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Efficient Entry to Diversely Functionalized Spirocyclic Oxindoles from Isatins through Carbonyl-Addition/Cyclization Reaction Sequences

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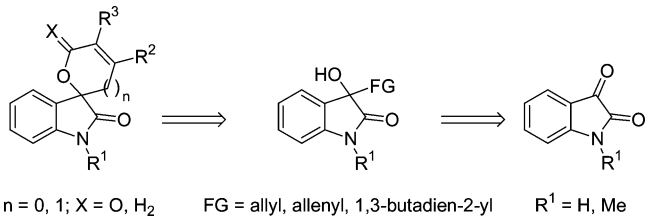

A novel approach to diversely functionalized spirocyclic oxindoles has been developed by using different metal-mediated carbonyl-addition/cyclization reaction sequences. Spirocyclization precursors, 2-indolinone-tethered homoallylic alcohols, (buta-1,3-dien-2-yl)methanols, and α-allenols have been obtained by regioselective addition of stabilized organoindium reagents to isatins in aqueous environment. Ruthenium-, silver-, and palladium-catalyzed reactions of the above unsaturated alcohol derivatives provided oxaspiro oxindoles.

Introduction

Spirocyclic compounds, which are systems containing one carbon atom common to two rings, are structurally quite interesting.[1] Among them, the heterocyclic spiro-oxindole framework is an important structural motif in biologically relevant compounds as natural products and pharmaceuticals.[2] Azaspiro derivatives are well-known,[3] but the preparation of the corresponding oxa analogues has evolved at a relatively slow pace.[4] In this context, we became aware that more of these syntheses were performed via cycloaddition or condensation reactions. In contrast to this literature scenario, we thought that the highly selective properties of metals would seem to recommend their application to the preparation of spirocycles. In connection with our current research interest in the preparation of biologically relevant nitrogenated compounds,[5] we now describe metal-mediated carbonyl-addition/cyclization reaction sequences as a novel entry to diversely functionalized spirocyclic oxindoles from commercially available isatins.

Results and Discussion

Starting substrates, homoallyl alcohol **2**, (buta-1,3-dien-2-yl) alcohol **3**, and α-allenyl alcohols **4a**−**c** were regiospecifically prepared using our recently developed metal-mediated Barbier-type carbonyl-allylation, -1,3-butadien-2-ylation, or -allenylation reactions of isatins **1** in aqueous media (Scheme 1).[6]

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(1) For selected reviews, see: (a) Sannigrahi, M. *Tetrahedron* **1999**, *55*, 9007. (b) Heathcock, C. H.; Graham, S. L.; Pirrung, M. C.; Plavac, F.; White, C. T. Spirocyclic Systems. In *The Total Synthesis of Natural* Products; ApSimon, J., Ed.; John Wiley and Sons: New York, 1983; Vol. 5, pp 264−313.

(2) For reviews, see: (a) Williams, R. M.; Cox, R. J. *Acc. Chem. Res.* **2003**, *36*, 127. (b) Da Silva, J. F. M.; Garden, S. J.; Pinto, A. C. *J. Braz. Chem. Soc.* **2001**, 273.

(3) For selected examples, see: (a) Ding, K.; Lu, Y.; Nikolovska-Coleska, Z.; Qiu, S.; Ding, Y.; Gao, W.; Stuckey, J.; Krajewski, K.; Roller, P. P.; Tomita, Y.; Parrish, D. A.; Deschamps, J. R.; Wang, S. *J. Am. Chem. Soc.* **2005**, *127*, 10130. (b) Chen, C.; Li, X.; Neumann, C. S.; Lo, M. M.-C.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 2249. (c) Bella, M.; Kobbelgaard, S.; JØrgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 3670. (d) Ready, J. M.; Reisman, S. E.; Hirata, M.; Weiss, M. M.; Tamaki, K.; Ovaska, T. V.; Wood, J. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1270. (e) Lo, M. M.-C.; Neumann, C. S.; Nagayama, S.; Perlstein, E. O.; Schreiber, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 16077. (f) Rehn, S.; Bergman, J.; Stensland, B. *Eur. J. Org. Chem.* **2004**, 413. (g) Nishikawa, T.; Kajii, S.; Isobe, M. *Synlett* **2004**, 2025. (h) Williams, R. M.; Cao, J.; Tsujishima, H.; Cox, R. J. *J. Am. Chem. Soc.* **2003**, *125*, 12172. (i) Bagul, T. D.; Lakshmaiah, G.; Kawabat, T.; Fuji, K. *Org. Lett.* **2002**, *4*, 249. (j) Lerchner, A.; Carreira, E. M. *J. Am. Chem. Soc.* **2002**, *124*, 14826. (k) Lin, X.; Weinreb, S. M. *Tetrahedron Lett.* **2001**, *42*, 2631. (l) Edmondson, S.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1138.

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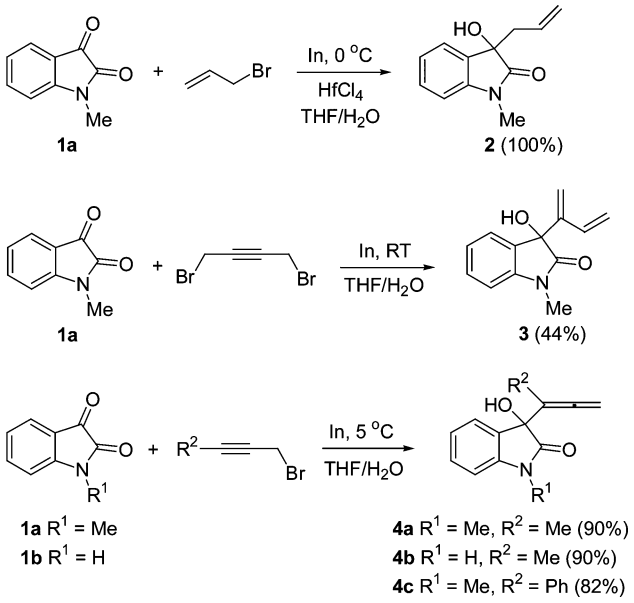
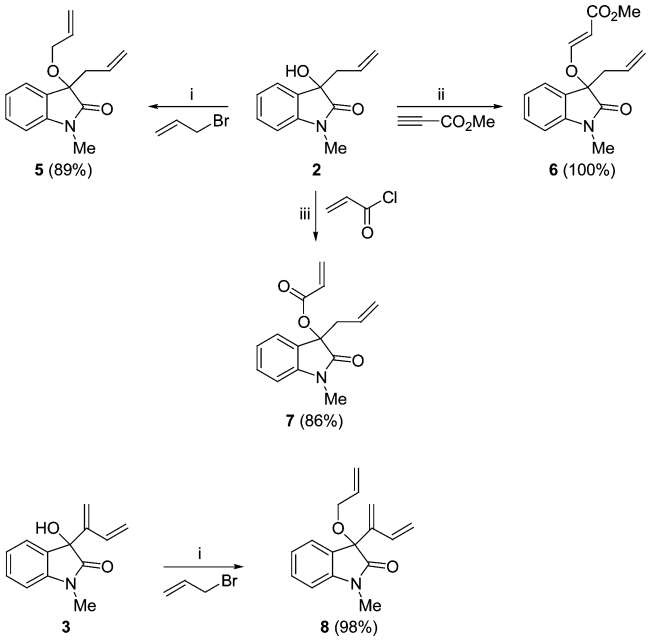
SCHEME 1



With the advent of well-defined, practically air-stable, and functional-group-tolerant metathesis catalysts, e.g., the first, $[Cl_2(PCy_3)_2Ru{=}CHPh]$, and second, $[Cl_2(Im)(Cy_3P)Ru{=}CHPh]$, generation of Grubbs' ruthenium-based catalysts, ring-closing metathesis (RCM) has become one of the most powerful and reliable approaches to construct a ring system.[7] Our first task was to develop a method for the synthesis of appropriately substituted metathesis precursors. The treatment of homoallyl alcohol **2** either with allyl bromide or methyl propiolate, under different basic conditions, gave dienes **5** and **6**, respectively (Scheme 2). Sodium hydride-promoted *O*-acylation of alcohol **2** with acryloyl chloride provides dienic substrate **7** (Scheme 2). To further expand the scope of substrates to submit to RCM, we thought of the buta-1,3-dien-2-yl moiety, bearing an extra

SCHEME 2 [a]



[a] Key: (i) TBAI (cat.), CH_2Cl_2, NaOH (aq 50%) (1:1), rt, 16 h; (ii) CH_2Cl_2, Et_3N (2 equiv), 0 °C, 1 h; (iii) NaH (2 equiv), THF, rt, 1 h.

alkene group. Following the same alkylation strategy used to obtain diene **5**, the required triene **8** was smoothly achieved from buta-1,3-dien-2-yl alcohol **3** (Scheme 2).

In view of the particular disposition of a variety of dienes to undergo spiro-forming RCM reaction, we sought to apply this methodology to our novel 2-indolinone-tethered diene substrates **5**−**8** for the synthesis of unusual oxindoles bearing a spiranic center substituted with a oxygen atom. The use of this approach in the synthesis of spirocyclic oxindoles has not been hitherto applied. Our objective was the synthesis of oxaspiro-oxindole structures containing five- and six-membered rings. Treatment of dienes **5**−**8** having a quaternary atom with first-generation Grubbs' carbene under smooth ring-closing metathesis conditions (5 mol %, CH_2Cl_2, 25 °C) did not furnish the desired spirocycles. The majority of the reaction mixture was composed of unreacted dienes. While the reasons for this lack of cyclization were not definitively established, we attributed the low reactivity of the structures **5**−**8** to either the ring strain inherent to the spirocyclic products or kinetic problems associated with its formation. Fortunately, we found that dienic substrates **5**−**8** require more vigorous conditions for ring closure. Under optimized conditions, we found that toluene at reflux temperature gave the best yields of oxindoles containing dihydrofuran, dyhydropyran, and dyhydropyranone spiranic rings. More active second-generation Grubbs' carbene was required for the spirocyclization taking place on terminally monosubstituted diene **6**. Exposure of dienes **5**−**8** to the Grubbs' ruthenium-based catalysts under our standard cyclization conditions (5 mol % of catalyst, 0.03 M, toluene, 110 °C) resulted in clean formation of the spirocycles **9**−**12** in good to excellent yields (57−89%) (Scheme 3). Grubbs' catalysts are known to be moderately thermally unstable, and the decomposition would inhibit productive metathesis.[8] To circumvent this problem, Grubbs' carbene was added in small portions (up to five) every 20 min

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(5) See, for instance: (a) Alcaide, B.; Almendros, P.; Aragoncillo, C.; Redondo, M. C.; Torres, M. R. *Chem. Eur. J.* **2006**, *12*, in press. (b) Alcaide, B.; Almendros, P.; Redondo, M. C.; Ruiz, M. P. *J. Org. Chem.* **2005**, *70*, 8890. (c) Alcaide, B.; Almendros, P.; Rodríguez-Acebes, R. *Chem. Eur. J.* **2005**, *11*, 5708. (d) Alcaide, B.; Almendros, P.; Cabrero, G.; Ruiz, M. P. *Org. Lett.* **2005**, *7*, 3981. (e) Alcaide, B.; Almendros, P.; Rodríguez-Acebes, R. *J. Org. Chem.* **2005**, *70*, 2713. (f) Alcaide, B.; Almendros, P.; Alonso, J. M. *J. Org. Chem.* **2004**, *69*, 993. (g) Alcaide, B.; Almendros, P.; Redondo, M. C. *Org. Lett.* **2004**, *6*, 1765.

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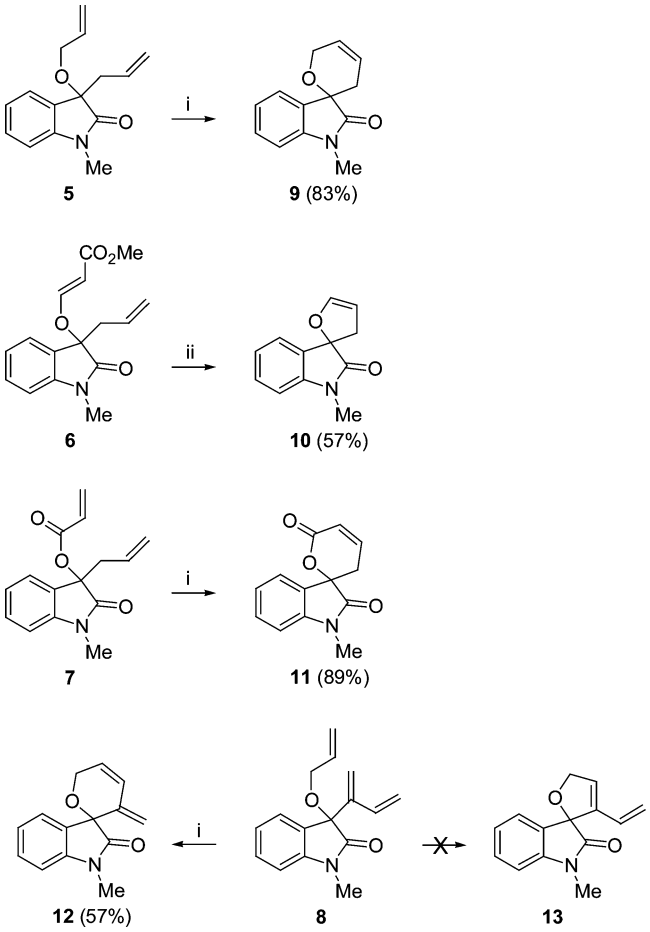
(8) (d) Hong, S. H.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2004**, *126*, 7414. (b) Ulman, M.; Grubbs, R. H. *J. Org. Chem.* **1999**, *64*, 7202.

SCHEME 3 [a]



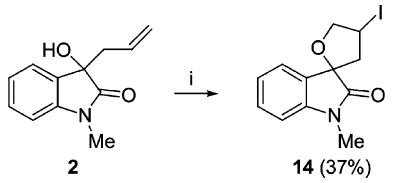
[a] Key: (i) 5 mol % of $[Cl_2(PCy_3)_2Ru{=}CHPh]$, toluene, reflux; **9**, 1 h; **11**, 38 h; **12**, 18 h; (ii) 5 mol % of $[Cl_2(Im)(Cy_3P)Ru{=}CHPh]$, toluene, reflux, 13 h.

(5 mol % is the overall amount of all the portions). Thus, the catalytic species is continuously being renewed by fresh Grubbs' carbene. The exposure of triene **8** to Grubbs' catalyst gave the six-membered spiro compound **12**, which bears an exocyclic methylene. No traces of the five-membered regioisomer **13** could be detected because only the least substituted double bond of the 1,3-diene system reacted (Scheme 3).

Having in hand the unsaturated alcohols **2**−**4**, our next target was to perform metal-mediated reactions in order to directly convert them to novel oxaspirocyclic oxindoles. For instance, homoallyl alcohol **2** was treated with iodine and silver(I) oxide in a 7:1 mixture of dioxetane−water at room temperature for 5 days[9] to give the corresponding iodotetrahydrofuran derivative **14** (Scheme 4).

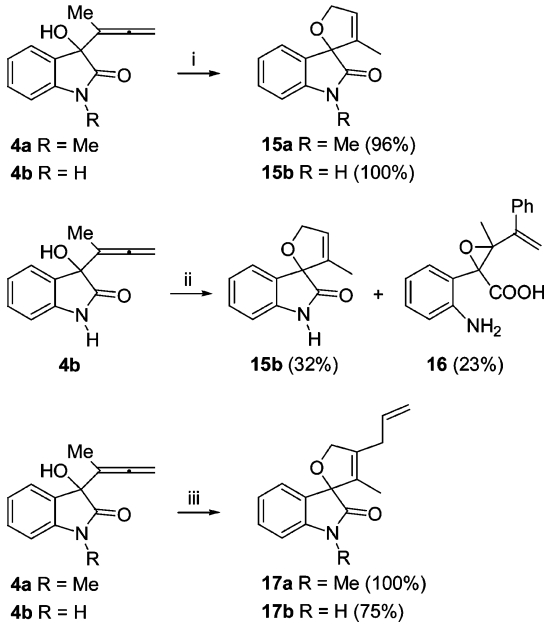
The combination of an allene moiety and a functional group in the same molecule provides many opportunities in metal-catalyzed processes.[10] However, allenes are still under utilized in heterocyclic synthesis. Application of this concept to install

SCHEME 4 [a]



[a] Key: (i) Ag_2O (1.5 equiv), I_2 (1.5 equiv), dioxane/water (7:1), rt, 5 days.

SCHEME 5 [a]



[a] Key: (i) $AgNO_3$ (1 equiv), acetone/water (1:1), reflux, 1 h; (ii) 5 mol % of $Pd(PPh_3)_4$, PhI (1.1 equiv), K_2CO_3 (4 equiv), toluene, reflux, 80 h; (iii) 5 mol % $PdCl_2$, allyl bromide (5 equiv), DMF, rt; **17a**, 2 h; **17b**, 1.5 h.

different spiranic dihydrofuran oxindole derivatives was explored starting from allenylcarbinols **4**. When treated with silver(I) nitrate, α-allenols **4** gave rise to spirocyclic dihydrofurans **15** in quantitative yields (Scheme 5).[11] Next, we focused our efforts on the palladium-catalyzed coupling-cyclization reaction of α-allenols **4** with organic halides.[12] After some trial and error, it was observed that the $Pd(PPh_3)_4$-catalyzed reaction of α-allenol **4b** and iodobenzene afforded as main product the spiranic dihydrofuran oxindole **15b**, together with the oxirane γ-amino acid **16** (Scheme 5). The formation of epoxide **16** involves concomitant ring opening of the γ-lactam nucleus, probably because of the ring strain of the intermediate spirocyclic epoxyoxindole which cannot survive under the reaction conditions. The transformation of the allenols **4a** and **4b** into the spirocyclic disubstituted dihydrofuran indolones **17a** and **17b** was readily achieved in quantitative and 75% yields by treatment with allyl bromide in the presence of palladium(II) chloride (5 mol %) (Scheme 5).

Scheme 6 outlines a mechanistic hypothesis for the formation of compound **16**. The Pd(0)-catalyzed insertion of iodobenzene

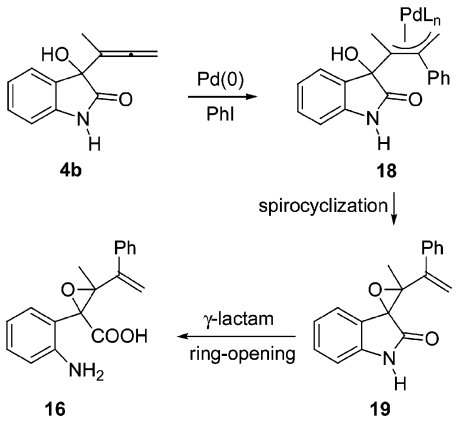
(9) Alonso, F.; Meléndez, J.; Yus, M. *Tetrahedron Lett.* **2004**, *45*, 1717.

(10) For reviews on transition metal catalyzed cyclizations of allenes, see: (a) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3590. (b) Bates, R. W.; Satcharoen, V. *Chem. Soc. Rev.* **2002**, *31*, 12. (c) Ma, S. *Acc.* Chem. Res. **2003**, *36*, 701. (d) *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, 2004; Vol. 2. (e) Hoffmann-Röder, A.; Krause, N. *Org. Biomol. Chem.* **2005**, *3*, 387. (f) Ma, S. *Chem. Rev.* **2005**, *105*, 2829.

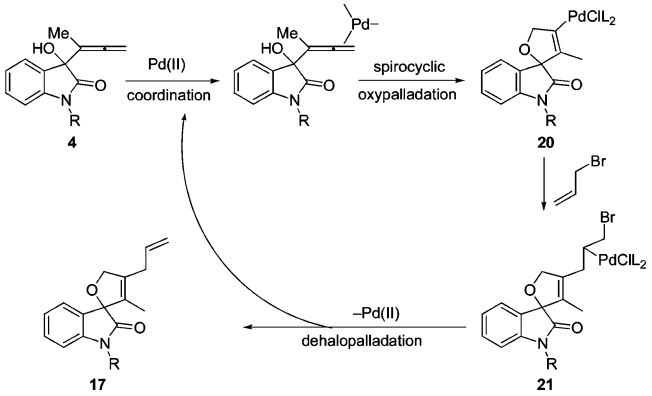
(11) For the Ag(I)-catalyzed cyclization of 2,3-allenols, see: (a) Marshall, J. A.; Yu, R. H.; Perkins, J. F. *J. Org. Chem.* **1995**, *60*, 5550. (b) Marshall, J. A.; Pinney, K. G. *J. Org. Chem.* **1993**, *58*, 7180.

(12) Xu, D.; Li, Z.; Ma, S. *Chem. Eur. J.* **2002**, *8*, 5012.

SCHEME 6



SCHEME 7

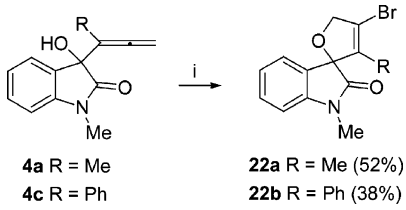


generated the corresponding (π-allyl)palladium intermediate **18**. Then, an intramolecular oxycyclization reaction on the (π-allyl)-palladium complex must account for the formation of the spiranic oxirane intermediate **19**. Subsequent γ-lactam ring opening of the spirocyclic epoxyoxindole **19** under the reaction conditions, afforded the oxirane γ-amino acid **16**. Compound **15b** should be formed without the intervention of PhI, via an allenepalladium complex which undergoes an intramolecular attack by the hydroxyl group (hydroalkoxylation).

The formation of spirocyclic allylmethyldihydrofuran indolones **17** could be explained following a Pd(II)-catalyzed mechanism.[13] Initial Pd(II) coordination followed by an intramolecular cycloetherification reaction gave the palladadihydrofuran species **20**. Intermediate **20** reacted with allyl bromide to form intermediate **21**, which after dehalopalladation generated spirooxindoles **17** with concomitant regeneration of the Pd(II) species (Scheme 7).

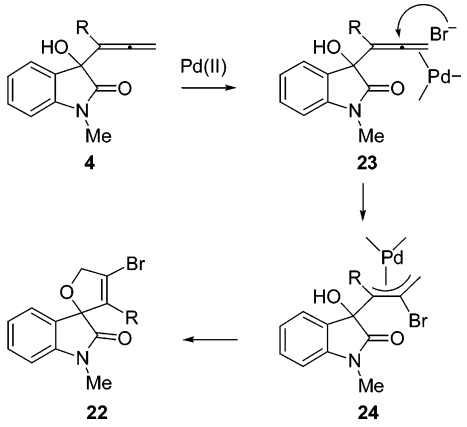
We next investigated the feasibility of synthesizing spirocyclic bromodihydrofuran-containing oxindoles by employing palladium(II)-induced intramolecular 2,3-oxybromination of α-allenols **4**. As shown in Scheme 8, the bromo-functionalized spirodihydrofuranoxindole derivatives **22** can be prepared as single isomers in reasonable yields. As far as we know, this is the first preparation of a furan derivative containing the bromovinyl moiety starting from allenols.[14] A likely mechanism for the generation of spirocycles **22** should involve the initial

SCHEME 8 [a]



[a] Key: (i) 9 mol % of Pd(OAc)$_2$, LiBr (5 equiv), Cu(OAc)$_2$ (2.1 equiv), K_2CO_3 (1.2 equiv), O_2, MeCN, rt; **22a**, 20 h; **22b**, 120 h.

SCHEME 9



formation of a (π-allyl)palladium species. The allenepalladium complex **23** is formed initially and suffers a nucleophilic attack by the bromide to produce a σ-allylpalladium species, which rapidly equilibrates to the corresponding (π-allyl)palladium intermediate **24**. Then, an intramolecular cycloetherification reaction on the (π-allyl)palladium complex must account for the formation of bromodihydrofuran intermediates **22** (Scheme 9).

Conclusions

In conclusion, the present study provides the first general methodology for the preparation of the oxacyclic spiro-oxindole framework, which is an important structural motif in some biologically relevant compounds. We have shown that combination of Barbier-type carbonyl-addition reactions and metal-mediated cyclizations is an useful methodology for the preparation of a variety of diversely functionalized oxaspirocyclic oxindoles from isatins.

Experimental Section

General Methods. The same experimental techniques were used as previously reported.[5]

General Procedure for the Ring-Closing Metathesis (RCM) Reaction of Diolefin Precursors 5−8. Preparation of Spirocyclic Oxindoles 9−12. To a solution protected from the sunlight of the appropriate diene (0.20 mmol) in anhydrous toluene (6 mL) was added in portions [$Cl_2(Cy_3P)_2Ru$=CHPh] or [Cl_2(Im)(Cy_3P)Ru=

(13) Ma, S.; Gao, W. *J. Org. Chem.* **2002**, *67*, 6104. One of the reviewers has suggested that compounds **17** might also arise from a π−allyl Pd intermediate similar to that involved in Scheme 6, which undergoes cyclization by nucleophilic attack to the distal allyl carbon atom.

(14) The palladium-catalyzed intramolecular cyclization of simple γ-allenic alcohols has been recently reported by Bäckvall and co-workers. However, it should be noted the dramatic change on the regioselectivity by the effect of the tether length. They obtained the 1,2-addition products, while we obtained the 2,3-addition products. See: Jonasson, C.; Horváth, A.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **2000**, *122*, 9600.

CHPh] (0.01 mmol) under argon. The resulting mixture was heated at reflux until complete disappearance of the starting material (TLC) and was concentrated under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexanes or ethyl acetate/dichloromethane mixtures gave analytically pure compounds **9**−**12**. Spectroscopic and analytical data for some representative pure forms of **9**−**12** follow.[15]

Spirocyclic Oxindole 11. From 49 mg (0.191 mmol) of diene **7**, 39 mg (89%) of compound **11** was obtained as a colorless oil after chromatography eluting with ethyl acetate/dichloromethane (1:30). ^{1}H NMR: δ 7.45 (d, 1H, J = 7.2 Hz), 7.37 (dd, 1H, J = 7.8, 1.2 Hz), 7.08 (td, 1H, J = 7.6, 1.1 Hz), 6.95 (dt, 1H, J = 9.9, 4.3 Hz), 6.86 (d, 1H, J = 7.8 Hz), 6.26 (dt, 1H, J = 9.9, 2.1 Hz), 3.19 (s, 3H), 2.93 and 2.75 (ddd, each 1H, J = 18.9, 4.2, 2.0 Hz). ^{13}C NMR: δ 172.6, 161.9, 143.1, 142.0, 131.1, 127.6, 124.0, 123.4, 121.4, 108.9, 80.0, 30.3, 26.4. IR ($CHCl_3$, cm^{-1}): ν 1720, 1710. MS (ES), *m*/*z*: 230 (M^+ + 1, 100), 229 (M^+, 25). Anal. Calcd for $C_{13}H_{11}NO_3$: C, 68.11; H, 4.84; N, 6.11. Found: C, 68.00; H, 4.86; N, 6.14.

Spirocyclic Oxindole 12. From 40 mg (0.157 mmol) of triene **8**, 21 mg (57%) of compound **12** was obtained as a colorless oil after chromatography eluting with ethyl acetate/hexanes (1:3). ^{1}H NMR: δ 7.36 (td, 1H, J = 7.7, 1.3 Hz), 7.31 (d, 1H, J = 6.9 Hz), 7.09 (td, 1H, J = 7.4, 1.1 Hz), 6.85 (d, 1H, J = 7.6 Hz), 6.48 (dt, 1H, J = 10.2, 2.2 Hz), 6.11 (d, 1H, J = 10.5 Hz), 4.98 (s, 1H), 4.91 (dm, 1H, J = 17.6 Hz), 4.55 (s, 1H), 4.42 (d, 1H, J = 17.6 Hz), 3.19 (s, 3H). ^{13}C NMR: δ 174.0, 144.2, 138.5, 130.1, 129.1, 128.0, 125.1, 125.0, 123.1, 113.4, 108.3, 77.2, 62.4, 26.0. IR ($CHCl_3$, cm^{-1}): ν 1707. MS (EI), *m*/*z*: 228 (M^+ + 1, 7), 227 (M^+, 100). Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.86; H, 5.80; N, 6.14.

Procedure for the Silver-Induced Reaction of Homoallyl Alcohol 2. Preparation of Spirocyclic Oxindole 14. Silver(I) oxide (108 mg, 0.465 mmol) and iodine (118 mg, 0.465 mmol) were sequentially added to a stirred solution of alkenol **2** (63 mg, 0.31 mmol) in dioxane/water (7:1) (4 mL). The reaction was stirred at room temperature for 120 h, before water (2 mL) was added. Then, the mixture was extracted with ethyl acetate (3 × 7 mL). The organic extract was washed with brine and dried ($MgSO_4$). Removal of solvent under reduced pressure yielded 38 mg (37%) of the spiranic iodotetrahydrofuran adduct **14** after chromatography eluting with ethyl acetate/dichloromethane (1:10).

Spirocyclic Oxindole 14. Colorless solid. Mp: 109−111 °C (hexanes/ethyl acetate). ^{1}H NMR: δ 7.60 (dd, 1H, J = 7.4, 1.2 Hz), 7.31 and 7.08 (td, each 1H, J = 7.5, 1.0 Hz), 6.80 (d, 1H, J = 7.7 Hz), 4.87 (m, 1H), 4.39 (dd, 1H, J = 9.7, 3.8 Hz), 4.16 (dd, 1H, J = 9.7, 1.5 Hz), 3.17 (s, 3H), 2.67 (dd, 1H, J = 13.7, 5.5 Hz), 2.20 (dt, 1H, J = 13.7, 1.8 Hz). ^{13}C NMR: δ 177.8, 143.8, 130.2, 129.9, 125.3, 123.4, 108.3, 82.9, 77.6, 73.2, 44.0, 26.2. IR ($CHCl_3$, cm^{-1}): ν 1711. MS (EI), *m*/*z*: 329 (M^+, 7), 160 (M^+, 100). Anal. Calcd for $C_{12}H_{12}INO_2$: C, 43.79; H, 3.67; N, 4.26. Found: C, 43.93; H, 3.64; N, 4.23.

General Procedure for the Silver-Induced Reaction of α-Allenols (+)-4. Preparation of Spirocyclic Oxindoles 15. Silver nitrate (0.20 mmol) was added to a stirred solution of the corresponding α-allenol **4** (0.20 mmol) in acetone/water (1:1) (0.4 mL). The reaction was refluxed until disappearance of the starting material (TLC). The mixture was allowed to reach room temperature before brine (2 mL) was added, and then it was extracted with ethyl acetate (4 × 5 mL). The organic extract was washed with brine and dried ($MgSO_4$). Removal of solvent under reduced pressure yielded the corresponding spiranic dihydrofuran adducts **15** in analytically pure form. Spectroscopic and analytical data for some representative pure forms of **15** follow.

Spirocyclic Oxindole 15b. From 26 mg (0.129 mmol) of α-allenol **4b**, 26 mg (100%) of compound **15b** was obtained as a colorless oil. ^{1}H NMR: δ 8.49 (br s, 1H), 7.24 (m, 2H), 7.06 (t, 1H, J = 7.3 Hz), 6.89 (d, 1H, J = 7.6 Hz), 5.99 (d, 1H, J = 1.5 Hz), 5.04 and 4.94 (dq, each 1H, J = 12.2, 2.0 Hz), 1.50 (d, 3H, J = 1.7 Hz). ^{13}C NMR: δ 178.1, 141.0, 135.9, 130.1, 128.8, 124.9, 124.8, 123.3, 110.3, 93.0, 76.6, 11.2. IR ($CHCl_3$, cm^{-1}): ν 3420, 1714. MS (EI), *m*/*z*: 202 (M^+ + 1, 5), 201 (M^+, 100). Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.51; H, 5.53; N, 6.99.

Pd(0)-Catalyzed Coupling Cyclization of α-Allenol 4b with PhI. Preparation of Spirocyclic Oxindole 15b and Oxirane γ-Amino Acid 16. [$Pd(PPh_3)_4$] (15 mg, 0.013 mmol) was added to a mixture of α-allenol **4b** (50 mg, 0.25 mmol), iodobenzene (54 mg, 0.27 mmol), and potassium carbonate (138 mg, 1.0 mmol) in DMF (2 mL) under Ar, and the resulting mixture was heated at 115 °C for 80 h. The reaction was then quenched with brine (2.5 mL), the mixture was extracted with ethyl acetate (4 × 5 mL), and the combined extracts were washed twice with brine and dried ($MgSO_4$). Removal of solvent under reduced pressure yielded 16 mg (32%) of the less polar compound **15b** and 17 mg (23%) of the more polar compound **16** after chromatography eluting with ethyl acetate/dichloromethane (1:15).

Oxirane γ-Amino Acid 16. ^{1}H NMR: δ 9.03 (br s, 1H), 7.96 (dd, 1H, J = 7.8, 1.5 Hz), 7.54 (ddd, 1H, J = 8.1, 7.3, 1.5 Hz), 7.13 (m, 6H), 6.86 (dd, 1H, J = 8.3, 0.7 Hz), 5.68 and 5.61 (s, each 1H), 1.77 (s, 3H). ^{13}C NMR: δ 173.7, 146.2, 140.3, 140.0, 136.1, 128.3, 128.1, 127.5, 127.1, 123.7, 118.8, 118.4, 116.2, 77.2, 62.4, 23.4. IR ($CHCl_3$, cm^{-1}): ν 3420, 3390, 1712. MS (ES), *m*/*z*: 296 (M^+ + 1, 100), 295 (M^+, 11). Anal. Calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.07; H, 5.82; N, 4.76.

General Procedure for the Palladium(II)-Catalyzed Coupling Reaction of α-Allenols 4 with Allyl Bromide. Preparation of Spirocyclic Oxindoles 17. Palladium(II) chloride (0.005 mmol) was added to a stirred solution of the corresponding α-allenol **4** (0.10 mmol) and allyl bromide (0.50 mmol) in *N*,*N*-dimethylformamide (0.6 mL). The reaction was stirred under argon atmosphere until disappearance of the starting material (TLC). Water (0.5 mL) was added before the mixture was extracted with ethyl acetate (3 × 4 mL). The organic phase was washed with water (2 × 2 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate mixtures gave analytically pure spiranic oxindoles **17**. Spectroscopic and analytical data for some representative pure forms of **17** follow.

Spirocyclic Oxindole 17a. From 48 mg (0.223 mmol) of α-allenol **4a**, 57 mg (100%) of compound **17a** was obtained as a colorless oil. ^{1}H NMR: δ 7.33 (td, 1H, J = 7.6, 1.5 Hz), 7.19 (dd, 1H, J = 7.2, 1.4 Hz), 7.07 (td, 1H, J = 7.5, 1.0 Hz), 6.83 (d, 1H, J = 7.6 Hz), 5.85 (ddt, 1H, J = 17.1, 10.0, 6.2 Hz), 5.19 (dq, 1H, J = 17.1, 1.5 Hz), 5.10 (dq, 1H, J = 10.0, 1.5 Hz), 4.97 and 4.86 (dd, each 1H, J = 12.0, 2.0 Hz), 3.20 (s, 3H), 2.99 (dt, 2H, J = 6.2, 1.5 Hz), 1.32 (t, 3H, J = 2.0 Hz). ^{13}C NMR: δ 175.9, 144.0, 134.5, 134.1, 130.0, 128.7, 128.6, 124.5, 123.1, 116.3, 108.2, 93.9, 78.5, 29.7, 26.3, 8.8. IR ($CHCl_3$, cm^{-1}): ν 1714. MS (EI), *m*/*z*: 256 (M^+ + 1, 7), 255 (M^+, 100). Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.39; H, 6.68; N, 5.47.

General Procedure for the Palladium(II)-Catalyzed Oxybromination of α-Allenols 4. Preparation of Spirocyclic Oxindoles 22. Palladium(II) acetate (0.012 mmol), lithium bromide (0.656 mmol), potassium carbonate (0.16 mmol), and copper(II) acetate (0.28 mmol) were sequentially added to a stirred solution of the corresponding α-allenol **4** (0.134 mmol) in acetonitrile (7 mL). The resulting suspension was stirred at room temperature under an oxygen atmosphere for 24 h at room temperature. The organic phase was diluted with brine (2 mL), extracted with ethyl acetate (3 × 5 mL), washed with brine (2 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue eluting with hexanes/ethyl acetate mixtures gave analytically pure spiranic oxindoles **22**. Spectroscopic and analytical data for some representative pure forms of **22** follow.

(15) Full spectroscopic and analytical data for compounds not included in this Experimental Section are described in the Supporting Information.

Spirocyclic Oxindole 22a. From 39 mg (0.18 mmol) of α-allenol **4a** was obtained 27 mg (52%) of compound **22a** as a colorless solid after chromatography eluting with ethyl acetate/hexanes (1:1). Mp: 230−231 °C (hexanes/ethyl acetate). ^{1}H NMR: δ 7.36 (td, 1H, J = 7.7, 1.5 Hz), 7.24 (ddd, 1H, J = 7.3, 1.5, 0.5 Hz), 7.10 (td, 1H, J = 7.4, 1.0 Hz), 6.85 (d, 1H, J = 7.8 Hz), 5.15 and 5.05 (dq, each 1H, J = 11.5, 2.0 Hz), 3.22 (s, 3H), 1.41 (t, 3H, J = 2.0 Hz). ^{13}C NMR: δ 175.3, 144.1, 133.3, 130.4, 129.3, 128.1, 124.5, 123.3, 108.4, 93.7, 77.2, 26.3, 10.8. IR ($CHCl_3$, cm^{-1}): ν 1712. MS (ES), *m*/*z*: 295 ($M^+ + 2 + H$, 100), 293 ($M^+ + H$, 98). Anal. Calcd for $C_{13}H_{12}BrNO_2$: C, 53.08; H, 4.11; N, 4.76. Found: C, 53.19; H, 4.09; N, 4.73.

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Supporting Information Available: Compound characterization data and experimental procedures for compounds **2**, **3**, **4a**−**c**, **5**−**8**, **9**, **10**, **15a**, **17b**, and **22b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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