Phosphine-Catalyzed [3+2] Cycloaddition of Aza-aurones and Allenoates: Enantioselective Synthesis of 2-Spirocyclopentyl-indolin-3-ones

Dr. Elisa Brambilla,[a] Camilla Pozza,[a] Prof. Silvia Rizzato,[b] Prof. Giorgio Abbiati[a] and Dr. Valentina Pirovano*[a]

[a] Dr. E. Brambilla, C. Pozza, Prof. G. Abbiati, Dr. Valentina Pirovano
Dipartimento di Scienze Farmaceutiche, Sezione di Chimica Generale e Organica "A. Marchesini"
Università degli Studi di Milano
Via G. Venezian 21, 20133 Milano, Italy
E-mail: valentina.pirovano@unimi.it
[b] Prof. S. Rizzato
Dipartimento di Chimica
Università degli Studi di Milano
Via C. Golgi 19, 20133 Milano, Italy

Abstract: An enantioselective phosphine-catalyzed [3+2] cycloaddition between aza-aurones and allenoates is here described. The reaction proceeded under mild reaction conditions to afford 2-spirocyclopentyl indolin-3-one derivatives as single γ-isomer and with high levels of stereocontrol.

Introduction

2-Spirocyclic indolinones constitute an intriguing class of spiro heterocycles often incorporated in the skeleton of numerous bioactive natural products.[1] In particular, the 2-spirocyclopentyl motif can be recognized in the structure of alkaloids brevianamide A, an insecticidal isolated from Penicillium brevicompactum[2] and Aristotelia chilensis derivative aristotelone,[3] as well in simple molecules employed as spiro-type functional fluorescent dyes.[4] (Figure 1).

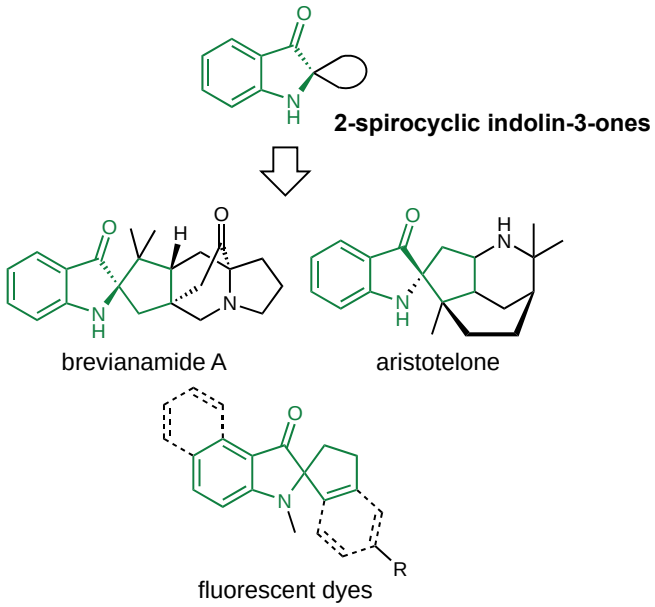
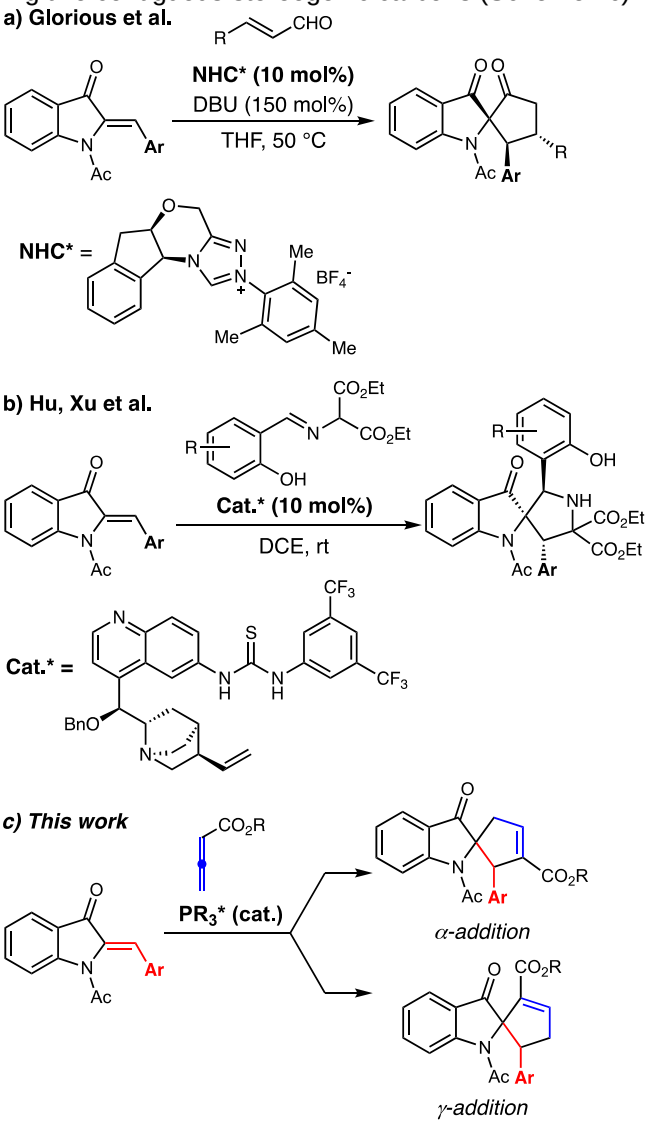


Figure 1: relevant molecules containing 2-spirocyclopentyl indolin-3-one core.

Despite their interesting properties, the preparation of 2-spirocyclopentyl-3-oxindoles remains a synthetic challenge and most of the recognized methods rely on oxidative rearrangements of [2,3]-fused-indoles or on intramolecular cyclizations of nitrogen-containing phenylacetylenes, reactions that generally afford racemic compounds.[5] Reported enantioselective syntheses are quite rare[6] and, in this scenario, [3+2] cycloadditions between (*Z*)-2-ylideneindolin-3-ones (namely aza-aurones) and suitable 3C synthons permit to build up molecular complexity in an efficient and stereoselective manner. Aza-aurones are generally scarcely used as 2C units in cycloadditions,[7] probably because of their low reactivity, especially if compared to widely-exploited isomeric 3-ylidene-indolin-2-ones.[8] The first example of an enantioselective synthesis of 2-spirocyclopentyl-indolin-3-ones by [3+2]

cycloaddition of aza-aurones has been reported in 2014 by Glorious and coworkers, which reacted them with enals under chiral N-heterocyclic carbene catalysis (Scheme 1a).[6b] Successively, in 2016, Hu and Xu synthesized enantioenriched 2,2'-pyrrolidinyl-spirooxindoles reacting aza-aurones with azomethine ylides in the presence of a bifunctional thiourea organocatalyst (Scheme 1b).[6c] Nevertheless, to the best of our knowledge, any report on the use of aza-aurone in [3+2] cycloadditions with allenoates has been reported yet. For this reason and as continuation of our studies in the synthesis of complex 3-indolinones,[9] including cycloaddition reaction of aza-aurones,[7c] we became interested in developing an enantioselective synthesis of 2-spirocyclopentyl indolinones derivatives via [3+2] cycloaddition between aza-aurones and allenoates under nucleophilic phosphine catalysis. Phosphine-catalyzed [3+2] cycloaddition reactions between allenes and electrophiles represent in fact an effective synthetic tool to build complex cyclopentene and dihydropyrrole derivatives. Starting from the seminal discovery of Lu in 1995,[10] this methodology has been widely studied and applied to a plethora of electron-poor alkenes and imines that reacted with allenoates to give functionalized carbo- and heterocycles.[11] In addition, the development of chiral phosphine catalysts has then expanded the applicability of this transformation providing elegant syntheses of enantioenriched five-membered rings.[12] According to the mechanism proposed by Lu and subsequent studies on related substrates,[13] [3+2] cycloaddition of aza-aurones and allenoate should lead in principle to the formation of α- and γ-addition isomers having two contiguous stereogenic carbons (Scheme 1c).

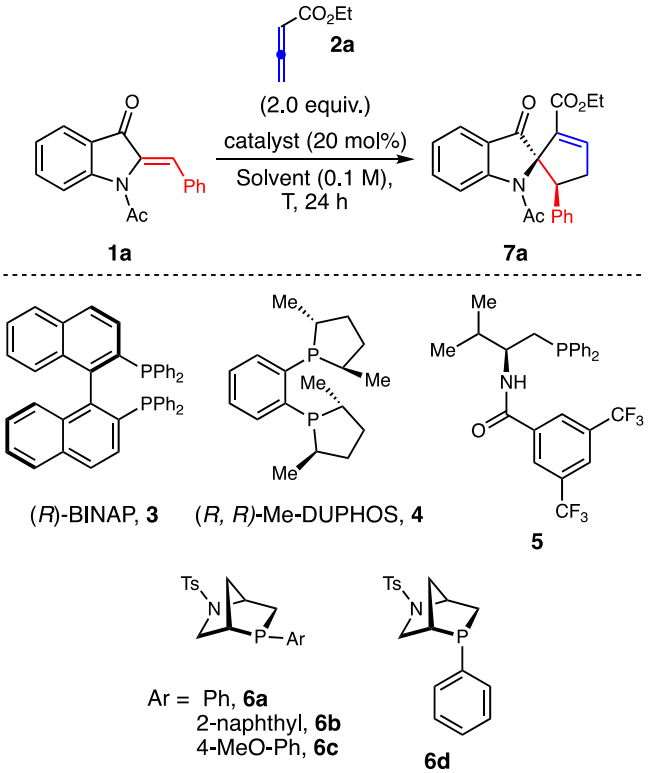


Scheme 1. Enantioselective syntheses of 2-spirocyclopentyl- indolin-3-ones and our proposal.

Results and Discussion

To verify the feasibility of our hypothesis, we selected aza-aurone **1a** and ethyl 2,3-butadienoate (**2a**) which were reacted in the presence of 20 mol% of chiral phosphines **3-6** under different reaction conditions. Obtained results are summarized in Table 1.

Table 1. Optimization of reaction conditions.



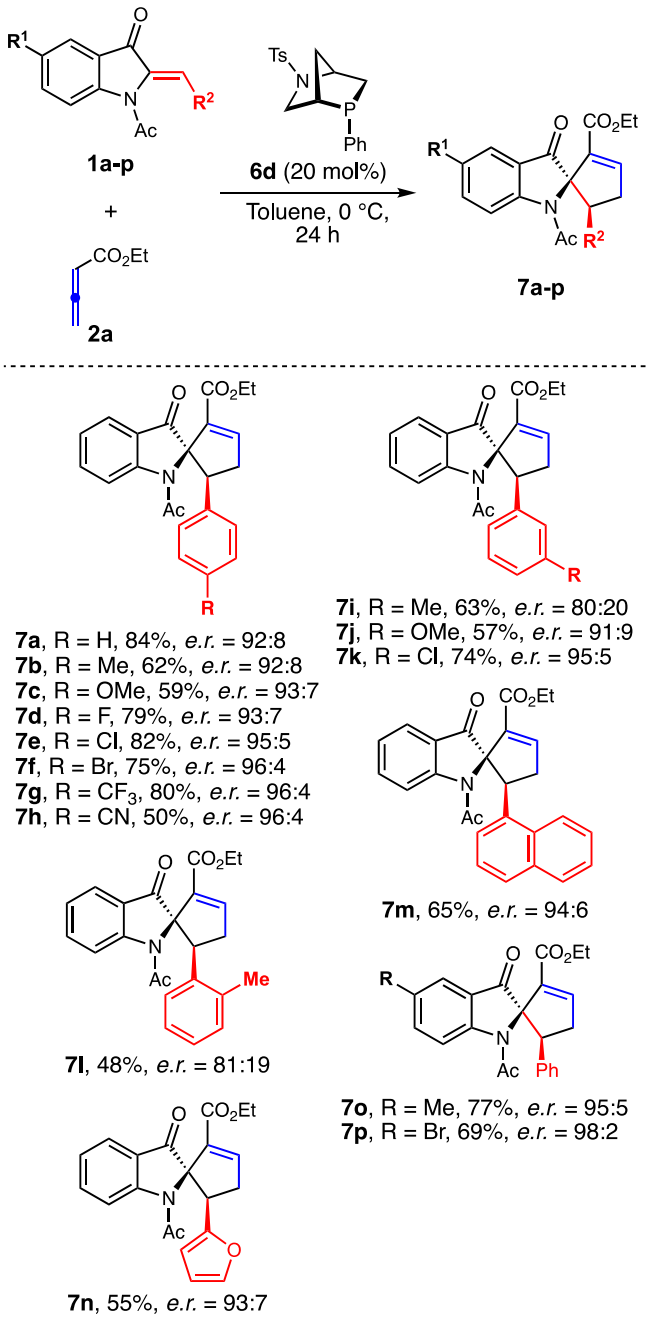
Entry[a]	Catalyst	Solvent	T, [°C]	Yield [%][b]	*e.r.*[c]
1	**3**	Toluene	rt	n.r.	-
2	**4**	Toluene	rt	n.r.	-
3	**5**	Toluene	rt	66	49:51
4	**6a**	Toluene	rt	77	86:14
5	**6a**	Toluene	0	72	89:11
6	**6b**	Toluene	0	53	85:15
7	**6c**	Toluene	0	67	79:21
8	**6d**	Toluene	0	84	92:8
9	**6d**	CH_2Cl_2	0	51	85:15
10	**6d**	C_6F_6	0	65	90:10

[a] Reaction was performed using **1a** (0.1 mmol), **2a** (0.2 mmol), catalyst (20 mol%) in the stated solvent (1 ml, 0.1 M) for 24 h at rt or 0 °C under N_2-atmosphere. [b] Isolated yield. [c] Determined by HPLC on the pure isolated product.

At the outset, we concentrated our attention on the choice of the best-performing chiral phosphine. We selected commercially available and/or easily synthesizable phosphines to provide and optimize a methodology that doesn't require long and/or complicated procedures to obtain reagents and catalysts. The first trial was performed using (*R*)-BINAP (**3**) as catalyst, in toluene at room temperature, but, even after 24 h, the reaction did not proceed and unreacted **1a** was visible in ^{1}H-NMR of the crude (entry 1). A similar result was obtained with (*R,R)*-Me-DUPHOS (**4**) which was ineffective (entry 2). We moved then to a simple amino acid-derived bifunctional chiral phosphines **5**, prepared from (*S*)-1-(diphenylphosphino)-3-methyl-2-butylamine in one step.[14] In this case, the reaction performed under the same conditions of entry 1, led to the formation of the desired 2-spirocyclopentylindolin-3-one **7a** in 66% yield, with complete γ-selectivity, however as a racemic mixture (*e.r.* = 49:51) (entry 3). Thus, we decided to test commercially available 2-aza-5-phosphabicyclo[2.2.1]heptane catalysts, developed by Kwon group,[15] which finally led to interesting results. When the reaction between **1a** and **2a** was catalyzed by exo-phenyl Kwon [2.2.1] bicyclic phosphine (**6a**) we were able to isolate the γ-adduct **7a** in 77% yield and with a moderate *e.r.* = 86:14 (entry 4). We performed the same reaction at a lower temperature (0 °C) and **7a** was isolated with a similar yield and a slightly increased *e.r.* = 89:11 (entry 5). Other related bicyclic phosphine, bearing different aromatic groups were

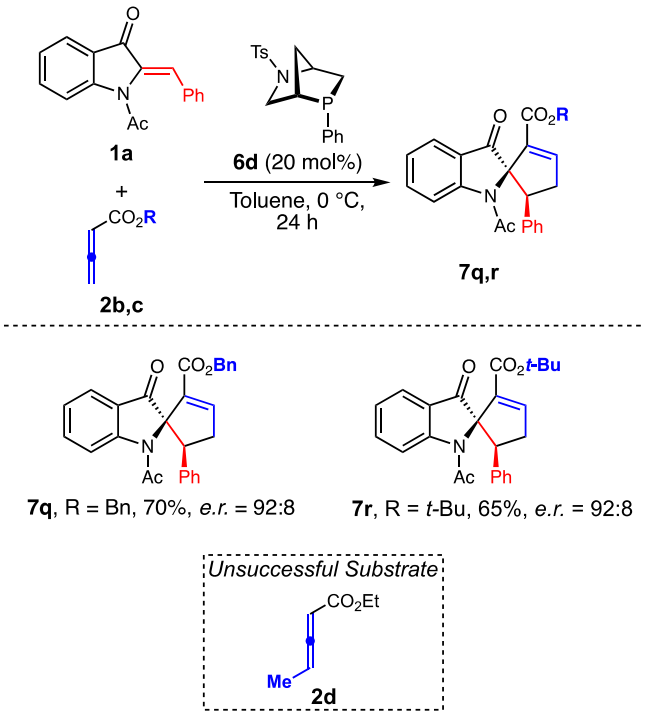
then tried at the same temperature, but neither 2-naphthyl substituted catalyst **6b** nor 4-methoxyphenyl derivative **6c** led to improved yield or enantioselectivity (entries 6-7). Finally, the best results were achieved with endo-phenyl Kwon [2.2.1] bicyclic phosphine (**6d**) that afforded spirocyclic indolinone **7a** in 84% with a good *e.r.* = 92:8 (entry 8) in toluene at 0 °C. Modifications of the solvent were then tried but the use of dichloromethane gave worse yield and *e.r.* (entry 9), while hexafluorobenzene led to similar *e.r*. but lower yield (entry 10). Based on the obtained results, the best reaction conditions required the use of 20 mol% of endo-phenyl Kwon [2.2.1] bicyclic phosphine (**6d**), in toluene (0.1 M) for 24 h at 0 °C.

Having the best conditions in hand, the substrate scope of the reaction was explored and a series of aza-aurones **1a-p**, bearing different functional groups on alkenyl aryl ring or indole nucleus, were reacted with allenoate **2a** to yield a series of enantiomerically enriched 2-spirocyclopentylindolin-3-ones **7a-p** (Scheme 2). Firstly, we concentrated our attention on the modification of the aza-aurone. The introduction of electron-rich substituents such as a methyl or of a methoxy in the 4-position of the benzylidene group was tolerated and the corresponding products **7b** and **7c** were isolated in slightly reduced yields (62% and 59%, respectively), but with better *e.r.* = 92:8 and 93:7. Halogen atoms (F, Cl, Br) and other electron-withdrawing groups (CF_3 and CN) could also be introduced at the same positions. In the case of halogens, the corresponding products **7d-f** were formed with good to excellent yields and with an *e.r.* ranging from 93:7 and 95:5 (F and Cl) up to 96:4 (Br). The same enantiomeric ratio (96:4) was observed in products **7g** and **7h**, synthesized from 4-CF_3 and 4-CN benzylidene derivatives in 80% and 50% yields, respectively. Substitution of the aromatic ring in other positions was also tolerated. Products **7i** and **7j** arising from 3-methyl and 3-methoxybenzylidene derivatives were formed in 63% and 57% yields, a result that is comparable to the one obtained with corresponding 4-substituted derivatives. Nevertheless, the enantiomeric ratio of **7j** was still good (*e.r.* = 91:9), while in the case of **7i** we observed a drop in the enantioselectivity with an *e.r.* = 80:20. Better results were obtained with 3-chloro derivative **7k** isolated in 74% yield and showing an *e.r.* = 95:5, while 2-methylbenzylidene aza-aurone gave an even worse yield (48%) than 3- and 4-methyl substituted aza-aurones and, similarly to **7i** the *e.r.* was 81:19. Other aromatic substituents on aza-aurone exocyclic double bond were tried, and naphthyl derived aza-aurone gave rise to spirocyclic indolinone **7m** in good 65% and *e.r.* = 94:6, while furyl substituted **7n** was obtained in 55% and *e.r.* = 93:7 from heteroaromatic aza-aurone **1n**. 5-methyl and 5-bromo substituted aza-aurones were then reacted with **2a** and, also in this case, the reactions efficiently led to the formation of **7o** and **7p** in 77% and 69% yields. Notably, in both cases, we observed high levels of enantioselectivity with *e.r.* ranging from 95:5 for **7o** to 98:2 for **7p**.



Scheme 2. Synthesis of 2-spirocyclopentyl-indolin-3-ones **7a-p**.

As final modification, we changed the nature of allenoate to verify a possible influence of the ester substituent in the reaction yield/enantioselectivity. Both benzyl ester **2b** and *tert*-butyl ester **2c** were reacted with **1a** under optimized conditions and 2-spirocyclopentyl-indolin-3-ones **7q** and **7r** were isolated in satisfactory 70% and 65% yield and *e.r.* = 92:8 for both reactions. Conversely, allenoate **2d** bearing a methyl group at the γ-position gave no reaction with **1a** and desired spirocyclopentyl-indolin-3-one or any other product couldn't be detected even after 48 h (Scheme 3).



Scheme 3. Modification of allenoates and synthesis of **7q** and **7r**.

All synthesized products were obtained with complete γ-selectivity and were characterized by NMR analyses. The structure of 2-spirocyclopentyl-3-indolinones was determined by single crystal X-ray diffraction analysis performed on species **7e** (Figure 2) whose data are presented in the Supportig Information.

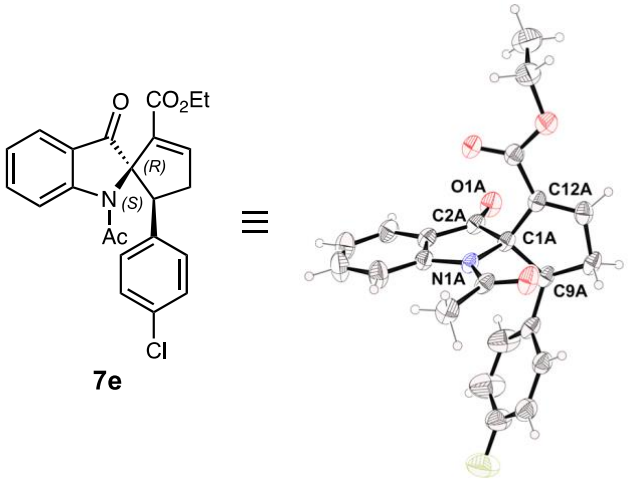
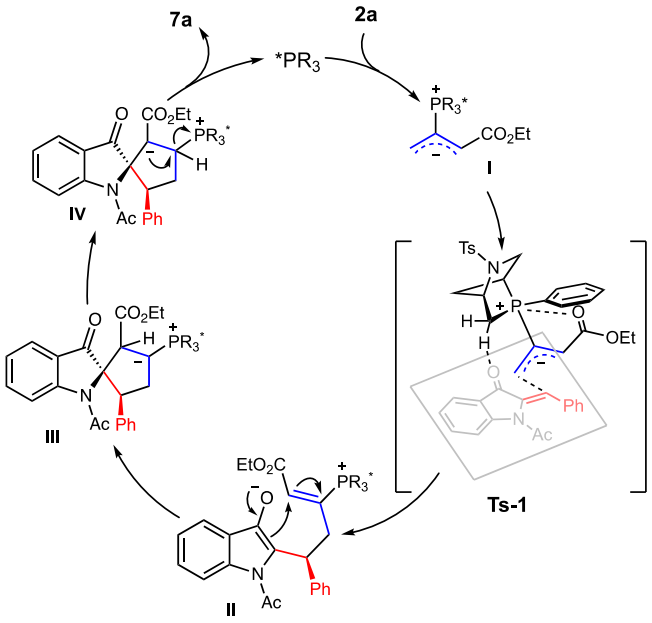


Figure 2. Absolute configuration of **7e** determined by single crystal X-Ray diffraction analysis. Thermal ellipsoid plot (30% probability) of one of the two independent molecules of **7e** in the crystal lattice.

Taking into account the obtained results and previous studies on phosphine-catalyzed [3+2] cycloaddition between electron-poor alkenes and allenoates,[16] including cyclizations of aurones[13a] and 2-arylidene-1,3-indandiones,[13b] as well as applications of Kwon's phosphines in allenoate cycloadditions,[15,17] the mechanism that we proposed for the formation of **7a** is illustrated in Scheme 4. The nucleophilic attack of the phosphine on central *sp* carbon of allenoate **2a** generates the zwitterionic intermediate **I**, which possesses two resonance forms with the negative charge delocalized on the α- and γ-carbon. Then, selective γ-addition of intermediate **I** on aza-aurone exocyclic double bond occurs on the *re*-face (**Ts-1**) giving rise to intermediate **II** that cyclizes to form [3+2] adduct **III**. In **Ts-1** formation of two distinct interactions, respectively between an acidic hydrogen alpha to the positively charged phosphorous atom and between this latter and the oxo function of allenoate **2**, occur and guide the stereoselective addition leading to the formation of adduct **II**. Finally, [1,2]-H shift from **III** and elimination of phosphine afford spirocyclic product **7a** with concomitant regeneration of the catalyst.



Scheme 4. Hypothesized reaction mechanism.

Conclusion

In conclusion, we have developed a novel methodology to synthesize 2-spirocyclpentyl-indolin-3-ones in a stereoselective way. Aza-aurones were employed as 2C carbon synthons in a phosphine-catalyzed [3+2] cycloaddition with allenoates to efficiently give spirocyclic products with complete regioselectivity. High levels of enantioselectivity were achieved using a commercially available phosphine catalyst that promoted the reaction of differently substituted substrates. We believe that this method is a complementary approach to 2-spirocyclic-3-oxindoles and represent a practical and effective strategy to synthesize enantioenriched 2-spirocyclopentyl-indolin-3-ones under mild reaction conditions starting from ready-available reagents and catalysts.

Experimental Section

General procedure for the synthesis of products 7a-r: to a nitrogen-flushed solution of aza-aurones **1a-p** (0.1 mmol) and endo-phenyl Kwon [2.2.1] bicyclic phosphine (20 mol%) in anhydrous toluene (1 ml), allenyl esters **2a-c** (0.2 mmol) were added at 0 °C. After 24 h the solvent was evaporated under vacuum and the crude was purified by flash chromatography on SiO_2 gel to yield the corresponding 2-spirocyclopentyl-indolin-3-one **7a-r**.

CCDC-2212561 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/structures**.

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Supporting Information Summary

Detailed experimental procedures for the synthesis of 2-spirocyclopentyl-indolin-3-one **7a-r**, HPLC analyses, crystal structure determinations of **7e**, spectra of new compounds are included in the supporting information file.

Keywords: asymmetric catalysis • cycloaddition • organocatalysis • phosphanes • spiro compounds

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