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Synthesis of Spirotetrahydrofuran Oxindoles via Palladium-Catalyzed [4 + 1] Cycloaddition of Diphenyl 2-Oxoindolin-3-yl Phosphates and 2-Methylidenetrimethylene Carbonate

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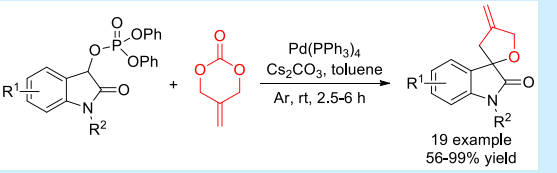
ABSTRACT: A novel palladium-catalyzed [4 + 1] cycloaddition to give spirotetrahydrofuran oxindoles has been developed, in which diphenyl 2-oxoindolin-3-yl phosphates were used as the both electrophilic and nucleophilic C_1 synthons at C-3 of the oxindole unit and 2-methylidenetrimethylene carbonate was used as the 1,4-dipole. The cycloannulation was performed at room temperature and provided the corresponding spirotetrahydrofuran oxindoles in good to excellent yields. The present method affords a new strategy for the construction of spirooxindole derivatives with unique three-dimensional structures.



Spirooxindole derivatives with the unique three-dimensional structures constitute privileged scaffolds in numerous natural products and pharmacologically relevant drugs,[1] and they are used as progesterone receptor modulators[2] and exhibit anticancer,[3] antitubercular,[4] antimalarial,[5] antifungal,[6] and anti-HIV activities.[7] As a key subtype of spirooxindoles, the 3,2′-tetrahydrofuryl spirooxindole (spirotetrahydrofuran oxindole) unit represents the core structures of a variety of alkaloids and pharmaceuticals.[8] For example, *N*-methylwelwitindolinone D (**A**) and HepG2 (**B**) are used as an anticancer agent and growth inhibitor, respectively,[9] compound **C** shows antifungal activity,[10] and compounds **D**−**F** display antitobacco mosaic virus and cytotoxic activities (Scheme 1a).[11] The construction of such skeletons has attracted significant attention from chemists, including Lewis acid-catalyzed [3 + 2] cycloaddition of vinyl silanes with isatins,[12] aminocatalytic 1,6-addition of 3-hydroxy-2-oxindoles to linear 2,4-dienals,[13] three-component reactions of isocyanides, substituted allenoates, and isatins,[14] palladium-catalyzed asymmetric [3 + 2] cycloaddition of vinyl cyclopropanes and isatins,[15] phosphine-catalyzed [3 + 2] cycloaddition of ynones and isatins,[16] and acid-catalyzed intramolecualr cyclization of 3-allyl-3-hydroxy-2-oxindoles.[17] In 2019, Aksenov, Rubin, and co-workers reoprted the [4 + 1] cycloadducts of indoles and nitrostyrenes.[18] However, the [4 + 1] cycloaddition leading to spirotetrahydrofuran oxindoles still is very limited using oxindole derivatives as the both electrophilic and nucleophilic C_1 synthons at C-3 of the oxindole unit.

2-Methylidenetrimethylene carbonate (**2**)[19a] and its derivative **A-6**[19b] in Scheme 1b are one kind of useful motif, and their palladium-catalyzed decarboxylation forms the corresponding zwitterionic allylpalladium intermediates. Further reactions of the intermediates provide the cyclic products, in which the reactions usually start with nucleophilic attack of the oxygen anion in the zwitterionic allylpalladium intermediates to the partners, after which palladium-catalyzed intramolecular allylation gives the target products. For example, palladium-catalyzed decarboxylation of **2** yields zwitterionic allylpalladium intermediate **A-3**. Then nucleophilic addition of the oxygen anion in **A-3** to the Michael acceptor (**A-1**) provides **A-4**, and intramolecular allyation of **A-4** affords the target product **A-2** (Scheme 1b). To realize our [4 + 1] cycloaddition strategy, we designed diphenyl 2-oxoindolin-3-yl phosphates **1** as the partners of **2**. We found that the two kinds of substrates were easily prepared: chemoselective 1,2-addition of diphenyl phosphite to *N*-alkylisatins and subsequent base-promoted migration of the diphenoxyphosphoryl moiety from carbon to oxygen provided **1** via the phospha-aldol-Brook rearrangement reaction,[20] and treatment of 2-methylenepropane-1,3-diol with triphosgene in the presence of base gave **2**.[19a] We designed a palladium-catalyzed [4 + 1] cycloaddition process of **1** and **2**. As shown in Scheme 1c, allylation of **1** with **A-3** at C-3 would give **A-8**, and intramolecular nucleophilic attack of the oxygen anion at C-3 would afford the target product **3** with release of diphenyl phosphate.

To verify our design in Scheme 1c, we used diphenyl 1-methyl-2-oxoindolin-3-yl phosphate (**1a**) and **2** as the model substrates to optimize the reaction conditions, including the catalyst, base, solvent, and reaction time. As shown in Table 1, the palladium-catalyzed [4 + 1] cycloaddition of the two substrates at room temperature provided the target product **3a**

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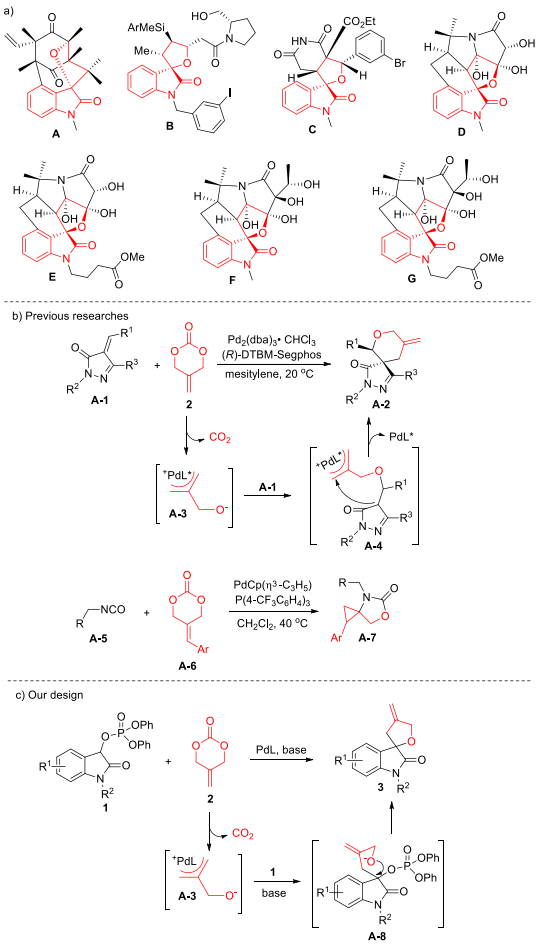
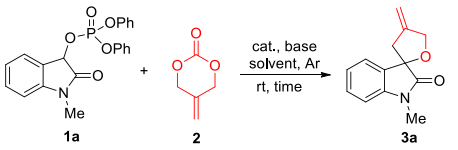
Scheme 1. (a) Representative Examples of Spirotetrahydrofuran Oxindoles with Various Biological Activities; (b) Previous Reactions of 2-Methylidenetrimethylene Carbonate and Its Derivatives; (c) Our Design for the Synthesis of Spirotetrahydrofuran Oxindoles



in 88% yield using $Pd(PPh_3)_4$ as the catalyst, K_2CO_3 as the base, and toluene as the solvent for 12 h (entry 1). We tested $Pd_2(dba)_3$ and $Pd(OAc)_2$ as the catalysts (entries 2 and 3, respectively), and they were inferior to $Pd(PPh_3)_4$ (compare entries 1−3). No reaction occurred in the absence of catalyst (entry 4). Five other solvents were tested (entries 5−9), and we found that toluene was suitable (compare entries 1 and 5−9). When Na_2CO_3, Cs_2CO_3, K_3PO_4, or Et_3N was used in place of K_2CO_3 as the base (entries 10−13), Cs_2CO_3 afforded the highest yield (96%) (entry 11). We investigated the reaction time and found that 6 h was satisfactory (compare entries 11 and 14).

With the optimized conditions in hand, the substrate scope for the [4 + 1] cycloaddition of **1** and **2** was surveyed (Scheme 2). First, we investigated variation of the R^2 substituent in **1** and found that methyl (**3a**, 96% yield), *n*-butyl (**3b**, 90% yield), allyl (**3c**, 94% yield), benzyl (**3d**, 97% yield), *o*-methylbenzyl (**3e**, 99% yield), *p*-methoxybenzyl (**3f**, 97% yield), methoxymethyl (**3g**, 92% yield), and phenyl (**3h**, 87% yield) were feasible. Subsequently, the effect of the R^1 substituent on the phenyl ring of **1** was surveyed, and substrates **1** containing electron-donating groups, including 5-Me (**3i** and **3l**, 99% and 90% yield, respectively), 7- or 6-Me

Table 1. Optimization of the Conditions for Catalytic [4 + 1] Cycloaddition of Diphenyl 1-Methyl-2-oxoindolin-3-yl Phosphate (1a) and 2-Methylidenetrimethylene Carbonate (2)[a]



entry	cat.	base	solvent	time (h)	yield (%)[b]
1	$Pd(PPh_3)_4$	K_2CO_3	toluene	12	88
2	$Pd_2(dba)_3$	K_2CO_3	toluene	12	NR
3	$Pd(OAc)_2$	K_2CO_3	toluene	12	NR
4	–	K_2CO_3	toluene	12	NR
5	$Pd(PPh_3)_4$	K_2CO_3	xylene	12	79
6	$Pd(PPh_3)_4$	K_2CO_3	MeCN	12	73
7	$Pd(PPh_3)_4$	K_2CO_3	CH_2Cl_2	12	74
8	$Pd(PPh_3)_4$	K_2CO_3	DCE	12	86
9	$Pd(PPh_3)_4$	K_2CO_3	DMF	12	65
10	$Pd(PPh_3)_4$	Na_2CO_3	toluene	12	48
11	$Pd(PPh_3)_4$	Cs_2CO_3	toluene	12	96
12	$Pd(PPh_3)_4$	K_3PO_4	toluene	12	30
13	$Pd(PPh_3)_4$	Et_3N	toluene	12	76
14	$Pd(PPh_3)_4$	Cs_2CO_3	toluene	6	96

[a]Reaction conditions: **1a** (0.15 mmol, 1.0 equiv), **2** (0.225 mmol, 1.5 equiv), catalyst (3.75 μmol, 2.5 mol %), base (0.3 mmol, 2.0 equiv) in the indicated solvent (1.5 mL) at the indicated temperature (rt, ∼25 °C) for the indicated time (6−12 h) in a sealed Schlenk tube under an argon atmosphere. DCE = 1,2-dichloroethane. DMF = *N*,*N*-dimethylformamide. [b]Isolated yields. NR = no reaction.

(**3j** and **3m**, 91% and 92% yield, respectively), and 5-MeO (**3s**, 85% yield), weak electron-withdrawing groups, including 5-F (**3n**, 56% yield), 5- or 6-Cl (**3k** and **3o**, 94% and 80% yield, respectively), and 5-Br (**3p** and **3r**, 89% and 64% yield, respectively), and strong electron-withdrawing groups, including 5-NO_2 (**3q**, 77% yield), provided satisfactory results. Therefore, the present method shows a wide substrate scope and tolerance of functional groups, and it will find extensive application in the synthesis of spirooxindole derivatives. In order to ascertain the structures of the newly synthesized products **3**, a single crystal of **3j** was prepared in a mixed solvent of *n*-hexane and ethyl acetate (4:1 v/v), and its structure was unambiguously confirmed by X-ray diffraction analysis (see the Supporting Information for details).

We attempted a one-pot two-step synthesis of **3a** using 1-methylindoline-2,3-dione (**4**), diphenyl phosphonate (**5**), and **2** as the starting materials: addition of the P−H bond in **5** (1.0 equiv) to the carbonyl at the 3-position of **4** and subsequent phospha-aldol-Brook rearrangement in the presence of 4-dimethylaminopyridine (DMAP) at room temperature for 10 min provided **1a**, and then 2.0 equiv of **2** was added to the resulting solution. The reaction of **1a** with **2** in the system was carried out under the standard conditions in Scheme 2, and the target product **3a** was obtained in 80% yield (Scheme 3a). A scaled-up synthesis of **3a** was also surveyed. As shown in Scheme 3b, the palladium-catalyzed reaction of **1a** (1 mmol, 395 mg) and **2** (2 mmol, 228 mg) under the standard conditions afforded **3a** in 95% yield, representing almost no loss of yield relative to the reaction of smaller amounts of the substrates. The results above show that our method is very efficient and practical.

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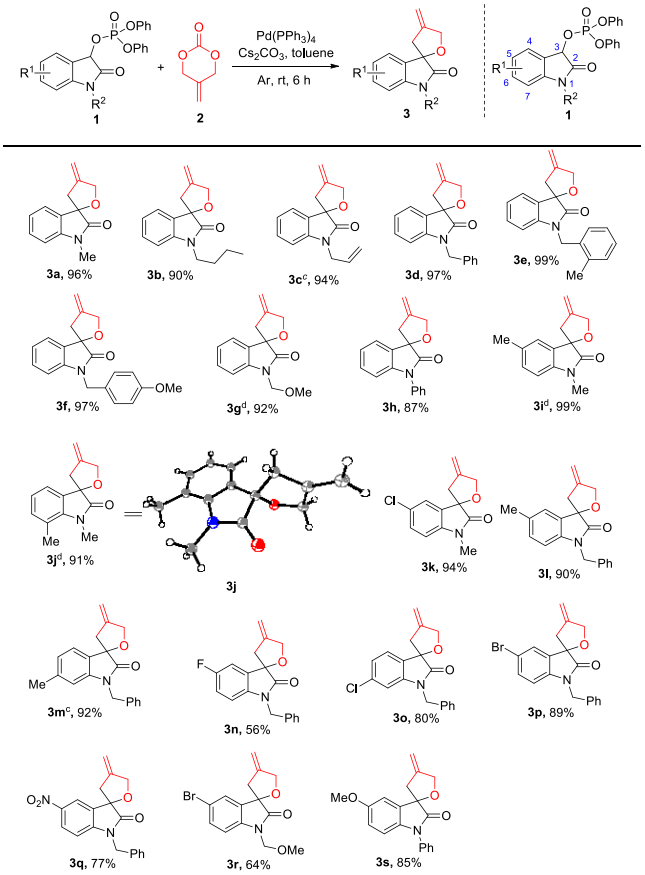
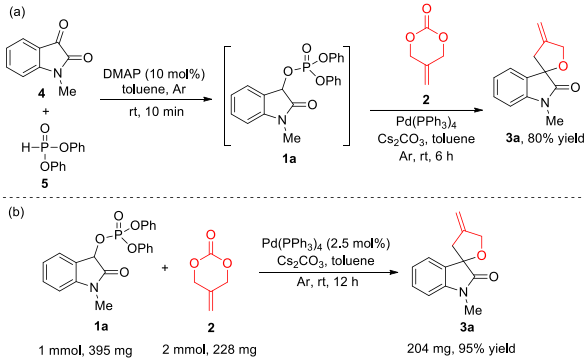
Scheme 2. Substrate Scope for the [4 + 1] Cycloaddition of 1 and 2[a,b]



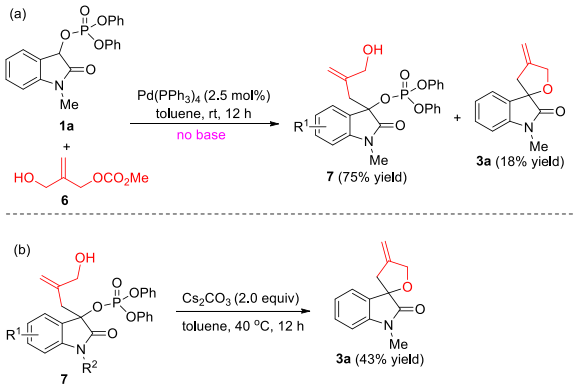
[a]**1** (0.15 mmol, 1.0 equiv), **2** (0.225 mmol, 1.5 equiv), $Pd(PPh_3)_4$ (3.75 μmol, 2.5 mol %), and Cs_2CO_3 (0.3 mmol, 2.0 equiv) in toluene (1.5 mL) at rt (~25 °C) for 6 h in a sealed Schlenk tube under an argon atmosphere. [b]Isolated yields are shown. [c]The reaction was run for 4 h. [d]The reaction was run for 2.5 h.

Scheme 3. (a) One-Pot Two-Step Synthesis of 3a and (b) Scaled-Up Synthesis of 3a



To explore the reaction mechanism for the synthesis of **3**, two control experiments were carried out. First, the $Pd(PPh_3)_4$-catalyzed reaction of **1a** with 2-(hydroxymethyl)allyl methyl carbonate (**6**) in the absence of base provided **7** as the major product in 75% isolated yield and **3a** as the minor product in 18% isolated yield (Scheme 4a). Second, treatment of **7** with Cs_2CO_3 produced **3a** in 43% isolated yield (Scheme 4b). These results showed that the reactions in Scheme 2

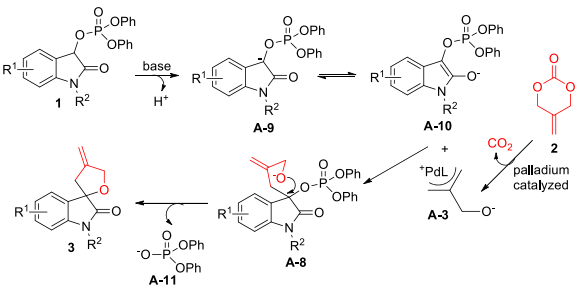
Scheme 4. (a) Palladium-Catalyzed Reaction of 1a with 6 in the Absence of Base and (b) Treatment of 7 with Cs_2CO_3



proceeded by a sequential two-step process including palladium-catalyzed allylation and nucleophilic substitution of oxygen anion at C-3 of **1**.

Furthermore, ^{31}P NMR tracking experiments were performed for the Pd-catalyzed reaction of **1a** with 1.5 equiv of **2** in $CDCl_3$ under the standard conditions. As shown in Figure S1, after the two substrates, $Pd(PPh_3)_4$, $CDCl_3$, and DMAP were mixed at room temperature, the resulting solution was immediately measured by ^{31}P NMR spectroscopy, and we observed two ^{31}P NMR peaks at δ_P = 29.70 and −10.75 ppm, corresponding to $Pd(PPh_3)_4$ and **1a**, respectively. After 5 min, three new signals appeared at δ_P = 30.47, −9.85, and −15.67 ppm, corresponding to **A-8**, **A-3**, and **A-11** in Scheme 5,

Scheme 5. Proposed Mechanism for the Reaction of 1 with 2



respectively. We measured the resulting solution after the reaction was performed for 10 and 30 min, respectively, and a new ^{31}P NMR peak at δ_P = −8.44 ppm was observed, corresponding to **A-9** or **A-10**. After 180 min, we only found two signals at δ_P = 29.70 and −15.67 ppm, corresponding to $Pd(PPh_3)_4$ and **A-11**, respectively, which indicated that the reaction was finished.

According to the above results, including the control experiments in Scheme 4 and the ^{31}P NMR tracking experiments in Figure S1, a possible mechanism is proposed. As shown in Scheme 5, deprotonation at C-3 of **1** by the base (Cs_2CO_3) forms anion **A-9**, and isomerization of **A-9** leads to **A-10**. Meanwhile, palladium-catalyzed decarboxylation of **2** yields zwitterionic allylpalladium intermediate **A-3**. Allylation of **A-10** with **A-3** gives **A-8**, and intramolecular nucleophilic attack of the oxygen anion at C-3 affords the target product **3** with release of diphenyl phosphate (**A-11**).

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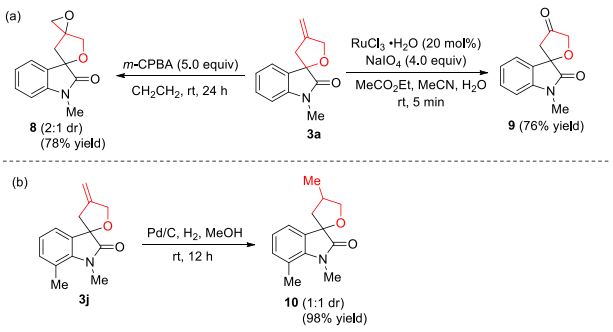
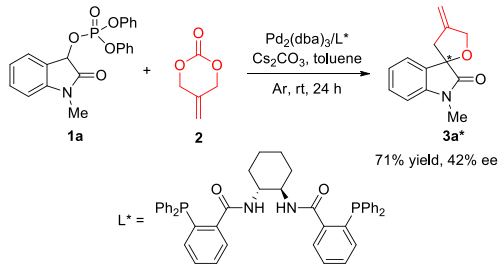
Subsequently, we demonstrated applications of the obtained products. Oxidation of **3a** with *m*-chloroperoxybenzoic acid (*m*-CPBA) or $NaIO_4$ in the presence of $RuCl_3{\cdot}H_2O$ (20 mol %) provided **8** and **9** in 78% and 76% yield, respectively (Scheme 6a). Palladium-catalyzed hydrogenation of **3j** gave **10** in 98% yield (Scheme 6b).

Scheme 6. Applications of the Obtained Products: (a) Oxidation of 3a; (b) Reduction of 3j



We attempted the asymmetric [4 + 1] cycloaddition of **1a** and **2**, and various catalysts and chiral ligands were screened (see Table S1 for the details). Unfortunately, the reaction provided only moderate enantioselectivity (42% ee) with $Pd_2(dba)_3$ as the catalyst in the presence of a chiral diphosphine ligand (Scheme 7).

Scheme 7. Preliminary Result of the Asymmetric Experiment



In summary, we have developed a new method for the synthesis of spirotetrahydrofuran oxindoles, in which diphenyl 2-oxoindolin-3-yl phosphates were used as the both electrophilic and nucleophilic C_1 synthons at C-3 of the oxindole unit and 2-methylidenetrimethylene carbonate was used as the 1,4-dipole. The palladium-catalyzed [4 + 1] cycloaddition of the two kinds of substrates at room temperature provided the corresponding target products in good to excellent yields. The novel [4 + 1] cycloaddition strategy affords a valuable pathway for the synthesis of other spirooxindole derivatives.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02306.

Full experimental details and characterization data, including ^1H, ^{13}C, and ^{31}P NMR spectra, for the synthesized products (**3a−s** and **7−10**), and crystallographic data for **3j** (PDF)

Accession Codes

CCDC 2088445 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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