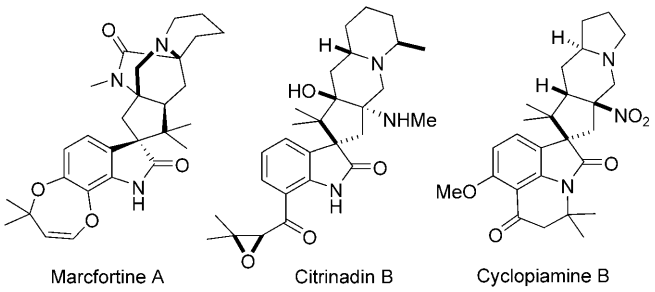
DOI: 10.1002/chem.201001791

# An Organocatalytic [3+2] Cyclisation Strategy for the Highly Enantioselective Synthesis of Spirooxindoles

**Arnaud Voituriez, Nathalie Pinto, Mathilde Neel, Pascal Retailleau, and Angela Marinetti*[a]**

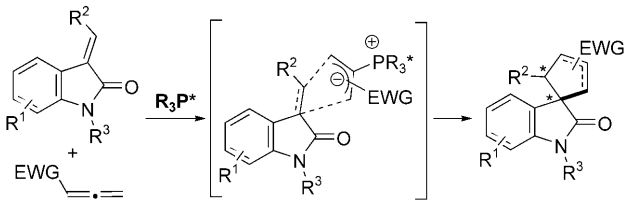
Spirooxindole cores are featured in a number of natural and unnatural biologically active compounds, as well as in drug candidates. Among them, pyrrolidin-3,3′-oxindole units are the most widespread,[1] however, spirocyclic oxindoles with carbocyclic five- or six-membered rings are not uncommon either. Specifically, 3-spirocyclopentane-2-oxindole scaffolds are embodied in natural alkaloid derivatives such as marcfortines,[2] citrinadins[3] cyclopiamines,[4] notoamides and versicolamides.[5] They also find applications in the area of medicinal chemistry.[6]




In this context, the development of efficient synthetic methods for the construction of spirocyclic oxindole scaffolds is of considerable importance. The challenging point is that biologically relevant spirooxindoles often display a stereogenic all-carbon quaternary centre at the C3-position, the stereochemistry of which must be controlled through appropriate synthetic strategies. This point has been quite commonly addressed for spirocyclic cores composed of pyrrolidin-3,3′-oxindole units.[7] However, efficient methodologies for the enantioselective synthesis of oxindoles with carbocyclic spiranic rings have been barely disclosed. Catalytic enantioselective approaches include three palladium-promoted processes, namely, the intramolecular Heck reaction, introduced by Overman et al.,[8] the [3+2] cycloaddition of trimethylenemethane on 3-alkylideneindolin-2-ones reported by Trost et al.,[9] as well as the cyclisation of 3-(4-pentynyl)-2-silyloxy indoles recently reported by Toste and Corkey.[10] Alternatively, aminocatalysis has been envisioned by Melchiorre, Gong and Chen who carried out cascade cyclisation reactions between 3-alkylideneindolin-2-ones and either suitable enones[11] or aldehydes[12].

Herein, we report on the first enantioselective approach for the construction of spirocyclic oxindolic cyclopentanes based on a phosphine-mediated organocatalytic process.

The [3+2] annulations between activated allenes and electron-poor olefins are among the seminal reactions in the field of phosphine organocatalysis.[13] When applied to 3-alkylideneindolin-2-ones, they would afford a straightforward approach to spirocyclic oxindolic cyclopentanes, through the formal reaction pathway shown in Scheme 1.[14] This strategy might also allow the stereocontrolled construction of the two contiguous stereocentres, since enantioselective variants of the [3+2] annulations are known to take place when using suitable chiral phosphorus catalysts.[15,16]




Scheme 1. Targeted approach to enantiomerically enriched oxindolic cyclopentanes. EWG = electron-withdrawing group.

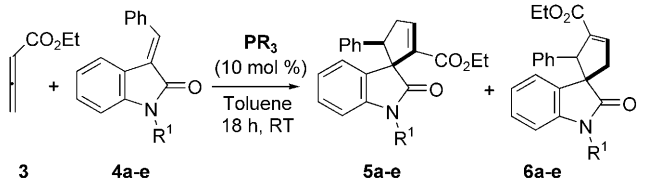
[a] Dr. A. Voituriez, N. Pinto, M. Neel, P. Retailleau, Dr. A. Marinetti
CNRS, UPR 2301, Institut de Chimie des Substances Naturelles
Centre de Recherche de Gif, 1, av. de la Terrasse, 91198 Gif-sur-Yvette (France)
Fax: (+33) 169077247
E-mail: angela.marinetti@icsn.cnrs-gif.fr

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201001791.

In our work, this synthetic approach has been established at first through [3+2] cyclisation experiments[17] between ethyl 2,3-butadienoate (**3**) and (*E*)-3-benzylideneindolin-2-ones **4a** ($R^1=CO_2Et$) or **4b** ($R^1=Ac$) in the presence of $PPh_3$ (entries 1 and 2 in Table 1). The expected reaction took place in mild conditions and afforded the desired spirooxindoles as 9:1 mixtures of the two regioisomers **5** and **6**, with the so-called "γ-adduct" **5** being the major isomer.

Table 1. Phosphine-promoted [3+2] annulation reactions of ethyl 2,3-butadienoate with (*E*)-3-benzylideneindolin-2-ones (**4**).

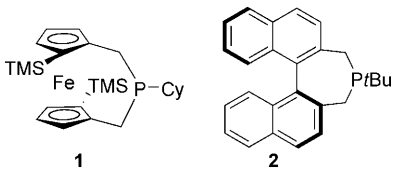



3 4a-e 5a-e 6a-e

$R^1$ = $CO_2Et$ (**a**), Ac (**b**), Boc (**c**), PMB (**d**), Me (**e**)

| Entry | $R^1$ | $PR_3$[a] | Yield [%] | **5/6** | **5** *ee* [%][b] |
|---|---|---|---|---|---|
| 1 | **4a** | $PPh_3$ | 81 | 85:15 | – |
| 2 | **4b** | $PPh_3$ | 89 | 90:10 | – |
| 3 | **4a** | **1** | 71 | 85:15 | 80 |
| 4 | **4b** | **1** | 98 | >95:5 | 96 |
| 5 | **4c** | **1** | 63 | 95:5 | 73 |
| 6 | **4d** | **1** | 82 | >95:5 | 88 |
| 7 | **4e** | **1** | 99 | >95:5[c] | 90 |
| 8 | **4b** | (*R,R*)-Me-DuPHOS | 90[d] | 79:21 | 55 |
| 9 | **4b** | (*R,R*)-Et-FerroTANE | 18[d] | 53:47 | 51 |
| 10 | **4b** | (*R*)-BINAP | 28[d] | 88:12 | 39 |
| 11 | **4b** | (*S*)-PHANEPHOS | 51[d] | 62:38 | 85 |
| 12 | **4b** | **2** | 95 | >95:5 | >99 |

[a] (*R,R*)-Me-DuPHOS = (−)-1,,2-bis((2*S*,5*S*)-2,5-dimethylphospholano)-benzene, (*R,R*)-Et-FerroTANE = (+)-1,1′-bis((2*R*,4*R*)-2,4-diethylphosphenato)ferrocene, (*R*)-BINAP = (*R*)-(+)-2,2′-bis(diphenylphosphino)-1,1′-binaphthalene, (*S*)-PHANEPHOS = (*S*)-(+)-4,12-bis(diphenlyphosphino)-[2,2]-paracycloheptane. [b] Enantiomeric excess (*ee*) values were determined by chiral HPLC. [c] The X-ray crystal structure of **5e** is given in the Supporting Information (CCDC-777517). [d] Conversion rates were determined by $^1H$ NMR spectroscopy.




1 2

Based on these preliminary results, we next considered the use of chiral phosphorus catalysts and especially that of (*S,S*)-FerroPHANE (**1**), a new chiral phosphine from our group, the efficiency of which as an organocatalyst in [3+2] annulation reactions has already been demonstrated.[15f–h] The annulation reactions were performed in toluene at room temperature with a catalyst loading of 10 mol% (Table 1, entries 3 and 4). Gratifyingly, the expected products were obtained in good yields, high regioselectivity and high stereochemical control, with *ee* values of 80 and 96% for **5a** and **5b**, respectively.

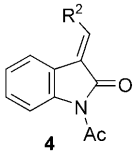
Then, in additional experiments, 3-benzylideneindolin-2-ones with *tert*-butyloxycarbonyl (Boc; **4c**), *p*-methoxybenzyl (PMB; **4d**) and Me (**4e**) groups as the N substituents have been subjected to the same cyclisation reactions (Table 1, entries 5–7). Screening revealed that all of these are suitable substrates, giving the expected products with good regioselectivity and moderate to high levels of enantioselectivity.

Although **1** afforded a satisfying enantiomeric excess in these initial cyclisation experiments ($ee_{max}=96\%$; Table 1, entry 4), a systematic screening of chiral phosphines was undertaken. Compound **4b** was used as the model substrate (entries 8–12 in Table 1). These additional tests demonstrated that (*R,R*)-Me-DuPHOS, (*R,R*)-Et-FerroTANE and (*R*)-BINAP give only moderate *ee* values (39–55% *ee*; entries 8–10 in Table 1). On the other hand, (*S*)-PHANEPHOS gave a significant 85% *ee* (Table 1, entry 11), the reaction displays, however, an unsatisfying regioselectivity, with a 62:38 ratio of the regioisomeric products **5b** and **6b**. Finally, (*S*)-*t*Bu-Binepine (**2**) was highlighted as an excellent organocatalyst for these annulations, giving quantitative yield and almost perfect enantioselectivity (Table 1, entry 12)[18]

Subsequently, the scope of the [3+2] cyclisation methodology was investigated with (*S*)-**2** as the catalyst, as summarised in Table 2 and Scheme 2. The reactions gave the desired spirocyclic indanones **5** with very high enantiomeric excesses from substrates with naphthyl groups (entries 2 and 3 in Table 2), substituted aryl groups (Table 2, entries 4–9) and heterocyclic moieties (Table 2, entries 10 and 11) on the exocyclic double bond.

Table 2. Phosphine-promoted [3+2] annulations on 3-alkylidene-oxindoles: variations of the olefin substituents $R^2$.[a]

| Entry | Substrate | $R^2$ | $PR_3$ | Yield [%] | **5/6** | **5** *ee* [%] |
|---|---|---|---|---|---|---|
| 1 | | Ph (**4b**) | **2** | 95 | >95:5 | >99 |
| 2 | | 1-naphthyl (**4f**) | **2** | 98 | >95:5 | >99[b] |
| 3 | | 2-naphthyl (**4g**) | **2** | 92 | >95:5 | 99 |
| 4 | | 4-Ph-$C_6H_4$ (**4h**) | **2** | 20 | 90:10 | 99 |
| 5 | | 4-$CF_3$-$C_6H_4$ (**4i**) | **2** | 62 | 85:15 | 99 |
| 6 | | 4-Br-$C_6H_4$(**4j**) | **2** | 63 | 90:10 | >99 |
| 7 | | 4-Cl-$C_6H_4$ (**4k**) | **2** | 80 | 92:8 | >99 |
| 8 | | 3-Br-$C_6H_4$ (**4l**) | **2** | 82 | 85:15 | >99 |
| 9 | | 4-Me-$C_6H_4$ (**4m**) | **2** | 99 | 88:12 | >99 |
| 10 | | 2-furyl (**4n**) | **2** | 25 | 76:24 | 97 |
| 11 | | 2-quinolyl (**4o**) | **2** | 75 | 90:10 | 97 |
| 12 | | −C≡C$C_5H_{11}$ (**4p**) | **2** | 38 | 74:26 | 97 |
| 13 | | 4-Ph-$C_6H_4$ (**4h**) | **1** | 61 | 92:8 | 92 |
| 14 | | 2-furyl (**4n**) | **1** | 80 | 77:23 | 90 |
| 15 | | −C≡C$C_5H_{11}$ (**4p**) | **1** | 56 | 80:20 | 86 |




4

[a] All reactions were performed under argon on a 0.15 mmol scale at a concentration of 0.3 M in toluene (0.5 mL); **3/4** ratio = 2:1. The **5/6** isomeric ratios were evaluated by NMR spectroscopy on the crude mixture; *ee* values were determined by chiral HPLC. Racemic samples of **4b–p** have been obtained by using $PPh_3$ as the catalyst. [b] According to X-ray data, compound **5f** has 1*S*,5*R* configuration.

Yields were usually good with the exception of reactions involving the biphenyl-, 2-furyl- and 1-heptynyl-substituted substrates **4h**, **4n** and **4p**. In such cases, the use of FerroPHANE **1** as the catalyst under the same reaction conditions allowed higher yields to be attained (61, 80 and 56%,

respectively), while retaining good levels of enantioselectivity (86–92% *ee*; Table 2, entries 13–15).

The reaction in entry 2 (Table 2) afforded **5f** as a crystalline compound, which was recrystallised twice from $CH_2Cl_2$/heptane to obtain crystals of enantiopure **5f** suitable for X-ray diffraction studies.[19] X-ray data confirmed the structural assignment and demonstrated that the stereochemistry of the annulation product reflects the *E* geometry of the double bond of the starting indolinone. The absolute configuration of **5f** was also assigned as *1S,5R* (Figure 1, see also the Supporting Information).[20]

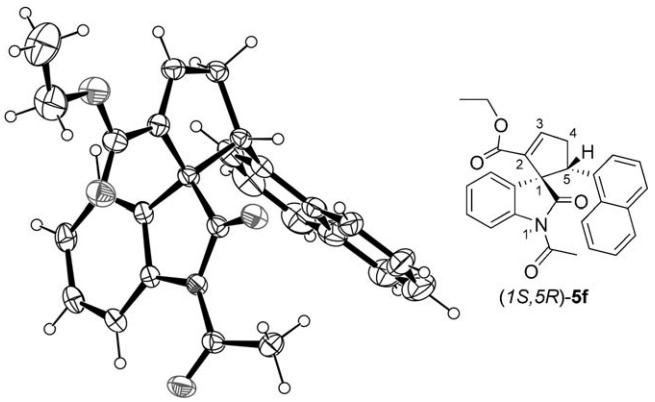
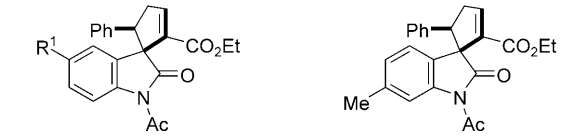



Figure 1. X-ray crystal structure of the spirocyclic oxindole (*1S,5R*)-**5f**.

The (*S*)-**2** promoted cyclisation reactions could be extended then to benzylidene indolinones with substituents on the 5′- and 6′-positions of the fused benzo rings.[21] The corresponding spirocyclic oxindoles **5q–t** were obtained in good yields (69–77%) and regioselectivity (>9:1 regioisomers ratios), with almost total enantioselectivity (Scheme 2).

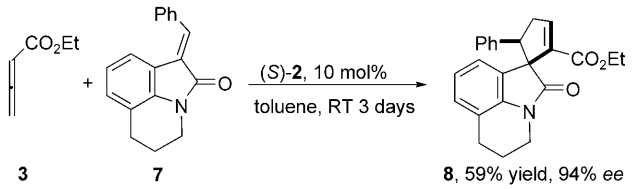



| | Yield [%] | 5/6 | 5 *ee* [%] |
|---|---|---|---|
| **5q**: $R^1$ = Br | 73 | 91:9 | >99 |
| **5r**: $R^1$ = Me | 69 | 95:5 | 99 |
| **5s**: $R^1$ = OMe | 72 | 90:10 | >99 |

| | Yield [%] | 5/6 | 5 *ee* [%] |
|---|---|---|---|
| **5t** | 77 | >95:5 | >99 |

Scheme 2. Spirocyclic indolinones from (*S*)-**2**-promoted annulation reactions on oxindoles with substituted aryl units.

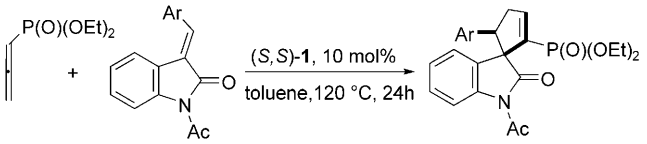
Furthermore, the reaction has been applied to the tricyclic indolinone **7**[21] to produce the unusual spirocyclic alkaloid scaffold **8** in acceptable isolated yield (59%) and 94% *ee*, after 3 days at room temperature (Scheme 3). The spirocyclic moiety of **8** constitutes the core unit of known natural products such as Cyclopiamine B.[4]




**3** **7** **8**, 59% yield, 94% *ee*

Scheme 3. Synthesis of the enantiomerically enriched tricyclic spirooxindole **8** under catalysis by **2**.

Finally, application of this methodology to the stereoselective synthesis of spirooxindoles with a phosphonate function has been envisioned, due to the extraordinary richness of organophosphorus compounds as reagents, ligands and biologically active derivatives.[22] Thus, the organocatalytic [3+2] cyclisation between allenylphosphonate **9** and **4f** has been investigated by using both **1** and **2** as the catalysts (Scheme 4). Catalyst **2** afforded a low conversion rate, mainly because of the relative inertness of allene **9** compared with allenoate **3**.[15h,23] Catalyst **1** led, however, to the desired spiranic phosphonate **10** in good yield through a highly regio- and stereoselective cyclisation reaction. Compound **10** was obtained as the major regioisomer (85:15 ratio) in 92% *ee* despite the harsh reaction conditions required for this reaction to take place.




**9** **4f**, Ar = 1-Naphthyl **10**, 70% yield, 92% *ee*

Scheme 4. Stereoselective synthesis of the α-phosphorylated spirooxindole **10** under catalysis by **1**.

In summary, the challenging goal of building the spirocyclic core of oxindolic cyclopentanes has been achieved through a new, highly stereoselective approach based on phosphine organocatalysis. The [3+2] cyclisation strategy allows the easy conversion of simple starting materials into the desired functionalised spirocyclic compounds, with almost perfect stereochemical control of two contiguous stereogenic centres, including the quaternary stereogenic centre joining the two rings. It constitutes an appropriate, efficient and synthetically useful method to access a valuable class of spirocyclic compounds.

## Acknowledgements

We are grateful to ICSN and to the Agence Nationale de la Recherche (ANR) for financial support. This work has been done within the PhoSciNet COST action.

**Keywords:** cyclization · organocatalysis · oxindoles · phosphanes · spiro compounds

[1] a) C. V. Galliford, K. A. Scheidt, *Angew. Chem.* **2007**, *119*, 8902–8912; *Angew. Chem. Int. Ed.* **2007**, *46*, 8748–8758; b) R. M. Williams, R. J. Cox, *Acc. Chem. Res.* **2003**, *36*, 127–139; c) S. Yu, D. Qin, S. Shangary, J. Chen, G. Wang, K. Ding, D. McEachern, S. Qiu, Z. Nikolovska-Coleska, R. Miller, S. Kang, D. Yang, S. Wang, *J. Med. Chem.* **2009**, *52*, 7970–7973; d) M. M.-C. Lo, C. S. Neumann, S. Nagayama, E. O. Perlstein, S. L. Schreiber, *J. Am. Chem. Soc.* **2004**, *126*, 16077–16086.

[2] J. M. Polonsky, M. A. Merrien, T. Prange, C. Pascard, *J. Chem. Soc. Chem. Commun.* **1980**, 601–602.

[3] T. Mugishima, M. Tsuda, Y. Kasai, H. Ishiyama, E. Fukushi, J. Kawabata, M. Watanabe, K. Akao, J. Kobayashi, *J. Org. Chem.* **2005**, *70*, 9430–9435.

[4] R. F. Bond, J. C. A. Boeyens, C. W. Holzapfel, P. S. Steyn, *J. Chem. Soc. Perkin Trans. 1* **1979**, 1751–1760.

[5] a) T. J. Greshock, A. W. Grubbs, P. Jiao, D. T. Wicklow, J. B. Gloer, R. M. Williams, *Angew. Chem.* **2008**, *120*, 3629–3633; *Angew. Chem. Int. Ed.* **2008**, *47*, 3573–3577; b) S. Tsukamoto, T. Kawabata, H. Kato, T. J. Greshock, H. Hirota, T. Ohta, R. M. Williams, *Org. Lett.* **2009**, *11*, 1297–1300.

[6] a) A. Fensome, W. R. Adams, A. L. Adams, T. J. Berrodin, J. Cohen, C. Huselton, A. Illenberger, J. C. Kern, V. A. Hudak, M. A. Marella, E. G. Melenski, C. C. McComas, C. A. Mugford, O. D. Slayden, M. Yudt, Z. Zhang, P. Zhang, Y. Zhu, R. C. Winneker, J. E. Wrobel, *J. Med. Chem.* **2008**, *51*, 1861–1873; b) P. R. Eastwood, J. Gonzalez Rodriguez, V. Giulio Matassa (Almirall S.A.), WO2009/132774, **2009**; c) J.-J. Liu (Hoffmann-La Roche Inc.), US 2009/0239889, **2009**.

[7] a) C. Marti, E. M. Carreira, *Eur. J. Org. Chem.* **2003**, 2209–2219; b) B. M. Trost, M. K. Brennan, *Synthesis* **2009**, 3003–3025; c) F. Zhou, Y-L. Liu, J. Zhou, *Adv. Synth. Catal.* **2010**, *352*, 1381–1407.

[8] a) A. Ashimori, B. Bachand, L. E. Overman, D. J. Poon, *J. Am. Chem. Soc.* **1998**, *120*, 6477–6487; b) A. B. Dounay, L. E. Overman, *Chem. Rev.* **2003**, *103*, 2945–2963.

[9] B. M. Trost, N. Cramer, S. M. Silverman, *J. Am. Chem. Soc.* **2007**, *129*, 12396–12397.

[10] B. K. Corkey, F. D. Toste, *J. Am. Chem. Soc.* **2007**, *129*, 2764–2765.

[11] a) G. Bencivenni, L.-Y. Wu, A. Mazzanti, B. Giannichi, F. Pesciaioli, M.-P. Song, G. M. Bartoli, P. Melchiorre, *Angew. Chem.* **2009**, *121*, 7336–7339; *Angew. Chem. Int. Ed.* **2009**, *48*, 7200–7203; b) Q. Wei, L.-Z. Gong, *Org. Lett.* **2010**, *12*, 1008–1011.

[12] K. Jiang, S.-J. Jia, S. Chen, L. Wu, Y.-C. Chen, *Chem. Eur. J.* **2010**, *16*, 2852–2856.

[13] 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.

[14] Other, non-enantioselective approaches to spirooxindoles based on phosphine organocatalysis: a) S. R. Yong, M. C. Williams, S. G. Pyne, A. T. Ung, B. W. Skelton, A. H. White, P. Turner, *Tetrahedron* **2005**, *61*, 8120–8129; b) K. Selvakumar, V. Vaithiyanathan, P. Shanmugam, *Chem. Commun.* **2010**, *46*, 2826–2828.

[15] For selected examples, see: a) G. Zhu, Z. Chen, Q. Jiang, D. Xiao, P. Cao, X. Zhang, *J. Am. Chem. Soc.* **1997**, *119*, 3836–3837; b) M. Sampath, T.-P. Loh, *Chem. Commun.* **2009**, 1568–1570; c) J. E. Wilson, G. C. Fu, *Angew. Chem.* **2006**, *118*, 1454–1457; *Angew. Chem. Int. Ed.* **2006**, *45*, 1426–1429; d) B. J. Cowen, S. J. Miller, *J. Am. Chem. Soc.* **2007**, *129*, 10988–10989; e) D. J. Wallace, R. L. Sidda, R. A. Reamer, *J. Org. Chem.* **2007**, *72*, 1051–1054; f) A. Voituriez, A. Panossian, N. Fleury-Brégeot, P. Retailleau, A. Marinetti, *J. Am. Chem. Soc.* **2008**, *130*, 14030–14031; g) A. Voituriez, A. Panossian, N. Fleury-Brégeot, P. Retailleau, A. Marinetti, *Adv. Synth. Catal.* **2009**, *351*, 1968–1976; h) N. Pinto, M. Neel, A. Panossian, P. Retailleau, G. Frison, A. Voituriez, A. Marinetti, *Chem. Eur. J.* **2010**, *16*, 1033–1045; i) H. Xiao, Z. Chai, C.-W. Zheng, Y.-Q. Yang, W. Liu, J.-K. Zhang, G. Zhao, *Angew. Chem. Int. Ed.* **2010**, *49*, 4467–4470.

[16] For a review on enantioselective phosphine organocatalysis, see: A. Marinetti, A. Voituriez, *Synlett* **2010**, 174–194.

[17] For related phosphine promoted [3+2] cyclisations, see: a) S. G. Pyne, K. Schafer, B. W. Skelton, A. H. White, *Chem. Commun.* **1997**, 2267–2268; b) T. Q. Pham, S. G. Pyne, B. W. Skelton, A. H. White, *Tetrahedron Lett.* **2002**, *43*, 5953–5956; c) 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; d) Y. Du, X. Lu, Y. Yu, *J. Org. Chem.* **2002**, *67*, 8901–8905; e) T. Q. Pham, S. G. Pyne, B. W. Skelton, A. H. White, *J. Org. Chem.* **2005**, *70*, 6369–6377.

[18] The high efficiency of **2** in enantioselective [4+2] and [3+2] organocatalytic cyclisation reactions has been disclosed at first in the pioneering work of Fu: a) reference [15c]; b) R. P. Wurz, G. C. Fu, *J. Am. Chem. Soc.* **2005**, *127*, 12234–12235.

[19] CCDC-777517 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.

[20] The two chiral ligands used in this study, **1** and **2**, afford the same enantiomers of **5** as the major products.

[21] For the synthesis of these substrates, see: S. Ueda, T. Okada, H. Nagasawa, *Chem. Commun.* **2010**, *46*, 2462–2464.

[22] For a recent review on the organocatalytic asymmetric synthesis of organophosphorus compounds, see: Ł. Albrecht, A. Anbrecht, H. Krawczyk, K. A. Jørgensen, *Chem. Eur. J.* **2010**, *16*, 28–48.

[23] A. Panossian, N. Fleury-Brégeot, A. Marinetti, *Eur. J. Org. Chem.* **2008**, 3826–3833.

Received: June 24, 2010
Published online: September 17, 2010