Organocatalytic enantioselective desymmetrization of cyclic enones *via* phosphine promoted [3 + 2] annulations†

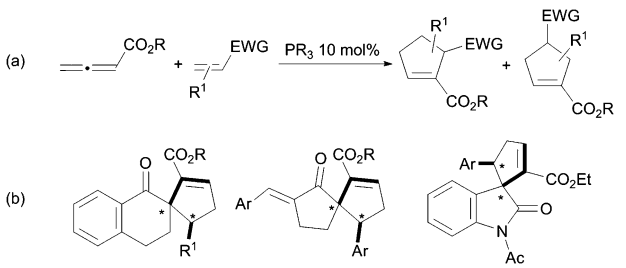
Nathalie Pinto, Pascal Retailleau, Arnaud Voituriez and Angela Marinetti*

Received 10th August 2010, Accepted 12th October 2010
DOI: 10.1039/c0cc03164j

Phosphine catalyzed enantioselective [3 + 2] cyclizations on 4-substituted 2,6-diarylidenecyclohexanones and 2,4-diarylidene-bicyclo[3.1.0]hexan-3-ones take place with high diastereo- and enantioselectivity levels. The process affords spirocyclic compounds with excellent stereochemical control of up to five stereogenic centres.

Desymmetrization is one of the most powerful synthetic tools for the stereocontrolled preparation of chiral molecules from simple and easily available starting materials. Among others, enantioselective organocatalytic methods have been successfully applied to these processes. Relevant recent examples are the desymmetrizations of prochiral cyclohexanones and cyclohexadienones *via* aldol or Michael type reactions which are performed in the presence of chiral Brønsted acids,[1] nitrogen bases[2] or ionic liquids.[3] As an extension of this strategy, we disclose here the first desymmetrization of cyclohexanone derivatives based on enantioselective phosphine organocatalysis.

Our approach starts from the [3 + 2] annulations of allenic esters and electron-poor olefins into functionalized cyclopentenes, also known as the Lu's reaction (Scheme 1a).[4] The well established synthetic potential of this methodology[5] mainly relates to the easy availability of the starting materials, to a simple experimental procedure as well as to the high regio- and diastereoselectivity levels. Moreover, high enantioselectivities have been attained by using chiral catalysts made of either cyclic phosphines with conformationally rigid molecular scaffolds[6] or acyclic multifunctional phosphines.[7] The method has been applied recently to the challenging synthesis of spirocyclic cyclopentenes, leading to good stereochemical control of two stereogenic carbons, including the quaternary carbon at the ring junction (Scheme 1b).[6b,7a,8]

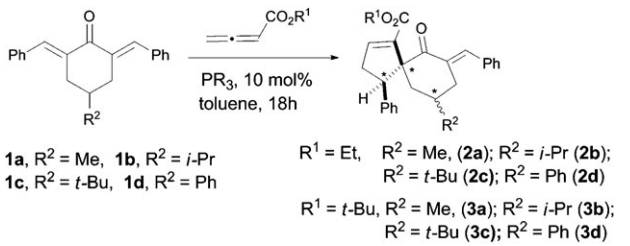


Scheme 1 (a) The Lu's phosphine-promoted [3 + 2] cyclizations between allenoates and electron-poor olefins. (b) Representative spirocyclic cyclopentenes available through enantioselective cyclizations.

The efficient stereochemical control attained in these annulation reactions makes them well suitable for implementing desymmetrization processes. Therefore, as a further step toward enantiomerically enriched molecules of increased complexity, we have envisioned application of the organocatalytic [3 + 2] cyclizations to the prochiral cyclic enones **1** and **4**. Our aim is to control the stereogenicity of the prochiral ring carbons, in order to create up to five stereogenic centres by a single process.

The first series of targeted substrates have been the 4-substituted 2,6-bis(benzylidene)cyclohexanones **1**,[9] which display two enantiotopic olefin functions and a prochiral carbon in the 4-position. To probe the viability of the cyclization process, enones **1a–d** have been submitted to annulations with ethyl allenoate in the presence of the achiral catalyst $(C_6H_{11})PPh_2$ (Scheme 2 and Table 1, entries 1–4).

The reactions afforded the spirocyclic compounds **2a–d** (R^1 = Et) in over 80% yield, with high regioselectivity and diastereoselectivity levels. Compounds **2** result from C–C bond formation between the γ-carbon of the allene and the β-olefinic carbon (γ-addition products). The corresponding



Scheme 2 Phosphine-catalyzed [3 + 2] annulations on prochiral arylidene cyclohexanones.

Table 1 [3 + 2] annulations promoted by $(C_6H_{11})PPh_2$

Entry	Product	R^1	R^2	Yield[a] (%)	dr[b]
1	**2a**	Et	Me	95	90 : 10
2	**2b**	Et	*i*-Pr	92	85 : 15
3	**2c**	Et	*t*-Bu	94	>95 : 5
4	**2d**	Et	Ph	86	90 : 10
5	**3a**	*t*-Bu	Me	90	85 : 15
6	**3b**	*t*-Bu	*i*-Pr	91	70 : 30
7	**3c**	*t*-Bu	*t*-Bu	87	90 : 10
8	**3d**	*t*-Bu	Ph	64	85 : 15

[a] Reactions performed at 40 °C. [b] By ^{1}H NMR of the crude reaction mixture.

Institut de Chimie des Substances Naturelles, CNRS UPR 2301, Centre de Recherche de Gif. 1, av. de la Terrasse, 91198 Gif-sur-Yvette, France. E-mail: angela.marinetti@icsn.cnrs-gif.fr; Fax: +33 (0)1 69 07 72 47; Tel: +33 (0)1 69 82 30 36

† Electronic supplementary information (ESI) available: Experimental procedures and characterization data. CCDC 787941. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0cc03164j

α-addition products have never been unambiguously observed in the reaction mixtures.

The spirocyclic cyclohexanones **2** are formed as mixtures of two diastereomers with opposite relative configurations of the stereogenic centres of the cyclohexanone moiety. Isomers ratios depend on the nature or the R^2 substituent which is expected, indeed, to dictate facial discrimination. Diastereomeric ratios are of approximatively 9 : 1 for **2a**, **2b** and **2d** (R^2 = Me, *i*-Pr and Ph, entries 1, 2 and 4 in Table 1), while the *tert*-butyl-substituted cyclohexanone **2c** was isolated as a single isomer (entry 3).

The structure of the major diastereomer of **2a** was assigned by X-ray diffraction studies (Fig. 1a). X-Ray data show that the favoured cyclization product results from the addition of the allenoate *syn* to the R^2 substituent. It can be assumed that, in the favoured conformer of the substrate, the R^2 substituent occupies an equatorial position. Then, the phosphine–allenoate adduct gives *syn*-addition in order to minimize the steric interactions between the incoming nucleophile and the axial H-substituent (Fig. 1b). In other words, the preferred conformation of the substrate prefigures the geometry of the final cyclization product **2a**.

X-Ray data also show that the cyclisation takes place with retention of the olefin *E*-configuration.

In additional experiments, enones **1a–d** were then reacted with *tert*-butyl allenoate (entries 5–8 in Table 1). We noticed that the increased steric hindrance of the allene tends to decrease the diastereoselectivity of the cyclizations. For instance, diastereomeric ratios of 85 : 15 and 70 : 30 have been obtained, for compounds **3a** and **3b** respectively (*vs.* 90 : 10 and 85 : 15 for the corresponding ethyl esters **2a,b**).

We next considered asymmetric variants of these annulation processes by using (*S*,*S*)-FerroPHANE, **A**,[10] and (*S*)-*t*-Bu-Binepine, **B**,[11] as the privileged catalysts. Representative results are compiled in Table 2.

The FerroPHANE catalyzed cyclization between **1a** and ethyl 2,3-butadienoate (entry 1) proceeded well, providing **2a** in good yield (91%), with only moderate diastereo- and enantioselectivity (75% ee).[12]

However, both the diastereo- and enantioselectivity could be improved by varying the R^2 substituent on the cyclohexanone. A satisfying level of stereoselectivity, that is a >95 : 5 dr and a 92% ee, was attained in the synthesis of **2c** from ethyl allenoate and the *t*-Bu-substituted cyclohexanone **1c** (entry 3). The 4-*i*-Pr- and 4-phenyl-substituted cyclohexanones **2b** and **2d** also gave high ees (82% and 92% ee respectively), with however lower diastereomer ratios (entries 2 and 4). In the starting allenoate, the ethyl group could be replaced by a *t*-Bu group (entries 5–7): the corresponding annulation products **3a–c** (R^1 = *t*-Bu) were produced with ees up to 95%, higher than those obtained from ethyl allenoate.

In parallel experiments, (*S*)-*t*-Bu-Binepine, **B**, has been evaluated as the catalyst for these cyclizations (entries 8–10). This catalyst gave comparable levels of diastereo- and enantioselectivity with respect to FerroPHANE. It displayed however a lower catalytic efficiency and comparatively lower yields.

Different substrates were examined then to test the scope of the [3 + 2] cyclizations above. Specifically, variations of the arylidene moiety have been performed on 4-*t*-Bu-substituted cyclohexanones. A set of substrates of this class (**1e–j**) have been prepared and reacted then with ethyl allenoate under FerroPHANE catalysis. The corresponding spirocyclic compounds **2e–j** have been obtained as depicted in Table 3.

The cyclization reactions afford good yields (72–95%), good diastereoselectivity and high enantioselectivity (85–94%) for Ar = naphthyls and *para*-substituted aryls (entries 1–5). The 2-furyl-substituted enone **1j** affords **2j** in 57% yield and a 75 : 25 diastereomeric ratio only, while the enantiomeric excess remains fully satisfying (92% ee).

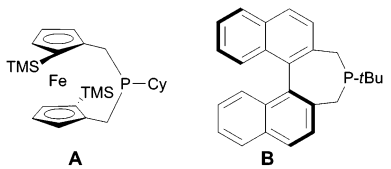
A further step toward increased product complexity has been taken then by considering the bicyclo[3.1.0]hexanes **4a** and *exo*-**4b** as the substrates. Compounds **4**[14] have been reacted with ethyl 2,3-butadienoate in the presence of the chiral phosphorus catalysts **A** and **B** (Scheme 3).

The FerroPHANE promoted cyclizations led to the 4-spiro-bicyclo[3.1.0]hexanes **5a** and **5b**, which display four

Table 2 Enantioselective [3 + 2] cyclizations on enones **1a–d** (Scheme 2)

Entry	Cat.	Product	R^1	R^2	Yield[a] (%)	dr	ee[b] (%)
1	**A**	**2a**	Et	Me	91	80 : 20	75
2	**A**	**2b**	Et	*i*-Pr	44	80 : 20	82
3	***A***	***2c***	*Et*	*t-Bu*	*98*	*>95 : 5*	*92*
4	**A**	**2d**	Et	Ph	98	85 : 15	92
5	**A**	**3a**	*t*-Bu	Me	86	80 : 20	90[c]
6	**A**	**3b**	*t*-Bu	*i*-Pr	60	70 : 30	86
7	**A**	**3c**	*t*-Bu	*t*-Bu	71	90 : 10	95
8	**B**	**2a**	Et	Me	75	85 : 15	82
9	**B**	**2c**	Et	*t*-Bu	50	>95 : 5	92
10	**B**	**3a**	*t*-Bu	Me	20	80 : 20	86

[a] Reactions performed at 80 °C. [b] Ee's have been measured by chiral HPLC. (*S*,*S*)-FerroPHANE and (*S*)-Binepine give the same sense of chiral induction.[13] [c] Minor isomer, ee = 92%.



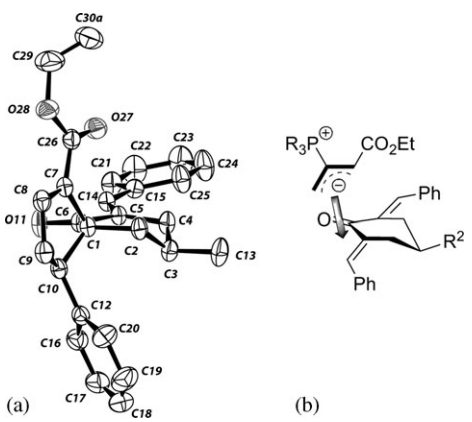
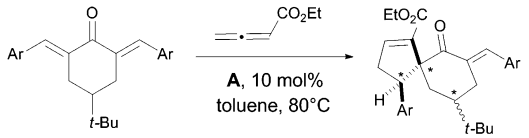


Fig. 1 (a) X-Ray crystal structure of the major diastereomer of **2a** (CCDC 787941). (b) Schematic drawing of the preferred addition of the phosphine–allenoate adduct to the enone.

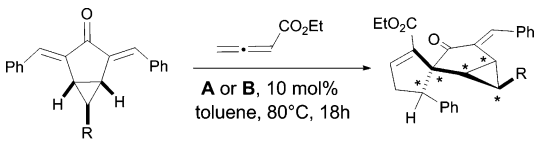
Table 3 (*S*,*S*)-FerroPHANE catalyzed [3 + 2] cyclizations on 2,6-diarylidene-4-*tert*-butyl-cyclohexanones



1e-j 2e-j

Entry	Product	Ar	Yield (%)	dr	ee[c] (%)
1	**2e**	*p*-MeOC$_6$H$_4$	91[a]	>95 : 5	94
2	**2f**	*p*-MeC$_6$H$_4$	77[a]	85 : 15	90
3	**2g**	*p*-ClC$_6$H$_4$	86[b]	95 : 5	86
4	**2h**	1-Naphthyl	95[a]	95 : 5	85
5	**2i**	2-Naphthyl	72[b]	95 : 5	90
6	**2j**	2-Furyl	57[b]	75 : 25	92

[a] Reaction time: 60 h. [b] Reaction time: 18 h. [c] By chiral HPLC. Samples of racemic **2e–j** have been obtained under CyPPh$_2$ catalysis.



4a, R = H,
4b, R = Me

5a,b

Cat.	Product	R	Yield (%)	e.e.(%)
A	**5a**	H	63	83
A	**5b**	Me	66	83
B	**5a**	H	20	86

Scheme 3 Enantioselective [3 + 2] cyclizations on the 2,5-dibenzylidene-bicyclo[3.1.0]hexanes **4**.

and five stereogenic carbons, respectively, with good diastereoselectivity. **5a** was isolated as a 9 : 1 mixture of isomers, while for **5b** only one out of eight possible isomers is produced in significant amount. The structures of the major isomers of **5a,b** have been tentatively assigned as shown in Scheme 3, by assuming that the cyclization takes place following the same stereochemical pathway as for substrates **2**, with the allenoate approaching the less hindered, *exo*-face of the bicyclic moiety. Under FerroPHANE catalysis, compounds **5a** (R^2 = H) and **5b** (R^2 = Me) are formed in comparable ee, showing that the additional Me substituent of **5b** does not affect the enantiocontrol. Under *t*-Bu-Binepine **A** catalysis, the bicyclic spiranic compound **5a** is obtained in a satisfying 86% ee, however the conversion rate is of only 22% after 18 h at 80 °C.

In summary, we have developed an efficient, highly stereoselective synthetic approach to the spirocyclic compounds **2**, as well as to the unique spiranic scaffolds **5**, involving the stereocontrolled formation of up to five stereogenic carbon centres in a single process. As far as we know, this is the first example of an enantioselective desymmetrization process based on phosphine promoted cyclizations.

We thank the Institut de Chimie des Substances Naturelles, the Agence Nationale de la Recherche (ANR) and the COST action CM0802 "PhoSciNet" for supporting this work.

Notes and references

1 Q. Gu, Z.-Q. Rong, C. Zheng and S.-L. You, *J. Am. Chem. Soc.*, 2010, **132**, 4056–4057.

2 (*a*) X. Companyó, G. Valero, L. Crovetto, A. Moyano and R. Rios, *Chem.–Eur. J.*, 2009, **15**, 6564–6568; (*b*) Y. Hayashi, H. Gotoh, T. Tamura, H. Yamaguchi, R. Masui and M. Shoji, *J. Am. Chem. Soc.*, 2005, **127**, 16028–16029; (*c*) J.-R. Chen, Y.-Y. Lai, H.-H. Lu, X.-F. Wang and W.-J. Xiao, *Tetrahedron*, 2009, **65**, 9238–9243; (*d*) J. Jiang, L. He, S.-W. Luo, L.-F. Cun and L.-Z. Gong, *Chem. Commun.*, 2007, 736–738.

3 (*a*) S. Luo, L. Zhang, X. Mi, Y. Qiao and J.-P. Cheng, *J. Org. Chem.*, 2007, **72**, 9350–9352; (*b*) L. Zhang, L. Cui, X. Li, S. Luo and J.-P. Cheng, *Chem.–Eur. J.*, 2010, **16**, 2045–2049.

4 (*a*) C. Zhang and X. Lu, *J. Org. Chem.*, 1995, **60**, 2906–2908; (*b*) X. Lu, C. Zhang and Z. Xu, *Acc. Chem. Res.*, 2001, **34**, 535–544.

5 (*a*) 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 and A. H. White, *J. Org. Chem.*, 2002, **67**, 227–233; (*b*) X. Lu, Z. Lu and X. Zhang, *Tetrahedron*, 2006, **62**, 457–460; (*c*) C. E. Henry and O. Kwon, *Org. Lett.*, 2007, **9**, 3069–3072; (*d*) J. L. Garcia Ruano, A. Nunez, M. R. Martin and A. Fraile, *J. Org. Chem.*, 2008, **73**, 9366–9371; (*e*) L.-W. Ye, J. Zhou and Y. Tang, *Chem. Soc. Rev.*, 2008, **37**, 1140–1152; (*f*) R. A. Jones and M. J. Krische, *Org. Lett.*, 2009, **11**, 1849–1851; (*g*) Y. Du and X. Lu, *J. Org. Chem.*, 2003, **68**, 6463–6465.

6 (*a*) G. Zhu, Z. Chen, Q. Jiang, D. Xiao, P. Cao and X. Zhang, *J. Am. Chem. Soc.*, 1997, **119**, 3836–3837; (*b*) J. E. Wilson and G. C. Fu, *Angew. Chem., Int. Ed.*, 2006, **45**, 1426–1429; (*c*) A. Voituriez, A. Panossian, N. Fleury-Brégeot, P. Retailleau and A. Marinetti, *J. Am. Chem. Soc.*, 2008, **130**, 14030–14031.

7 (*a*) B. J. Cowen and S. J. Miller, *J. Am. Chem. Soc.*, 2007, **129**, 10988–10989; (*b*) H. Xiao, Z. Chai, C.-W. Zheng, Y.-Q. Yang, W. Liu, J.-K. Zhang and G. Zhao, *Angew. Chem., Int. Ed.*, 2010, **49**, 4467–4470.

8 (*a*) D. J. Wallace, R. L. Sidda and R. A. Reamer, *J. Org. Chem.*, 2007, **72**, 1051–1054; (*b*) A. Voituriez, A. Panossian, N. Fleury-Brégeot, P. Retailleau and A. Marinetti, *Adv. Synth. Catal.*, 2009, **351**, 1968–1976; (*c*) N. Pinto, M. Neel, A. Panossian, P. Retailleau, G. Frison, A. Voituriez and A. Marinetti, *Chem.–Eur. J.*, 2010, **16**, 1033–1045; (*d*) A. Voituriez, N. Pinto, M. Neel, P. Retailleau and A. Marinetti, *Chem.–Eur. J.*, 2010, DOI: 10.1002/chem.201001791.

9 (*a*) H. Frey, *Synthesis*, 1992, 387–390; (*b*) J. R. Dimmock, M. P. Padmanilayam, G. A. Zello, K. H. Nienaber, T. M. Allen, C. L. Santos, E. De Clercq, J. Balzarini, E. K. Manavathu and J. P. Stables, *Eur. J. Med. Chem.*, 2003, **38**, 169–177.

10 For uses of FerroPHANE in [3 + 2] cyclizations on bis-(benzylidene)-cyclopentanones and cyclohexanones, see ref. 8*b*,*c*.

11 The use of (*R*)-*t*-Bu-Binepine in [3 + 2] cyclizations on 2,5-dibenzylidenecyclohexanone (93% ee) has been reported in ref. 6*b*.

12 In previous studies, the analogous cyclization on the 4-unsubstituted 2,6-dibenzylidenecyclohexanone gave a 85% ee. See ref. 8*c*.

13 If we assume that FerroPHANE displays the same sense of chiral induction as previously demonstrated for analogous cyclization reactions,[8c,d] compounds **2** and **3** should have 4*R*,5*R*,9*R* configurations.

14 (*a*) M. L. Kearley and P. M. Lahti, *Tetrahedron Lett.*, 1991, **32**, 5869–5872; (*b*) M. L. Kearley, A. S. Ichimura and P. M. Lahti, *J. Am. Chem. Soc.*, 1995, **117**, 5235–5244.