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Multicomponent Reactions of Phosphines, Enynedioates and Cinnamaldimines Give γ-Lactams with a 1,3,5-Hexatriene Moiety for Facile 6π Electrocyclization: Access to Oxindoles, Isatins and Isoxazolinones

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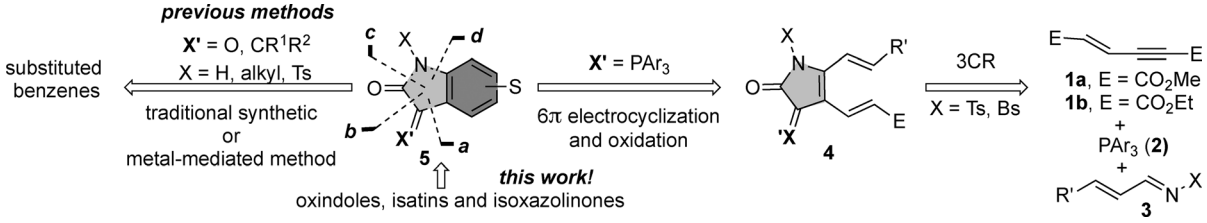
Abstract: Multicomponent reactions of phosphines, enynedioates and cinnamaldimines generated 3-phosphorus ylide γ-lactams having a 1,3,5-hexatriene moiety with low activation energy barrier for 6π electrocyclization, through initial formation of 1,3-dipoles from the α(δ′)-Michael addition of phosphines to enynedioates. The reactive 1,3-dipoles underwent addition to cinnamaldimines, lactamization, 6π electrocyclization and oxidation to give 3-phosphorus ylide oxindoles as platform molecules toward isatins and isoxazolinones. The key step, 6π electrocyclization, was further examined by a kinetic and a computational study.

Keywords: electrocyclic reactions; Michael addition; multicomponent reactions; phosphorus; transition states

Introduction

Oxindoles, structurally indispensable heterocyclics in pharmaceutical applications, possess numerous bioactive properties,[1] and are important precursors for the synthesis of potential drugs, such as physostigmine for treatment of glaucoma and Alzheimer's disease,[2] and tenidap for treatment of inflammation and arthritis,[3] as well as a new class of spiro-oxindoles such as non-peptide MDM2 inhibitors for inhibiting tumor cell growth.[4] Methodology towards the preparation of structurally-diverse oxindoles such as 1*H*-indole-2,3-diones (isatins, X′=O), 3-alkylideneoxindoles (X′=CR^1R^2), and 3,3-disubstituted oxindoles has therefore become a significant synthetic topic (Scheme 1). The developed synthetic methodology toward oxindoles **5** can be divided into four bond formation pathways ***a***–***d*** for generating the γ-lactam moiety from substituted benzenes. For bond formation through ***a***, isatins can be obtained by cyclization of isonitrosoacetanilide in the presence of sulfuric acid;[5] in addition, 3-alkylideneoxindoles[6] and 3,3-disubstituted oxindoles[7] were made available *via* transition metal-catalyzed cyclization of *N*-arylpropiolamides, *N*-arylacrylamides and diazo-β-ketoanilide. For bond formation through ***b***, 3-alkylideneoxindoles can be achieved by palladium-catalyzed cyclization of 2-(alkynyl)aryl isocyanates, intramolecular cyanoamidation of alkynyl and alkenyl cyanoformamides, and cyclization of carbamoyl chlorides with a proximate alkenyl or alkynyl moiety[8] or by taking advantage of rhodium[9] or iron catalysis[10] with the above substrates. Further ap-



Scheme 1. Traditional and our proposed synthetic strategy toward oxindoles **5**.

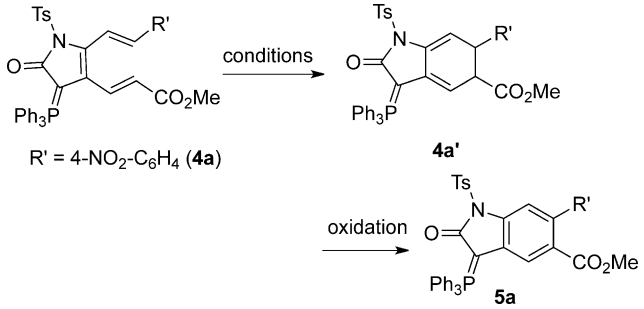
proaches to oxindoles through amidic bond formation *via* ***c*** generally involve insertion of carbon monoxide under metal catalysis; for example, carbonylative cycloaddition of 2-alkynylanilines or 2-alkenylanilines to give 3-alkylideneoxindoles by Co, Pd or Rh catalysis.[11] In this bond formation pathway, isatins can also be synthesized by amination of the C–H bond from 2-aminoaryl methyl ketone under an oxygen atmosphere by Cu(I) catalysis.[12] Lastly, the highly efficient *N*-arylation methodology provided oxindoles from 2-arylpropanamides by Cu, Pd or Ag catalysis through formation of bond ***d***.[13] The common feature of previous versatile synthetic methods to oxindoles was the use of substituted benzenes as their starting substrates and no synthetic reports ever concerned approaches *via* the initial set-up of a γ-lactam moiety followed by construction of the fused benzene moiety. We have developed three-component reactions (3CRs) of organophosphines with alkynoates,[14] such as dimethyl acetylenedicarboxylate (DMAD),[14b] (*E*)-hex-2-en-4-ynedioic acid dimethyl ester,[15] and oligoynoates,[16] generating zwitterions, followed by addition to electrophiles, such as aldehydes and imines, to give highly substituted γ-lactones or lactams. In principle, the developed methodology could be employed to prepare oxindole derivatives, provided that both β- and γ-carbons of γ-lactams were equipped with an alkenyl moiety for subsequent 6π electrocyclization and oxidation (Scheme 1). This approach would be synthetically challenging since placement of an alkenyl functionality on both β- and γ-carbons on lactams to give **4** is non-trivial by conventional methods. Furthermore, to the best of our knowledge, 6π electrocyclization of hexatrienes was relatively disfavored to give 1,3-cyclohexadiene with a free energy of activation $\Delta G^{\ddagger}$ of 30.7 kcal·mol^{-1} at 298 K [see Supporting Information, Scheme S1 (a)] and could proceed under thermodynamic and photochemical conditions for application in natural products synthesis.[17] A study towards understanding the thermodynamics and kinetics of the 6π electrocyclization of 1-dimethylamino-1,3,5-hexatriene relevant to substitution effects by hybrid density functional calculations revealed a decreased activation barrier of 17–25 kcal·mol^{-1} by placement of an electron-withdrawing group (EWG) at C-2.[18] Significant findings through the two-layer ONIOM method by Fu and Liu suggested approaches to promote the sluggish electrocyclization of 1,3,5-hexatrienes by specific captodative substitution.[19] In this context, monosubstitution of hexatriene at C-1 showed minute effects on the activation energy and that at C-2 or C-3 may reduce the activation energy by up to 6 kcal·mol^{-1} (24.8–31.9 kcal·mol^{-1}). Furthermore, a particular captodative disubstitution of hexatrienes may cause a decrease of the activation energy by up to 10 kcal·mol^{-1}.

Examples of facile 6π electrocyclization of disubstituted hexatrienes at room temperature were rare[20] and those with higher substituted hexatrienes were even scarcely available for practical study. We noted that 3,4-thienyl-fused 1,3,4,5-tetrasubstituted hexatrienes **A** required 6 h for electrocyclization at 200 °C[21] and 3,4-indolo-fused **B** furnished electrocyclization products only at reflux in xylenes (138–140 °C) for 24 h [Supporting Information, Scheme S1 (b)].[22] In another context, photochromic materials have been developed for practical applications through light-controlled isomerization involving 6π electrocyclization of diarylethene photoswitches.[23] Hampered by synthetic availability, our knowledge on 6π electrocyclization of 3,4-aromatic ring-fused 1,3,4,6-tetrasubstituted hexatrienes was relatively limited. Our synthetically available γ-lactams through one-pot 3CRs prompted us to explore the 6π electrocyclization of 3,4-γ-lactam-fused hexatrienes and understand the corresponding changes of activation energy. The cyclization led to useful 3-phosphorus ylide oxindoles as platform molecules toward isatins and isoxazolinones. Herein, we report the syntheses of 3-phosphorus ylide oxindoles through facile 6π electrocyclization of 3,4-γ-lactam-fused 1,3,4,6-tetrasubstituted hexatrienes. The 3,4-γ-lactam-fused hexatrienes were prepared through three-component reactions of phosphines, enynedioates and cinnamaldimines and were found to undergo slow 6π electrocyclization at room temperature in the absence of light. The key step, 6π electrocyclization, was also observed to be accelerated by light, thermal conditions and acid additives, and was corroborated with kinetic and computational transition state studies. Furthermore, 3-phosphorus ylide oxindoles were used as platform molecules toward biologically important isatins and isoxazolinones upon oxidation.

Results and Discussion

To commence this study, lactams **4** were prepared through three-component reactions of enynedioates **1**, phosphines **2** and cinnamaldimines **3**, *via* α(δ′)-Michael addition of phosphines to **1** followed by addition to cinnamaldimines.[15c] Dark purple colored lactams **4** can be prepared in 28–68% yields in one pot, but cannot be isolated in pure form since they underwent 6π electrocyclization spontaneously and subsequent oxidation gradually to give less polar yellowish compounds **5** (2–16%) under ambient conditions. Thus, retrieving pure **4** for spectroscopic characterization was implausible. Furthermore, *N*-substituted α,β-conjugated imines **3** with an aliphatic chain (X = alkyl) were not suitable for the synthesis of **4** due to their labile property upon isolation (Scheme 1).[24] Upon silica gel chromatography in aerobic conditions,

Table 1. Optimization of the reaction conditions.[a]



R' = 4-NO_2-C_6H_4 (**4a**)

Entry	Solvent	Temp. [°C]	Time [h]	Conc. [mM]	Yield [%][b]
1	EA	r.t.	24	0.25	14
2	EA	77	24	0.25	26
3	ACN	83	24	0.25	46
4	DCE	84	24	0.25	70
5	$CHCl_3$	62	24	0.25	62
6	DCM	40	24	0.25	45
7	*o*-DCB	84	24	0.25	57
8	PhCl	84	24	0.25	52
9	toluene	111	24	0.25	21
10[c]	DCE	84	24	0.25	41
11[c]	DCE	84	3	0.25	79
12[c]	DCE	84	3	0.13	79
13[c]	DCE	84	3	0.50	75
14[c,d]	DCE	84	3	0.50	63
15[c,d]	DCE	84	1	0.50	92
16[e]	DCE	84	24	0.50	3

[a] Reactions were carried out with **4a** (0.010 mmol) in denoted solvents under aerobic conditions unless otherwise noted.

[b] Yields were determined by ^{1}H NMR spectroscopy with mesitylene as an internal standard.

[c] Irradiated by a 500 W halogen lamp at a distance of 25 cm.

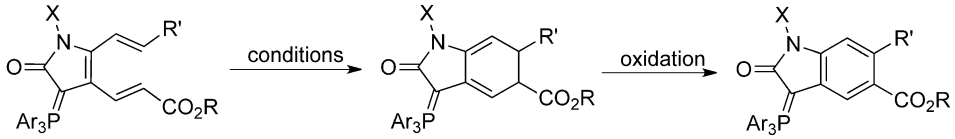
[d] 3 equiv. of acetic acid were added as an additive.

[e] 3 equiv. of Cs_2CO_3 were added as an additive and the mixture was bubbled with O_2.

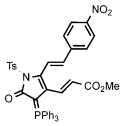
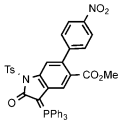
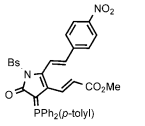
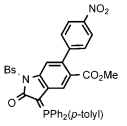
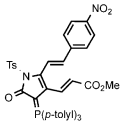
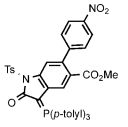
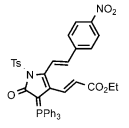
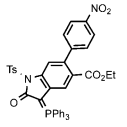
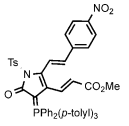
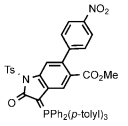
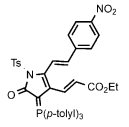
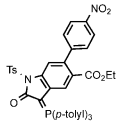
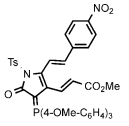
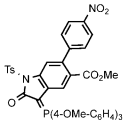
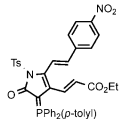
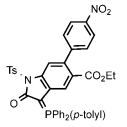
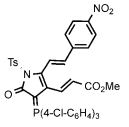
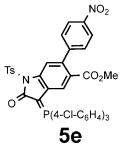
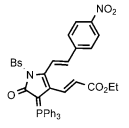
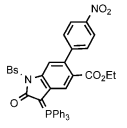
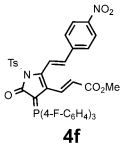
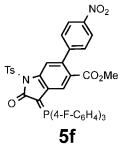
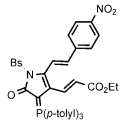
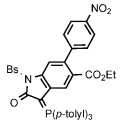
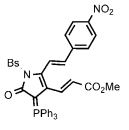
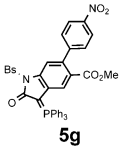
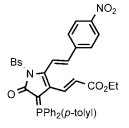
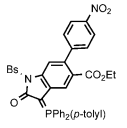
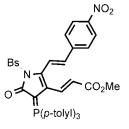
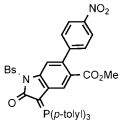
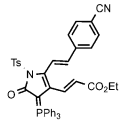
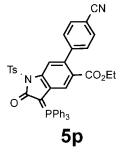
we observed that **4** also slowly underwent 6π electrocyclization to give oxindoles **5**. We investigated the optimal conditions for their transformation to **5** through 6π electrocyclization in a freshly prepared solution containing both **4** and 2–16% of **5** (Table 1). Lactam **4a** (0.25 mM in solvents) was chosen as the model substrate for optimization of the conditions of the 6π electrocyclization under aerobic and thermal conditions. Although lactam **4a** was easily converted to **5a** during column chromatography, we found that its transformation to **5a** was sluggish in ethyl acetate (14% and 26% yields, entries 1 and 2) and moderate in acetonitrile (46%, entry 3) – this finding indicated that such a cyclization may be promoted by slightly acidic silica gel. We further noted that reactions in chlorinated solvents, such as 1,2-dichloroethane (DCE), $CHCl_3$, dichloromethane (DCM), *o*-dichlorobenzene (*o*-DCB) and chlorobenzene, gave promising outcomes (entries 4–8; 70%, 62%, 45%, 57% and 52%, respectively); but that in the non-chlorinated aromatic solvent, toluene, did not. Furthermore, the reaction rate of the 6π electrocyclization can be accelerated under photochemical conditions with halogen lamp irradiation, providing good yields of **5a** (entries 10 and 11). Doubly reducing or increasing the solution concentration also gave comparable yields under photochemical conditions (entries 12 and 13). To our delight, the reaction rate of 6π electrocyclization was accelerated evidently by the addition of acetic acid (entries 14 and 15). We obtained 92% yield with 3 equiv. of acetic acid as an additive under photochemical conditions for 1 h. A control experiment displayed that the use of bases as additives such as Cs_2CO_3 impeded the performance of the 6π electrocyclization, resulting in a poor yield (3%, entry 16). In contrast to the oxidation of cyclohexadienyl to the benzene moiety with a catalytic amount of Pd/C as reported by Srinivasan and co-workers,[25] we found that cyclohexadienyl fused γ-lactam intermediate **4a′** can be readily oxidized to **5a** in air without additional Pd/C. In short, this 6π cyclization was accelerated by thermal and photochemical conditions[26] as well as by the use of acid additives.

After optimizing the reaction conditions for the 6π electrocyclization, we next scaled up the reaction and examined the reaction scope (Table 2). We found that increasing the reaction scale by 3-fold did not require extension of the reaction time for the 6π electrocyclization to achieve comparable yields (Table 2, entry 1, 1 h, 88% *versus* Table 1, entry 15, 1 h, 92%). Changes of the substitution on lactams **4** resulted in different reactivities in the 6π electrocyclization step. Lactams **4** equipped with electron-releasing phosphines were found to be more reactive – electrocyclization of intermediates **4b** and **4c** equipped with electron-releasing phosphines resulted in good yields (entries 2 and 3; 85 and 80%) under the same irradiation time as compared to that with unsubstituted triphenylphosphine **4a**, and lactam **4d** required even less halogen lamp irradiation time for comparable yields (entry 4, 85%). However, intermediates **4e** and **4f** with electron-withdrawing phosphines demanded for more irradiation time to give comparably good yields (entry 5, 88%; entry 6, 85%). Furthermore, a minor influence on the reactivity of **4** was observed with differing *N*-substitution. When the tosyl (Ts) substitution on the lactam nitrogen was altered to benzenesulfonyl (Bs), the intermediates **4** became slightly less reactive toward cyclization (entry 7, 87%; entry 8, 80%; entry 9, 84%). When **4** were equipped with ethyl esters, their reactivity also became lower – an extended reaction time was required to achieve good yields (entries 10–15, 81–89%). Lastly, the 4-cyanocinnamaldimine derived lactam **4p** accelerated its 6π electro-

Table 2. Scope of the reaction.[a]



R' = 4-NO_2-C_6H_4 or 4-CN-C_6H_4 (**4**)

Entry	**4**	Product (**5**)	Time; Yield[b]	Entry	**4**	Product (**5**)	Time; Yield[b]
1	 **4a**	 **5a**	1 h; 88 %	9	 **4i**	 **5i**	1 h; 84 %
2	 **4b**	 **5b**	1 h; 85 %	10	 **4j**	 **5j**	1.5 h; 86 %
3	 **4c**	 **5c**	1 h; 80 %	11	 **4k**	 **5k**	1.5 h; 81 %
4	 **4d**	 **5d**	0.5 h; 85 %	12	 **4l**	 **5l**	1.5 h; 89 %
5	 **4e**	 **5e**	1.5 h; 88 %	13	 **4m**	 **5m**	2 h; 86 %
6	 **4f**	 **5f**	1.5 h; 85 %	14	 **4n**	 **5n**	2 h; 85 %
7	 **4g**	 **5g**	1.5 h; 87 %	15	 **4o**	 **5o**	2 h; 85 %
8	 **4h**	 **5h**	1.5 h; 80 %	16	 **4p**	 **5p**	0.5 h; 70 %

[a] Reactions were carried out with **4** in DCE (0.030 mmol; conc. = 0.50 mM) and 3 equiv. of acetic acid as an additive, and irradiated by a 500 W halogen lamp at a distance of 25 cm. [b] Isolated yields (%).

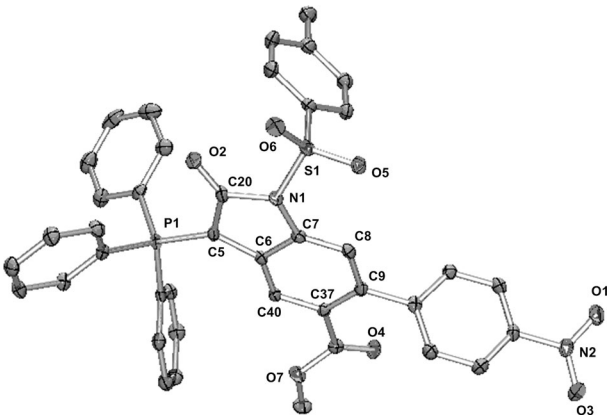


Figure 1. X-ray single crystal structure of compound **5a**.

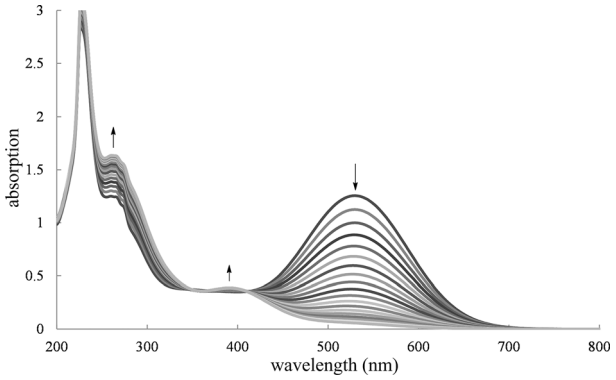


Figure 2. UV-*vis* absorption spectra of **4a** in DCE under halogen lamp irradiation at 25 °C, measured every 15 min.

cyclization but with relatively lower yield (entry 16, 70%). Overall, the more electron-rich the lactams **4**, the higher is the reactivity that **4** exhibited.

We characterized the isolated 3-phosphorus ylide oxindoles **5a**–**p** by ^{1}H, ^{13}C, ^{31}P NMR spectroscopy, IR, ESI-MS, and X-ray crystallography. Taking compound **5a** as an example, we found two singlet signals at $\delta =$ 2.45 and 3.43 ppm corresponding to the methyl moiety on the tosyl and methoxy groups, respectively, in the ^{1}H NMR spectrum. The two protons on C-8 and C-40 (Figure 1) appeared at $\delta = 5.97$ and 7.91 ppm, respectively. In the ^{13}C NMR spectrum, a doublet centered at $\delta = 54.8$ ppm represented the phosphorus ylidic carbon C-5 with $^{1}J_{P,C} = 132.1$ Hz and the two carbonyl groups, from the lactam moiety and the carboxylic ester, appeared at $\delta = 166.8$ ($^{2}J_{P,C} =$ 17.1 Hz) and 168.1 ppm, respectively. We observed a typical singlet at $\delta = 12.2$ ppm in the ^{31}P NMR spectrum. The carbonyl stretching bands of the lactam and ester appeared at 1660 and 1723 cm^{-1} in the IR spectrum, respectively. Furthermore, a single crystal of **5a** was grown from a chloroform solution for X-ray diffraction analysis (Figure 1).[27] The β and γ carbons of the lactam moiety were covalently bonded to the benzene moiety, proving the core structure of the oxindole. The oxindole skeleton was close to planar, as evidenced by the torsional angles of C-6–C-7–C-8–C-9 and N-1–C-7–C-8–C-9, –0.1(4)° and 178.6(3)°, respectively. Due to negative charge delocalization from the ylidic carbon C-5 to the carbonyl group (C-20–O-2), the C-5–C-20 bond was shorter, 1.424(4) Å, than a typical carbon-carbon single bond.

We further investigated the reaction rate of the 6π electrocyclization with **4a** under thermal and photochemical conditions by ^{1}H NMR and UV-vis spectroscopy, respectively. As reflected from the descending absorption at 529 nm and slight ascending absorption at 392 nm, the purple coloured solution faded and became a yellowish solution of **5a**. The reaction rate was found to be $6.02 \pm 0.14 \times 10^{-6}$ s^{-1} at 25 °C with 200 equiv. of acetic acid in the absence of light (Supporting Information, Figure S58). Furthermore, the reaction rate was measured to be $1.48 \pm 0.03 \times 10^{-4}$ s^{-1} under halogen lamp irradiation (Figure 2 and Supporting Information, Figure S59).

Furthermore, we calculated the activation energy for the 6π electrocyclization of **4a** to **4a′** at the B3LYP 6-31G(d) level of theory and found two possible transition state structures, **TS1** and **TS2** (Figure 3), for formation of electrocyclization intermediates **4a$_1$′** and **4a$_2$′** through a suprafacial fashion, respectively. Transition structure **TS2** with 4-nitrophenyl and methyl ester groups *syn* to the 4-methylphenyl moiety of the tosyl group possessed an unusually low activation energy (E_a) of 12.6 kcal·mol^{-1}, while the other transi-

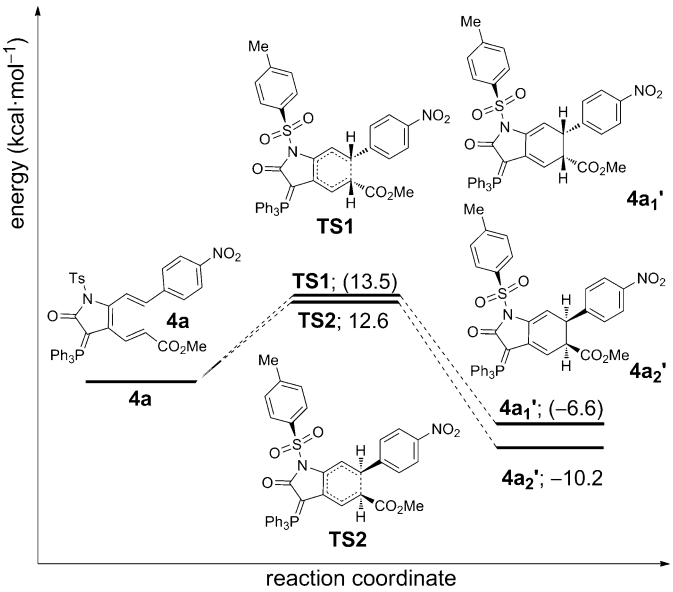
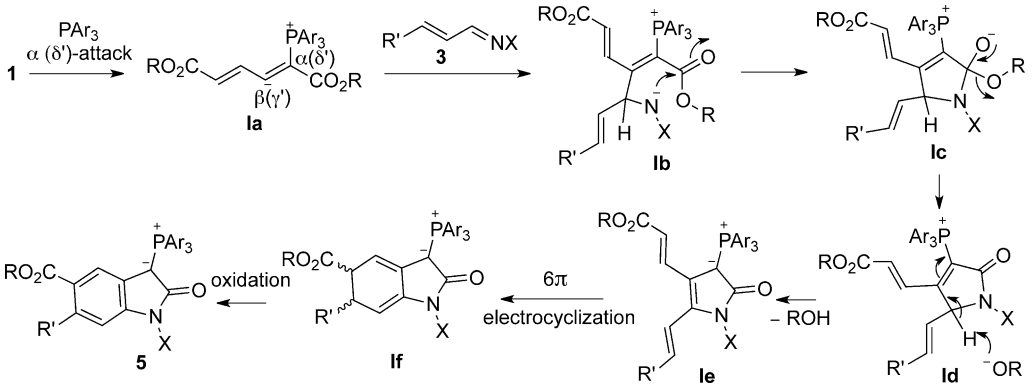


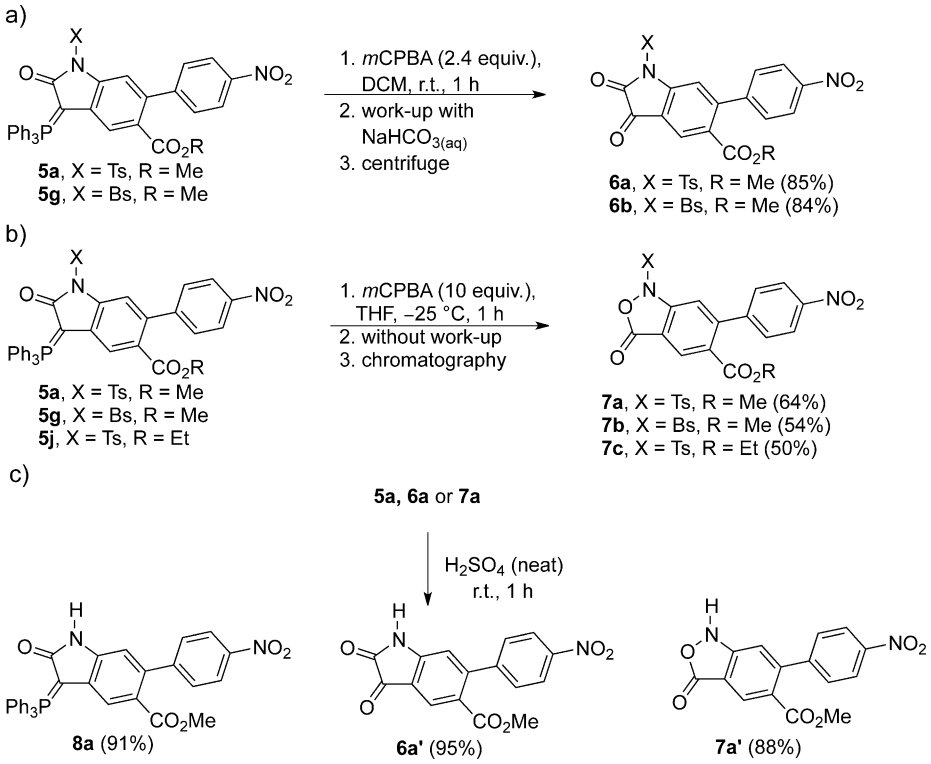
Figure 3. Relative energies (kcal·mol^{-1}) of the thermal 6π electrocyclization pathways computed at the B3LYP 6-31G(d) level of theory; values in parentheses were the relative energies of this electrocyclization through transition state **TS1**.



Scheme 2. Proposed mechanism for the formation of 3-phosphorus ylide oxindoles 5.

tion structure **TS1** with 4-nitrophenyl and methyl ester groups *anti* to the 4-methylphenyl moiety of the tosyl group showed E_a of 13.5 kcal·mol^{-1}. These computed activation energies (E_a) for 6π electrocyclization were close to the results of our kinetic study with $E_a = 13.6 \pm 0.4$ kcal·mol^{-1} by ^{1}H NMR spectroscopy tracing (Supporting Information, Figures S60 and S61). The measured thermal 6π electrocyclization rates were found to be $1.06 \pm 0.05 \times 10^{-4}$ s^{-1}, $1.83 \pm 0.07 \times 10^{-4}$ s^{-1}, $3.20 \pm 0.09 \times 10^{-4}$ s^{-1}, and $5.77 \pm 0.16 \times 10^{-4}$ s^{-1} at 60, 70, 80 and 90 °C, respectively.

We accounted for this overall studied reaction with the following mechanism. First, PAr_3 underwent nucleophilic attack to the α(δ′)-carbon of enynedioates **1** (Scheme 2), generating zwitterions **Ia** with a negative charge on the β(γ′)-carbon. Addition of **Ia** to the carbon-nitrogen double bond of cinnamaldimines **3**, followed by intramolecular cyclization of **Ib**, gave intermediates **Ic**. After alkoxides had been released, deprotonation of **Id** took place to form labile intermediates **Ie**. Oxindoles **5** were then formed after 6π electrocyclization and air oxidation from **Ie** through cyclohexadiene intermediates **If**.



Scheme 3. a) Synthesis of isatins **6a**, **b** from oxindoles **5a** and **5g**. b) Synthesis of isoxazolinones **7a–c** from oxindoles **5a**, **5g** and **5j**. c) Deprotection of the Ts group of **5a**, **6a** and **7a** by treatment with concentrated sulfuric acid to give oxindole **8a**, isatin **6a′** and isoxazolinone **7a′**, respectively.

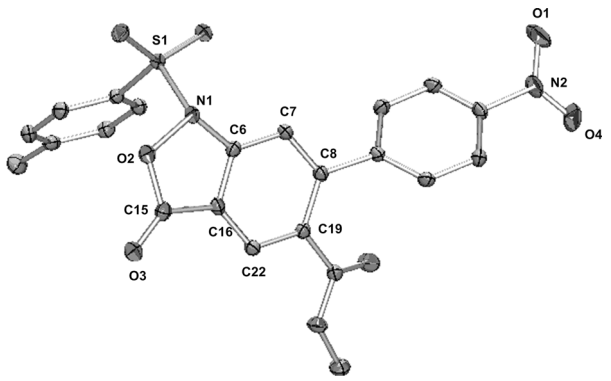
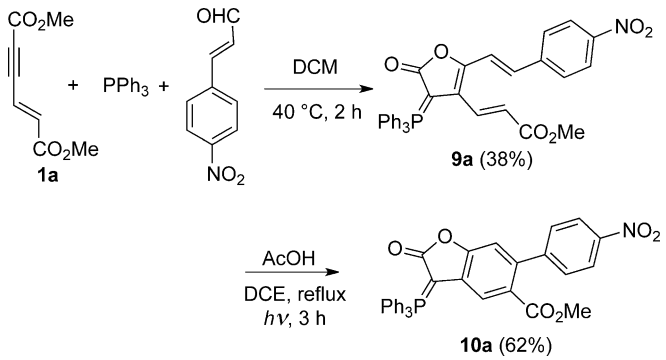


Figure 4. X-ray single crystal structure of isoxazolinone **7a**.



Scheme 4. Synthesis of γ-lactone **9a** and benzofuranone **10a**.

3-Phosphorus oxindoles **5** were reactive toward both oxidizing and reducing agents. To convert compound **5a** to functional substituted isatins, we attempted to oxidize its ylidic C=P bond to a carbonyl moiety. As our first choice, we used $NaIO_4$[28] as oxidant in ethanol/H_2O as co-solvents, but no expected reaction occurred under reflux for overnight. Another attempted oxidation of **5a** by O_2 in dichloromethane under photochemical conditions for 24 h was also ineffective.[29] To our delight, formation of isatins **6a**, **b** was observed on using *m*CPBA[30] as an oxidant (Scheme 3a). Oxidative cleavage of the C=P bond required more than two equivalents of *m*CPBA (2.4 equiv.) for providing oxygen to by-product phosphine oxides and isatins. Oxindole **5a** was not consumed completely with an insufficient amount of *m*CPBA (1.2 equiv.) at −25 °C, evidenced by two sets of aromatic signals corresponding to **5a** and isatin **6a** in the ^{1}H NMR spectra of the crude mixture. To obtain pure isatins **6a**, **b**, the reaction mixtures were quenched and extracted with saturated sodium bicarbonate first for removal of unreacted *m*CPBA. Pure orange solid isatins **6a**, **b** were isolated in *ca.* 85% yield by precipitation of **6a**, **b** with *n*-hexane. The isatin derivatives are biologically active compounds that could exhibit antitumor and antibacterial activities.[31]

Furthermore, overoxidation of oxindoles **5a**, **5g**, and **5j** with excess *m*CPBA (10 equiv.) at −25 °C gave isoxazolinones **7a–c** as the major products (50–64%), respectively (Scheme 3b). Compound **7a** was unambiguously characterized by its single crystal structure (Figure 4).[32] Isoxazolinones, normally synthesized by reduction of methyl *ortho*-nitrobenzoate with zinc and NH_4Cl[33] or photolysis of *ortho*-azidobenzoic acid,[34] possess anticonvulsant, antimicrobial and antileukemic activities.[35] Last, the tosyl group (Ts) of oxindole **5a** can be removed with sodium naphthalenide[36] to give only 10% yield of **8a**. However, **8a** was formed in 91% yield under treatment with neat H_2SO_4 at room temperature; deprotected isatin **6a′** and isoxazolinone **7a′** can also be obtained by treatment of concentrated H_2SO_4, respectively (Scheme 3c).[37]

The reactivity of 4-nitrocinnamaldehyde was lower than those of 4-nitro- and 4-cyanocinnamaldimines in the three-component reaction with phosphines and enynedioates. A thermally stable γ-lactone **9a** was isolated in 38% yield. The 6π electrocyclization was also found to be slower under standard conditions, giving benzofuranone **10a**[38] in 62% yield (Scheme 4). Reactions with cinnamaldehyde and cinnamaldimine did not yield the corresponding lactone and lactam due to their poor reactivity.

Conclusions

In conclusion, we have successfully developed distinguished approaches to 3-phosphorus oxindoles, isatins and isoxazolinones from three-component reactions of phosphines, enynedioates and cinnamaldimines – *via* α(δ′)-Michael addition of phosphines to enynedioates followed by addition to cinnamaldimines, and further 6π electrocyclization and oxidation. The overall reaction involves a facile 6π electrocyclization of 3,4-γ-lactam-fused 1,3,4,6-tetrasubstituted 1,3,5-hexatrienes with an unusually low activation barrier according to computational and kinetic studies. The C=P bond of 3-phosphorus ylide oxindoles can be oxidized to a carbonyl group to give isatins with appropriate amounts of *m*CPBA and to provide isoxazolinones with excess *m*CPBA by overoxidation. This methodology provides a distinguished protocol to the 3-phosphorus oxindole derivatives, isatins and isoxazolinones through α(δ′)-Michael addition and 6π electrocyclization as key steps.

Experimental Section

General Procedure for the Synthesis of Oxindole Derivatives 5a–p

A benzene solution containing enynedioate **1** (0.45 mmol) and cinnamaldimine **3** (0.15 mmol) was distilled to remove moisture residues for three time (anhydrous benzene, 10 mL × 3) with a Dean–Stark apparatus. Then, 22.5 mL of anhydrous dichloromethane (DCM) were added to the resulting mixture followed by addition of phosphine **2** (0.45 mmol). The mixture was stirred under 0 °C for 2 h, and then at room temperature for 22 h. Upon completion of the reaction, DCM was removed under vacuum and the residue then subjected to flash chromatography. Elution with EA/hexanes (3/1) gave purple lactam intermediates **4a–d**, **4g–o** and orange lactam intermediates **4p**; with EA/hexanes (1/1) gave purple lactam intermediates **4e**, **f**, respectively. The amount of **4a–p** was determined by ^{1}H NMR spectroscopy with mesitylene as an internal standard. Appropriate amounts of intermediates **4** (0.030 mmol) was dissolved in 60 mL of anhydrous 1,2-dichloroethane (DCE, 0.50 mM) and then acetic acid (5.1 μL, 0.090 mmol) was added to the solution. The mixture was irradiated by a halogen lamp at reflux (*ca.* 84 °C) for 1 to 2 h and the solution colour changed from purple to orange during this period. Upon completion of the reaction, DCE was removed under vacuum and the resulting mixture was subjected to flash chromatography. Elution with EA/hexanes (1/1) gave yellow oxindole derivatives **5a–p**.

General Procedure for the Synthesis of Isatins 6a, b

To 20 mL of anhydrous DCM solution containing oxindole **5a** or **5g** (0.014 mmol) was added 10 mL of DCM containing *m*CPBA (0.034 mmol) through syringe slowly in 30 min at room temperature. The mixture was then stirred for another 30 min. Upon completion of the reaction, the solution was quenched with saturated sodium bicarbonate and extracted with DCM. The extract was dried with sodium sulfate. After evaporation of DCM, the resulting solids were re-dissolved in chloroform (2 mL), precipitated with *n*-hexane (6 mL) and centrifuged for three times to give pure solids **6**.

General Procedure for the Synthesis of Isoxazolinones 7a–c

To 20 mL of anhydrous THF solution containing *m*CPBA (0.28 mmol) was added 10 mL of THF containing **5a**, **5g**, or **5j** (0.028 mmol) through syringe in 30 min at −25 °C. The mixture was then stirred for another 30 min. Upon completion of the reaction, THF was removed under vacuum and the resulting mixture was subjected to flash chromatography. Elution with EA/hexanes (1/2) gave white solids **7**.

General Procedure for the Synthesis of 6a′, 7a′ and 8a

Tosyl protected compound **5a, 6a** or **7a** (0.028 mmol) was added to 1.2 mL of 98% H_2SO_4 and stirred for 1 h at room temperature, respectively. After completion of the reaction, the solution was diluted with 20 mL of EA and neutralized with saturated sodium bicarbonate at 0 °C for 30 min, followed by extraction with EA. The resulting mixture was subjected to flash chromatography with EA/MeOH or EA/hexanes as eluents to give white solid **6a′** and yellow solids **7a′** and **8a**.

General Procedure for the Synthesis of 9a

A benzene solution containing enynedioate **1a** (0.90 mmol) and 4-nitrocinnamaldehyde (0.30 mmol) was distilled to remove moisture residues for three time (benzene, 10 mL × 3) with a Dean–Stark apparatus. Then, 7.5 mL of DCM were added to the resulting mixture followed by addition of triphenylphosphine (0.90 mmol). The mixture was stirred under 40 °C for 2 h. Upon completion of the reaction, the mixture was then subjected to flash chromatography after removal of DCM under vacuum. Elution with EA/hexanes (2/1) gave purple product **9a**.

General Procedure for the Synthesis of 10a

To 60 mL of DCE solution containing **9a** (0.017 g, 0.030 mmol, 0.50 mM) was added acetic acid (3 equiv., 5.15 μL). The mixture was irradiated by a halogen lamp at reflux (*ca.* 84 °C) for 3 h and the solution colour changed from purple to orange during this period. Upon completion of the reaction, DCE was removed under vacuum and the resulting mixture was subjected to flash chromatography. Elution with EA/hexanes (2/1) gave yellow oxindole derivative **10a**.

Acknowledgements

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$C_{41}H_{31}N_2O_7PS$; crystal system: triclinic; space group: P −1; $d = 1.420\ mg\,m^{-13}$, $V = 1699.24(12)$ Å^3; $a = 10.1828(4)$ Å.; $b = 10.7540(4)$ Å; $c = 16.2764(7)$ Å; $\alpha = 81.419(2)°$; $\beta = 74.852(2)°$; $\gamma = 85.151(2)°$; $R_1 = 0.0454$; $R_w = 0.1255$.

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