DOI: 10.1002/adsc.201100748

Heterocyclic Spiranes and Dispiranes *via* Enantioselective Phosphine-Catalyzed [3+2] Annulations

Deepti Duvvuru,[a] Nathalie Pinto,[a] Catherine Gomez,[a] Jean-François Betzer,[a] Pascal Retailleau,[a] Arnaud Voituriez,[a,*] and Angela Marinetti[a,*]

[a] Institut de Chimie des Substances Naturelles, CNRS UPR 2301, Centre de Recherche de Gif, 1 av. de la Terrasse, 91198 Gif-sur-Yvette, France
Fax: (+33)-1-6907-7247; e-mail: arnaud.voituriez@icsn.cnrs-gif.fr or angela.marinetti@icsn.cnrs-gif.fr

Received: September 27, 2011; Published online: February 9, 2012

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201100748.

Abstract: The synthesis of highly functionalized heterocyclic spiranes has been carried out by [3+2] cyclizations between allenoates and enones, under phosphine catalysis. Excellent enantioselectivity levels (*ee*s up to 99%) have been attained in FerroPHANE-promoted cyclizations of this class, leading to chiral sulfides with unprecedented spiranic structures. The corresponding sulfoxides have been obtained then *via* a subsequent, highly diastereoselective oxidation of the prostereogenic sulfur centre.

Keywords: [3+2] cyclization; enantioselective organocatalysis; phosphines; spiro compounds; sulfoxides

Introduction

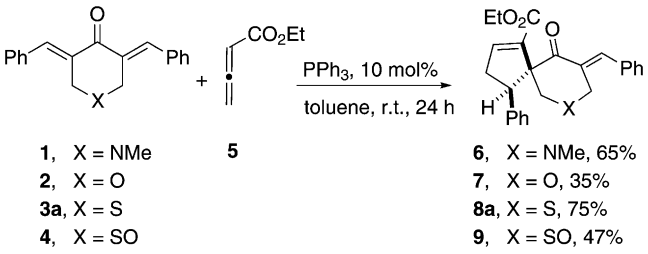
The [3+2] cyclization between olefins and electron-deficient allenes or alkynes, usually referred to as the Lu reaction, has become a benchmark reaction in the field of phosphine organocatalysis.[1] A variety of reaction partners has been considered for synthetic purposes[2] and enantioselective variants have been also developed,[3,4] following on from the pioneering studies reported by Zhang in 1997.[5] Noteworthy, these enantioselective [3+2] cyclizations represent highly efficient tools to access spirocyclic derivatives with quaternary, all-carbon stereogenic centres. Such challenging synthetic targets can be attained easily, in mild conditions, with high levels of stereoselectivity.[2i,4b,6] The method has been applied notably to the facile, stereoselective creation of spirocyclopentene oxindole moieties.[7] Also, phosphine-promoted [3+2] cyclizations on cyclic bis-arylidene ketones afforded unique spiranic scaffolds with good stereocontrol of up to five stereogenic centres.[4b,8]

As a further step towards molecular complexity, we consider here the use of heterocyclic α,β-unsaturated ketones, such as 3,5-bis(arylidene)-4-piperidones **1**, dihydropyranones **2**, dihydrothiopyranones **3**, and dihydrothiopyranone oxides **4**, as substrates in [3+2] cyclization processes. The enantioselective [3+2] cyclizations are expected to afford spiroheterocycles with unprecedented molecular scaffolds.

The potential usefulness of the targeted heterocycles can be anticipated, based on the well-established importance of analogous compounds in either medicinal chemistry or enantioselective synthesis. For instance, piperidinones **1** themselves[9] and some spirocyclic derivatives thereof[10] are known to display cytotoxic or antimycobacterial activities, while cyclic amines,[11] sulfides and sulfoxides[12] afford countless chiral auxiliaries for both stoichiometric syntheses and organic or organometallic catalysis.

Results and Discussion

In this work, we have investigated the phosphine-catalyzed [3+2] cyclizations between ethyl 2,3-butadienoate and the heterocyclic bis-arylidene ketones **1–4** as a suitable synthetic approach to spiranic heterocycles. The bis-arylidene ketones **1**–**3a** (Scheme 1) have been prepared by two subsequent aldol condensations on the corresponding unsubstituted cyclic ketones, according to known procedures.[13] The thiopyran-4-one **3a** was then converted into the corresponding sulfoxide **4** by oxidation with $NaIO_4$.[13a] The four substrates **1–4** were reacted with ethyl butadienoate **5** in the



1, X = NMe
2, X = O
3a, X = S
4, X = SO

5

6, X = NMe, 65%
7, X = O, 35%
8a, X = S, 75%
9, X = SO, 47%

Scheme 1. Triphenylphosphine promoted [3+2] cyclizations on heterocyclic bis-arylidene ketones.

presence of a 10 mol% amount of PPh_3 as the nucleophilic catalyst.

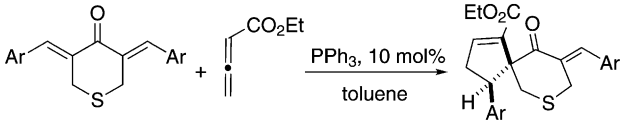
The desired cyclizations took place at room temperature and afforded the spirocyclic derivatives **6–8a** in moderate to good yields. Only minor amounts of side products are observed in the crude reaction mixtures. The isolated products are the so-called γ-adducts. They formally result from Michael additions of the allenoate **5**, *via* its γ-carbon, to the enone function of the electrophilic partners. The outcome of these reactions is therefore fully consistent with the previously observed γ-regioselectivity[2n,4b,8a] of most reactions involving non-substituted allenoates and β-substituted α,β-unsaturated ketones, under phosphine catalysis.[14]

Sulfoxide **4** displayed a more complex behaviour. The prochiral substrate **4** was converted into a mixture of cyclization products, which include the two diastereomeric γ-adducts with opposite configurations of the stereogenic sulfur function, as well as small amounts of the corresponding α-adducts. Due to its low selectivity, the [3+2] cyclization on sulfoxide **4** cannot be considered so far as a synthetically useful method, while the cyclization on the corresponding sulfide **3a** proved to be a fully convenient, selective approach to spiranic derivatives. Therefore, after the preliminary experiments in Scheme 1, cyclic sulfides have been selected as preferred substrates for more extended studies.

The cyclization reactions have been extended to thiopyranones with various arylidene moieties (Table 1): with triphenylphosphine as catalyst, the corresponding spirocyclic derivatives **8b–h** have been obtained as single regioisomers in good yields, after optimization of the reaction conditions. The cyclization reactions usually proceed at room temperature, by combining the enones **3** and ethyl butadienoate **5** in a 1:2 ratio, in the presence of a 10 mol% amount of PPh_3. The reaction of **3d** has been run in refluxing toluene to attain good conversion rates, since the electron-rich aryl group decreases the reactivity of the double bond.

As mentioned above, it is well known, from literature data as well as from our own work, that suitable chiral phosphines are able to induce high enantioselectivity in analogous [3+2] cyclizations on enones.

Table 1. Triphenylphosphine-promoted [3+2] annulations on arylidene thiopyranones.



3b – h **5** **8b – h**

Entry	Substrate	Ar	Product	Yield [%][a]
1	**3b**	2-naphthyl	**8b**	77
2	**3c**	9-phenanthryl	**8c**	98
3	**3d**	4-$MeOC_6H_4$	**8d**	75[b]
4	**3e**	4-$NO_2C_6H_4$	**8e**	78[c]
5	**3f**	4-ClC_6H_4	**8f**	66
6	**3g**	4-MeC_6H_4	**8g**	70
7	**3h**	thiophen-2-yl	**8h**	67

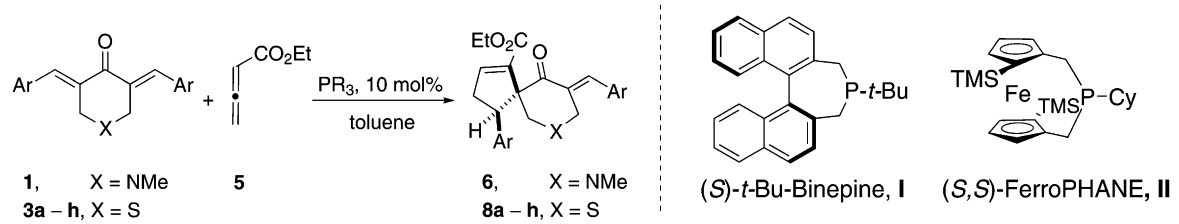
[a] *General conditions*: **3**:**5** ratio = 1:2, room temperature, 16 h.
[b] In refluxing toluene.
[c] 1:1 substrate ratios.

Therefore, we next investigated asymmetric variants of these annulations and our results are shown in Table 2. Thiopyranone **3a** was selected as a representative substrate for preliminary studies. It was reacted with ethyl allenoate in the presence of several chiral phosphorus catalysts, including PhanePhos, DIOP, Me-DuPhos, Binap, Binepines and FerroPHANE.[15] Among these phosphorus derivatives, the two catalysts previously identified as the best ones in [3+2] cyclizations, namely *t*-Bu-Binepine **I**,[4b] and FerroPHANE **II**, recently developed in our group,[4c] also proved the best ones in these reactions. (*S*)-*t*-Bu-Binepine afforded **8a** in 66% yield, 89% *ee* while (*S,S*)-FerroPHANE gave an 84% yield and a 92% *ee* in the same reaction (entries 1 and 2 in Table 2). We assume that the final spirocycle **8a** obtained in (*S,S*)-FerroPHANE-catalyzed cyclizations has a (4*S*,5*R*)-configuration, based on the known stereochemical outcome of analogous annulations on both acyclic enones[8a] and arylidene-oxindoles.[7a]

More extended experiments have been conducted then with FerroPHANE as the catalyst, showing that high levels of enantioselectivity can be attained in these cyclizations starting from thiopyranones **3** with various aryl substituents on the vinyl functions (93–99% *ee*, entries 3–9 in Table 2). Also, cyclization on piperidinone **1** could be performed in analogous conditions to afford the corresponding spirocyclic amine **6** in 86% enantiomeric excess (entry 10).

From the results in Table 2, it appears that cyclization on the *p*-nitrophenyl-substituted thiopyranone **3e** takes place with an especially high enantioselectivity level, leading to **8e** in >99% *ee*. The excellent enantioselectivity of these reactions, as well as the potential usefulness of enantiomerically pure, C_2-symmetri-

Table 2. Enantioselective [3+2] cyclizations promoted by (*S*)-*t*-Bu-Binepine **I**, and (*S,S*)-FerroPHANE **II**.

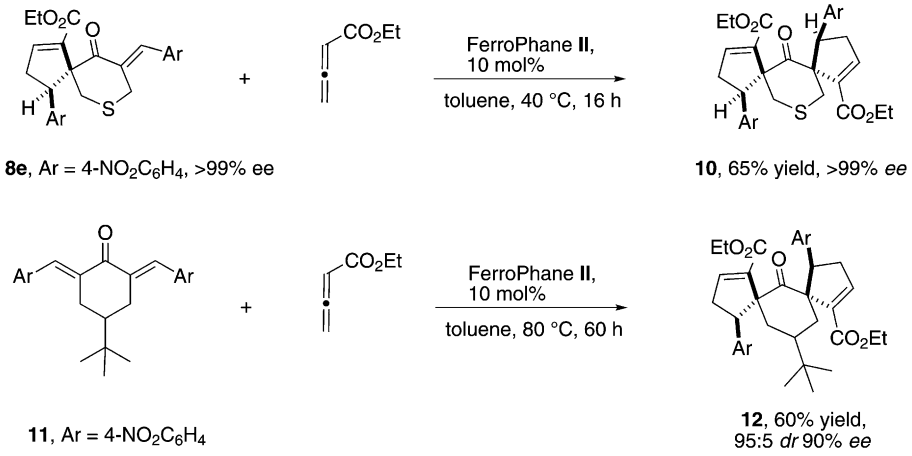


Entry	Substrate	X	Ar	Product	PR_3	Yield [%][a]	*ee* [%]
1	**3a**	S	Ph	**8a**	**I**	66	89
2	**3a**	S	Ph	**8a**	**II**	84	92
3	**3b**	S	2-naphthyl	**8b**	**II**	86	94
4	**3c**	S	9-phenanthryl	**8c**	**II**	90	95
5	**3d**	S	4-$MeOC_6H_4$	**8d**	**II**	84[b]	93
6	**3e**	S	4-$NO_2C_6H_4$	**8e**	**II**	65[c]	>99
7	**3f**	S	4-ClC_6H_4	**8f**	**II**	65	93
8	**3g**	S	4-MeC_6H_4	**8g**	**II**	75	95
9	**3h**	S	thiophen-2-yl	**8h**	**II**	80[d]	97
10	**1**	NMe	Ph	**6**	**II**	70[e]	86

[a] *Conditions*: **3**:**5** ratio = 1:2, toluene, 40 °C, 24 h.
[b] In refluxing toluene.
[c] **3e**:**5** ratio = 1:1.
[d] At room temperature.
[e] **1**:**5** ratio = 1:1, 80 °C.

cal sulfides,[12b–d] led us to envision a further extension of the method to the synthesis of analogous C_2 symmetrical sulfides by a double annulation process. Our previous work on [3+2] cyclizations demonstrated that double annulation processes can take place on acyclic bis-enones with good diastereo- and enantiocontrol,[8a] however, the double annulations on cyclic substrates had never been reported before. They are expected to be somewhat more challenging since they involve the creation of two quaternary stereogenic carbon centres in a rather hindered environment. The cyclization reaction between **8e** and ethyl allenoate **5** was thus attempted in the presence of an excess allenoate (Scheme 2). With (*S,S*)-FerroPHANE as the catalyst, the desired dispiranic derivative **10** could be obtained in 65% yield and >99% enantiomeric excess, according to HPLC analysis. It represents the first example of C_2-symmetrical bis-spirocyclic derivatives of this class.[16]

According to our experiments, this double cyclization process requires activation of the enone by electron-withdrawing groups, since it proceeds with enone **8e** only.



Scheme 2. Synthesis of the dispiro[4.1.4.3]-7-thiotetradecanone **10** and the carbon analogue **12**.

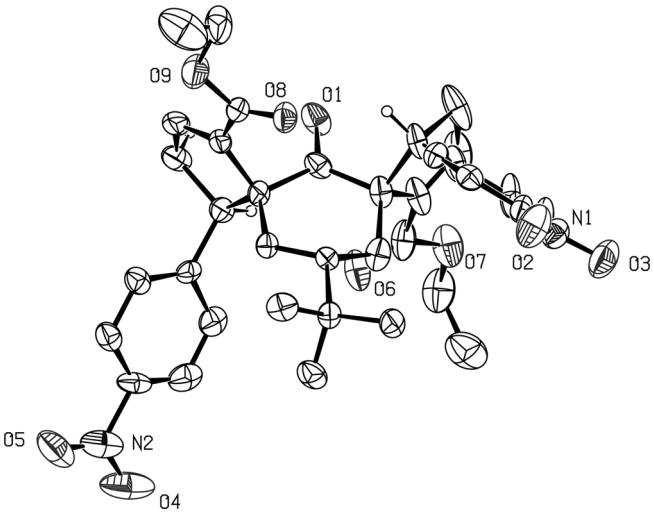


Figure 1. ORTEP view of the bis-spiranic derivative **12** (CCDC 834027, these data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif).

Interestingly, the scope of the double [3+2] annulation process could be extended also to non-heterocyclic substrates: an analogous bis-spiranic scaffold could be obtained from the cyclohexanone derivative **11**, where the double bonds are activated by the electron-withdrawing *p*-$NO_2C_6H_4$ groups.

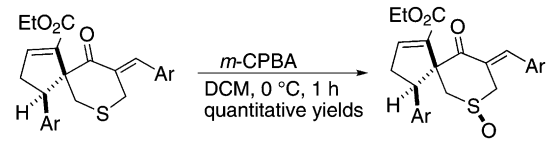
An X-ray crystal structure of **12** (Figure 1) allowed the stereochemistry of the bis-spiranic moiety to be established unambiguously.

In summary, the spiranic and bis-spiranic sulfides **8** and **10** are easily available in enantiomerically enriched form, *via* the [3+2] annulations as shown in Table 2 and Scheme 2, respectively. The chiral catalyst FerroPHANE proved to be able to induce effective regio- and stereocontrol in both annulation steps leading to the stereocontrolled formation of sulfides with unusual molecular scaffolds.

Overall, of the four types of cyclic enones that we envisioned initially as potential substrates for phosphine promoted [3+2] cyclizations (Scheme 1), only sulfoxide **4** failed to produce the corresponding [4,5]-spirocycle in synthetically useful yields and selectivity. A possible strategy to get round this limitation and access spirocyclic sulfoxides, would be to carry out a controlled oxidation of sulfides **8**. We therefore investigated this alternative strategy also.

We were able to achieve the desired diastereoselective oxidations of sulfides **8** into the corresponding sulfoxides **9**, as shown in Scheme 3.

The experimental procedure which involves oxidation of **8** with *m*-CPBA at 0 °C, affords sulfoxides **9** in quantitative yields and total diastereoselectivity. By this method, a whole range of enantiomerically enriched sulfoxides could be obtained easily, starting from the corresponding sulfides (Scheme 3). The relative configurations of the sulfoxide group and the cyclopentene unit have been established by X-ray diffraction studies on **9a** (Figure 2).



8a, Ar = Ph, 92% *ee* — **9a**, Ar = Ph
8b, Ar = 2-naphthyl, 94% *ee* — **9b**, Ar = 2-naphthyl
8c, Ar = 9-phenanthryl, 95% *ee* — **9c**, Ar = 9-phenanthryl
8d, Ar = 4-$MeOC_6H_4$, 93% *ee* — **9d**, Ar = 4-$MeOC_6H_4$
8e, Ar = 4-$NO_2C_6H_4$, >99% *ee* — **9e**, Ar = 4-$NO_2C_6H_4$
8f, Ar = 4-ClC_6H_4, 93% *ee* — **9f**, Ar = 4-ClC_6H_4
8g, Ar = 4-MeC_6H_4, 95% *ee* — **9g**, Ar = 4-MeC_6H_4
8h, Ar = thiophen-2-yl, 97% *ee* — **9h**, Ar = thiophen-2-yl

Scheme 3. Diastereoselective oxidation of the spirocyclic sulfides **8**.

X-ray data show that oxidation takes place exclusively from the less hindered face of the dihydro-thiopyranone moiety, that is, from the face opposite to the phenyl substituent of the spirocyclic substrate **8a**.

Although diastereoselective oxidations of chiral sulfides into the corresponding sulfoxides are largely documented,[17] the perfect diastereoselectivity observed in the synthesis of **9** remains exceptional. It is likely to be related to the well-defined, rigid and highly disymmetric steric environment of the sulfur centre generated by the spirocyclic scaffold. Also,

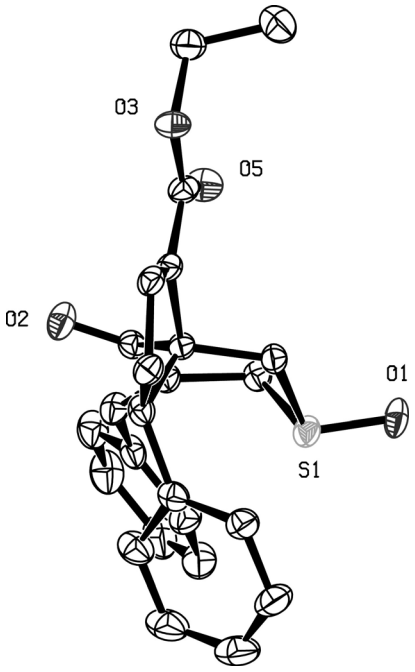
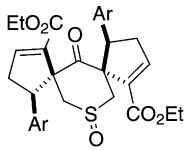


Figure 2. ORTEP view of **9a** (CCDC 834028, these data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif).



13, Ar = 4-$NO_2C_6H_4$, 60% yield, >99% *ee*

Scheme 4. Sulfoxide **13** obtained by *m*-CPBA oxidation of **10**.

weak interactions between the functional groups of the substrates and the oxidizing agent might contribute to the stereochemical control of these reactions. This excellent steric discrimination shows promise for future applications of the chiral sulfoxides **9**, sulfides **8** and analogous spiranic heterocycles as chiral auxiliaries in enantioselective processes.

Finally, the same oxidation procedure has been applied to the synthesis of the dispiranic sulfoxide **13** shown in Scheme 4.

The highly hindered environment of the sulfur centre in the bis-spiranic derivative **10**, induces a lower reaction rate with respect to the analogous oxidations in Scheme 3. Nevertheless, the desired sulfoxide **13** could be obtained in acceptable yield and fully characterized.

Conclusions

In conclusion, we have demonstrated that phosphine-promoted organocatalytic [3+2] annulations afford a convenient access to chiral cyclic amines and sulfides with unprecedented spiranic scaffolds. (*S,S*)-FerroPHANE is a convenient chiral catalyst giving highly enantioselective annulations of this compound class. Especially reactions on sulfides occur with very high diastereo- and enantioselectivity levels. Moreover, spiranic chiral sulfoxides of the same series are easily available from the corresponding sulfides *via* a quantitative and totally diastereoselective oxidation procedure. A bis-spiranic C_2-symmetrical sulfide and the corresponding sulfoxide have also been prepared by applying the same methods. Further studies will be oriented towards the use of these new heterocyclic derivatives as chiral auxiliaries in organic and organometallic catalysis.

Experimental Section

General Remarks

All non-aqueous reactions were run under an argon atmosphere, by using standard techniques for manipulating air-sensitive compounds. All reagents and solvents were of commercial quality and were used without further purification. Flash column chromatography was performed using 40–63 mesh silica. The bis-arylidene ketones were prepared following known procedures.[13,18,19] FerroPHANE was synthesized according to our previous work.[4c]

Representative Procedure for the Catalytic [3+2] Annulations of Ethyl Buta-2,3-dienoate 5 with Enones 1–3 (Table 1 and Table 2)

Ethyl 2,3-butadienoate (0.20 mmol) was added to a mixture of enone (0.20 mmol) and the phosphorus catalyst [PPh_3, (*S*)-*t*-Bu-Binepine or (*S,S*)-FerroPHANE, 0.020 mmol] in degassed toluene (0.7 mL) under an argon atmosphere. After 8 h stirring at the given temperature (see Scheme 2, Table 1 and Table 2), an additional 0.20 mmol amount of 2,3-butadienoate was added and the solution was stirred overnight at the same temperature. The crude mixture was concentrated under vacuum and the final product was purified by flash chromatography on silica gel.

Ethyl 9-benzylidene-10-oxo-4-phenyl-7-thiaspiro[4.5]dec-1-ene-1-carboxylate (8a): R_f 0.3 (10% EtOAc/heptanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.64 (bs, 1H), 7.40–7.20 (m, 10H), 7.09 (t, J=2.6 Hz, 1H), 4.25 (t, J=8.4 Hz, 1H), 4.18 (q, J=7.2 Hz, 2H), 3.75 (dd, J=14.7, 1.8 Hz, 1H), 3.67 (dd, J=14.7, 2.7 Hz, 1H), 3.27 (d, J=14.3 Hz, 1H), 2.94 (dd, J=8.5, 2.6 Hz, 2H), 2.74 (dd, J=14.3, 2.8 Hz, 1H), 1.28 (t, J=7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=202.3 (C), 163.6 (C), 145.0 (CH), 141.7 (C), 138.4 (C), 135.5 (CH), 135.2 (C), 134.7 (C), 130.0 (CH), 128.9 (CH), 128.6 (CH), 128.4 (CH), 128.2 (CH), 127.3 (CH), 64.1 (C), 60.7 (CH_2), 55.1 (CH), 36.2 (CH_2), 32.2 (CH_2), 30.1 (CH_2), 14.1 (CH_3); IR: ν_{max}=1706, 1593, 1492, 1454, 1371, 1329, 1262, 1246, 1109, 1028, 764, 751, 699 cm^{-1}; HR-MS (ESI): m/z=427.1342, calcd. for $C_{25}H_{24}NaO_3S$ [M+Na]$^+$: 427.1344; $[\alpha]_D^{22}$: +353 (*c* 0.5, $CHCl_3$); HPLC (Daicel CHIRACEL IA, 30 °C, 10% *i*-PrOH/*n*-heptane, 1 mL min^{-1}, 295 nm) retention times: 9.4 min (minor) and 13.0 min (major), 92% *ee*.

Ethyl 9-benzylidene-7-methyl-10-oxo-4-phenyl-7-azaspiro-[4.5]dec-1-ene-1-carboxylate (6): R_f 0.3 (15% EtOAc/heptanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.69 (bs, 1H), 7.45–7.32 (m, 5H), 7.25–7.15 (m, 5H), 7.11 (t, J=2.6 Hz, 1H), 4.25–4.05 (m, 3H), 3.67 (d, J=14.4 Hz, 1H), 3.37 (dd, J=14.4, 2.4 Hz, 1H), 2.92 (dt, J=8.1, 2.6 Hz, 2H), 2.64 (bs, 2H), 1.82 (s, 3H), 1.23 (t, J=7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=201.7 (C), 164.0 (C), 146.0 (CH), 140.1 (C), 139.9 (C), 135.5 (CH), 133.3 (C), 130.7 (CH), 128.6 (CH), 128.5 (CH+C), 127.9 (CH), 126.8 (CH), 64.0 (C), 60.7 (CH_2), 57.5 (CH_2), 56.7 (CH_2), 54.4 (CH), 45.5 (CH_3), 36.7 (CH_2), 14.2 (CH_3); IR: ν_{max}=1707, 1677, 1597, 1492, 1446, 1369, 1328, 1264, 1172, 1107, 1050, 909, 728 cm^{-1}; HR-MS (ESI): m/z=424.1908, calcd. for $C_{26}H_{27}NNaO_3$ [M+Na]$^+$: 424.1889; $[\alpha]_D^{22}$: +447 (*c* 0.9, $CHCl_3$); HPLC (Daicel CHIRACEL IA, 30 °C, 5% *i*-PrOH/*n*-heptane, 1 mL min^{-1}, 295 nm): retention times: 12.5 (minor) and 14.2 min (major), 86% *ee*.

Ethyl 9-benzylidene-10-oxo-4-phenyl-7-oxaspiro[4.5]dec-1-ene-1-carboxylate (7): R_f 0.35 (20% EtOAc/heptanes); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.70 (bs, 1H), 7.35–7.27 (m, 3H), 7.25–7.10 (m, 7H), 7.05 (t, J=2.7 Hz, 1H), 4.65 (dd, J=14.7, 1.5 Hz, 1H), 4.59 (dd, J=14.7, 2.1 Hz, 1H), 4.2–4.05 (m, 3H), 3.89 (d, J_{AB}=12.4 Hz, 1H), 3.84 (d, J_{AB}=12.4 Hz, 1H), 2.91 (ddd, J=18.3, 9.3, 2.1 Hz, 1H), 2.80 (ddd,

$J=18.3$, 10.2, 2.7 Hz, 1H), 1.17 (t, $J=7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=200.4$ (C), 163.6 (C), 146.6 (CH), 138.7 (C), 138.6 (C), 136.1 (CH), 134.8 (C), 133.1 (C), 130.8 (CH), 129.4 (CH), 128.7 (CH), 128.5 (CH), 128.4 (CH), 127.3 (CH), 68.6 (CH_2), 68.3 (CH_2), 63.4 (C), 60.9 (CH_2), 54.3 (CH), 35.8 (CH_2), 14.2 (CH_3); IR: $\nu_{max}=2930$, 1708, 1681, 1597, 1492, 1446, 1371, 1331, 1261, 1231, 1196, 1127, 1028, 751, 698 cm^{-1}; HR-MS (ESI): $m/z=411.1584$, calcd. for $C_{25}H_{24}NaO_4$ $[M+Na]^+$: 411.1572.

Synthesis of 10

Compound **10** was obtained by FerroPHANE-promoted [3+2] cyclization of **8e** with ethyl butadienoate **5**, according to the general procedure described above. R_f 0.3 (10% EtOAc/heptanes); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=8.08$ (d, $J=8.9$ Hz, 4H), 7.56 (d, $J=8.9$ Hz, 4H), 7.23 (t, $J=2.6$ Hz, 2H), 4.25 (q, $J=6.9$ Hz, 4H), 4.19 (dd, $J=8.7$, 2.4 Hz, 2H), 3.80 (d, $J=13.7$ Hz, 2H), 3.09 (ddd, $J=19.2$, 8.6, 2.5 Hz, 2H), 2.58 (dt, $J=19.2$, 2.7 Hz, 2H), 2.29 (d, $J=13.7$ Hz, 2H), 1.36 (t, $J=7.2$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=205.9$ (C), 164.1 (C), 149.3 (C), 147.4 (CH+C), 137.9 (C), 129.9 (CH), 123.3 (CH), 65.8 (C), 61.1 (CH_2), 50.5 (CH), 41.0 (CH_2), 26.5 (CH_2), 14.4 (CH_3); IR: $\nu_{max}=1706$, 1597, 1518, 1346, 1278, 1109, 1070, 1018, 848, 747 cm^{-1}; HR-MS (ESI): $m/z=629.1595$, calcd. for $C_{31}H_{30}N_2NaO_9S$ $[M+Na]^+$: 629.1570, found: ; $[\alpha]_D^{22}$: +435 (*c* 0.7, $CHCl_3$); HPLC (Daicel CHIRACEL IA, 30 °C, 8% *i*-PrOH/*n*-heptane, 1 mL min^{-1}, 295 nm): retention times: 26.4 (minor) and 29.2 min (major), >99% *ee*.

Synthesis of the Bis-spiranic Cyclohexanone 12

Ethyl 2,3 butadienoate (0,45 mmol) was added to a mixture of (2*E*,6*E*)-2,6-bis(*p*-nitrobenzylidene)-4-*tert*-butylcyclohexanone **11** (0.15 mmol) and FerroPHANE, **II** (10 mol%, 0.015 mmol) in degassed toluene (0.5 mL) under an argon atmosphere. The solution was stirred at 80 °C for 60 h. The crude mixture was concentrated under vacuum. The final product was purified by flash chromatography on silica gel with an EtOAc/heptane gradient (5:95 to 20:80). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=8.14$ (d, $J=8.4$ Hz, 2H), 8.13 (d, $J=8.4$ Hz, 2H), 7.54 (d, $J=8.4$ Hz, 2H), 7.49 (d, $J=8.4$ Hz, 2H), 7.15 (dt, $J=14.6$, 2.3 Hz, 2H), 4.28 (q, $J=7.1$ Hz, 4H), 4.11 (d, $J=8.7$, 1H), 3.98 (d, $J=8.7$ Hz, 1H), 3.3–3.2 (m, 2H), 2.60 (d, $J=19.3$, 1H), 2.47 (d, $J=19.3$, 1H), 1.95 (t, $J=13.3$ Hz, 1H), 1.64 (t, $J=13.2$ Hz, 1H), 1.55 (m, 1H), 1.38 (t, $J=7.1$ Hz, 3H), 1.37 (t, $J=7.1$ Hz, 3H), 1.3 (m, 1H), 0.10 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=216.0$ (C), 164.9 (C), 164.5 (C), 152.2 (C), 151.7 (C), 147.0 (C), 146.9 (C), 146.8 (CH), 145.7 (CH), 143.6 (C), 140.9 (C), 130.5 (CH), 130.2 (CH), 123.72 (CH), 64.9 (C), 62.8 (C), 60.9 (CH_2), 60.8 (CH_2), 54.8 (CH), 52.3 (CH), 42.5 (CH_2), 41.2 (CH_2), 38.0 (CH), 33.4 (CH_2), 32.3 (C), 28.2 (CH_2), 26.1 [$C(CH_3)_3$], 14.4 (CH_3); IR: $\nu_{max}=2958$, 1702, 1517, 1345, 1281, 1127, 1063, 850, 747 cm^{-1}; HR-MS (ESI): $m/z=667.2606$, calcd. for $C_{36}H_{40}N_2NaO_9$ $[M+Na]^+$: 667.2632; $[\alpha]_D^{22}$: +68 (*c* 1.0, $CHCl_3$).

Synthesis of Sulfoxides 9

3-Chloroperoxybenzoic acid (0.12 mmol) in DCM (2 mL) was added over 0.5 h to a solution of sulfide **8** (0.1 mmol) in DCM (3 mL) at 0 °C under an argon atmosphere. The mixture was stirred at 0 °C for 0.5 h. The reaction mixture was diluted with CH_2Cl_2, then quenched with saturated $NaHCO_3$ solution and washed with brine and water. The organic layer was dried over $MgSO_4$ and concentrated under vacuum to afford the pure sulfoxides **9**.

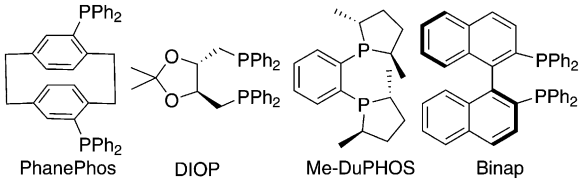
Ethyl 9-benzylidene-10-oxo-4-phenyl-7-thiaspiro[4.5]dec-1-ene-1-carboxylate 7-oxide (9a): R_f 0.3 (90% EtOAc/heptanes); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=7.80$ (bs, 1H), 7.45–7.35 (m, 3H), 7.32–7.25 (m, 5H), 7.20–7.10 (m, 2H), 7.06 (t, $J=2.6$ Hz, 1H), 4.38 (dd, $J=3.7$, 2.6 Hz, 1H), 4.24–4.08 (m, 3H), 3.80 (dd, $J=12.6$, 2.1 Hz, 1H), 3.39 (dd, $J=12.6$, 3.7 Hz, 1H), 3.30 (d, $J=12.7$ Hz, 1H), 3.07 (ddd, $J=18.6$, 10.1, 2.1 Hz, 1H), 2.87 (ddd, $J=18.6$, 7.7, 3.1 Hz, 1H), 1.29 (t, $J=7.1$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=199.9$ (C), 163.1 (C), 144.9 (CH), 143.5 (CH), 140.7 (C), 137.0 (C), 134.1 (C), 129.8 (CH), 129.6 (CH), 129.3 (CH), 129.0 (CH), 128.7 (CH), 128.5 (C), 64.6 (C), 61.3 (CH_2), 55.8 (CH), 55.1 (CH_2), 51.9 (CH_2), 35.4 (CH_2), 14.2 (CH_3); IR: $\nu_{max}=1700$, 1591, 1446, 1371, 1329, 1243,1126,1105, 1040, 901, 733, 697 cm^{-1}; HR-MS (ESI): $m/z=421.1457$, calcd. for $C_{25}H_{25}O_4S$ $[M+H]^+$ 421.1474; $[\alpha]_D^{22}$: +120 (*c* 0.3, $CHCl_3$); HPLC (Daicel CHIRACEL IA, 30 °C, 30% *i*-PrOH/*n*-heptane, 1 mL min^{-1}, 295 nm): retention times: 12.0 (minor) and 17.3 min (major), 90% *ee*. Compound **9a** has been characterized by X-ray diffraction studies, registration number: CCDC 834028. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

References

[1] a) C. Zhang, X. Lu, *J. Org. Chem.* **1995**, *60*, 2906–2908; b) X. Lu, C. Zhang, Z. Xu, *Acc. Chem. Res.* **2001**, *34*, 535–544; c) L.-W. Ye, J. Zhou, Y. Tang, *Chem. Soc. Rev.* **2008**, *37*, 1140–1152.

[2] a) S. G. Pyne, K. Schafer, B. W. Skelton, A. H. White, *Chem. Commun.* **1997**, 2267–2268; b) L.-H. Shu, W.-Q. Sun, D.-W. Zhang, S.-H. Wu, H.-M. Wu, J.-F. Xu, X.-F Lao, *Chem. Commun.* **1997**, 79–80; c) B. F. O'Donovan, P. B. Hitchcock, M. F. Meidine, H. W. Kroto, R. Taylor, D. R. M. Walton, *Chem. Commun.* **1997**, 81–82; d) A. T. Ung, K. Schafer, K. B. Lindsay, S. G. Pyne, K. Amornraksa, R. Wouters, I. Van der Linden, I. Biesmans, A. S. J. Lesage, B. W. Skelton, A. H. White, *J. Org. Chem.* **2002**, *67*, 227–233; e) T. Q. Pham, S. G. Pyne, B. W. Skelton, A. H. White, *J. Org. Chem.* **2005**, *70*, 6369–6377; f) Y. Du, X. Lu, Y. Yu, *J. Org. Chem.* **2002**, *67*, 8901–8905; g) Y. Du, X. Lu, *J. Org. Chem.* **2003**, *68*, 6463–6465; h) X. Lu, Z. Lu, X. Zhang, *Tetrahedron* **2006**, *62*, 457–460; i) D. J. Wallace, R. L. Sidda, R. A. Reamer, *J. Org. Chem.* **2007**, *72*, 1051–1054; j) C. E. Henry, O. Kwon, *Org. Lett.* **2007**, *9*, 3069–3072; k) J. L. García Ruano, A. Nunez, M. R. Martin, A. Fraile, *J. Org. Chem.* **2008**, *73*, 9366–9371; l) X.-Y. Guan, M. Shi, *J. Org. Chem.* **2009**, ***74***, 1977–1981; m) X.-C. Zhang, S.-H. Cao, Y. Wei, M. Shi, *Chem. Commun.* **2011**, *47*, 1548–1550; n) Y.-Q. Zou, C. Li, J. Rong, H. Yan, J.-R. Chen, W.-J. Xiao, *Synlett* **2011**, 1000–1004.

[3] For a review, see: A. Marinetti, A. Voituriez, *Synlett* **2010**, 174–194.
[4] For selected examples, see: a) Z. Pakulski, O. M. Demchuk, J. Frelek, R. Luboradzki, K. M. Pietrusiewicz, *Eur. J. Org. Chem.* **2004**, 3913–3918; b) J. E. Wilson, G. C. Fu, *Angew. Chem.* **2006**, *118*, 1454–1457; *Angew. Chem. Int. Ed.* **2006**, *45*, 1426–1429; c) A. Voituriez, A. Panossian, N. Fleury-Brégeot, P. Retailleau, A. Marinetti, *J. Am. Chem. Soc.* **2008**, *130*, 14030–14031; d) M. Sampath, T.-P. Loh, *Chem. Commun.* **2009**, 1568–1570; e) M. Sampath, T.-P. Loh, *Chem. Sci.* **2010**, *1*, 739–742; f) H. Xiao, Z. Chai, C.-W. Zheng, Y.-Q. Yang, W. Liu, J.-K. Zhang, G. Zhao, *Angew. Chem.* **2010**, *122*, 4569–4572; *Angew. Chem. Int. Ed.* **2010**, *49*, 4467–4470; g) X. Han, S.-X. Wang, F. Zhong, Y. Lu, *Synthesis* **2011**, 1859–1864; h) M. Neel, J. Gouin, A. Voituriez, A. Marinetti, *Synthesis* **2011**, 2003–2009; i) Y. Fujiwara, G. C. Fu, *J. Am. Chem. Soc.* **2011**, *133*, 12293–12297.
[5] G. Zhu, Z. Chen, Q. Jiang, D. Xiao, P. Cao, X. Zhang, *J. Am. Chem. Soc.* **1997**, *119*, 3836–3837.
[6] a) B. J. Cowen, S. J. Miller, *J. Am. Chem. Soc.* **2007**, *129*, 10988–10989; b) A. Voituriez, A. Panossian, N. Fleury-Brégeot, P. Retailleau, A. Marinetti, *Adv. Synth. Catal.* **2009**, *351*, 1968–1976.
[7] a) A. Voituriez, N. Pinto, M. Neel, P. Retailleau, A. Marinetti, *Chem. Eur. J.* **2010**, *16*, 12541–12544; b) X. Han, Y. Wang, F. Zhong, Y. Lu, *J. Am. Chem. Soc.* **2011**, *133*, 1726–1729; c) B. Tan, N. R. Candeias, C. F. Barbas III, *J. Am. Chem. Soc.* **2011**, *133*, 4672–4675.
[8] a) N. Pinto, M. Neel, A. Panossian, P. Retailleau, G. Frison, A. Voituriez, A. Marinetti, *Chem. Eur. J.* **2010**, *16*, 1033–1045; b) N. Pinto, P. Retailleau, A. Voituriez, A. Marinetti, *Chem. Commun.* **2011**, *47*, 1015–1017.
[9] J. R. Dimmock, M. P. Padmanilayam, R. N. Puthucode, A. J. Nazarali, N. L. Motaganahalli, G. A. Zello, J. W. Quail, E. O. Oloo, H.-B. Kraatz, J. S. Prisciak, T. M. Allen, C. L. Santos, J. Balzarini, E. De Clercq, E. K. Manavathu, *J. Med. Chem.* **2001**, *44*, 586–593.
[10] R. Suresh Kumar, S. Perumal, K. Arun Shetty, P. Yogeeswari, D. Sriram, *Eur. J. Med. Chem.* **2010**, *45*, 124–133.
[11] a) P. Melchiorre, M. Marigo, A. Carlone, G. Bartoli, *Angew. Chem.* **2008**, *120*, 6232–6265; *Angew. Chem. Int. Ed.* **2008**, *47*, 6138–6171; b) S. Bertelsen, K. A Jørgensen, *Chem. Soc. Rev.* **2009**, *38*, 2178–2189; c) F. Fache, E. Schulz, M. L. Tommasino, M. Lemaire, *Chem. Rev.* **2000**, *100*, 2159–2231; d) S. E. Denmark, N. D. Gould, L. M. Wolf, *J. Org. Chem.* **2011**, *76*, 4260–4336.
[12] a) I. Fernández, N. Khiar, *Chem. Rev.* **2003**, *103*, 3651–3705; b) H. Pellissier, *Tetrahedron* **2007**, *63*, 1297–1330; c) M. Mellah, A. Voituriez, E. Schulz, *Chem. Rev.* **2007**, *107*, 5133–5209; d) E. M. McGarrigle, E. L. Myers, O. Illa, M. A. Shaw, S. L. Riches, V. K. Aggarwal, *Chem. Rev.* **2007**, *107*, 5841–5883; e) M. C. Carreño, G. Hernández-Torres, M. Ribagorda, A. Urbano, *Chem. Commun.* **2009**, 6129–6144.
[13] a) M. S. Puar, G. C. Rovnyak, A. I. Cohen, B. Toeplitz, J. Z. Gougoutas, *J. Org. Chem.* **1979**, *44*, 2513–2518; b) R. Suresh Kumar, S. M. Rajesh, S. Perumal, P. Yogeeswari, D. Sriram, *Tetrahedron: Asymmetry* **2010**, *21*, 1315–1327; c) G. C. Rovnyak, R. C. Millonig, J. Schwartz, V. Shu, *J. Med. Chem.* **1982**, *25*, 1482–1488.
[14] α-Regioisomers may be formed preferentially in analogous annulations involving different substrate pairs: see a) refs.[2g–i]; b) ref.[2m]; c) ref.[6a]; d) T. Q. Pham, S. G. Pyne, B. W. Skelton, A. H. White, *Tetrahedron Lett.* **2002**, *43*, 5953–5956.
[15] The chiral phosphines shown hereafter afforded enantiomeric excesses in the range 29–43%.



[16] For other synthetic approaches to polyspiranic scaffolds, see: a) ref.[13b]; b) J. Brugidou, H. Christol, *Bull. Soc. Chim. Fr.* **1968**, 1141–1144; c) B. M. Trost, Y. Shi, *J. Am. Chem. Soc.* **1993**, *115*, 9421–9438; d) J. Leuger, G. Blond, R. Fröhlich, T. Billard, G. Haufe, B. R. Langlois, *J. Org. Chem.* **2006**, *71*, 2735–2739.
[17] E. Wojaczyńska, J. Wojaczyński, *Chem. Rev.* **2010**, *110*, 4303–4356.
[18] a) M. S. Abaee, M. M. Mojtahedi, M. M. Zahedi, A. W. Mesbah, N. M. Ghandchi, W. Massa *Phosphorus Sulfur Silicon Rel. El.* **2007**, *182*, 2891–2895; b) M. S. Abaee, M. M. Mojtahedi, M. M. Zahedi, R. Sharifi, *Heteroat. Chem.* **2007**, *18*, 44–49; c) M. S. Abaee, M. M. Mojtahedi, M. M. Zahedi, *Synlett* **2005**, *15*, 2317–2320; d) G. C. Rovnyak, V. Shu, *J. Org. Chem.* **1979**, *44*, 2518–2522; e) N. J. Leonard, D. Choudhury, *J. Am. Chem. Soc.* **1957**, *79*, 156–160.
[19] a) Z.-G. Han, S.-J. Tu, B. Jiang, S. Yan, X.-H. Zhang, S.-S. Wu, W.-J. Hao, X.-D. Cao, F. Shi, G. Zhang, N. Ma, *Synthesis* **2009**, *10*, 1639–1646; b) H. N. Pati, U. Das, S. Das, B. Bandy, E. De Clercq, J. Balzarini, M. Kawase, H. Sakagami, J. W. Quail, J. P. Stables, J. R. Dimmock, *Eur. J. Med. Chem.* **2009**, *44*, 54–62; c) L. Yuan, B. G. Sumpter, K. A. Abboud, R. K. Castellano, *New. J. Chem.* **2008**, *32*, 1924–1934; d) J. Krapcho, C. F. Turk, *J. Med. Chem.* **1979**, *22*, 207–210.

