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Synthesis of 3,3′-Spirocyclic Oxindoles via Phosphine Catalyzed [4 + 2] Cyclizations

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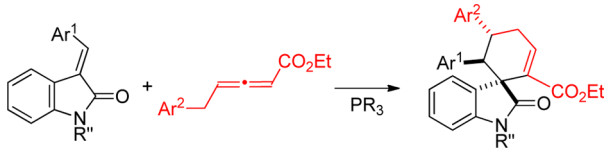
ABSTRACT



Triphenylphosphine promoted reactions between 3-arylideneoxindoles and δ-aryl-substituted penta-2,3-dienoates afford an unprecedented access to spirocyclic oxindoles with functionalized six-membered rings. In these new [4 + 2] cyclization processes, the allenoates operate as the four-carbon synthons, thanks to the involvement of the substituted δ-carbons. These reactions give excellent control of the relative stereochemistry of the three stereogenic centers. The stereochemistry of the final product has been ascertained by X-ray diffraction studies.

Carbocyclic 3,3′-spirooxindoles constitute common structural units for a number of bioactive compounds, therapeutic agents, and natural products. For their synthesis, organometallic and organocatalytic cyclizations on isatin derivatives are well established strategies.[1] Among others, phosphine organocatalysis has emerged recently in this field, as a very efficient and selective approach.[2] Thus, for instance, Barbas,[3a] Lu,[3b] and Shi[3c] have disclosed [3 + 2] cyclization processes based on Baylis−Hillman adducts as the three atom components. Our group[4a,b] and others[4c] have envisioned [3 + 2] cyclizations between allenoates and isatin-derived olefins to efficiently access spiranic oxindoles with cyclopentene scaffolds.[5] Thus, after initial studies on reactions involving nonsubstituted butadienoates, which led to disubstituted cyclopentene units,[4a] we have investigated γ-substituted allenoates as precursors for 2,3,5-trisubstituted cyclopentene rings (Scheme 1a).[4b] During this work we have noticed that a benzyl-substituted allenoate (R = Ph, R′ = Et) did not afford the expected spirocyclopentene derivative; it gave however a new reaction, i.e. conversion of the reactants into a formal [4 + 2] cyclization product (Scheme 1b).

Since spirooxindoles with six-membered cyclic backbones are relevant synthetic targets found in both natural products and bioactive compounds, such as Gelsemine, **1**,[6] and the MDM2-p53 inhibitor **2**[7] (Figure 1), we decided to

(1) (a) Westermann, B.; Ayaz, M.; van Berkel, S. S. *Angew. Chem., Int. Ed.* **2010**, *49*, 846. (b) Singh, G. S.; Desta, Z. Y. *Chem. Rev.* **2012**, *112*, 6104. (c) Ball-Jones, N. R.; Badillo, J. J.; Franz, A. K. *Org. Biomol. Chem.* **2012**, *10*, 5165. (d) Dalpozzo, R.; Bartoli, G.; Bencivenni, G. *Chem. Soc. Rev.* **2012**, *41*, 7247. (e) Hong, L.; Wang, R. *Adv. Synth. Catal.* **2013**, *355*, 1023. (f) Franz, A. K.; Hanhan, N. V.; Ball-Jones, N. R. *ACS Catal.* **2013**, *3*, 540.

(2) (a) Selvakumar, K.; Vaithiyanathan, V.; Shanmugam, P. *Chem. Commun.* **2010**, *46*, 2826. (b) Wang, Y.; Liu, L.; Zhang, T.; Zhong, N.-J.; Wang, D.; Chen, Y.-J. *J. Org. Chem.* **2012**, *77*, 4143. (c) Zhong, F.; Han, X.; Wang, Y.; Lu, Y. *Chem. Sci.* **2012**, *3*, 1231. (d) Gomez, C.; Betzer, J.-F.; Voituriez, A.; Marinetti, A. *ChemCatChem* **2013**, *5*, 1055.

(3) (a) Tan, B.; Candeias, N. R.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2011**, *133*, 4672. (b) Zhong, F.; Han, X.; Wang, Y.; Lu, Y. *Angew. Chem., Int. Ed.* **2011**, *50*, 7837. (c) Deng, H.-P.; Wei, Y.; Shi, M. *Org. Lett.* **2011**, *13*, 3348.

(4) (a) Voituriez, A.; Pinto, N.; Neel, M.; Retailleau, P.; Marinetti, A. *Chem.—Eur. J.* **2010**, *16*, 12541. (b) Gomez, C.; Gicquel, M.; Carry, J.-C.; Schio, L.; Retailleau, P.; Voituriez, A.; Marinetti, A. *J. Org. Chem.* **2013**, *78*, 1488. (c) Zhang, X.-C.; Cao, S.-H.; Wei, Y.; Shi, M. *Chem. Commun.* **2011**, *47*, 1548.

(5) For leading references on [3 + 2] annulations between allenoates and electron-poor olefins under phosphine catalysis, see: (a) Zhang, C.; Lu, X. *J. Org. Chem.* **1995**, *60*, 2906. (b) Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535. (c) Wilson, J. E.; Fu, G. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1426. (d) Cowen, B. J.; Miller, S. J. *J. Am. Chem. Soc.* **2007**, *129*, 10988. (e) Voituriez, A.; Panossian, A.; Fleury-Brégeot, N.; Retailleau, P.; Marinetti, A. *J. Am. Chem. Soc.* **2008**, *130*, 14030. (f) Han, X.; Wang, Y.; Zhong, F.; Lu, Y. *J. Am. Chem. Soc.* **2011**, *133*, 1726.

(6) Lin, H.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 36.

(7) Liu, J.-J.; Zhang, Z. (Hoffmann-La Roche AG) PCT Int. Appl. WO2008/055812, 2008.

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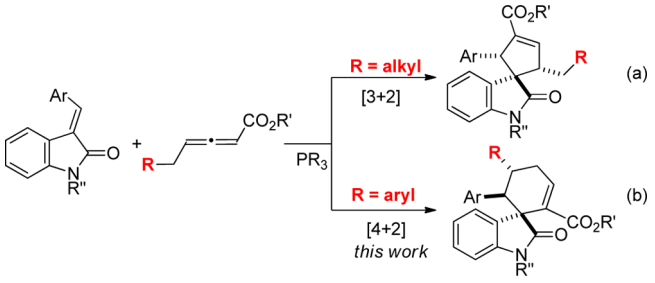
Scheme 1. Divergent Behavior of δ-Alkyl and δ-Aryl-Substituted Allenoates in Phosphine Promoted Cyclization Reactions



investigate the phosphine promoted cyclizations of arylideneoxindoles with δ-aryl-substituted allenes in more depth. These reactions might represent an alternative tool for the synthesis of this important class of compounds.[8] The main results of these studies are reported hereafter.

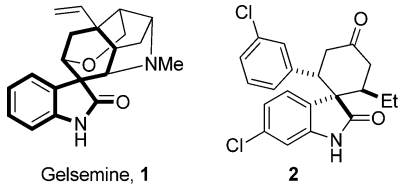
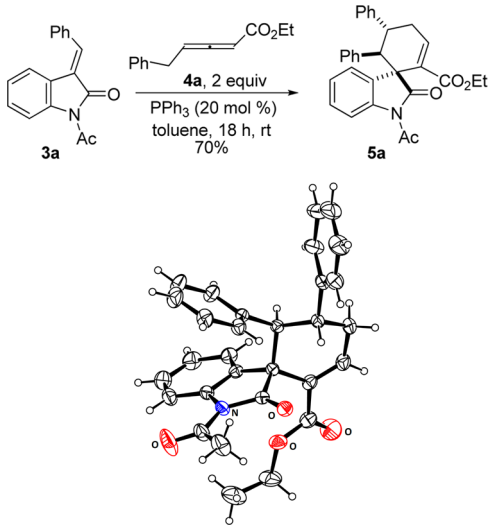


Figure 1. Examples of natural (**1**) and bioactive compounds (**2**) with spirocyclohexane oxindole architectures.

Our first experiment has been the reaction between *N*-acetyl 3-benzylideneoxindole **3a** and ethyl 5-phenyl-2,3-pentadienoate **4a** in the presence of 20 mol % of PPh_3 (Scheme 2). After 18 h at rt, the spirocyclohexeneoxindole **5a** has been isolated in 70% yield, as a single diastereomer (>95:5 isomer ratio in the crude mixture).[9] Its molecular structure has been established by X-ray diffraction studies (see ORTEP drawing in Scheme 2), showing that the product displays *cis, trans* relative arrangements of the

Scheme 2. [4 + 2] Cyclization of 5-Phenyl-2,3-pentadienoate **4a**; X-ray Crystal Structure of the Cyclization Product **5a**



two phenyl substituents, with respect to the oxindole carbonyl group.

In the ^{1}H NMR spectrum of **5a**, signals for the CH-6 and CH-5 groups are observed at δ 3.53 and 4.14 ppm respectively, with a ^3J coupling constant of 12.5 Hz.

The observed *cis* relative arrangement of the phenyl group at the C6 position and the CO group means that the *trans* stereochemistry of the starting olefin has been lost during the cyclization reaction and suggests therefore a nonconcerted reaction mechanism. A plausible mechanistic proposal (Scheme 3) involves addition of the phosphine to the β-position of the allenoate to form **I**, followed by a formal 1,4-H-shift[10] which moves the negative charge to the δ-position. The key role of the phenyl group here is to favor this rearrangement by stabilizing intermediate **II**, in which the negative charge will be on a benzylic carbon. This effect accounts for the divergent behavior of allenoate **4a** with respect to δ-alkyl substituted (or unsubstituted) penta-2,3-dienoates which usually give [3 + 2] cyclizations.[4c,5d,11] Intermediate **II** is assumed to give δ-addition to the olefinic substrate, so as to generate **III**. Then, a cyclization step giving **IV**, an H-shift, and release of the phosphorus catalyst will achieve the reaction pathway. An analogous mechanistic proposal has been postulated by Huang who, during submission of this manuscript, has

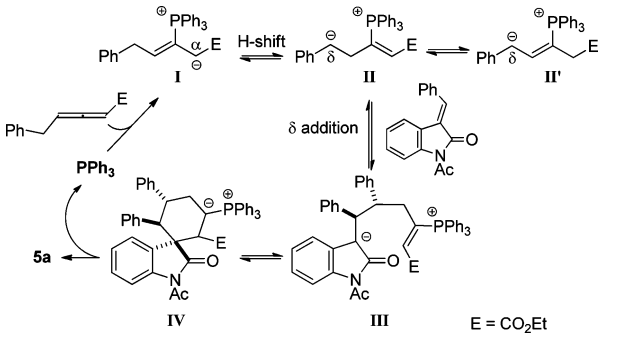
(8) For selected recent examples of organocatalytic approaches to spirocyclohexane oxindoles, see: (a) Bencivenni, G.; Wu, L.-Y.; Mazzanti, A.; Giannichi, B.; Pesciaioli, F.; Song, M.-P.; Bartoli, G.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 7200. (b) Wang, L.-L.; Peng, L.; Bai, J.-F.; Huang, Q.-C.; Xu, X.-Y.; Wang, L.-X. *Chem. Commun.* **2010**, *46*, 8064. (c) Zeng, X.; Ni, Q.; Raabe, G.; Enders, D. *Angew. Chem., Int. Ed.* **2013**, *52*, 2977. (d) Huang, X.-F.; Liu, Z.-M.; Geng, Z.-C.; Zhang, S.-Y.; Wang, Y.; Wang, X.-W. *Org. Biomol. Chem.* **2012**, *10*, 8794. (e) Liu, Y.; Nappi, M.; Arceo, E.; Vera, S.; Melchiorre, P. *J. Am. Chem. Soc.* **2011**, *133*, 15212. (f) Shen, L.-T.; Jia, W.-Q.; Ye, S. *Angew. Chem., Int. Ed.* **2013**, *52*, 585. (g) Wang, L.-L.; Peng, L.; Bai, J.-F.; Jia, L.-N.; Luo, X.-Y.; Huang, Q.-C.; Xu, X.-Y.; Wang, L.-X. *Chem. Commun.* **2011**, *47*, 5593. (h) Jia, Z.-J.; Jiang, H.; Li, J.-L.; Gschwend, B.; Li, Q.-Z.; Yin, X.; Grouleff, J.; Chen, Y.-C.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2011**, *133*, 5053. (i) Wei, Q.; Gong, L.-Z. *Org. Lett.* **2010**, *12*, 1008. (l) Tan, B.; Hernández-Torres, G.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2011**, *133*, 12354.

(9) Nitrogen-based nucleophiles, such as DABCO or DBU, do not catalyze these cyclizations. The reaction conditions have been optimized by considering various solvents (CH_2Cl_2, THF, toluene), concentrations, catalyst loadings (10−20 mol %), amount of allene (1−2 equiv), and reaction temperatures (0−60 °C). The best conditions are given in Scheme 2.

(10) Water promoted H-shifts have been demonstrated previously to be key steps in phosphine promoted cyclization reactions. See for instance: (a) Xia, Y.; Liang, Y.; Chen, Y.; Wang, M.; Jiao, L.; Huang, F.; Liu, S.; Li, Y.; Yu, Z.-X. *J. Am. Chem. Soc.* **2007**, *129*, 3470. (b) Mercier, E.; Fonovic, B.; Henry, C.; Kwon, O.; Dudding, T. *Tetrahedron Lett.* **2007**, *48*, 3617. (c) Liang, Y.; Liu, S.; Xia, Y.; Li, Y.; Yu, Z.-X. *Chem.—Eur. J.* **2008**, *14*, 4361.

(11) (a) Pyne, S. G.; Schafer, K.; Skelton, B. W.; White, A. H. *Chem. Commun.* **1997**, 2267. (b) Sampath, M.; Loh, T.-P. *Chem. Sci.* **2010**, *1*, 739. (c) Fujiwara, Y.; Fu, G. C. *J. Am. Chem. Soc.* **2011**, *133*, 12293. (d) γ-Substituted allenoates have been used also as two-atom components in 4 + 2 cyclizations: Meng, X.; Huang, Y.; Zhao, H.; Xie, P.; Ma, J.; Chen, R. *Org. Lett.* **2009**, *11*, 991.

Scheme 3. Proposed Mechanism for [4 + 2] Annulations



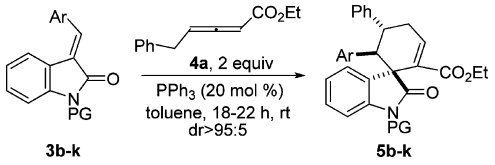
disclosed a [4 + 2] annulation of the same allenoate **4a** on 2-arylidene-1H-indenediones.[12,13]

The experiment in Scheme 2 above affords, together with Huang's work, the first examples of phosphine promoted [4 + 2] cyclizations involving the δ-carbon of an allenoate. Prior to these studies, only α-substituted allenoates were used as 4-C synthons in phosphine promoted cyclization reactions. These reactions involved the β'-carbon atom of the allene.[2c,14]

In the next step of our work, we have investigated the scope of the [4 + 2] cyclizations by varying the 3-arylideneoxindole substrates. The results are shown in Table 1. Moderate to good yields of the desired products **5** have been obtained from oxindoles with benzoyl and ethoxycarbonyl protecting groups (entries 1 and 2), as well as from various arylidene-substituted oxindoles (entries 3−10). Most of these reactions are highly diastereoselective, the spirocyclohexenes **5b**−**g,i,k** being obtained mostly as single isomers. Only reactions in entries 7 and 9 afforded 6:4 and 9:1 mixtures of isomers respectively. Based on NMR data, the isomeric oxindoles **5h** have been tentatively assigned as the two diastereomers with opposite configurations of the quaternary carbon, with respect to the neighboring CHPh group.

Additional experiments have been carried out on oxindoles bearing Cl or Me substituents on their benzo-units. The corresponding spirooxindoles have been isolated in 66−85% yields (Table 2, entries 1−7). Finally, the allenic partner has been changed, showing that the reaction

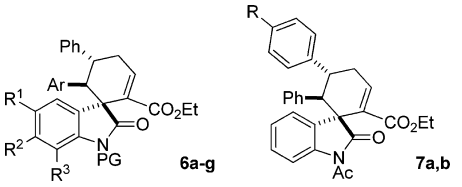
Table 1. Scope of the Reaction: Variation of the Arylideneoxindole Substrates



entry	PG	Ar	product	yield (%)
1	Bz	Ph	**5b**	87
2	CO_2Et	Ph	**5c**	63
3	Ac	p-CF_3-C_6H_4	**5d**	77
4	Ac	p-Cl-C_6H_4	**5e**	62
5	Ac	p-Br-C_6H_4	**5f**	89
6	Ac	p-Me-C_6H_4	**5g**	73[a]
7	Ac	m-Br-C_6H_4	**5h**	74[b]
8	Ac	o-Br-C_6H_4	**5i**	48
9	Ac	p-CN-C_6H_4	**5j**	78[c]
10	Ac	2-quinolyl	**5k**	48

[a] PPh_3, 50 mol %. [b] 6:4 mixture of two diastereoisomers. [c] 9:1 mixture of two isomers.

Table 2. Additional Examples of Substituted Cyclohexene-Spirooxindoles Obtained *via* PPh_3 Promoted [4 + 2] Annulations[a]



entry	compd	Ar/R	R^1	R^2	R^3	yield (%)
1	**6a**	Ph	Cl	H	H	86
2	**6b**	Ph	H	Cl	H	66
3	**6c**	Ph	H	H	Cl	66
4	**6d**	Ph[b]	Me	H	H	79
5	**6e**	Ph[b]	H	H	Me	85
6	**6f**	m-Cl-C_6H_4	H	Cl	H	68[c]
7	**6g**	o-F-m-Cl-C_6H_4	H	Cl	H	80[d]
8	**7a**	CF_3	H	H	H	64[e]
9	**7b**	MeO	H	H	H	64

[a] PG = Ac, unless otherwise noted. [b] PG = Bz. [c] 6:4 mixture of two diastereoisomers. [d] 9:1 isomer mixture. [e] PPh_3, 50 mol %.

tolerates allenoates with both electron-withdrawing (CF_3) and electron-donating (OMe) substituents on the δ-aryl group (Table 2, entries 8 and 9). The trifluoromethylphenyl-substituted allenoate (entry 8) required a higher catalyst loading to achieve a good conversion rate (64% yield, after 18 h in the presence of a 50 mol % amount of PPh_3).

Preliminary experiments toward enantioselective variants of these reactions have shown that (*S,S*)-2,4-bis-(diphenylphosphino)pentane ((*S,S*)-BDPP) promotes the

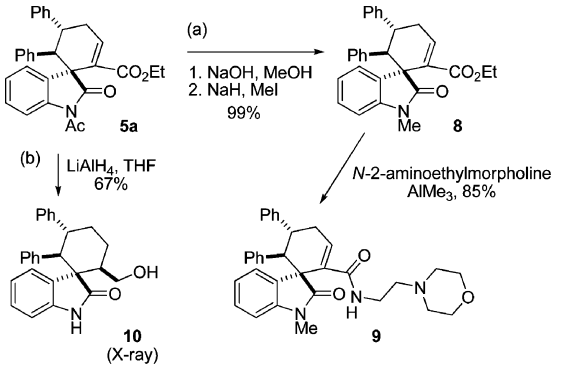
(12) Li, E.; Huang, Y.; Liang, L.; Xie, P. *Org. Lett.* **2013**, *15*, 3138.

(13) (a) An alternative reaction pathway might involve the allylic phosphorus ylide **II′** as the reaction intermediate. (b) The six-membered ring might also be formed by a Diels−Alder type reaction between the olefin and a conjugated diene generated by isomerization of the allenoate. A Diels−Alder process is expected however to take place with retention of the geometry of the starting olefin. Moreover, we did not observe any cycloaddition product when heating a mixture of **3a** and ethyl 5-phenyl-2,4-pentadienoate.

(14) (a) Zhu, X.-F.; Lan, J.; Kwon, O. *J. Am. Chem. Soc.* **2003**, *125*, 4716. (b) Wurz, R. P.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 12234. (c) Zhu, X.-F.; Schaffner, A.-P.; Li, R. C.; Kwon, O. *Org. Lett.* **2005**, *7*, 2977. (d) Tran, Y. S.; Kwon, O. *J. Am. Chem. Soc.* **2007**, *129*, 12632. (e) Castellano, S.; Fiji, H. D. G.; Kinderman, S. S.; Watanabe, M.; de Leon, P.; Tamanoi, F.; Kwon, O. *J. Am. Chem. Soc.* **2007**, *129*, 5843. (f) Wang, T.; Ye, S. *Org. Lett.* **2010**, *12*, 4168. (g) Tran, Y. S.; Martin, T. J.; Kwon, O. *Chem.—Asian J.* **2011**, *6*, 2101. (h) Zhao, L.; Wen, M.; Wang, Z.-X. *Eur. J. Org. Chem.* **2012**, 3587.

cyclization reaction in Scheme 2, affording the expected spiranic derivative **5a** in 60% ee. Also, the spirocyclohexene **7b** (Table 2) has been obtained in 50% yield and a 83:17 enantiomer ratio (66% ee). These results demonstrate the potential of developing enantioselective reactions by using chiral phosphorus catalysts. Further studies toward this end are ongoing in our group.

Scheme 4. Examples of Functional Group Transformation on the Spiranic Oxindole **5a**



Next, with the aim of using compounds **5**–**7** as intermediates for the synthesis of differently substituted spiranic derivatives, we have started investigating the reactivity of **5a**. Representative reactions are shown in Scheme 4. (a) The ester function of the spirocyclic derivative **5a** could be converted into an amide function in good yields, *via* $AlMe_3$ promoted amidation. Amide **9** was obtained in 84% yield over three steps. (b) The olefinic bond and the ester function of **5a** could be reduced simultaneously with $LiAlH_4$, giving the saturated spiro-cyclohexaneoxindole **10** in good yield, with total diastereoselectivity. The relative stereochemistry of the four contiguous stereogenic centers has been established by X-ray diffraction studies (see Supporting Information). Reduction of the olefinic bond with $LiAlH_4$ takes place selectively on the face opposite to the carbonyl function of the oxindole unit, leading to the saturated ring in a stereocontrolled manner.

In summary, these new phosphine promoted [4 + 2] cyclization reactions offer an easy, unprecedented access to functionalized spiro-cyclohexeneoxindoles, with efficient control of the relative stereochemistry of three contiguous stereogenic centers. The method suitably complements the previously described phosphine promoted reactions which exclusively apply to the synthesis of spirocyclic oxindoles with five-membered cyclic scaffolds.

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Supporting Information Available. Experimental procedures and characterization of the new compounds **5**–**10**. X-ray data for **5a** and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.