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Palladium-Catalyzed Annulation of Allenes with Indole-2-carboxylic Acid Derivatives: Synthesis of Indolo[2,3-*c*]pyrane-1-ones via Ar−I Reactivity or C−H Functionalization

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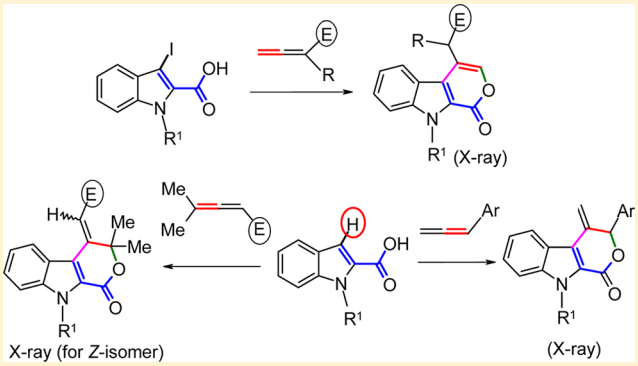
Supporting Information

ABSTRACT: Two methodologies, one involving Ar−I reactivity and the other through C−H functionalization, for the formation of indolo[2,3-*c*]pyrane-1-ones via the corresponding allenes, are presented. A highly efficient approach to indolo[2,3-*c*]pyrane-1-one derivatives through the Pd-catalyzed regioselective annulation of allenes with 3-iodo-1-alkylindole-2-carboxylic acids is described. This method is fairly general for a wide range of allenes affording the respective indolo[2,3-*c*]pyrane-1-ones in good to excellent yields. In addition, a Pd(II)-catalyzed oxidative coupling of indole-2-caboxylic acid derivatives with allenes via direct C−H functionalization to afford the corresponding indolo[2,3-*c*]pyrane-1-ones in moderate to good yields has been developed.



INTRODUCTION

Allenes are versatile synthons and can be used as precursors for a variety of biologically important heterocycles such as furanones, γ- and δ-lactones, functionalized dihydrofurans, benzofurans, imidazoles, chromenes, and many more.[1] In particular, transition-metal-catalyzed[2] or organocatalyzed[3] reactions of allenes for C−C or C−Het (Het = a heteroatom) bond formation has emerged as a prominent area in organic synthesis. Allenylphosphonates (phosphorylated allenes) and allenylphosphine oxides can also be employed as useful precursors in organic synthesis.[4,5] We have recently reported the synthesis of phosphono-benzofurans, phosphono-indenones, and phosphono-isocoumarins by the palladium-catalyzed reactions of allenylphosphonates.[6] Since indole derivatives have a wide range of biological activity,[7] we considered the palladium-catalyzed reactions of allenes with indole-2-carboxylic acid derivatives that may lead to indolo[2,3-*c*]pyrane-1-ones as a worthwhile study. The efficacy of indolo[2,3-*c*]pyrano [also termed as pyrano[3,4-*b*]indoles] scaffolds as inhibitors for hepatitis C virus NS5B polymerase has been studied extensively.[8] It is also noteworthy that the indolo[2,3-*c*]pyrane-1-one derivatives are good precursors for the synthesis of pharmaceutically valuable β-carbolines.[9,10] In the literature, very few methods have been reported for the synthesis of indolo[2,3-*c*]pyrane-1-ones, including a copper(I) catalyzed cyclization of iodo-indole-2-carboxylic acids with terminal alkynes[9a] and gold(III) chloride catalyzed cycloisomerization of 3-ethynyl-indole-2-carboxylic acid.[9c] However, the former protocol has the drawback of using stoichiometric amount of the copper reagent at high reaction temperature (120 °C) with average to good yields, while the latter method is expensive. Alternatively, we visualized that the indolo[2,3-*c*]pyrane-1-ones can be presumably constructed by the Pd-catalyzed annulation of allenes with indole-2-carboxylic acid derivatives by C−H functionalization. Moreover, the transition-metal-catalyzed direct C−H functionalization of indole derivatives for the arylation/alkenylation at either the C(2)- or C(3)-position of indole and oxidative annulations with internal alkynes that lead to fused heterocyclic compounds have been successfully achieved.[11,12] Although rhodium-catalyzed annulation of allene via C−H activation is known,[13] Pd-catalyzed oxidative annulations of indole-2-caboxylic acids with allenes via direct C−H functionalization to produce the corresponding indolo-[2,3-*c*]pyrane-1-ones (lactones) has not been established yet. In this paper, we describe the reactions of allenes with 3-iodo-indole-2-carboxylic acid derivatives and our initial results on the direct annulations of allenes with indole-2-carboxylic acid derivatives by C−H activation under palladium catalysis.

RESULTS AND DISCUSSION

The allene precursors shown in the Chart 1 were prepared by standard methods.[14−17] We shall first discuss the Pd-catalyzed cyclization using iodo-indole carboxylic acids; this will be followed by reactions using free indole-carboxylic acids that involve C−H activation.

(i) Pd-Catalyzed Annulation of Allenes with 3-Iodo-1-alkyl-indole-2-carboxylic Acids. We first treated the allene $(OCH_2CMe_2CH_2O)P(O)C(Ph)=C=CH_2$ (**1**) with 1-meth-

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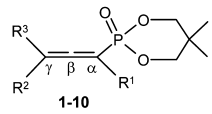
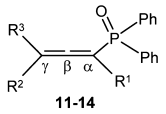
Chart 1. Allene Precursors Used in the Present Study



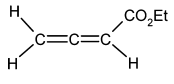
1-10



11-14

R^1 = Ph, R^2 = R^3 = H	[**1**, δ(P): 6.6]
R^1 = 4-Me-C_6H_4, R^2 = R^3 = H	[**2**, δ(P): 7.8]
R^1 = 4-MeO-C_6H_4, R^2 = R^3 = H	[**3**, δ(P): 7.5]
R^1 = 4-Cl-C_6H_4, R^2 = R^3 = H	[**4**, δ(P): 6.8]
R^1 = 1-naphthyl, R^2 = R^3 = H	[**5**, δ(P): 8.3]
R^1 = Me, R^2 = R^3 = H	[**6**, δ(P): 11.2]
R^1 = R^2 = R^3 = H	[**7**, δ(P): 8.7]
R^1 = R^2 = H, R^3 = Me	[**8**, δ(P): 8.9]
R^1 = H, R^2 = R^3 = Me	[**9**, δ(P): 8.8]
R^1 = H, R^2,R^3 = -$(CH_2)_5$-	[**10**, δ(P): 8.8]

R^1 = Ph, R^2 = R^3 = H	[**11**, δ(P): 30.2]
R^1 = R^2 = R^3 = H	[**12**, δ(P): 24.6]
R^1 = H, R^2 = R^3 = Me	[**13**, δ(P): 27.1]
R^1 = H, R^2, R^3 = -$(CH_2)_5$-	[**14**, δ(P): 26.5]



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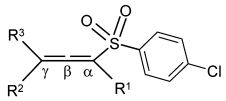
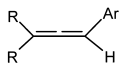


R^1 = Ph, R^2 = R^3 = H (**16**)
R^1 = Me, R^2 = R^3 = H (**17**)



R = H, Ar = Ph (**18**)
R = H, Ar = C_6H_4-4-Me (**19**)
R = Me, Ar = Ph (**20**)

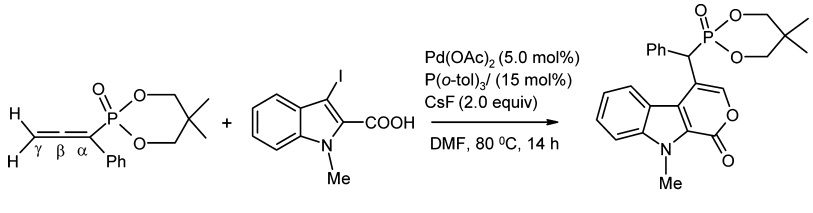
yl-3-iodo-indole-2-carboxylic acid (**21a**) in the presence of $Pd(OAc)_2$ (5 mol %) and CsF (2.0 equiv) in PEG-400 (5.0 mL).[6b] Under these conditions, the desired product could not be observed (^{31}P NMR). When the reaction was conducted in the presence of $Pd(OAc)_2$ (5 mol %), P(*o*-tol)$_3$ (15 mol %), and CsF (2.0 equiv) in DMF as the solvent for 14 h, the corresponding indolo[2,3-*c*]pyrane-1-one (**22**) was obtained in 94% isolated yield (Scheme 1); the cyclization occurred even in the absence of P(*o*-tol)$_3$, but the yield was lower (78% isolated). Changing the base from CsF to K_2CO_3 and in the presence of the phosphine [$Pd(OAc)_2$ (5 mol %)/P(*o*-tol)$_3$ (15 mol %)/K_2CO_3 (2.0 equiv)], compound **22** was obtained in 73% isolated yield. Thus CsF as a base worked better here. The structure of compound **22** was confirmed by X-ray crystallography (Figure S1 in Supporting Information); the P-**C**(Ph)−**C** distance of 1.527(3) Å clearly shows that the double bond that was initially present at this position in the allene is now a single bond as depicted in Scheme 1, confirming that a proton shift also has occurred. With these conditions in hand, we then explored the scope of this catalytic system for the synthesis of pyrano-indole derivatives **23**−**29** (Scheme 2a); in the reaction using allenes **6** and **9**, the products obtained were vinylphosphonates **28** and **29**. The X-ray structure of **29** is determined; on this basis, compound **28** was assigned a similar configuration. The phosphono-allene was completely consumed in this reaction, suggesting that the reaction is quantitative with respect to the allene. In the case of allenes **7** and **8** with a terminal $=CH_2$ or $=CH(Me)$ group, the reactions leading to **30** and **31** (cf. Scheme 2b) were conducted in the absence of P(*o*-tol)$_3$ because of the isomerization of allene to alkyne when P(*o*-tol)$_3$ was used.[6a] Similar to allene **6**, the other precursor **10** also led to vinylphosphonate **32** (Table 1, see Figure S3 in Supporting Information for X-ray structure). The allenylphosphine oxides **11**−**14** with **21a** behaved similarly and afforded the cyclized products **33**−**36** in good yield. The broader applicability of this system is also evidenced by the isolation of indolo[2,3-*c*]pyrane-1-ones **37** and **38** by using the allenoate **15**. Furthermore, this chemistry was extendable to the sulfonyl substituted allenes **16** and **17** (leading to compounds **39** and **40**) and aryl substituted allene **20** (leading to pyranoindole **41**).[18] These data are also presented in Table 1. In the reactions leading to **39** and **40** though the yield was better when K_2CO_3 was used in place of CsF. The important feature of this work is that essentially one product is formed regioselectively.

In the ^{13}C NMR spectrum of **28**, the carbon attached to phosphorus shows a doublet at δ 123.6 [^1J(P−C) = 180.0 Hz]. The large value of ^1J(P−C) is consistent with the sp^2 hybridized carbon being connected to phosphorus as depicted.[14] The major isomer is assigned a (*Z*) configuration based on X-ray data for compounds **29**/**32**. For further confirmation of the stereochemistry, we have determined the X-ray structure of **37** (Supporting Information, Figure S4). As regards products **28** and **39**, the phosphonyl product **28** is vinylic (with respect to phosphorus), whereas the corresponding the sulfonyl substituted pyranone product **39** is allylic (with respect to sulfur). Hence, in order to doubly make sure of our assignment, compound **39** was characterized by single crystal X-ray crystallography (Supporting Information, Figure S5).

Formation of pyranoindole derivatives can be rationalized by the pathway shown in Scheme 3.[6a] The arylpalladium complex **I** upon reacting with the allene gives the π-allyl palladium complex **II** through the insertion reaction at the β-carbon of allene. Elimination of HI (by the base) and the palladium moiety leads to species **III**. The cyclization then occurs to provide the compound **IV**; rearrangement (proton shift) leading to **V** may occur depending on the substituents present. Thus, the reaction of allenes **1**−**17** and **20** with 1-alkyl-iodo-indole-2-carboxylic acid afforded β,γ-cyclization products (with respect to phosphorus) most likely due to the stabilization of allylic carbocation **III** by alkyl (or -H) groups at the γ-position.[19]

(ii) Pd-Catalyzed Annulation of Allenes with 1-Alkyl-indole-2-carboxylic Acids via C−H Functionalization. As a part of our investigations on allenes, the oxidative coupling of indole-2-carboxylic acids **42a**−**d** with allenes **9**, **10**, **13**−**15**, and **18**−**20** by Pd catalysis via C−H functionalization has also been explored (Scheme 4a); the pyranoindoles thus obtained were **29**, **32**, **35**−**37**, **41**, and **43**−**49**. For this purpose, we first established reaction conditions for the oxidative annulation of allene **18** with the indole-2-carboxylic acid **42a** (Scheme 4b).

Scheme 1. Reaction of Allene 1 with 3-Iodo-1-methylindole-2-carboxylic Acid (21a) Leading to Phosphono-indolopyranone 22



1 **21a** **22** (94%, X- ray)

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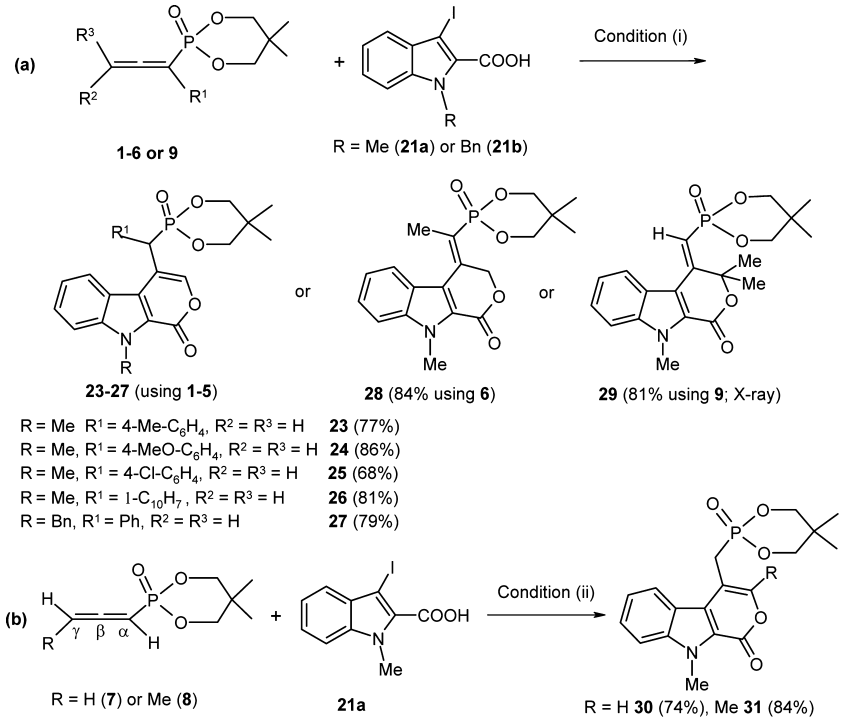
Scheme 2. Synthesis of Phosphono-indolo[2,3-*c*]pyrane-1-ones 23−31



We were pleased to discover that the reaction was feasible for the formation of **44** as the major product. However, at least three other isomeric products in minor quantities (GC−MS evidence) are also formed.[20] Hence, the principal challenge in optimization centered upon increasing the yield of **44** at the expense of the other isomers. Initially, the reaction was conducted in the presence of $Pd(OAc)_2$, stochiometric $Cu(OAc)_2$ as the oxidant, and LiOAc as the base [a catalytic system recently employed by Miura[10e]] in dimethyl acetamide (DMA) as the solvent at 120 °C/12 h (Table 2, entry 1). Under these conditions, the yield of compound **44** after isolation was 39% along with traces of isomers. When the catalyst was changed to $PdCl_2$, the yield of **44** (entry 2) was lower. No increase in the yield was observed by changing the oxidant from $Cu(OAc)_2$ to Ag_2CO_3 (entry 3). Quite pleasingly though, the yield (after isolation) and selectivity of **44** was dramatically increased to 67% using $Pd(OAc)_2$ in conjunction with stochiometric Ag_2CO_3 as the oxidant/base and CH_3CN as the solvent (entry 4). Screening of other palladium salts/oxidants/solvents led to the formation of **44** in only modest yield/selectivity (entries 5−11). Thus, $Pd(OAc)_2$ as the catalyst, Ag_2CO_3 as the oxidant/base, CH_3CN as the solvent, 80 °C as the reaction temperature, and 12−14 h reaction time were selected as optimal conditions. The results, leading to compounds **29**, **32**, **35**−**37**, **41**, and **43**−**49** are shown in Table 3.

The salient features of cyclization involving this C−H functionalization are summarized below:

(a) The phosphorus based allenes **9**, **10**, **13**, and **14** with 1-methyl-indole-2-carboxylic acid **42a** afforded the [*β*,*γ*] products **29**, **32**, **35**, and **36** (Table 3). Compound **29** is the same as that obtained using **9** and 3-iodo-1-methyl-indole-2-carboxylic acid; the configuration is (*Z*) at the exocyclic double bond.

(b) While the allenylphosphonates **9** and **10** afforded single isomers [(*Z*)-**29** or (*Z*)-**32**], allenylphosphine oxides **13** and **14** led to (*Z* + *E*) isomeric products **35** and **36**, with the major isomer having (*Z*) configuration. All of these are also (*β*,*γ*)-cyclized products.

(c) The allenoate **15** also afforded (*β*,*γ*)-cyclized products **37** and **43** in the ratio 1:3; compound **37** probably results from isomerization of **43**.[21]

(d) Reaction of the aryl allenes (**18**−**20**) with 1-methyl-indole-2-carboxylic acids **42a**−**d** using the above conditions readily afforded the indolopyranones [**44**−**49** and **41**; Table 3]. The structure for the cyclized product pyranoindole **47** is established by X-ray crystallography (Supporting Information, Figure S6). The point to be noted here is that **44**−**49** derived from allenes **18** and **19** are (*α*,*β*)-cyclized, whereas product **41** derived from the allene **20** is (*β*,*γ*)-cyclized.[22] Such greater reactivity of the $=CMe_2$ end as in **20** has been observed before.[6a]

(e) The reaction was not feasible in the case of *α*-aryl allenylphosphonate **1**, probably due to steric factors; hence reaction using similar allenes **2**−**6** and **11** was not attempted. As mentioned elsewhere, phosphorus allenes **7** and **12** rearrange to give alkynes in the presence of a base.[6a]

A possible pathway based on the literature reports[12d−f,h] is proposed in Scheme 5. Initially, exchange of an acetate group in $Pd(OAc)_2$ by the indole carboxylate leads to a species with the liberation of AcOH without undergoing decarboxylation (at the indole residue) in the presence of silver salts.[23] Then this species undergoes carbo-palladation at the C(3)-position, forming a palladacycle intermediate **VI** that subsequently inserts into allenes to produce allylic palladium(II) intermediates **VII** or **VII′**. Subsequent reductive elimination generates the lactones as well as Pd(0) species; the latter is

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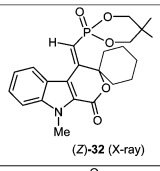
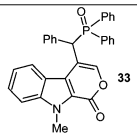
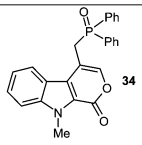
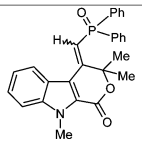
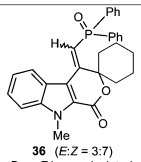
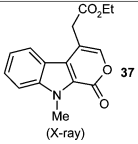
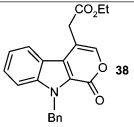
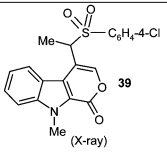
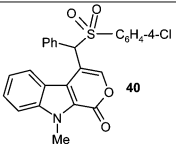
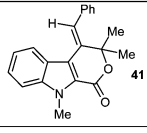
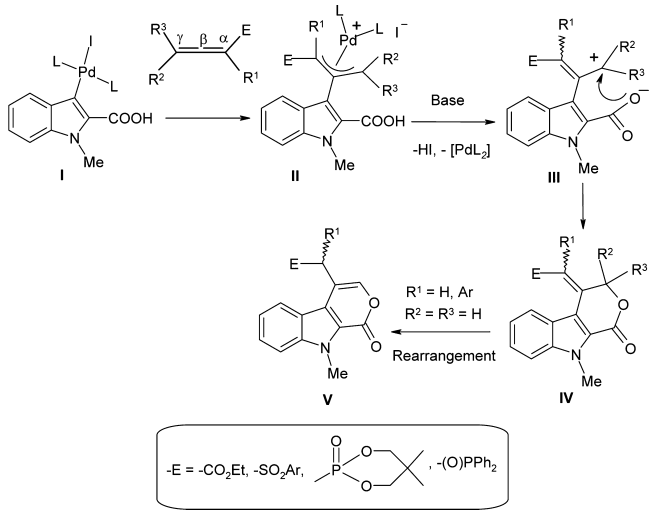
Table 1. Details of the Synthesis of Pyranoindoles 32−41

Entry	Allene	Indole-2-carboxylic acid	Condition (cf. Scheme 2)	Pyrano-indole Product	Isolated yield (%)
1	**10**	**21a**	**(i)**	 (*Z*)-**32** (X-ray)	65
2	**11**	**21a**	**(i)**	 **33**	64
3	**12**	**21a**	**(ii)**	 **34**	92
4	**13**	**21a**	**(i)**	 **35** (*E*:*Z* = 2:8)	63 (*E*+*Z*)[a]
5	**14**	**21a**	**(i)**	 **36** (*E*:*Z* = 3:7) Pure *Z* isomer isolated	54 (*Z*)[a]
6	**15**	**21a**	**(ii)**	 (X-ray)	81[b]
7	**15**	**21b**	**(ii)**	 **38**	83[b]
8	**16**	**21a**	**(ii)**	 **39** (X-ray)	56
			(iii)[a]		85[c]
9	**17**	**21a**	**(ii)**	 **40**	48
			(iii)		66[c]
10	**20**	**21a**	**(i)**	 **41**	72[d]

[a]The combined yield of the *E* + *Z* isomers was essentially quantitative (^{31}P NMR). The major isomer is assigned Z configuration on the basis of the X-ray structures of compounds **29**/**32**. [b]Here, the reaction was complete within 10 h. [c]In these cases, the reaction conditions were similar to (i) except that K_2CO_3 was used in place of CsF. [d]Assignment of stereochemistry is based on the structure of (**A**) mentioned in ref 18.

Scheme 3. Proposed Pathway for the Annulation Reaction



reoxidized to the Pd(II) species by silver or copper salts. While the oxidative coupling of 1-methyl-indole-2-carboxylic acids with allenes **9**, **10**, **13**−**15**, and **20** led to *β*,*γ*-cyclization products, that of allenes **18** and **19** occurred at the *β*,*α*-site (with respect to phenyl or *p*-tolyl group) is observed in the case. The reason for this preference is not clear at the moment.

SUMMARY

In summary, the present study gives an illuminating account of comparison between C−H functionalization and Ar−I reactivity in the formation of indolo[2,3-*c*]pyrane-1-ones. We have described the Pd-catalyzed regioselective cyclization reactions of allenylphosphonates/allenylphosphine oxides, allenoate $EtO_2CCH{=}C{=}CH_2$, and allenylsulfones [4-Cl-C_6H_4−$S(O)_2CR{=}C{=}CH_2$] with 3-iodo-indole-2-carboxylic acids that led to indolo[2,3-*c*]pyrane-1-ones (pyranoindoles) in high yields essentially as single isomers. This is a new route for indolo[2,3-*c*]pyrane-1-ones from allenes. More importantly, the Pd-catalyzed oxidative annulation of allenes via direct C−H functionalization with 1-alkyl-indole-2-carboxylic acid derivatives at the C3-position affording corresponding indolo pyranones in moderate to good yields has been demonstrated. The formation of lactones without undergoing decarboxylation of indole-2-carboxylic acids is notable. The present method highlights the synthesis in good yields of various phosphono-indolo[2,3-*c*]pyrane-1-ones that are not readily available by conventional synthetic routes.

EXPERIMENTAL SECTION

General Comments. Solvents were dried according to known methods as appropriate.[24] ^{1}H, ^{13}C, and ^{31}P NMR spectra (^{1}H, 400 MHz or 500 MHz; ^{13}C, 100 or 125 MHz; and ^{31}P, 162 or 202 MHz) were recorded using a 400 or 500 MHz spectrometer in $CDCl_3$ (unless stated otherwise) with shifts referenced to $SiMe_4$ (δ = 0) or 85% H_3PO_4 (δ = 0). IR spectra were recorded on an FTIR spectrophotometer. Melting points were determined by using a local hot-stage melting point apparatus and are uncorrected. Elemental analyses were carried out on a CHN analyzer. Mass spectra were recorded using GC−MS/LC−MS equipment. HRMS was recorded using an ESI-TOF analyzer. The allenylphosphonates/phosphine oxides **1**−**14**,[14] allenoate **15**,[16] allenylsulfones **16** and **17**,[17a] and phenyl-substituted allenes **18**−**20**[17b] were prepared by literature procedures.

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Scheme 4. Formation of Pyranoindoles by C−H Functionalization of Indole Carboxylic Acids

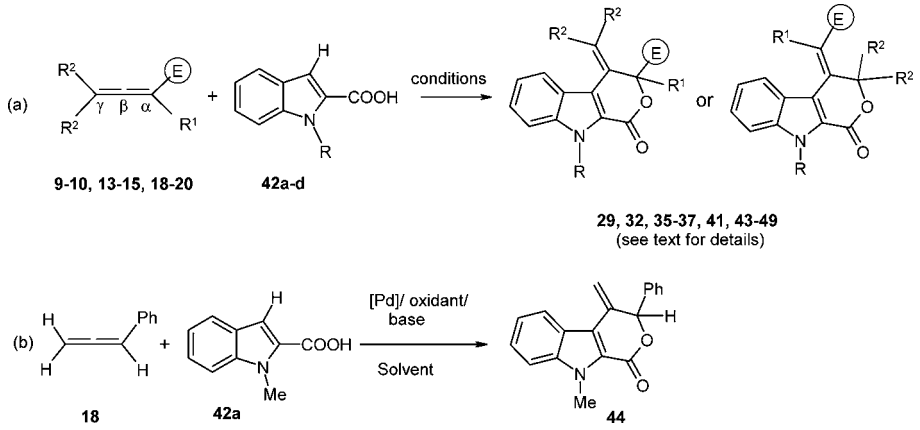

Table 2. Optimization of Reaction Conditions for the Annulation of Phenylallene 18 with Indole Carboxylic Acid 42a Leading to Product 44[a]

entry	Pd source	oxidant	base	solvent	temp (°C)	(%)yield of **44**[b]
1	$Pd(OAc)_2$	$Cu(OAc)_2$	LiOAc	DMA	120	39[c]
2	$PdCl_2$	$Cu(OAc)_2$	LiOAc	DMA	120	21[c]
3	$Pd(OAc)_2$	Ag_2CO_3		DMA	120	28
4	**$Pd(OAc)_2$**	**Ag_2CO_3**		**CH_3CN**	**80**	**67**[c]
5	$PdCl_2$	Ag_2CO_3		CH_3CN	90	42[c]
6	$Pd(OAc)_2$	$Cu(OAc)_2$	LiOAc	CH_3CN	90	22[c]
7	$PdCl_2$	$Cu(OAc)_2$	LiOAc	CH_3CN	80	29[c]
8	$Pd(OAc)_2$	Ag_2CO_3		DMF	120	29
9	$PdCl_2$	Ag_2CO_3		DMF	120	19[c]
10	$PdCl_2$	Ag_2CO_3		DMA	120	51
11	$PdCl_2(CH_3CN)_2$	Ag_2CO_3		DMA	120	53[c]

[a]Reaction conditions: indole-2-carboxylic acid (0.25 mmol), phenylallene (0.375 mmol), catalyst (10 mol %), oxidant $Cu(OAc)_2$ (0.5 mmol) or Ag_2CO_3 (0.375 mmol), base (0.5 mmol), solvent (5 mL); 10−16 h (reaction time is not optimized). [b]Isolated yield based on the amount of **42a** after column chromatography; **42a** was completely consumed. [c]A mixture of products was obtained (GC−MS).

(i) General Procedures for the Synthesis of 3-Iodo-1-methylindole-2-carboxylic Acid (21a), 1-Benzyl-3-iodo-indole-2-carboxylic Acid (21b), and Indole Carboxylic Acids 42a−d. **(a)** To a stirred solution of 3-iodo-indole-2-ethylcarboxylate (1.0 equiv) in dimethylformamide (DMF, 0.3 M with respect to iodo compound) at rt were added tetrabutylammonium bromide (TBAB) (10 mol %) and K_2CO_3 (2.0 equiv). To this was added iodomethane (5 equiv) or benzyl chloride (2.0 equiv), and the round-bottomed flask (RBF) was sealed with a glass stopper. The contents were stirred at rt for 12 h. After the completion of the reaction (TLC), the mixture was diluted with dichloromethane (DCM), washed with brine, dried over Na_2SO_4, and filtered, and the solvent was removed by rotary evaporator. The crude product was purified by column chromatography (hexane/EtOAc; 9:1) to get the 1-benzyl or 1-methyl-3-iodo-indole-2-ethylcarboxylate pure product in 96% or 88% yield, respectively.

(b) The 1-benzyl or 3-iodo-1-methylindole-2-ethylcarboxylate as obtained in **(a)** was dissolved in EtOH (0.3 M), and the contents were heated under reflux before addition of KOH (3.0 equiv) in water (0.15 M). This mixture was heated again under reflux for 16 h, the solvent was removed by rotary evaporator, and the crude material was extracted with ethyl acetate. The organic layer (EtOAc) was dried with anhydrous Na_2SO_4, and the solvent was removed by rotary evaporator to get the carboxylic acid (**21a** or **21b**) in 91−90% yield.

The acids **42a−d** were also prepared by the hydrolysis of the corresponding ethyl esters which were obtained by the above procedure. These are known.[25]

*Compound **21a**.* Yield: 1.89 g (90%; using 7.00 mmol of 3-iodo-1-methyl-indole-2-ethylcarboxylate). Mp: 174−176 °C (white solid), lit.[26] (177−178 °C). IR (KBr): 3058, 2924, 2591, 1672, 1501, 1350, 1265, 928 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.12 (s, 3H), 7.19−7.27 (m, 1H), 7.42−7.73 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 31.8, 110.4, 110.7, 112.5, 120.8, 122.9, 124.3, 125.7, 126.9, 167.2. LC−MS: m/z 302 $[M + H]^+$. Anal. Calcd for $C_{10}H_8INO_2$: C, 39.89; H, 2.68; N, 4.65. Found: C, 39.95; H, 2.62; N, 4.61.

(ii) General Procedure for the Preparation of Indolo[2,3-*c*]pyrane-1-ones (22−41). Into an oven-dried 25 mL round-bottomed flask were added $Pd(OAc)_2$ (5.0 mol %), P(*o*-tol)$_3$ (15 mol %), 3-iodo-1-methylindole-2-carboxylic acid **21a** or **21b** (0.55 mmol), CsF (or K_2CO_3) (1.0 mmol), and DMF (5.0 mL), and the mixture was kept stirring at rt for 5 min. After that, allene (0.5 mmol) was added. The RBF was flushed with N_2 and sealed. Then the contents were heated at 80 °C with stirring for 14 h. After the completion of the reaction (TLC), the mixture was cooled to rt, diluted with ethyl acetate (30 mL), washed with brine (3 × 10 mL), dried over anhydrous Na_2SO_4, and filtered, and the solvent was removed by rotary evaporator. The crude products were purified by column chromatography (hexane/EtOAc; 1:1.5) to get the pure products in 54−94% yield. Compounds **22−38** were prepared by this method, by using 0.55 mol of the indole carboxylic acid, unless stated otherwise.

*Compound **22**.* Yield: 0.205 g (94%; white solid). Mp: 222−224 °C. IR (KBr): 2965, 1696, 1476, 1262, 1020, 874, 799 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.79 (s, 3H), 0.99 (s, 3H), 3.68−3.77 (m, 2H), 4.23−4.28 (m, 5H), 5.16 (d, J = 26.8 Hz, 1H), 7.18−7.58 (m, 8H), 7.90 (d, J = 8.0 Hz, 1H), 8.02 (d, J = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.4, 21.5, 31.5, 32.7 (d, J = 6.5 Hz), 43.3 (d, J = 136.6 Hz), 75.9 (d, J = 6.8 Hz), 76.0 (d, J = 6.6 Hz), 110.9, 112.8 (d, J = 3.3 Hz), 120.3, 121.3, 122.2, 122.6, 123.5 (d, J = 14.5 Hz), 127.5, 128.1 (d, J = 3.3 Hz), 128.9 (d, J = 2.8 Hz), 129.7 (d, J = 5.8 Hz),

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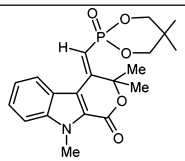
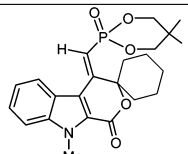
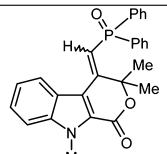
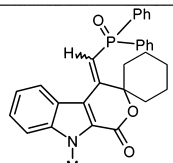
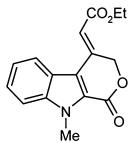
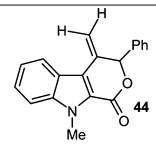
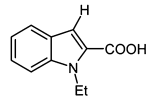
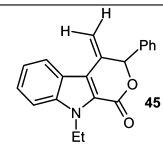
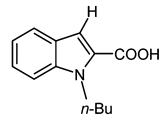
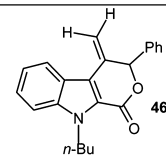
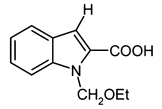
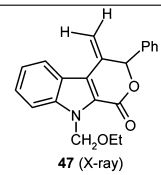
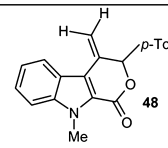
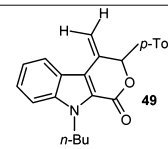
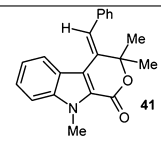
Table 3. Reaction of Allenes 9, 10, 13−15, and 18−20 with 42a−d via C−H Functionalization: Formation of Indolopyranones 29, 32, 35−37, 41, and 43−49[a,b]

Entry	Allene	Indole-2-carboxylic acid	Pyrano-indole Product	Isolated yield (%)
1	**9**	**42a**	 (*Z*)-**29** (X-ray)	68
2	**10**	**42a**	 (*Z*)-**32** (X-ray)	65
3	**13**	**42a**	 **35** (*E*:*Z* = 3:7)	61 (*E*+*Z*)[c]
4	**14**	**42a**	 **36** (*E*:*Z* = 3:7)	51 (*Z*)[c]
5	**15**	**42a**	**37** +  **43** (ratio 1:3)[e]	15 (pure **43**)[d]
6	**18**	**42a**	 **44**	68
7	**18**	**42b**		62
			 **45**	
8	**18**	**42c**		62
			 **46**	
9	**18**	**42d**		43
			 **47** (X-ray)	
10	**19**	**42a**	 **48**	63
11	**19**	**42c**	 **49**	65
12	**20**	**42a**	 **41**	64

[a]Reaction conditions: for entries 1−4, indole-2-carboxylic acid (0.55 mmol), allene (0.5 mmol), $Pd(OAc)_2$ (10 mol %), Ag_2CO_3 (0.75 mmol), CH_3CN (5 mL), 12 h. For entries 5−12, 0.5 mmol of indole-2-carboxylic acid and 0.75 mmol of allene were used. [b]Isolated yield based on the amount of the allene for entries 1−4 and indole-2-carboxylic acid (**42a**) for entries 5−12. [c]The combined yield of the *E* + Z isomers was essentially quantitative (^{31}P NMR); isomer ratio was ∼3:7. The major isomer is assigned (*Z*) configuration on the basis of the compounds **29**/**32**. [d]The reaction was complete but the yield of isolated pure compound **43** is lower because of the closeness in R_f values of **37** and **43**. Total isolated yield of the unseparated products **37** + **43** was >58%. For pure compound **37** (X-ray), see Table 1. [e]Based on GC−MS data.

133.8 (d, *J* = 7.7 Hz), 141.1, 143.0 (d, *J* = 7.3 Hz), 157.0. ^{31}P NMR (162 MHz, $CDCl_3$): δ 18.8. HRMS (ESI) calcd for $C_{24}H_{24}NO_5P$ (M + H)$^+$ 438.1392l, found 438.1392. This compound was crystallized from DCM containing traces of hexane.

Compound ***23***. Yield: 0.052 g (77%; white solid; using 0.15 mmol of allene **2**). Mp: 216−218 °C. IR (KBr): 2967, 1711, 1512, 1474, 1277, 1061, 831 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.85 (s, 3H), 1.00 (s, 3H), 2.30 (s, 3H), 3.67−3.77 (m, 2H), 4.23−4.27 (m, 5H), 5.12 (d, *J* = 26.5 Hz, 1H), 7.16−7.23 (m, 3H), 7.43−7.51 (m, 4H), 7.92 (d, *J* = 8.0 Hz, 1H), 8.02 (br, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.1, 21.5, 31.5, 32.7 (d, *J* = 6.2 Hz), 42.8 (d, *J* = 137.0 Hz), 75.9 (d, *J* = 6.5 Hz), 76.0 (d, *J* = 6.8 Hz), 110.9, 113.0 (d, *J* = 2.9 Hz), 120.4, 121.3, 122.3, 122.7, 123.6 (d, *J* = 14.4 Hz), 127.4, 129.6$_0$ (d, *J* = 6.0 Hz), 129.6$_4$ (d, *J* = 2.6 Hz), 130.6 (d, *J* = 7.6 Hz), 137.9 (d, *J* = 3.4 Hz), 141.1, 143.0 (d, *J* = 7.3 Hz), 157.0. ^{31}P NMR (162 MHz, $CDCl_3$): δ 18.9. LC−MS: *m*/*z* 452 [M + H]$^+$. Anal. Calcd for $C_{25}H_{26}NO_5P$: C, 66.51; H, 5.80; N, 3.10. Found: C, 66.45; H, 5.85; N, 3.18.

Compound ***24***. Yield: 0.200 g (86%; white solid). Mp: 230−232 °C. IR (KBr): 3058, 2955, 1719, 1613, 1510, 1246, 1051, 735 cm^{-1}. ^{1}H NMR (500 MHz): δ 0.85 (s, 3H), 1.00 (s, 3H), 3.67−3.79 (m, 5H), 4.23−4.28 (m, 5H), 5.10 (d, *J* = 33.0 Hz, 1H), 6.87−6.89 (m,

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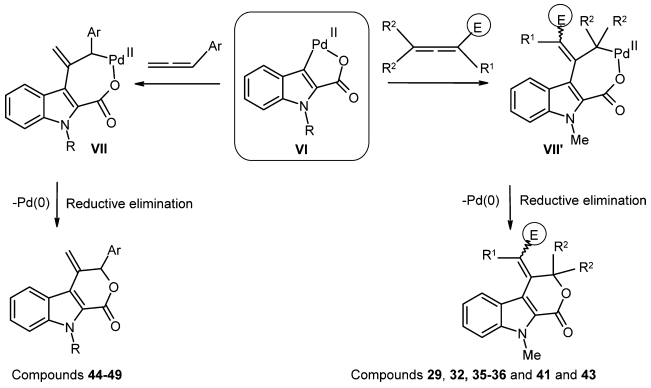
Scheme 5. Possible Pathway for the Formation of Pyranoindoles (Lactones)



2H), 7.19–7.23 (m, 1H), 7.44–7.51 (m, 4H), 7.89 (d, J = 8.0 Hz, 1H), 8.02 (br, 1H). ^{13}C NMR (125 MHz): δ 21.5, 31.5, 32.7 (d, J = 6.4 Hz), 42.3 (d, J = 137.6 Hz), 55.3, 75.8 (d, J = 6.8 Hz), 75.9 (d, J = 6.7 Hz), 110.9, 133.0 (d, J = 2.7 Hz), 114.3 (d, J = 2.7 Hz), 120.3, 121.3, 122.2, 122.7, 123.5 (d, J = 14.5 Hz), 125.4 (d, J = 14.5 Hz), 127.4, 130.8 (d, J = 5.7 Hz), 141.1, 142.8 (d, J = 7.1 Hz), 157.0, 159.4 (d, J = 3.3 Hz). ^{31}P NMR (202 MHz, $CDCl_3$): δ 19.1. LC–MS: m/z 467 $[M]^+$. Anal. Calcd for $C_{25}H_{26}NO_6P$: C, 64.24; H, 5.61; N, 3.00. Found: C, 64.41; H, 5.56; N, 3.07.

Compound ***25***. Yield: 0.159 g (68%; white solid; using 0.15 mmol of allene **2**). Mp: 212–216 °C. IR (KBr): 2957, 1715, 1617, 1489, 1339, 1285, 1057, 785 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (s, 3H), 0.98 (s, 3H), 3.70–3.82 (m, 2H), 4.23–4.32 (m, 5H), 5.12 (d, J = 26.8 Hz, 1H), 7.19–7.23 (m, 1H), 7.32–7.34 (m, 2H), 7.46–7.52 (m, 4H), 7.82 (d, J = 8.0 Hz, 1H), 8.01 (br, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.4, 21.6, 31.5, 32.8 (d, J = 5.9 Hz), 42.5 (d, J = 137.1 Hz), 75.7 (d, J = 6.6 Hz), 75.8 (d, J = 6.6 Hz), 111.0, 112.4, 120.2, 121.4, 122.2, 122.3, 123.1 (d, J = 14.1 Hz), 127.6, 129.1 (d, J = 2.7 Hz), 131.0 (d, J = 5.8 Hz), 132.4 (d, J = 7.4 Hz), 134.1 (d, J = 4.2 Hz), 141.1, 143.1 (d, J = 7.1 Hz), 156.8. ^{31}P NMR (162 MHz, $CDCl_3$): δ 18.6. LC–MS: m/z 471 and 473 $[M]^+$. Anal. Calcd for $C_{24}H_{23}ClNO_5P$: C, 61.09; H, 4.91; N, 2.97. Found: C, 61.22; H, 4.98; N, 2.91.

Compound ***26***. Yield: 0.198 g (81%; brown solid). Mp: 278–280 °C. IR (KBr): 3104, 1725, 1609, 1470, 1238, 1061, 743 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.72 (s, 3H), 0.90 (s, 3H), 3.37–3.55 (m, 2H), 4.15–4.24 (m, 5H), 6.00 (d, J = 26.0 Hz, 1H), 7.05–7.09 (m, 1H), 7.44–7.55 (m, 5H), 7.71–8.00 (m, 5H), 8.15 (d, J = 7.6 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.3, 31.4, 32.5 (d, J = 6.5 Hz), 39.3 (d, J = 139.9 Hz), 75.6 (d, J = 3.0 Hz,), 75.7 (d, J = 2.9 Hz), 110.8, 113.6 (d, J = 5.6 Hz), 120.5, 121.2, 121.8, 122.8, 123.2, 123.5 (d, J = 10.1 Hz), 125.4 (d, J = 2.6 Hz), 125.9, 126.8, 127.4, 127.8 (d, J = 6.4 Hz), 129.0 (d, J = 2.2 Hz), 129.3, 130.2 (d, J = 4.9 Hz), 131.6 (d, J = 8.5 Hz), 134.3, 141.0, 144.1 (d, J = 7.6 Hz), 156.8. ^{31}P NMR (202 MHz, $CDCl_3$): δ 20.1. LC–MS: m/z 487 $[M]^+$. Anal. Calcd for $C_{28}H_{26}NO_5P$: C, 68.99; H, 5.38; N, 2.87. Found: C, 68.79; H, 5.31; N, 2.95.

Compound ***27***. Yield: 0.163 g (79%; white solid; using 0.4 mmol of allene **1**). Mp: 224–228 °C. IR (KBr): 3058, 2971, 1717, 1613, 1462, 1277, 1059, 741 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.79 (s, 3H), 0.99 (s, 3H), 3.68–3.77 (m, 2H), 4.24–4.28 (m, 2H), 5.19 (d, J = 27.0 Hz, 1H), 5.90 (d, J = 16.0 Hz, 1H), 6.04 (d, J = 16.0 Hz, 1H), 7.18–7.27 (m, 7H), 7.36–7.44 (m, 4H), 7.58–7.59 (m, 2H), 7.93 (d, J = 8.5 Hz, 1H), 8.07 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.4, 21.5, 32.7 (d, J = 6.4 Hz), 43.4 (d, J = 136.5 Hz), 48.1, 75.9 (d, J = 6.8 Hz), 76.0 (d, J = 6.6 Hz), 111.7, 112.8 (d, J = 3.3 Hz), 120.8, 121.5, 121.9, 122.7, 124.1 (d, J = 14.0 Hz), 127.1, 127.6 (d, J = 3.1 Hz), 128.1 (d, J = 3.1 Hz), 128.8, 128.9 (d, J = 2.6 Hz), 129.8$_0$, 129.8$_1$, 129.8 (d, J = 5.9 Hz), 133.8 (d, J = 7.5 Hz), 137.3, 140.7, 143.4 (d, J = 7.3 Hz), 156.7. ^{31}P NMR (162 MHz, $CDCl_3$): δ 18.7. LC–MS: m/z 514 $[M + H]^+$. Anal. Calcd for $C_{30}H_{28}NO_5P$: C, 70.17; H, 5.50; N, 2.73. Found: C, 70.08; H, 5.56; N, 2.81.

Compound ***28***. Yield: 0.158 g (84%; white solid). Mp: 140–146 °C. IR (KBr): 2924, 1715, 1609, 1507, 1252, 1055, 785 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.01 (s, 3H), 1.26 (s, 3H), 2.34 (d, J = 15.0 Hz, 3H), 3.88 (dd, $J \approx$ 17.0 Hz, $J \approx$ 11.0 Hz, 2H), 4.14 (s, 3H), 4.41 (dd, $J \approx$ 11.0 Hz, $J \approx$ 6.0 Hz, 2H), 5.55 (s, 2H), 7.28–7.47 (m, 3H), 7.66 (d, J = 8.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.0 (d, J = 8.4 Hz), 21.5, 22.2, 31.3, 32.7 (d, J = 5.5 Hz), 71.6 (d, J = 7.6 Hz), 74.8 (d, J = 5.9 Hz), 77.3, 120.2, 120.4, 122.5 (d, J = 180.0 Hz), 121.9, 122.2, 123.7, 124.1, 126.2, 139.7, 140.0 (d, J = 15.5 Hz), 160.0. ^{31}P NMR (202 MHz, $CDCl_3$): δ 15.9. HRMS (ESI) calcd for $C_{19}H_{22}NO_5P$ $(M + Na)^+$ 398.1134, found 398.1134.

Compound ***29***. Yield: 0.158 g (81%; white solid). Mp: 118–122 °C. IR (KBr): 2965, 2884, 1715, 1586, 1269, 1059, 745 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): 1.14 (s, 6H), 2.01 (s, 6H), 3.96 (dd→t, $J \approx$ 12.0 Hz, 2H), 4.19 (s, 3H), 4.26 (dd→t, $J \approx$ 10.0 Hz, 2H), 6.42 (d, J = 8.0 Hz, 1H), 7.37–7.54 (m, 3H), 8.00 (d, J = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 21.6, 21.7, 29.0, 31.7, 32.7 (d, J = 5.3 Hz), 75.6, 75.7, 88.5 (d, J = 5.8 Hz), 106.4 (d, J = 194.7 Hz), 111.6, 118.7 (d, J = 24.5 Hz), 121.7, 122.3, 123.3, 124.0, 126.8, 140.7, 155.5 (d, J = 7.2 Hz), 158.5. ^{31}P NMR (162 MHz, $CDCl_3$): δ 12.2. HRMS (ESI) calcd for $C_{20}H_{24}NO_5P$ $(M + H)^+$ 389.1392, found 389.1392. This compound was crystallized from ethyl acetate containing traces of hexane.

Compound ***30***. Yield: 0.133 g (74%; white solid). Mp: 216–218 °C. IR (KBr): 3081, 2971, 1705, 1607, 1476, 1267, 1065, 735 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (s, 3H), 0.93(s, 3H), 3.51 (d, J = 20.4 Hz, 2H), 3.67 (dd, J = 16.6 Hz, $J \approx$ 11.0 Hz, 2H), 4.20–4.23 (m, 5H), 7.28–7.33 (m, 2H), 7.48–7.56 (m, 2H), 8.12 (d, J = 8.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.3, 21.6, 25.6 (d, J = 141.0 Hz), 31.4, 32.6 (d, J = 6.0 Hz), 75.1$_0$, 75.1$_4$, 108.5 (d, J = 11.0 Hz), 110.7, 120.9, 121.4$_0$, 121.4$_5$, 123.1, 123.8 (d, J = 4.0 Hz), 127.8, 141.2, 141.6 (d, J = 11.0 Hz), 157.0. ^{31}P NMR (162 MHz, $CDCl_3$): δ 21.3. HRMS (ESI) calcd for $C_{18}H_{20}NO_5P$ $(M + Na)^+$ 384.0977, found 384.0977.

Compound ***31***. Yield: 0.158 g (84%; white solid). Mp: 250–252 °C. IR (KBr): 2959, 2888, 1710, 1611, 1474, 1266, 1057, 806 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): 0.84 (s, 3H), 0.87 (s, 3H), 2.41 (d, J = 4.4 Hz, 3H), 3.55 (d, J = 14.8 Hz, 2H), 3.59 (dd, $J = J \approx$ 11.4 Hz, 2H), 4.19–4.21 (m, 5H), 7.25–7.28 (m, 1H), 7.45–7.53 (m, 2H), 8.13 (d, J = 8.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 17.0, 21.2, 21.4, 25.9 (d, J = 141.0 Hz), 31.3, 32.5 (d, J = 5.8 Hz), 74.8$_0$, 74.8$_2$, 104.1 (d, J = 11.2 Hz), 110.5, 120.5, 120.7, 120.9, 123.4, 125.3, 127.5, 141.4, 150.8 (d, J = 10.0 Hz), 157.2. ^{31}P NMR (162 MHz, $CDCl_3$). HRMS (ESI) calcd for $C_{19}H_{22}NO_5P$ $(M + Na)^+$ 398.1134, found 398.1134.

Compound ***32***. Yield: 0.14 g (65%; white solid). Mp: 198–200 °C. IR (KBr): 2932, 1713, 1609, 1485, 1273, 1057, 822 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.75 (s, 3H), 1.15 (s, 3H), 1.67–2.12 (m, 10H), 3.58–3.69 (m, 4H), 4.16 (s, 3H), 5.92 (d, J = 9.6 Hz, 1H), 7.33–7.45 (m, 3H), 8.54 (d, J = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 20.7, 21.7, 21.8, 25.2, 31.4, 32.3 (d, J = 7.0 Hz), 35.5, 76.6, 77.2, 88.1 (d, J = 21.0 Hz), 109.2 (d, J = 179.0 Hz), 110.2, 117.7 (d, J = 9.0 Hz), 122.3, 123.4, 123.8, 124.7, 126.6, 139.7, 152.2, 159.2. ^{31}P NMR (162 MHz, $CDCl_3$): δ 11.0. LC–MS: m/z 429 $[M]^+$. Anal. Calcd for $C_{23}H_{28}NO_5P$: C, 64.33; H, 6.57; N, 3.26. Found: C, 64.48; H, 6.65; N, 3.18. This compound was crystallized from DCM containing traces of hexane.

Compound ***33***. Yield: 0.158 g (64%; white solid). Mp: 288–292 °C. IR (KBr): 3056, 1701, 1599, 1476, 1206, 1036, 739, 511 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.20 (s, 3H), 5.32 (d, J = 11.0 Hz, 1H), 7.17–7.18 (m, 3H), 7.25–7.29 (m, 2H), 7.36–7.53 (m, 11H), 7.83–7.87 (m, 2H), 8.06 (d, J = 8.5 Hz, 1H), 8.48 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 31.5, 45.5 (d, J = 64.1 Hz), 111.1, 114.9 (d, J = 3.5 Hz), 120.5, 121.4, 122.3$_0$, 122.3$_1$, 123.4 (d, J = 10.1 Hz), 127.5, 127.6 (d, J = 2.6 Hz), 128.3, 128.4, 129.0 (d, J = 11.3 Hz), 130.3 (d, J = 4.6 Hz), 131.2 (d, J = 8.4 Hz), 131.4 (d, J = 9.0 Hz), 131.9 (d, J = 2.8 Hz), 132.0 (d, J = 2.5 Hz), 132.2 (d, J = 57.1 Hz), 132.6, 133.1 (d, J = 5.8 Hz), 141.1, 143.8 (d, J = 7.8 Hz), 157.0. ^{31}P NMR (202 MHz,

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$CDCl_3$): δ 32.3. HRMS (ESI) *m/z*: calcd for $C_{31}H_{24}NO_3P$ $(M + H)^+$ 490.1572, found 490.1572.

Compound ***34***. Yield: 0.191 g (92%; brown solid). Mp: 248−252 °C. IR (KBr): 2948, 1707, 1435, 1331, 1183, 1030, 847, 735 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 3.90 (d, *J* = 12.5 Hz, 2H), 4.16 (s, 3H), 7.07 (d, *J* = 4.0 Hz, 1H), 7.21−7.24 (m, 1H), 7.42−7.55 (m, 8H), 7.78−7.82 (m, 4H), 8.05 (d, *J* = 8.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 30.0 (d, *J* = 67.8 Hz), 31.3, 108.6 (d, *J* = 8.1 Hz), 110.7, 121.0, 121.2, 121.6, 122.9, 124.2 (d, *J* = 4.5 Hz), 127.5, 128.8, 128.9, 131.1_0, 131.1_4, 131.7, 132.2 (d, *J* = 2.3 Hz), 132.4, 141.1, 141.7 (d, *J* = 8.0 Hz), 156.9. ^{31}P NMR (202 MHz, $CDCl_3$): δ 29.1. HRMS (ESI) calcd for $C_{25}H_{20}NO_3P$ $(M + H)^+$ 414.1181, found 414.1181.

Compound ***35***. Yield: 0.140 g (63%; white solid). Mp: 156−160 °C. IR (KBr): 3058, 2988, 1715, 1563, 1485, 1254, 1094, 721 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.99 (s, 6H), 4.19 (s, 3H), 6.89 (d, *J* = 15.6 Hz, 1H), 7.25−7.27 (m, 1H), 7.50−7.56 (m, 8H), 7.70−7.84 (m, 5H). There was also a minor isomer: δ 1.69, 4.01, 6.45(d) [other peaks were buried in the signals due to the major isomer]. ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.8, 31.7, 89.1, 111.5, 113.7 (d, *J* = 103.3 Hz), 121.5, 122.4, 123.2, 126.6, 128.9 (d, *J* = 12.0 Hz), 130.9 (d, *J* = 9.7 Hz), 131.8, 135.1, 136.1, 140.7, 154.3, 158.7. ^{31}P NMR (162 MHz, $CDCl_3$): δ 20.7 [major, ca. 75%], 18.7 [minor, ca. 25%]. LC−MS: *m/z* 441 $[M]^+$. Anal. Calcd for $C_{27}H_{24}NO_3P$: C, 73.46; H, 5.48; N, 3.17. Found: C, 73.56; H, 5.41; N, 3.22.

Compound ***36***. Yield: 0.130 g (54%; white solid). Mp: 210−212 °C. IR (KBr): 2926, 1707, 1561, 1437, 1350, 1267, 1098, 828 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.56−1.98 (m, 8H), 2.75−2.82 (m, 2H), 4.18 (s, 3H), 6.84 (d, *J* = 15.6 Hz, 1H), 7.46−7.56 (m, 9H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.81−7.86 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5, 24.0, 31.6, 37.1, 89.9 (d, *J* = 3.0 Hz), 111.5, 113.5 (d, *J* = 104.0 Hz), 119.4 (d, *J* = 19.0 Hz), 121.5, 121.7, 122.5, 123.1, 123.5, 126.5, 128.1 (d, *J* = 12.0 Hz), 128.8 (d, *J* = 12.0 Hz), 130.7, 131.0 (d, *J* = 10.0 Hz), 131.3, 131.7, 135.2, 136.3, 140.7, 155.0, 158.5. ^{31}P NMR (162 MHz, $CDCl_3$): δ 21.5. LC−MS: *m/z* 481 $[M]^+$. Anal. Calcd for $C_{30}H_{28}NO_3P$: C, 74.83; H, 5.86; N, 2.91. Found: C, 74.65; H, 5.81; N, 2.99.

Compound ***37***. Yield: 0.116 g (81%; white solid; using 0.5 mmol of **21a** and 0.6 mmol of allene **15**). Mp: 106−110 °C. IR (KBr): 3083, 1730, 1707, 1624, 1478, 1275, 1017, 737 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): 1.23 (t, *J* ≈ 7.0 Hz, 3H), 3.80 (s, 2H), 4.16−4.21 (m, 5H), 7.24−7.28 (m, 2H), 7.45−7.53 (m, 2H), 7.91 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.2, 31.3, 34.5, 61.5, 110.8, 111.0, 120.8, 121.3, 121.5, 122.4, 124.0, 127.6, 141.1, 141.3, 157.2, 170.5. HRMS (ESI) calcd for $C_{16}H_{15}NO_4$ $(M + H)^+$ 286.1001, found 286.1001. This compound was crystallized from DCM containing traces of hexane.

Compound ***38***. Yield: 0.090 g (83%; white solid; using 0.3 mmol of **21b** and 0.36 mmol of allene **15**). Mp: 220−222 °C. IR (KBr): 3034, 2980, 1730, 1707, 1622, 1495, 1277, 1022, 741 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): 1.25 (t, *J* = 7.2 Hz, 3H), 3.85 (s, 2H), 4.65 (q, *J* = 7.2 Hz, 2H), 5.98 (s, 2H), 7.20−7.30 (m, 7H), 7.46−7.51 (m, 2H), 7.97 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 14.2, 34.5, 48.0, 61.6, 111.1, 111.7, 121.3, 121.6, 122.6, 124.7, 126.5, 127.1, 127.6, 127.9, 128.8, 137.4, 140.7, 141.7, 157.0, 170.5. LC−MS: *m/z* 361 $[M]^+$. Anal. Calcd for $C_{22}H_{19}NO_4$: C, 73.12; H, 5.30; N, 3.88. Found: C, 73.32; H, 5.38; N, 3.81.

Compound ***39***. Yield: 0.170 g (85%; white solid). Mp: 204−208 °C. IR (KBr): 3117, 1721, 1707, 1615, 1476, 1314, 1146, 1024 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 1.80 (d, *J* = 9.0 Hz, 3H), 4.24 (s, 3H), 5.09−5.10 (br, 1H), 7.24−7.39 (m, 4H), 7.49−7.59 (m, 2H), 7.69−7.72 (m, 2H), 8.00 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.9, 31.5, 59.1, 111.1, 112.5, 120.4, 121.3, 121.6, 122.8, 123.0, 127.9, 129.3, 131.1, 134.7, 141.0, 141.3, 143.0, 156.5. LC−MS: *m/z* 402 and 404 $[M]^+$. HRMS (ESI) calcd for $C_{20}H_{16}ClNO_4S$ $(M + Na)^+$ 424.0387, found 424.0387. This compound was crystallized from DCM contianing traces of hexane.

Compound ***40***. Yield: 0.152 g (66%; brown solid). Mp: 156−160 °C. IR (KBr): 3063, 2924, 1609, 1476, 1319, 1148, 702 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 4.21 (s, 3H), 5.03 (s, 1H), 7.16−7.56 (m, 10H), 7.68−7.70 (m, 2H), 7.85 (d, *J* = 8.4 Hz, 1H), 8.27 (br, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 31.5, 69.1, 111.1, 111.3, 120.0, 121.7, 122.0, 122.4, 127.7, 129.1, 129.5, 129.7, 130.2, 130.6$_0$, 130.6$_4$, 136.4, 140.9, 141.1, 143.1, 156.4. LC−MS: *m/z* 464 and 466 $[M]^+$. Anal. Calcd for $C_{25}H_{18}ClNO_4S$: C, 64.72; H, 3.91; N, 3.02. Found: C, 64.82; H, 3.85; N, 3.12.

Compound ***41***. Yield: 0.114 g (72%; white solid; using 0.5 mmol of **21a** and 0.6 mmol of allene **20**). Mp: 134−138 °C. IR (KBr): 3058, 2984, 1701, 1509, 1483, 1267, 1090, 747 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): 1.75 (s, 6H), 4.16 (s, 3H), 6.36 (d, *J* = 8.4 Hz, 1H), 6.74−6.78 (m, 1H), 6.85 (s, 1H), 7.21−7.55 (m, 7H). ^{13}C NMR (100 MHz, $CDCl_3$): 27.7, 31.4, 87.7, 110.3, 119.6, 120.6, 122.1, 124.0, 124.5, 125.3, 125.7, 127.5, 128.4, 129.5, 133.6, 137.6, 140.1, 160.4. HRMS (ESI) calcd for $C_{21}H_{19}NO_2$ $(M + H)^+$ 318.1496, found 318.1494.

(iii) Pd-Catalyzed Annulation of Allenes with 1-Alkyl-indole-2-carboxylic Acids via C−H Functionalization: Synthesis of compounds 29, 32, 35−37, 41, and 43−49. *Standardization of Reaction Conditions.* An oven-dried 10 mL RBF was charged with the Pd(II) complex (10 mol %), oxidant [Ag_2CO_3 or $Cu(OAc)_2$; 0.375−0.500 mmol], 1-methyl-indole-2-carboxylic acid **42a** (0.25 mmol), and the base [LiOAc, CsF or K_2CO_3]. The RBF was evacuated for 5 min and filled with N_2. To this was added solvent [CH_3CN, DMF, or dimethyl acetamide; 2.5 mL], and the contents were stirred at rt for 5 min. After this, allene **18** (0.375 mmol) was added via a micropipet. The RBF was flushed with N_2 and sealed. The contents were stirred in preheated oil bath (80−120 °C) for the indicated period of time. After the completion of the reaction (GC−MS), the mixture was cooled to rt, diluted with ethyl acetate (15 mL), washed with brine (3 × 5 mL), dried over Na_2SO_4, and filtered, and the solvent was removed from the filtrate. The crude product was purified by column chromatography (silica gel, ethyl acetate−hexane) to get the pure product (**44**). Other details are presented in Table 2.

Standardized Procedure for the Preparation of Compounds ***29, 32, 35−37, 41, and 43−49***. In an oven-dried 25 mL RBF was taken silver carbonate (0.75 mmol) and dried *in vacuo* while heating with a hot air gun for 0.5 h. After cooling (5 min), $Pd(OAc)_2$ (10 mol %), 1-alkylindole-2-carboxylic acid (0.5−0.55 mmol), and CH_3CN (5.0 mL) were added. The mixture was kept stirring at rt for 5 min. After that, allene (0.50−0.75 mmol) was added, and the RBF was sealed with a stopper. The resulting mixture was heated with stirring at 80 °C (oil bath) for 10−12 h. After the completion of the reaction (GC−MS)/^{31}P NMR), the solvent was removed by rotary evaporator and the mixture subjected to flash chromatography (silica gel, ethyl acetate/hexane 1:19) to obtain the pure products in 43−68% yield. Compounds **29**, **32**, **35−37**, **41**, and **43−49** were prepared by this procedure.

Compound ***43***. Yield: total yield 62%. Combined yield (**37** + **43**): 0.089 g [47%; using **15** (0.75 mmol) and **42a** (0.50 mmol)] Isolated yield for **43**: 0.022 g (15%; white solid). Mp: 120−122 °C. IR (KBr): 2961, 1717, 1697, 1601, 1489, 1262, 1030 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.36 (t, *J* ≈ 7.6 Hz, 3H), 4.19 (s, 3H), 4.26 (q, *J* = 7.2 Hz, 2H), 5.90 (d, *J* = 2.4 Hz, 2H), 6.57 (dd→t, *J* ≈ 2.2 Hz, 1H), 7.38−7.40 (m, 1H), 7.52−7.53 (m, 2H), 8.03 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 31.8, 60.5, 70.7, 111.4, 118.3, 121.7, 122.3, 123.3, 124.1, 127.0, 140.4, 143.4, 159.0, 166.4. HRMS (ESI) calcd for $C_{16}H_{15}NO_4$ $(M + Na)^+$ 308.0899, found 308.0895.

Compound ***44***. Yield: 0.098 g (68%; white solid; using 0.5 mmol of **42a** and 0.75 mmol of **18**). Mp: 154−156 °C. IR (KBr): 3036, 2932, 1701, 1480, 1308, 1096, 733 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.11 (s, 3H), 5.16 (s, 1H), 5.94 (s, 1H), 6.19 (s, 1H), 7.27−7.36 (m, 4H), 7.43−7.49 (m, 4H), 7.95 (d, *J* = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 31.4, 85.1, 111.0, 113.2, 120.6, 122.0, 122.7, 126.7, 127.3, 128.3, 128.5, 128.7, 129.0, 130.3, 136.6, 138.0, 140.6, 159.7. HRMS (ESI) calcd for $C_{19}H_{15}NO_2$ $(M + Na)^+$ 312.1001, found 312.1001.

Compound ***45***. Yield: 0.094 g (62%; white solid; using 0.5 mmol of **42c** and 0.75 mmol of **18**). Mp: 130−134 °C. IR (KBr): 2924, 1707, 1466, 1231, 1092, 905, 735 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.43 (t, *J* = 7.2 Hz, 3H), 4.65 (m, 2H), 5.14 (s, 1H), 5.93 (s, 1H), 6.19 (s, 1H), 7.27−7.49 (m, 8H), 7.96 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.5, 39.7, 85.1, 111.0, 113.1, 120.8, 122.0, 122.1,

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122.2, 126.6, 127.3, 128.5, 128.7, 136.8, 138.0, 139.6, 159.4. HRMS (ESI) calcd for $C_{20}H_{17}NO_2$ $(M + H)^+$ 304.1339, found 304.1337.

Compound ***46***. Yield: 0.103 g (62%; white solid; using 0.5 mmol of **42c** and 0.75 mmol of **18**). Mp: 94−98 °C. IR (KBr): 2955, 1713, 1522, 1471, 1341, 1184, 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 0.93 (t, J = 7.2 Hz, 3H), 1.34−1.38 (m, 2H), 1.78−1.82 (m, 2H), 4.60−4.63 (m, 2H), 5.17 (d, J = 1.6 Hz, 1H), 5.94 (d, J = 1.2 Hz, 1H), 6.19 (s, 1H), 7.27−7.50 (m, 8H), 7.96 (d, J = 8.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 20.1, 32.5, 44.5, 85.1, 111.3, 113.1, 120.6, 121.9, 122.0$_5$, 122.0$_9$, 122.3, 126.5, 127.2, 128.5, 128.6, 136.8, 138.1, 139.9, 159.5. HRMS (ESI) calcd for $C_{22}H_{21}NO_2$ $(M + H)^+$ 332.1652, found 332.1650.

Compound ***47***. Yield: 0.072 g (43%; white solid; using 0.5 mmol of **42d** and 0.75 mmol of **18**). Mp: 100−104 °C. IR (KBr): 2975, 1703, 1464, 1337, 1196, 1096, 999, 749 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.11 (t, $J \sim$ 7.0 Hz, 3H), 3.46−3.54 (m, 2H), 5.23 (s, 1H), 5.99 (s, 1H), 6.03−6.10 (m, 2H), 6.20 (s, 1H), 7.31−7.39 (m, 4H), 7.47−7.67 (m, 4H), 7.95 (d, J = 8.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.0, 64.1, 73.5, 85.0, 112.4, 114.4, 121.9, 122.2, 122.5, 122.7, 127.2, 128.5, 128.7, 136.5, 137.8, 140.4, 159.5. HRMS (ESI) calcd for $C_{21}H_{19}NO_3$ $(M + Na)^+$ 356.1263, found 356.1263. It was crystallized from chloroform at 30 °C.

Compound ***48***. Yield: 0.096 g (63%; white solid; using 0.5 mmol of **42a** and 0.75 mmol of **19**). Mp: 126−130 °C. IR (KBr): 2955, 1703, 1478, 1308, 1229, 1200, 1090, 808, 735 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 2.34 (s, 3H), 4.11 (s, 3H), 5.17 (s, 1H), 5.93 (s, 1H), 6.16 (s, 1H), 7.15−7.17 (m, 2H), 7.27−7.30 (m, 1H), 7.35−7.37 (m, 2H), 7.42−7.49 (m, 2H), 7.95 (d, J = 8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.2, 31.4, 85.1, 111.0, 113.1, 120.6, 121.9$_6$, 122.0$_0$, 122.7, 126.6, 127.2, 129.2, 129.3, 135.1, 136.6, 138.5, 140.6, 159.8. HRMS (ESI) calcd for $C_{20}H_{17}NO_2$ $(M + H)^+$ 304.1339, found 304.1337.

Compound ***49***. Yield: 0.112 g (65%; white solid; using 0.5 mmol of **42c** and 0.75 mmol of **19**). Mp: 100−104 °C. IR (KBr): 2955, 1705, 520, 1472, 1237, 1190, 1098, 741 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 0.94 (t, J = 7.5 Hz, 3H), 1.35−1.37 (m, 2H), 1.79−1.82 (m, 2H), 2.36 (s, 3H), 4.60−4.63 (m, 2H), 5.17 (s, 1H), 5.92 (s, 1H), 6.17 (s, 1H), 7.17−7.28 (m, 3H), 7.36−7.38 (m, 2H), 7.46−7.47 (m, 2H), 7.96 (d, J = 8.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 20.1, 21.2, 32.5, 44.5, 85.1, 111.3, 112.9, 120.7, 121.9, 122.1, 122.2, 122.4, 126.4, 127.2, 129.3, 135.2, 137.0, 138.4, 139.9, 159.5. HRMS (ESI) calcd for $C_{23}H_{23}NO_2$ $(M + H)^+$ 346.1809, found 346.1807.

(iv) X-ray Data. X-ray data for compounds **22**, **29**, **32**, **37**, **39**, **47**, and **A** were collected using Mo Kα (λ = 0.71073 Å) radiation. The structures were solved and refined by standard methods.[27] CCDC numbers are CCDC 8844798−884804.

Crystal Data. **22**: $C_{24}H_{24}NO_5P$, M = 437.41, monoclinic, space group $P2(1)/c$, a = 11.2790(3), b = 13.8867(4), c = 14.0971(4) Å, β = 95.564°, V = 2197.60(11) Å^3, Z = 4, μ = 0.161 mm^{-1}, data/restraints/parameters: 3876/0/284, R indices ($I > 2\sigma(I)$): R1 = 0.0451, $wR2$ (all data) = 0.1233. CCDC no. 8844798.

29: $C_{20}H_{24}NO_5P$, M = 389.37, monoclinic, space group $P2(1)/c$, a = 13.8122(6), b = 13.1379(4), c = 11.7893(6) Å, β = 112.165(6)°, V = 1981.23(15) Å^3, Z = 4, μ = 0.169 mm^{-1}, data/restraints/parameters: 3475/0/250, R indices ($I > 2\sigma(I)$): R1 = 0.0416, $wR2$ (all data) = 0.1046. CCDC no. 8844799.

32: $C_{23}H_{28}NO_5P$, M = 429.43, monoclinic, space group $P2(1)/c$, a = 7.1222(9), b = 17.729(2), c = 16.957(2) Å, β = 93.189°, V = 2137.9(5) Å^3, Z = 4, μ = 0.164 mm^{-1}, data/restraints/parameters: 3772/0/274, R indices ($I > 2\sigma(I)$): R1 = 0.1213, $wR2$ (all data) = 0.2163. CCDC no. 8844800.

37: $C_{16}H_{15}NO_4$, M = 285.29, monoclinic, space group $P2(1)/c$, a = 13.362(3), b = 13.883(3), c = 7.8491(17) Å, β = 103.842(3)°, V = 1413.7(6) Å^3, Z = 4, μ = 0.097 mm^{-1}, data/restraints/parameters: 2484/0/193, R indices ($I > 2\sigma(I)$): R1 = 0.0501, $wR2$ (all data) = 0.1351. CCDC no. 8844801.

39: $C_{21}H_{18}Cl_3NO_4S$, M = 486.79, triclinic, space group $P\bar{1}$, a = 9.1437(8), b = 9.3147(7), c = 12.7844(16) Å, α= 92.975(8)°, β = 95.650(9)°, γ= 91.661(6)°, V = 1081.48(18) Å^3, Z = 4, μ = 0.549 mm^{-1}, data/restraints/parameters: 3802/0/274, R indices ($I > 2\sigma(I)$): R1 = 0.0536, $wR2$ (all data) =. 0.1581. CCDC no. 8844802.

47: $C_{21}H_{19}NO_3$, M = 333.39, monoclinic, space group $P2(1)/c$, a = 13.0768(16), b = 16.069(2), c = 8.6435(9) Å, β = 105.021(13)°, V = 1754.3(4) Å^3, Z = 4, μ = 0.084 mm^{-1}, data/restraints/parameters: 3093/1/230, R indices ($I > 2\sigma(I)$): R1 = 0.0583, $wR2$ (all data) = 0.1277. CCDC no. 8844803.

A: C_{38} H_{30} N_2 O_4, M = 578.64, monoclinic, space group $C2/c$, a = 24.956(5), b = 8.9926(8), c = 16.635(3) Å, β = 129.57(3)°, V = 2877.8(9) Å^3, Z = 4, μ = 0.087 mm^{-1}, data/restraints/parameters: 2404/0/200, R indices ($I > 2\sigma(I)$): R1 = 0.0566, $wR2$ (all data) = 0.1302. CCDC no. 8844804.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

More experimental data, additional molecular drawings, CIF files, copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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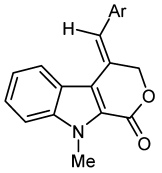
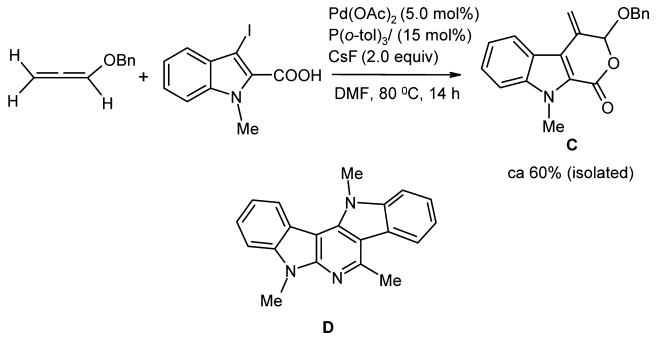
(18) The arylallenes **18** and **19** on reaction with **21a** afford products **A** and **B** that are analogous to **29**. The isolation of a pure isomer was difficult in these cases due to closeness of R_f values; however, a couple of crystals of (**A**) amenable for X-ray structure diffraction (Supporting Information, Figure S7) could be obtained and the structure could be determined.

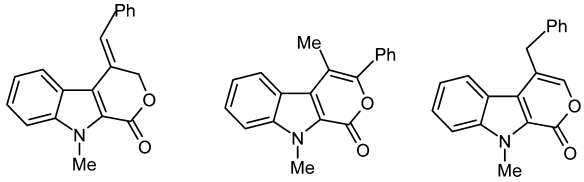


Ar = Ph **A** (X-ray, 81% isomeric purity using **21a**)
Ar = C_6H_4-4-Me **B** (93% isomeric purity using **21a**)

(19) When the allene $H_2C{=}C{=}CH(OCH_2Ph)$ containing an electron-donating group (OCH_2Ph) was treated with 3-iodo-1-methylindole-2-carboxylic acid, the result was the β,α-cyclized product (**C**) [Mp: 148−150 °C. IR (KBr): 2932, 1711, 1480, 1211, 1109, 1053, 982 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 4.13 (s, 3H), 4.87 (d, $J \approx 12.20$ Hz, 1H), 5.02 (d, $J \approx 12.2$ Hz, 1H), 5.51 (s, 1H), 5.87 and 5.92 (2 s, 2H), 7.26−7.47 (m, 8H), 7.92 (d, $J = 8.4$ Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 31.4, 70.7, 102.7, 110.9, 113.3, 118.9, 121.6, 122.0, 122.2, 126.7, 128.2, 128.3, 128.6, 134.1, 136.4, 140.5, 158.7. HRMS (ESI) calcd for $C_{20}H_{17}NO_3Na$ $(M + Na)^+$ 342.1106, found 342.1106]. The reaction of this allene with 1-methylindole-2-carboxylic acid in CH_3CN was rather sluggish but showed three products on tlc; however, since the only product (**D**, triaza-indeno-fluorene) (m/z 300) that we could isolate did not contain the allene residue (^1H NMR, partial X-ray structure), we did not proceed further.



(20) The other three possible isomers are shown below:



(21) Interestingly, when $Cu(OAc)_2$ (0.75 mmol) + LiOAc (1.0 mmol) was used in place of Ag_2CO_3, with the reaction time being 8 h; 0.75 mmol of the allenoate, only compound **37** was preferentially formed.
(22) Compound **41** was obtained with 64% isolated yield from 0.5 mmol of **42a** and 0.75 mmol of **20**.

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