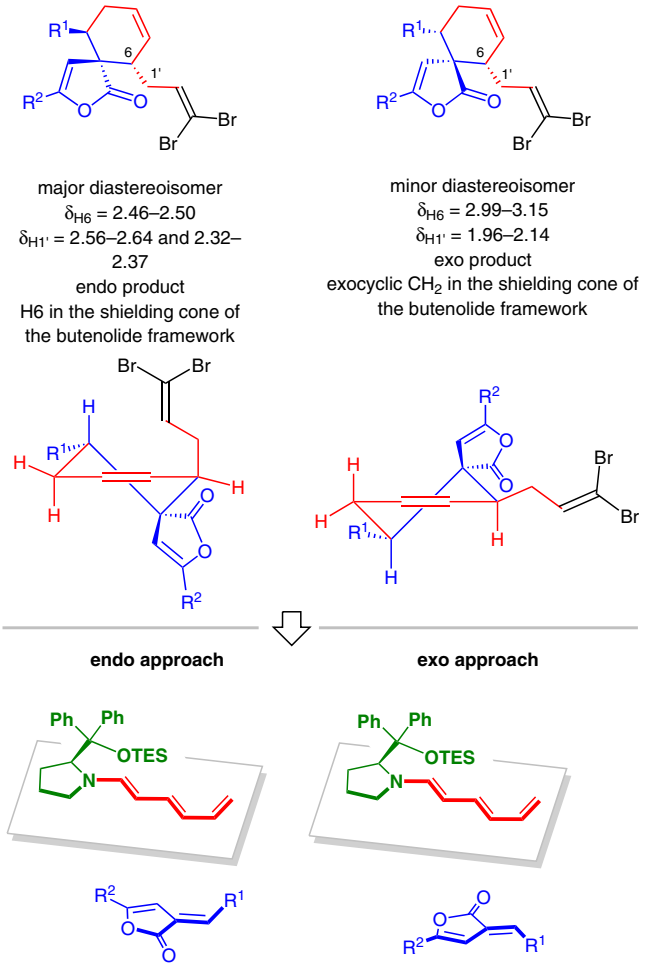


Scheme 4 Enantioselective synthesis of $\Delta^{\beta,\gamma}$-butenolides **4**: reaction mechanism and configurational assignments of the major diastereoisomer

The relative configuration of the minor diastereoisomer was elucidated by the means of the ^{1}H NMR spectroscopy (Scheme 5). It was found that the main difference in the spectra of the two diastereoisomers was the chemical shift of the proton in the C6 position and in the exocyclic methylene moiety (1′ position). While in the major diastereoisomers the chemical shift of the H6 proton was in the range δ = 2.46–2.50, it shifted quite dramatically in the minor diasteroisomers' spectra (δ = 2.99–3.15 ppm). A similar but opposite trend was observed for the H1′ protons (a shift from δ = 2.56–2.64 ppm and δ = 2.32–2.37 ppm for the major diastereoisomers to δ = 1.96–2.14 ppm for the minor diastereoisomers). Such a pronounced change in the chemical shifts of the protons in the direct neighbourhood of the C6 stereogenic centre can be explained by the *endo*/*exo* approach of the dienophile. The most stable half-chair conformations of both diastereoisomers are depicted in Scheme 5. The observed effect can be attributed to the shielding effect of the π-electrons of the butenolide moiety exerted on the substituent occupying the C6 pseudoequatorial position on the cyclohexene framework. Therefore, in the major *endo* diastereoisomer H6 proton is strongly shielded by the butenolide ring causing its upfield shift and downfield shift of the deshielded exocyclic CH_2 group at the same time. Notably, this is in accordance with the outcome of the single crystal X-ray analysis (see Scheme 4). On the other hand, in the minor/*exo* product exocyclic CH_2 group occupies a pseudoequatorial position. Therefore, due to the mentioned shielding effect its signal in the ^{1}H NMR spectra appears in the upfield. Consequently, the H6 proton chemical shift is shifted downfield.



Scheme 5 Assignment of the configuration of the minor diastereoisomer and further mechanistic consideration

In conclusion, we have developed a novel approach to spirocyclic butenolide-containing cyclohexene derivatives **5** with three contiguous stereogenic centres including one quaternary.[10] The reaction was found to proceed for a wide variety of 2,4-dienals and olefinic butenolides offering a general approach to this class of compounds. For the isolation purposes the products were directly subjected to the Ramirez olefination and the target products were iso-

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lated as geminal-dibromo derivatives. It is noteworthy that the developed synthetic strategy is highly enantioselective and benefits from operational simplicity. Furthermore, it opens access to a novel class of spirocyclic butenolides with intriguing biological properties.

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(7) **Representative Procedure**: An ordinary screw-cap vial was charged with a magnetic stirring bar, the corresponding (*E*)-3-arylidene-5-arylfuran-2(3*H*)-one **2** (0.2 mmol, 1 equiv), catalyst **3b** (0.04 mmol, 0.2 equiv), CH_2Cl_2 (0.4 mL) and the corresponding 2,4-dienal **1** (0.6 mmol, 3 equiv). The reaction mixture was stirred at r.t. and monitored by ^1H NMR spectroscopy. After 24 h the reaction mixture was directly submitted to Ramirez olefination. In a separate screw-cap vial carbon tetrabromide (0.3 mmol, 3.0 equiv) was dissolved in CH_2Cl_2 (0.5 mL) and cooled to –5 °C. Triphenylphosphine (0.6 mmol, 6.0 equiv) was added in one portion and after 5 min the reaction mixture was added dropwise at –5 °C. After 10 min at 0 °C the reaction mixture was directly subjected to flash chromatography on silica gel to afford the target product **5**.

(8) CCDC 1007871 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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(10) Data for **5a**: 6-(3,3-Dibromoallyl)-3,10-diphenyl-2-oxaspiro[4.5]deca-3,7-dien-1-one (Table 2, Entry 1): Following the general procedure, **5a** was isolated by flash chromatography on silica (gradient: hexane–Et_2O from 100:0 to 100:6) in 65% yield as a colourless oil (dr = 3.5:1). (5*S*,6*S*,10*R*)-**5a**: ^1H NMR (700 MHz, $CDCl_3$): δ = 7.56–7.59 (m, 2 H), 7.38–7.43 (m, 3 H), 7.24–7.31 (m, 5 H), 6.48 (dd, *J* = 8.2, 6.6 Hz, 1 H), 6.10 (ddt, *J* = 10.3, 3.7, 1.8 Hz, 1 H), 5.85 (ddd, *J* = 10.0, 3.8, 2.0 Hz, 1 H), 5.72 (s, 1 H), 3.33 (t, *J* = 6.6 Hz, 1 H), 2.79 (dddd, *J* = 16.9, 6.2, 3.9, 2.0 Hz, 1 H), 2.62 (ddd, *J* = 14.4, 6.6, 4.3 Hz, 1 H), 2.44–2.53 (m, 2 H), 2.36 (ddd, *J* = 14.3, 10.1, 8.2 Hz, 1 H). ^{13}C NMR (176 MHz, $CDCl_3$): δ = 177.1, 152.2, 140.5, 136.1, 129.9, 128.8 (2 × C), 128.8 (2 × C), 128.3, 128.5 (2 × C), 127.9, 127.6, 126.7, 125.1 (2 × C), 105.8, 90.9, 55.6, 43.1, 39.7, 34.4, 29.6. HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{24}H_{20}Br_2O_2$: 522.9707; found: 522.9710. The ee was determined by HPLC using a Chiralpak IA column [hexane–*i*-PrOH (98:2)]; flow rate: 1.0 mL/min; t_R (major) = 13.2 min, t_R (minor) = 11.5 min (98% ee); $[\alpha]_D^{20}$ +0.8 (*c* = 1.2, $CHCl_3$).

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