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One-pot Sequential [3+3] Dipolar Cycloaddition of Aldehyde or Ketone, Hydroxylamine with Spirocyclopropyl Oxindole

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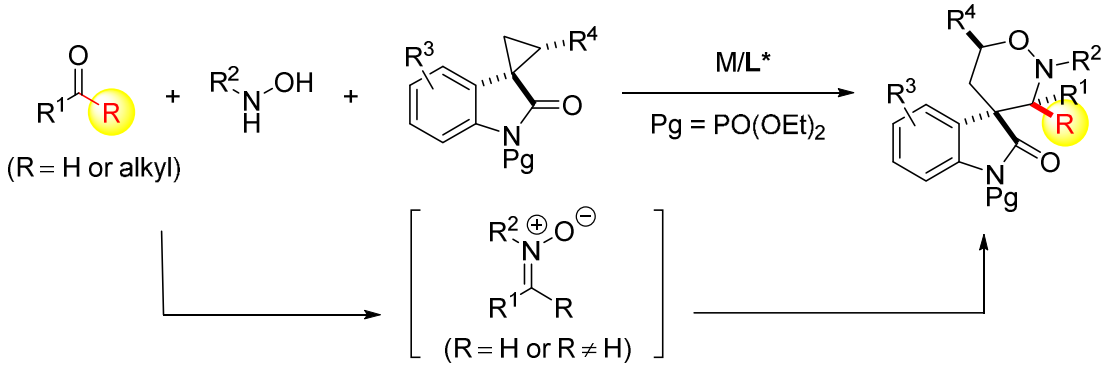


♣ One-pot sequential operation ♣ Both aldehydes and ketones ♣ Biological evaluation

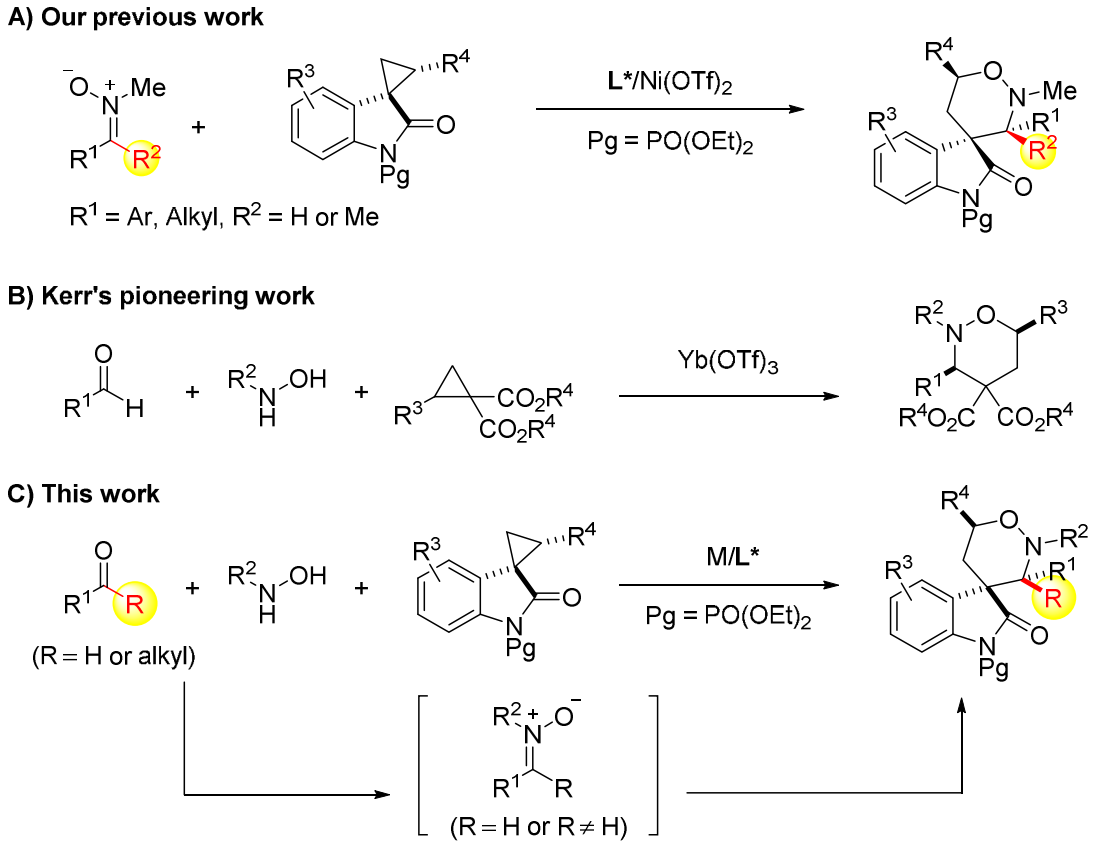
Abstract: A $Sc(OTf)_3$ catalyzed highly diastereoselective one-pot sequential [3+3] dipolar cycloaddition reaction of aldehyde or ketone, *N*-alkyl hydroxylamine and spirocyclopropyl oxindole is developed, allowing facile construction of spirocyclic oxindole-tetrahydro-1,2-oxazines in sufficient structural diversity. The corresponding catalytic enantioselective one-pot protocol of aldehydes is also reported, affording the desired adducts in up to 97% ee. The biological evaluation of selected oxindole-based spirocyclic tetrahydro-1,2-oxazines revealed that they exerted cytotoxic effects on human prostate cancer cells with the capacity to inhibit NFκB signaling in prostate cancer cells.

Introduction

Spiro skeletons are widely distributed in bioactive natural products and pharmaceutically active compounds.[1] Notably, spirocyclic compounds play an active role in modern drug discovery & development, because the incorporation of spiro-ring fusion can reduce the conformational entropy penalty upon binding with a protein target.[2] As a result, much attention has been paid to the efficient construction of densely functionalized spirocyclic compounds with structural diversity.[3] This is further fueled by the demand of probe- and drug-discovery programmes for synthetic libraries that replicate the structural features of natural products, to enhance the returns of high-throughput screenings.[4] In particular, spirocyclic compounds derived from privileged scaffolds are highly desirable.

Tetrahydro-1,2-oxazine moiety present in bioactive natural products such as nakadomarin A, (+)-phyllantidine, FR900482 and FR 66979, as well as in synthetic bioactive compounds FK317 and FK973.[5] The merger of this heterocycle into spirocycles is interesting to develop novel molecules for medicinal studies. Recently, inspired by the pioneering work of Young and Kerr in [3+3] cycloaddition of nitrones and donor-acceptor (D–A) cyclopropanes for the flexible construction of tetrahydro-1,2-oxazines,[6] as well as the efforts of Sibi and Tang groups in developing catalytic asymmetric versions,[7] we developed a highly diastereo- and enantioselective [3+3] cycloaddition of spirocyclopropyl oxindoles[8] with both aldonitrones and ketonitrones (Scheme 1A).[9] This enables the facile synthesis of oxindole based spirocyclic tetrahydro-1,2-oxazines. It is worth mentioning that spirocyclic oxindoles are prominent structural motifs in drugs and bioactive compounds as well, the diverse construction of this framework is of current interest.[10] Because some nitrones are not easy to prepare or unstable due to oligomerization under acidic conditions, along with their highly hydroscopic nature, the development of more convenient and efficient protocols using nitrones formed in situ, without the isolation and handling of the nitrones, is very helpful to build up libraries of oxindole based spirocyclic 1,2-oxazines for medicinal studies.

Scheme 1. One-pot [3+3] Cycloaddition of Aldehyde or Ketone, Hydroxylamine with D-A Cyclopropane.



- One-pot sequential operation using either aldehydes or ketones
- Facile construction of spirocyclic oxindole-tetrahydro-1,2-oxazines for biological evaluation

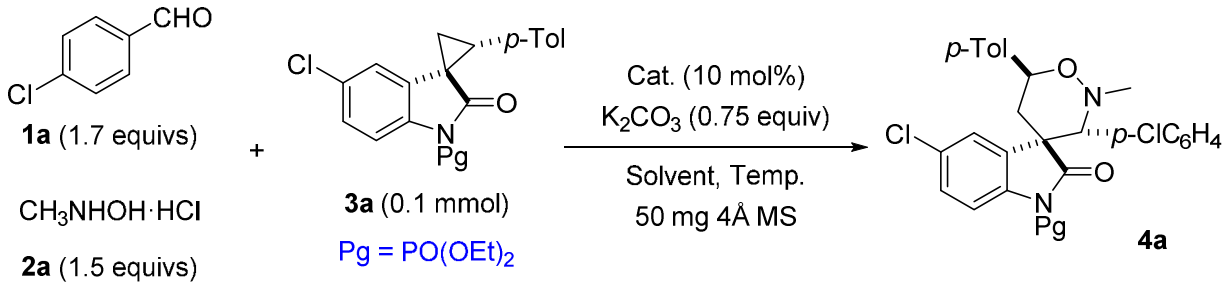
In 2004, Kerr et al. developed an elegant three component protocol using aldehydes, hydroxylamines and D–A cyclopropanes (Scheme 1B).[11] This strategy was further successfully applied to the total synthesis of nakadomarin A[12a] and (+)-phyllantidine[12b] as well as the construction of other privileged scaffolds.[12c-e] Their meaningful results encouraged us to develop a one-pot method for the facile construction of a library of spirocylic oxindole-1,2-oxazines for biological evaluation, although ketones have not been incorporated to such one-pot protocol and the corresponding catalytic enantioselective one-pot version remains undeveloped. As part of our research program for the efficient construction of spirocyclic oxindoles for biological evaluation,[9,13] we attempt to develop a highly diastereoselective one-pot [3+3] cycloaddition of aldehydes or ketones, hydroxylamines with spirocyclopropyl oxindoles,

along with a catalytic enantioselective version (Scheme 1C). Here, we wish to report our research work and the initial results of biological evaluation.

Results and discussion

We began our research by using the [3+3] cycloaddition of 4-chlorobenzaldehyde **1a**, *N*-methylhydroxylamine hydrochloride **2a** and *N*-diethoxyphosphoryl spirocyclopropyl oxindole **3a** as model reaction, with K_2CO_3 as base to neutralize the reaction. Typically, **1a** and **2a** were combined initially in the presence of 4 Å molecular sieves (MS), 10 mol% Lewis acid catalyst and 0.75 equiv K_2CO_3 at 50 °C for 1 h. After the complete formation of nitrone, **3a** was added and the resulting reaction mixture was stirred until **3a** was fully consumed.

Table 1. Conditions Optimization



Entry	Cat.	Solvent	Temp. (°C)	Time (h)	Dr[a]	Yield (%)
1	$Ni(OTf)_2$	DCE	50	72	>20:1	42
2	$Ni(OTf)_2$	DCE	80	6	3.7:1	70
3	$Mg(OTf)_2$	DCE	50	72	9.6:1	56
4	$Mg(OTf)_2$	DCE	80	6	4.0:1	69
5	$Bi(OTf)_3$	DCE	50	24	>20:1	24
6	$Er(OTf)_3$	DCE	50	5	4.6:1	70
7	$Y(OTf)_3$	DCE	50	5	4.7:1	66
8	$Yb(OTf)_3$	DCE	50	5	4.7:1	73
9	$Sc(OTf)_3$	DCE	50	5	5.5:1	72
11	$Sc(OTf)_3$	THF	50	24	8.3:1	73
12	$Sc(OTf)_3$	Toluene	50	6	7.6:1	80
13	$Sc(OTf)_3$	EtOAc	50	6	10.3:1	85

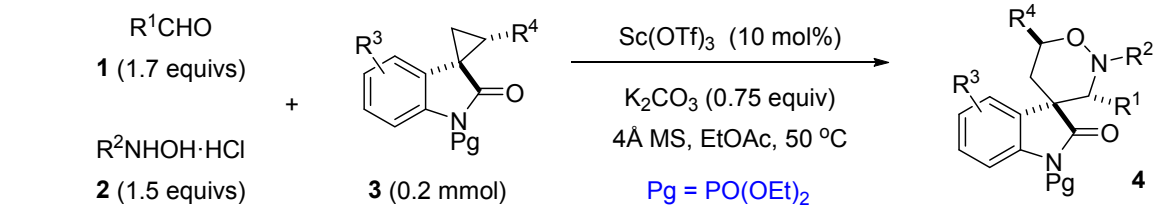
[a] Determined by ^{1}H NMR analysis. Note: **3a** was not fully consumed in entry 1.

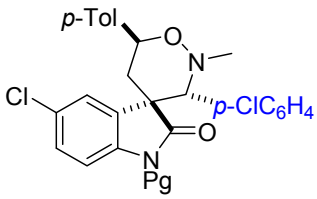
Initially, the performance of different metal triflates was investigated using dichloroethane (DCE) as solvent. When the reaction of **1a**, **2a** and **3a** were conducted in the absence of Lewis acid catalyst, the nitrone could be formed smoothly, but no further cycloaddition reaction could be detected. $Ni(OTf)_2$, the best catalyst we identified in previous work[9], catalyzed the reaction to give the desired product **4a** in > 20:1 dr, but resulted in incompletion of the [3+3] cycloaddition, and **4a** was obtained in only 42% yield even after 72 h (entry 1, Table 1). The relative configuration of **4a** was determined by NMR analysis combined with the reference of previous work[9]. Raising reaction temperature from 50 ^oC to 80 ^oC allowed the reaction to finish within 6 h, but afforded **4a** in a much lower 3.7:1 dr (entry 2). Similar results were observed when using $Mg(OTf)_2$ as catalyst (entries 3-4). $Bi(OTf)_3$ was a less active catalyst for this reaction, giving **4a** in only 24% yield (entry 5). Rare earth metal triflates such as $Er(OTf)_3$, $Y(OTf)_3$, $Yb(OTf)_3$, and $Sc(OTf)_3$ could allow the reaction to finish in 5 h (entries 6-9), but $Sc(OTf)_3$ gave the best result in term of reaction yield and dr value (entry 9). Subsequently, the solvent effects of the reaction catalyzed by $Sc(OTf)_3$ were investigated to improve the diastereoselectivity. THF as the solvent resulted in higher dr but slower reaction rate (entry 11); however, the reaction in toluene could finish in 6 h, affording **4a** in 80% yield with 7.6:1 dr (entry 12). Gratifyingly, ethyl acetate (EtOAc) turned out to be the best solvent of choice, and the reaction went for a completion within 6 h to give **4a** in 85% yield and 10.3:1 dr (entry 13). Finally, we determined to run the reaction at 50 ^oC in EtOAc, using 10 mol% $Sc(OTf)_3$ as the catalyst.

The substrate scope of this one-pot sequential protocol with respect to differently substituted aldehydes **1**, *N*-alkyl hydroxylamines **2** and oxindoles **3** was then studied (Scheme 2). In general, phenyl aldehydes with either electron-deficient or electron-rich substituents were all viable substrates, giving the desired products **4a-g** in 77-83% yield and 6.5:1-10.0:1 dr. 2-Naphthaldehyde, 2-furanaldehyde and 2-thenaldehyde gave the corresponding products **4h-j** in high yield and dr values. Aliphatic aldehydes with an isopropyl or a cyclohexyl group also worked well, giving the corresponding products **4k** and **4l**

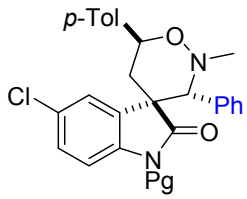
in high yield and diastereroselectivity. α,β-Unsaturated aldehydes were compatible substrates as well, as shown by the conversion of cinnamaldehyde to **4m** in 90% yield and 14.0:1 dr. Furthermore, differently substituted hydroxyamines and spirocyclopropyl oxindoles were examined. BnNHOH gave the desired product **4n** in 87% yield with 18.1:1 dr. On the other hand, the oxindoles **3** bearing a fluorine atom on C5 position of oxindole ring or a 2-naphthyl group on the cyclopropane ring all readily furnished the corresponding products **4o-p** in good yield and diastereoselectivity.

Scheme 2. Substrate Scope with Aldehyde

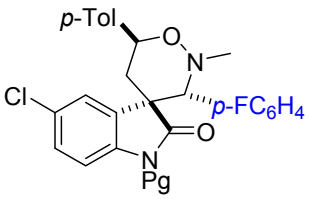




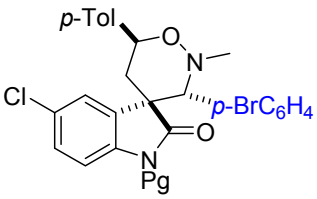
4a: 5 h, 83%, 10.0:1 dr



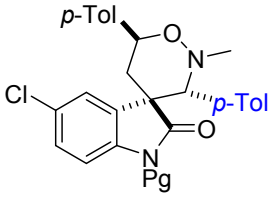
4b: 6 h, 83%, 9.2:1 dr



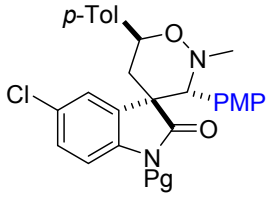
4c: 6 h, 79%, 8.1:1 dr



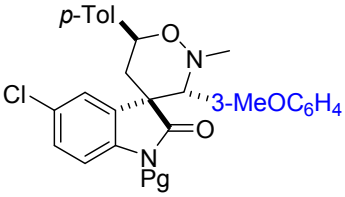
4d: 4 h, 77%, 9.3:1 dr



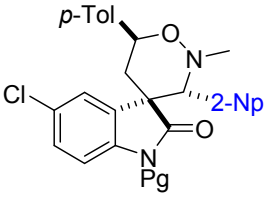
4e: 6 h, 81%, 8.0:1 dr



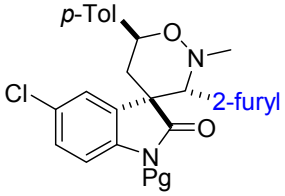
4f: 5 h, 78%, 6.5:1 dr



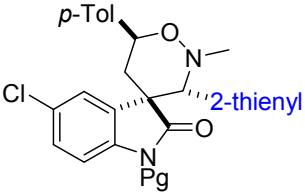
4g: 6 h, 83%, 8.4:1 dr



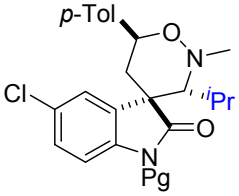
4h: 4 h, 69%, 8.0:1 dr



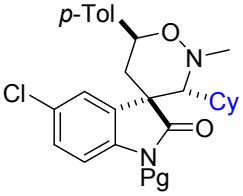
4i: 4 h, 81%, 10.0:1 dr



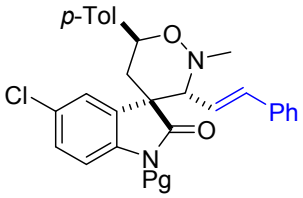
4j: 4 h, 81%, 11.3:1 dr



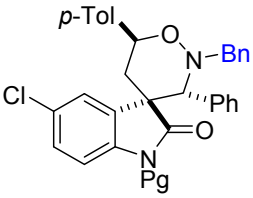
4k: 6 h, 86%, 8.6:1 dr[b]



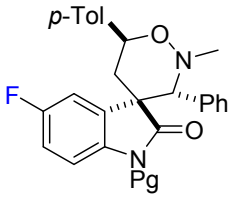
4l: 6 h, 86%, 10.9:1 dr



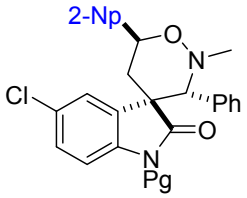
4m: 4 h, 90%, 14.0:1 dr



4n: 4 h, 87%, 18.1:1 dr[c]



4o: 4 h, 83%, 11.6:1 dr



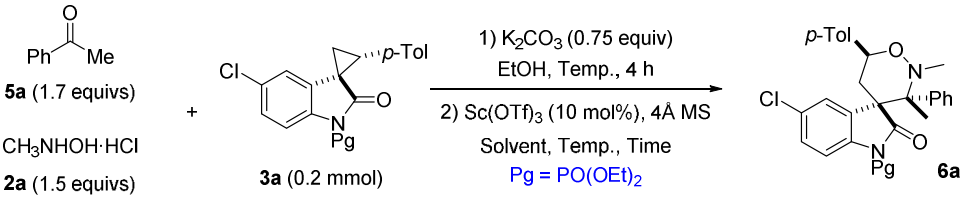
4p: 4 h, 85%, 8.1:1 dr

[a] Dr value was determined by ^{1}H NMR. [b] 2.0 mmol isobutyraldehyde was used. [c] Reaction run without K_2CO_3.

In the following, we investigated the feasibility of merging ketones into the one-pot procedure to construct spirocyclic tetrahydro-1,2-oxazines with adjacent quaternary and tetrasubstituted carbons. Since ketonitrones formation was more difficult, the corresponding procedure of the one-pot manipulation was modified slightly in that EtOH was used as solvent for ketonitrone formation.[14] While the [3+3] cycloaddition of the thus obtained ketonitrone and spirocyclopropyl oxindoles could not take

place in EtOH, we then tried to remove EtOH after the formation of ketonitrone and use other solvents for the [3+3] cycloaddition reaction. All of the solvents screened could give the product **6a** successfully, albeit with different reaction outcome (Table 2). When DCE or THF was used, product **6a** could be obtained in 40% and 43% yield with 4.6:1 and 4.2:1 dr respectively (entry 1-2, Table 2). A higher yield could be obtained using toluene and EtOAc as solvent, but the diastereoselectivity decreased slightly (entries 3-4). Finally, when using ^{i}PrOAc as solvent, the reaction could finish in 24 h giving product **6a** in 57% yield with 4.0:1 dr (entry 5, Table 2). We also tried to run the reaction in ^{i}PrOAc at 80 ^{o}C to improve the efficiency of nitrone formation and the [3+3] cycloaddition of ketonitrone and spirocyclopropyl oxindoles, but **6a** was only obtained in 33% yield. (entry 6, Table 2). Finally, we determined to run the reaction of ketones at 50 ^{o}C in EtOAc.

Table 2. Screening of Solvents for One-pot Sequential [3+3] Cycloaddition Using Ketone



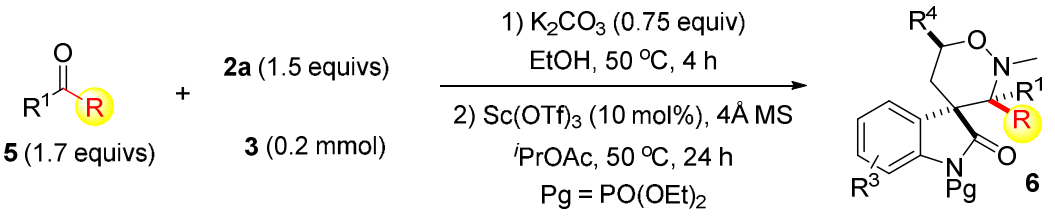
Entry	Solvent	Temp. (^{o}C)	Time (h)	Dr[a]	Yield (%)[b]
1	DCE	50	36	4.6:1	40
2	THF	50	36	4.2:1	43
3	Toluene	50	36	3.5:1	49
4	EtOAc	50	36	3.7:1	54
5	^{i}PrOAc	50	24	4.0:1	57
6	^{i}PrOAc	80	24	mess	33

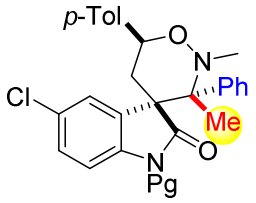
[a] Determined by ^{1}H NMR analysis of crude mixture.

Under this condition, acetophenones with different phenyl substituents, along with methyl *trans*-styrylketone were readily coordinated to the one-pot synthesis to afford the desired spirocyclic tetrahydro-1,2-oxazines **6a-e** in 42-51% yields and moderate dr values (Scheme 3). Spirocyclopropyl oxindoles with different substituents at the oxindole framework or at the cyclopropane moiety all worked well to give the corresponding adducts **6f-6h** in reasonable yield and moderate dr value. The reaction of cyclopentone was conducted at 80 ^{o}C, furnishing the product **6i** in excellent 20:1 dr, albeit with moderate yield. The low yield may cause by the low conversion of nitrone formation step and the

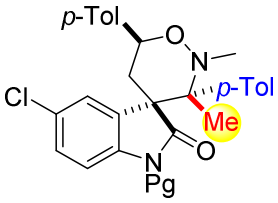
instability of the nitrone. We have also tried to isolate the ketonitrone derivated from cyclopentone but failed. Despite the room for further improvement in terms of diasteresoselectivity, our results clearly suggested the potential of in situ formation of unactivated ketonitrones for diverted-oriented synthesis.

Scheme 3. Substrate Scope with Ketone

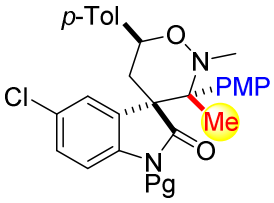




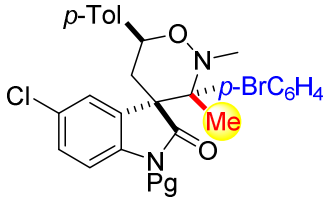
6a: 50%, 3.9:1 dr



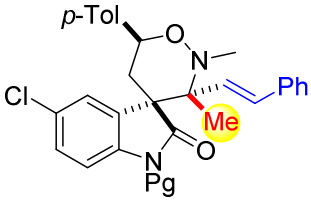
6b: 48%, 4.2:1 dr



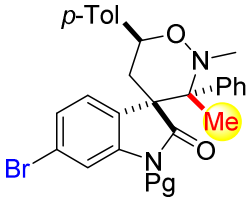
6c: 51%, 4.5:1 dr



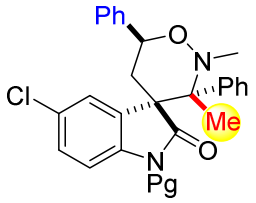
6d: 46%, 2.3:1 dr



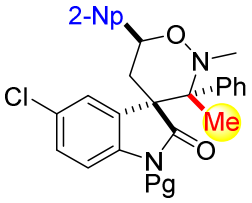
6e: 42%, 5.3:1 dr



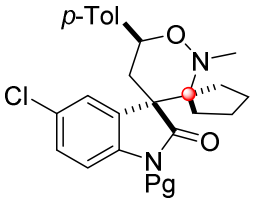
6f: 50%, 3.5:1 dr



6g: 49%, 3.0:1 dr



6h: 55%, 3.0:1 dr

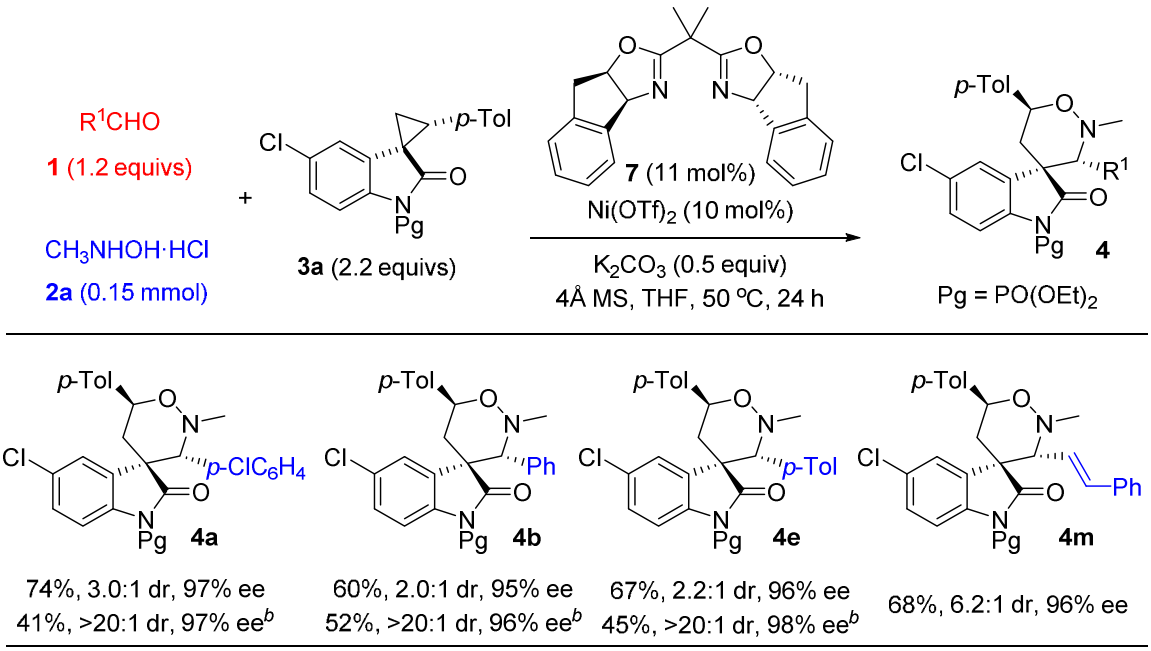


6i: 22%, >20:1 dr[b]

[a] Dr determined by ^{1}H NMR analysis. [b] Nitrone preparation and cycloaddition reaction were conducted at 80 °C.

We also tried the catalytic asymmetric version of the one-pot sequential [3+3] cycloaddition reaction. Chiral bisoxazoline **7**/Ni(OTf)$_2$, the previously established catalyst,[9] was found to mediate the one-pot transformation well, affording the chiral spirocyclic products **4a-b**, **4e** and **4m** in considerable yield and excellent ee value, albeit with diminished dr value as compared with the corresponding enantioselective cycloaddition of pre-prepared aldonitrones[9] (Scheme 4).

Scheme 4. Asymmetric One-pot Sequential [3+3] Dipolar Cycloaddition Reaction



[a] Dr determined by ^{1}H NMR analysis of the crude reaction mixture. [b] Previous results using pre-formed nitrone and 0.3 mmol **3a** (ref 9).

Biological Studies

Next, we investigated the biological activities of the thus obtained spirocylic oxindole-1,2-oxazines in a NFκB signaling inhibitory assay. As a transcription factor, nuclear factor κB (NFκB) plays key roles in regulation of cell proliferation, survival and immune responses.[15] Constitutive activation of NFκB signaling pathway is often detected in hormone refractory prostate cancer, which is the resistance stage to androgen deprivation therapy. Moreover, the inhibition of NFκB activation has proved to be a promising approach for prostate cancer treatment.[16] Therefore, small molecule inhibitors that inhibit NFκB transcriptional activity would be potential candidate to treat hormone refractory prostate cancer. Several potent NFκB signaling inhibitors, such as JSH-23, have been recently reported.[17]

We tested whether the thus obtained spirocylic oxindole-1,2-oxazines can suppress NFκB activity in a hormone refractory prostate cancer DU145 cell line. As a well-known inducer of NFκB activity, TNFα treatment successfully increased the NFκB transcriptional activity (Figure 1). Notably, all of the four selected compounds (**4b**, **4f**, **6a** and **6c)** significantly inhibited the transcriptional activity of NFκB in DU145 cells in a dose-dependent manner.

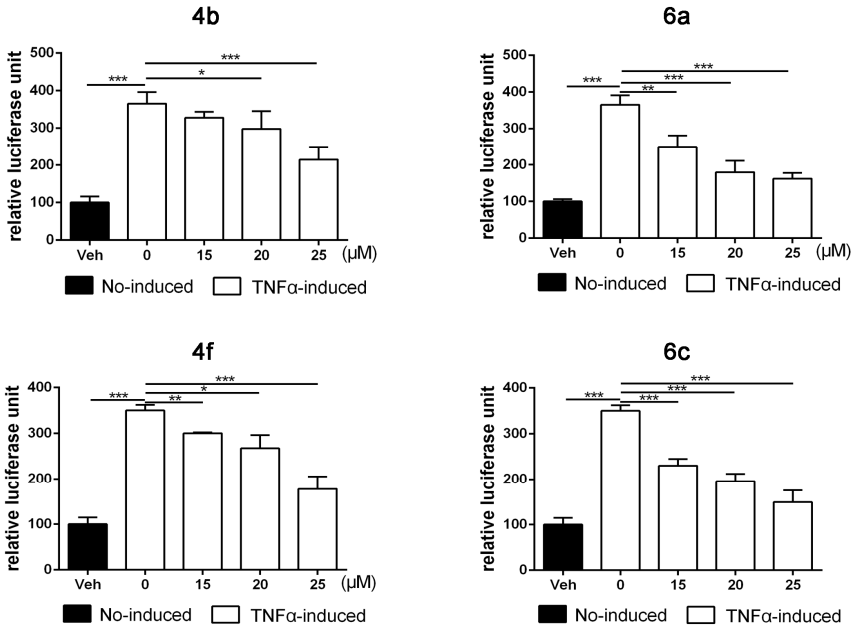


Figure 1. Compounds **4b**, **4f**, **6a** and **6c** inhibited NFκB signaling pathway. DU145 cells were transfected with 6xNFκB-luciferase reporter plasmid. After 24 h, the cells were pre-treated with **4b**, **4f**, **6a** and **6c** for 4 h, followed by 10 ng/mL TNFα treatment. The luciferase activities were calculated as a rate of firefly luciferase activity/total protein. The relative luciferase activity of vehicle control was set as 100%. N = 3. The data were repeated in three biological independent replicates and presented as mean ± SD. *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$.

Since constitutive activation of NFκB signaling is positively associated with prostate cancer cell proliferation and survival, we next examine whether these four compounds (**4b**, **4f**, **6a** and **6c)** can induce cytotoxicity on hormone refractory prostate cancer cells. Two human hormone refractory prostate cancer cell lines (DU145 and PC3) and one non-malignant prostate epithelial cell line (BPH1) with four compounds for 48 h and then measured the cell viability using the MTT assay. The half-maximal inhibitory concentration (IC50) values were measured in DU145, PC3 and BPH1 cells. All the compounds given in Table 3 showed cytotoxic effects to prostate cancer cells. Interestingly, DU145 and PC3 cells showed more sensitivity to these four compounds than BPH1 cells. Next, we compared these four compounds with a well-known NFκB inhibitor (JSH-23) on cytotoxic effects. The IC50 of JSH-23 is higher than **4b**, **4f**, **6a** and **6c** in DU145 and PC3 cells (Table 3). Overall, these four new compounds can be taken as potent inhibitors of NFκB signaling pathway and have higher cytotoxic effects than JSH-23 in DU145 and PC3 cells.

Table 3. IC50 Values of Four Compounds in a Non-malignant Prostate Epithelial BPH1 Cells and two Hormone Refractory Prostate Cancer DU145 and PC3 Cells

Compound	IC50 (μM, mean ± SD)		
	DU145 cell line	PC3 cell line	BPH1 cell line
4b	19.09±2.19	22.87±5.21	>30
4f	16.50±3.13	20.00±3.52	>30
6a	15.45±0.95	22.03±5.92	>30
6c	14.57±1.90	18.92±2.71	>30
JSH-23	110.47	70.64	-

Conclusion

In summary, we have developed a one-pot sequential [3+3] dipolar cycloaddition reaction of aldehyde/ketone, *N*-alkyl hydroxylamines and spirocyclopropyl oxindoles for the facile synthesis of oxindole-based spirocyclic tetrahydro-1,2-oxazines. The biological studies indicate that the thus obtained spirocyclic oxindole-1,2-oxazines possess cytotoxic effect on hormone refractory prostate cancer cells with the capacity to inhibit NFκB transcriptional activity. Further structural modification and bioactivity studies of the thus obtained spirocyclic tetrahydro-1,2-oxazines are on going in our lab.

Experimental Section

General Information. Reactions were monitored by thin layer chromatography using UV light to visualize the course of reaction. Purification of reaction products was carried out by flash chromatography on silica gel. Chemical yields referred to pure isolated substances. Infrared (IR) spectra were obtained using a Bruker tensor 27 infrared spectrometer. ^{1}H NMR, ^{13}C{^{1}H}NMR, ^{31}P NMR and ^{19}F NMR spectra were obtained using Bruker DPX-400 or DPX-300 MHz spectrometer. Chemical shifts were reported in ppm from tetramethylsilane with the solvent resonance. The following abbreviations were used to designate chemical shift multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, h = heptet, m = multiplet, br = broad.

All reactions were run in an atmosphere of N_2 except noted. Anhydrous CH_2ClCH_2Cl (DCE) and CH_3CN were prepared by first distillation over P_2O_5 and then from CaH_2. Toluene and THF were prepared by distillation over sodium-benzophenone ketyl prior to use. Anhydrous EtOAc and ^{i}PrOAc were prepared by distillation over activated calcium sulfate and 5Å MS prior use. Activated molecular sieves powder 4Å (MS 4 Å) was dried at 150 °C in vacuum before use. Metal triflates were purchased from Strem Chemicals and used as it received. *N*-diethoxyphosphoryl spirocyclopropyl oxindoles were synthesized according to the literature procedures.[9] (**4a-l**, **4o-p**, **6a-b**, **6d**, **6f-h** are reported compound,[9] **4m-n**, **6c**, **6e**, **6i** are new coupound)

General procedure for one-pot sequential [3+3] dipolar cycloaddition with aldehyde.

To a Schlenk tube were sequentially added aldehydes **1** (0.34 mmol), hydroxyamines **2** (0.30 mmol), 4Å MS (100 mg), $Sc(OTf)_3$ (9.8 mg, 0.02 mmol, 10 mol %) and K_2CO_3 (0.15 mmol, 20.7 mg), followed by the addition of anhydrous EtOAc (2.0 mL). After the resulting solution was stirred at 50 ^{o}C for 1 h, spirocyclopropyl oxindoles **3** (0.20 mmol) was added. The reaction was kept stirring at 50 ^{o}C till the full consumption of **3** by TLC analysis. Then EtOAc was removed under reduced pressure. The residue was dissolved in CH_2Cl_2, rapidly passed through a glass funnel with a thin layer (2 cm) of silica gel, washed with 10 mL CH_2Cl_2/EtOAc (5/1, v/v), and concentrated under reduced pressure. To determine the dr value of the products, the residue was first dissolved in $CDCl_3$, and took a little portion to determine diastereoselectivity by ^{1}H NMR analysis. Then the sample for analysis and rest crude product were recombined for column chromatography purification to afford product **4**, using CH_2Cl_2/EtOAc (40/1, v/v) as the eluent.

Spirocyclic oxindole-tetrahydro-1,2-oxazines 4a: White solid; 97.7 mg, yield 83%; ^{1}H NMR analysis revealed that the dr is 10.0:1. ^{1}H NMR (400 MHz, $CDCl_3$): 8.32 (s, 1H), 7.58 (d, J = 8.4 Hz, 1H), 7.34 (d, J = 8.0 Hz, 2H), 7.29 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H), 7.23-7.07 (m, 4H), 6.94 (d, J = 8.8 Hz, 1H), 6.61 (d, J = 8.4 Hz, 1H), 5.50 (dd, J_1 = 12.4 Hz, J_2 = 2.4 Hz, 1H), 4.16 (s, 1H), 4.13-4.07 (m, 1H), 3.97-3.90 (m, 1H), 3.84-3.78 (m, 1H), 3.59-3.52 (m, 1H), 2.57-2.50 (m, 1H), 2.49 (s, 3H), 2.35 (s,

3H), 1.89 (dd, J_1 = 13.2 Hz, J_2 = 2.4 Hz, 1H), 1.25 (td, J_1 = 7.2 Hz, J_2 = 0.8 Hz, 3H), 1.18 (td, J_1 = 7.2 Hz, J_2 = 0.8 Hz, 3H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): 178.0, 139.1 (d, J = 6.9 Hz), 138.3, 136.4, 134.1, 134.0, 132.2 (d, J = 9.3 Hz), 131.9, 129.3, 129.1, 129.0, 128.8, 128.1, 126.9, 126.6, 115.3, 75.6, 74.9, 64.7 (d, J = 5.7 Hz), 64.2 (d, J = 5.8 Hz), 54.4 (d, J = 5.8 Hz), 44.7, 41.1, 21.2, 15.9 (d, J = 6.9 Hz), 15.8 (d, J = 7.4 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): -7.32;

Spirocyclic oxindole-tetrahydro-1,2-oxazines 4b: White solid; 92.0 mg, 83% yield; ^1H NMR analysis showed the dr value is 9.2:1. ^1H NMR (400 MHz, $CDCl_3$): 8.36 (s, 1H), 7.58 (d, J = 8.8 Hz, 1H), 7.35 (d, J = 8.0 Hz, 2H), 7.28 (dd, J_1 = 8.8 Hz, J_2 = 2.4 Hz, 1H), 7.22-7.08 (m, 5H), 7.00-6.90 (m, 1H), 6.72-6.61 (m, 1H), 5.52 (dd, J_1 = 12.0 Hz, J_2 = 2.4 Hz, 1H), 4.18 (s, 1H), 4.14-4.08 (m, 1H), 3.96-3.92 (m, 1H), 3.76-3.70 (m, 1H), 3.51-3.45 (m, 1H), 2.60-2.51 (m, 1H), 2.50 (s, 3H), 2.35 (s, 3H), 1.89 (dd, J_1 = 13.2 Hz, J_2 = 2.4 Hz, 1H), 1.24 (td, J_1 = 7.2 Hz, J_2 = 0.8 Hz, 3H), 1.15 (td, J_1 = 7.2 Hz, J_2 = 0.8 Hz, 3H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): 178.3, 139.2 (d, J = 7.1 Hz), 138.2, 136.6, 135.6, 132.6 (d, J = 9.4 Hz), 130.6, 129.3, 128.9, 128.6, 128.1, 127.9, 127.7, 127.0, 126.6, 115.2, 75.6, 64.6 (d, J = 5.7 Hz), 64.0 (d, J = 5.5 Hz), 54.4 (d, J = 5.7 Hz), 44.7, 41.3, 21.2, 16.0 (d, J = 7.0 Hz) , 15.9 (d, J = 7.8 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): -7.28;

Spirocyclic oxindole-tetrahydro-1,2-oxazines 4c: White solid; 90.1 mg, 79% yield; ^1H NMR analysis revealed that the dr is 8.1:1. ^1H NMR (400 MHz, $CDCl_3$): 8.33 (s, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.34 (d, J = 8.4 Hz, 2H), 7.29 (dd, J_1 = 8.8 Hz, J_2 = 2.4 Hz, 1H), 7.25-7.14 (m, 3H), 6.90-6.80 (m, 1H), 6.74-6.59 (m, 2H), 5.50 (dd, J_1 = 12.0 Hz, J_2 = 2.4 Hz, 1H), 4.17 (s, 1H), 4.16-4.08 (m, 1H), 3.98-3.92 (m, 1H), 3.86-3.80 (m, 1H), 3.60-3.54 (m, 1H), 2.55-2.49 (m, 1H), 2.49 (s, 3H), 2.35 (s, 3H), 1.89 (dd, J_1 = 13.2 Hz, J_2 = 2.4 Hz, 1H), 1.25 (td, J_1 = 7.2 Hz, J_2 = 0.8 Hz, 3H), 1.18 (td, J_1 = 7.2 Hz, J_2 = 0.8 Hz, 3H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): 178.2, 162.6 (d, J = 246.5 Hz), 139.1 (d, J = 7.0 Hz), 138.3, 136.4, 132.4 (d, J = 9.5 Hz), 132.2 (d, J = 7.9 Hz), 131.4 (d, J = 3.3 Hz), 129.4, 129.3, 129.1, 128.8, 126.9, 126.6, 115.3, 115.0, 114.8, 114. 6, 75.6, 74.7, 64.7 (d, J = 5.6 Hz), 64.2 (d, J = 5.6 Hz), 54.4 (d, J = 5.6 Hz), 44.6, 41.1, 21.2, 16.0 (d, J = 6.8 Hz), 15.9 (d, J = 7.6 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): -.7.27; ^{19}F NMR (282 MHz, $CDCl_3$): -113.24;

Spirocyclic oxindole-tetrahydro-1,2-oxazines 4d: White solid; 97.5 mg, 77% yield; ^{1}H NMR analysis revealed that the dr is 9.3:1. ^{1}H NMR (400 MHz, $CDCl_3$): 8.32 (s, 1H), 7.58 (d, J = 8.8 Hz, 1H), 7.36-7.27 (m, 4H), 7.19 (d, J = 8.0 Hz, 2H), 7.15-7.01 (m, 2H), 6.55 (d, J = 7.6 Hz, 1H), 5.50 (dd, J_1 = 12.4 Hz, J_2 = 2.4 Hz, 1H), 4.15 (s, 1H), 4.14-4.07 (m, 1H), 3.98-3.88 (m, 1H), 3.84-3.76 (m, 1H), 3.59-3.49 (m, 1H), 2.54-2.49 (m, 1H), 2.48 (s, 3H), 2.35 (s, 3H), 1.89 (dd, J_1 = 12.8 Hz, J_2 = 2.4 Hz, 1H), 1.26 (td, J_1 = 7.2 Hz, J_2 = 0.8 Hz, 3H), 1.19 (td, J_1 = 7.2 Hz, J_2 = 0.8 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): 178.0, 139.1 (d, J = 7.0 Hz), 138.3, 136.3, 134.5, 132.2, 132.1, 131.1 (d, J = 5.3 Hz), 129.3, 129.1, 128.8, 126. 9, 126.6, 122.3, 115.3, 75.6, 74.9, 64.7 (d, J = 5.5 Hz), 64.2 (d, J = 5.5 Hz), 54.3 (d, J = 5.7 Hz), 44.7, 41.0, 21.2, 16.0 (d, J = 7.2 Hz), 15.9 (d, J = 7.8 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): -7.32;

Spirocyclic oxindole-tetrahydro-1,2-oxazines 4e: White solid; 92.3 mg, 81% yield; ^{1}H NMR analysis revealed that the dr is 8.0:1. ^{1}H NMR (400 MHz, $CDCl_3$): 8.35 (s, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.34 (d, J = 8.0 Hz, 2H), 7.30-7.26 (m, 1H), 7.19 (d, J = 8.0 Hz, 2H), 7.09 (d, J = 8.8 Hz, 1H), 6.95 (d, J = 7.6 Hz, 1H), 6.75 (d, J = 8.0 Hz, 1H), 6.52 (d, J = 8.0 Hz, 1H), 5.51 (dd, J_1 = 12.0 Hz, J_2 = 2.4 Hz, 1H), 4.14 (s, 1H), 4.12-4.06 (m, 1H), 3.96-3.90 (m, 1H), 3.73-3.67 (m, 1H), 3.46-3.40 (m, 1H), 2.54-2.51 (m, 1H), 2.48 (s, 3H), 2.35 (s, 3H), 2.17 (s, 3H), 1.87 (dd, J_1 = 13.2 Hz, J_2 = 2.4 Hz, 1H), 1.23 (td, J_1 = 7.2 Hz, J_2 = 0.8 Hz, 3H), 1.13 (td, J_1 = 7.2 Hz, J_2 = 0.8 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): 178.3, 139.1 (d, J = 6.9 Hz), 138.1, 137.7, 136.5, 132.7 (d, J = 9.5 Hz), 132.4, 130.6, 129.2, 128.9, 128.7, 128.5, 128.5, 127.4, 127.0, 126.6, 115.1, 75.6, 75.3, 64.6 (d, J = 5.6 Hz), 63.9 (d, J = 5.5 Hz), 54.4 (d, J = 5.7 Hz), 44.6, 41.2, 21.2, 21.0, 16.0 (d, J = 7.0 Hz) , 15.9 (d, J = 7.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): -7.27;

Spirocyclic oxindole-tetrahydro-1,2-oxazines 4f: White solid; 91.1 mg, 78% yield; ^{1}H NMR analysis revealed that the dr is 6.5:1. ^{1}H NMR (400 MHz, $CDCl_3$): 8.35 (s, 1H), 7.60 (d, J = 8.8 Hz, 1H), 7.35 (d, J = 8.0 Hz, 2H), 7.29 (dd, J_1 = 8.8, J_2 = 2.0, 1H), 7.19 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 8.4 Hz, 1H), 6.67 (d, J = 9.2 Hz, 1H), 6.55 (d, J = 8.4 Hz, 1H), 6.49 (d, J = 8.8 Hz, 1H), 5.51 (dd, J_1 = 12.0 Hz, J_2 = 2.0 Hz, 1H), 4.13 (s, 1H), 4.12-4.08 (m, 1H), 3.97-3.90 (m, 1H), 3.77-3.71 (m, 1H), 3.67 (s,

3H), 3.52-3.46 (m, 1H), 2.54-2.51 (m, 1H), 2.48 (s, 3H), 2.35 (s, 3H), 1.88 (dd, J_1 = 13.2 Hz, J_2 = 2.4 Hz, 1H), 1.24 (td, J_1 = 7.2 Hz, J_2 = 0.8 Hz, 3H), 1.15 (td, J_1 = 7.2 Hz, J_2 = 0.8 Hz, 3H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): 178.4, 159.2, 139.2 (d, J = 7.0 Hz), 138.2, 136.6, 132.8 (d, J = 9.4 Hz), 131.9, 129.3, 128.9, 128.6, 128.6, 127.5, 126.9, 126.6, 115.2, 113.5, 113.0, 75.6, 75.0, 64.6 (d, J = 5.7 Hz), 64.0 (d, J = 5.5 Hz), 55.0, 54.5 (d, J = 5.7 Hz), 44.6, 41.3, 21.2, 16.0 (d, J = 6.9 Hz), 15.9 (d, J = 7.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): -7.26;

Spirocyclic oxindole-tetrahydro-1,2-oxazines 4g: White solid; 97.0 mg, 83% yield; ^{1}H NMR analysis revealed that the dr is 8.4:1. ^{1}H NMR (400 MHz, $CDCl_3$): 8.38-8.32 (m, 1H), 7.64-7.58 (m, 1H), 7.34 (d, J = 7.6 Hz, 2H), 7.29-7.26 (m, 1H), 7.19 (d, J = 8.0 Hz, 2H), 7.05-6.62 (m, 3H), 6.25-6.20 (m, 1H), 5.51 (dd, J_1 = 12.0 Hz, J_2 = 2.4 Hz, 1H), 4.16-4.09 (m, 2H), 4.00-3.94 (m, 1H), 3.78-3.72 (m, 2H), 3.57-3.41 (m, 3H), 2.58-2.45 (m, 1H), 2.52 (s, 3H), 2.35 (s, 3H), 1.95-1.82 (m, 1H), 1.25 (td, J_1 = 7.2 Hz, J_2 = 0.8 Hz, 3H), 1.17 (td, J_1 = 7.2 Hz, J_2 = 0.8 Hz, 3H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): 178.2, 159.0, 139.5, 139.4, 139.2, 138.2, 136.9, 136.6, 133.0, 133.0, 129.2, 128.9, 128.7, 128.5, 126.9, 126.6, 122.7, 120.1, 116.4, 116.2, 115.4, 115.2, 112.8, 111.2, 75.7, 75.6, 75.2, 64.7, 64.7, 64.1, 64.1, 54.9, 54.3, 54.3, 44.6, 41.3, 41.2, 21.2, 16.0, 15.9, 15.8; ^{31}P NMR (162 MHz, $CDCl_3$): -7.29;

Spirocyclic oxindole-tetrahydro-1,2-oxazines 4h: White solid; 83.4 mg, 69% yield; ^{1}H NMR analysis revealed that the dr is 8.0:1. ^{1}H NMR (400 MHz, $CDCl_3$): 8.44-8.43 (m, 1H), 7.77-7.37 (m, 9H), 7.29-7.26 (m, 1H), 7.21 (d, J = 8.0 Hz, 2H), 7.09-6.78 (m, 1H), 5.59-5.56 (m, 1H), 4.36-4.35 (m, 1H), 4.06-3.89 (m, 1H), 3.84-3.67 (m, 1H), 3.48-3.00 (m, 2H), 2.62-2.56 (m, 1H), 2.53 (s, 3H), 2.36 (s, 3H), 1.99-1.91 (m, 1H), 1.13-1.07 (m, 3H), 0.96-0.67 (m, 3H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): 178.2, 139.1, 139.0, 138.3, 136.6, 133.2, 132.8, 132.7, 129.6, 129.3, 129.0, 128.7, 128.2, 127.8, 127.5, 127.4, 127.1, 126.6, 126.4, 126.3, 124.8, 115.1, 75.8, 75.7, 75.6, 64.6, 64.5, 63.8, 63.8, 54.7, 54.6, 44.9, 44.7, 41.2, 21.2, 15.8, 15.8, 15.4, 15.4; ^{31}P NMR (162 MHz, $CDCl_3$): -7.47;

Spirocyclic oxindole-tetrahydro-1,2-oxazines 4i: White solid; 88.0 mg, 81% yield; ^{1}H NMR analysis revealed that the dr is 10.0:1. ^{1}H NMR (400 MHz, $CDCl_3$): 8.29 (s, 1H), 7.80 (d, J = 8.8 Hz, 1H), 7.37-7.30 (m, 3H), 7.22-7.14 (m, 3H), 6.08 (dd, J_1 = 3.2 Hz, J_2 = 1.6 Hz, 1H), 5.47 (d, J = 3.6 Hz,

1H), 5.43 (dd, J_1 = 12.0 Hz, J_2 = 2.4 Hz, 1H), 4.31 (s, 1H), 4.24-4.10 (m, 2H), 3.88-3.81 (m, 1H), 3.62-3.56 (m, 1H), 2.53-2.39 (m, 1H), 2.45 (s, 3H), 2.34 (s, 3H), 1.88 (dd, J_1 = 13.2 Hz, J_2 = 2.4 Hz, 1H), 1.29 (td, J_1 = 7.2 Hz, J_2 = 0.8 Hz, 3H), 1.15 (td, J_1 = 7.2 Hz, J_2 = 1.2 Hz, 3H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): 178.1, 149.0, 142.3, 139.4 (d, J = 7.0 Hz), 138.2, 136.4, 133.2 (d, J = 9.4 Hz), 129.3, 129.1, 128.8, 126.9, 126.6, 115.3, 110.4, 109.5, 75.8, 68.6, 64.9 (d, J = 5.8 Hz), 64.2 (d, J = 5.6 Hz), 52.6 (d, J = 5.8 Hz), 44.2, 41.2, 21.2, 16.0 (d, J = 6.7 Hz), 15.8 (d, J = 7.5 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): -7.30;

Spirocyclic oxindole-tetrahydro-1,2-oxazines 4j: White solid; 90.8 mg, 81% yield; ^{1}H NMR analysis revealed that the dr is 11.3:1. ^{1}H NMR (400 MHz, $CDCl_3$): 8.34 (s, 1H), 7.74 (d, J = 8.8 Hz, 1H), 7.36 (dd, J_1 = 8.8 Hz, J_2 = 2.4 Hz, 1H), 7.33 (d, J = 8.0 Hz , 2H), 7.18 (d, J = 7.6 Hz , 2H), 7.07 (d, J = 5.2 Hz, 1H), 6.83 (s, br, 1H), 6.77-6.76 (m, 1H), 5.49 (dd, J_1 = 12.0 Hz, J_2 = 2.4 Hz, 1H), 4.48 (s, 1H), 4.20-4.12 (m, 1H), 4.08-3.98 (m, 1H), 3.73-3.63 (m, 1H), 3.39-3.29 (m, 1H), 2.53-2.46 (m, 1H), 2.44 (s, 3H), 2.34 (s, 3H), 1.93 (dd, J_1 = 13.2 Hz, J_2 = 2.4 Hz, 1H), 1.26 (td, J_1 = 7.2 Hz, J_2 = 0.8 Hz, 3H), 1.09 (td, J_1 = 7.2 Hz, J_2 = 0.8 Hz, 3H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): 178.0, 139.9 (d, J = 7.0 Hz), 138.3, 136.4, 136.3, 132.6 (d, J = 9.4 Hz), 129.3, 129.2, 129.1, 128.7, 127.3, 127.2, 126.6, 125.5, 115.3, 75.6, 71.4, 64.8 (d, J = 5.8 Hz), 64.8 (d, J = 5.5 Hz), 53.9 (d, J = 5.8 Hz), 44.4, 41.0, 21.2, 16.0 (d, J = 6.9 Hz), 15.8 (d, J = 7.8 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): -7.31;

Spirocyclic oxindole-tetrahydro-1,2-oxazines 4k: Colorless oil; 89.5 mg, 86% yield; ^{1}H NMR analysis revealed that the dr is 8.6:1. ^{1}H NMR (400 MHz, $CDCl_3$): 8.14 (s, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.31 (dd, J_1 = 8.8 Hz, J_2 = 2.4 Hz, 1H), 7.25 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H), 5.24 (dd, J_1 = 12.0 Hz, J_2 = 2.4 Hz, 1H), 4.37-4.08 (m, 4H), 3.16 (d, J = 3.2 Hz, 1H), 2.76 (s, 3H), 2.32-2.31 (m, 4H), 1.84-1.74 (m, 1H), 1.60 (dd, J_1 = 13.2 Hz, J_2 = 2.4 Hz, 1H), 1.36 (td, J_1 = 7.2 Hz, J_2 = 0.8 Hz, 3H), 1.31 (td, J_1 = 7.2 Hz, J_2 = 0.8 Hz, 3H), 0.69 (dd, J_1 = 13.2 Hz, J_2 = 6.8 Hz, 6H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): 179.8, 138.7 (d, J = 7.2 Hz), 138.0, 136.6, 134.0 (d, J = 9.6 Hz), 129.2, 129.0, 128.3, 127.5, 126.5, 115.5, 75.1, 73.2, 65.1 (d, J = 6.1 Hz), 64.7 (d, J = 5.9 Hz), 52.3 (d, J = 5.5 Hz), 45.1,

44.2, 29.9, 21.3, 21.1, 19.3, 16.1 (d, J = 5.4 Hz), 16.0 (d, J = 5.1 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): -6.72;

Spirocyclic oxindole-tetrahydro-1,2-oxazines 4l: White solid; 96.5 mg, 86% yield; ^{1}H NMR analysis revealed that the dr is 10.9:1. ^{1}H NMR (400 MHz, $CDCl_3$): 8.13 (s, 1H), 7.89 (d, J = 8.4 Hz, 1H), 7.32 (dd, J_1 = 8.8 Hz, J_2 = 2.4 Hz, 1H), 7.24 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H), 5.23 (dd, J_1 = 12.0 Hz, J_2 = 2.0 Hz, 1H), 4.37-4.10 (m, 4H), 3.16 (d, J = 3.2 Hz, 1H), 2.77 (s, 3H), 2.37-2.25 (m, 1H), 2.32 (s, 3H), 1.58-1.47 (m, 7H), 1.38 (td, J_1 = 6.8 Hz, J_2 = 0.8 Hz, 3H), 1.32 (td, J_1 = 7.2 Hz, J_2 = 0.8 Hz, 3H), 0.98-0.79 (m, 4H), 0.50-0.44(m, 1H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): 179.7, 138.4 (d, J = 7.2 Hz), 138.0, 136.6, 134.4 (d, J = 9.7 Hz), 129.2, 128.9, 128.3, 127.4, 126.5, 115.4, 75.1, 73.4, 65.0 (d, J = 6.0 Hz), 64.6 (d, J = 6.0 Hz), 51.9 (d, J = 5.6 Hz), 44.9, 44.6, 41.9, 31.0, 30.6, 27.4, 27.4, 26.4, 21.2, 16.1 (d, J = 7.1 Hz), 16.0 (d, J = 6.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): -6.64;

Spirocyclic oxindole-tetrahydro-1,2-oxazines 4m: White solid; 104.6 mg, 90% yield; m.p. 69-70 ^{o}C; ^{1}H NMR analysis revealed that the dr is 14.0:1. ^{1}H NMR (400 MHz, $CDCl_3$): 8.20 (s, 1H), 7.36 (dd, J_1 = 8.8 Hz, J_2 = 2.4 Hz, 1H), 7.31 (d, J = 8.0 Hz , 1H), 7.21-7.16 (m, 5H), 7.07-7.05 (m, 2H), 5.61 (d, J = 12.0 Hz, 1H), 5.39 (dd, J_1 = 12.0 Hz, J_2 = 9.6 Hz, 1H), 5.35 (d, J = 9.6 Hz, 1H), 4.20-4.13 (m, 1H), 4.07-4.01 (m, 1H), 3.85-3.79 (m, 1H), 3.73 (d, J = 9.6 Hz, 1H), 3.67-3.61 (m, 1H), 2.65 (s, 3H), 2.42 (dd, J_1 = 13.2 Hz, J_2 = 12.0 Hz, 1H), 2.34 (s, 3H), 1.82 (dd, J_1 = 13.2 Hz, J_2 = 2.4 Hz, 1H), 1.22 (td, J_1 = 6.8 Hz, J_2 = 1.2 Hz, 3H), 0.90 (td, J_1 = 7.2 Hz, J_2 = 0.8 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): 178.6, 139.2 (d, J = 7.0 Hz), 138.2, 136.6, 135.6, 135.3, 132.8 (d, J = 9.5 Hz), 129.3, 129.2, 128.7, 128.6, 128.3, 126.5, 126.5, 126.4, 123.5, 115.3, 75.8, 73.5, 64.8 (d, J = 5.6 Hz), 64.3 (d, J = 5.5 Hz), 53.8 (d, J = 5.6 Hz), 44.8, 40.6, 21.2, 16.0 (d, J = 6.8 Hz), 15.6 (d, J = 7.4 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): -7.00; IR (ATR): 2915, 1743, 1464, 1308, 1286, 1149, 1022 cm^{-1}; MS (EI): 580 (M^+, 4), 419 (58), 162 (36), 144 (100), 115 (30), 91 (35), 77 (21), 43 (23); HRMS (EI-TOF): Exact mass calcd for $C_{31}H_{34}N_2O_5P^{35}Cl$ $[M]^+$: 580.1894, Found: 580.1891.

Spirocyclic oxindole-tetrahydro-1,2-oxazines 4n: White solid; 109.8 mg, 87% yield; m.p. 180-181 ^{o}C; ^{1}H NMR analysis revealed that the dr is 18.1:1. ^{1}H NMR (400 MHz, $CDCl_3$): 8.38 (s, 1H), 7.59 (d, J

= 8.8 Hz , 1H), 7.29-7.26 (m, 5H), 7.20-7.18 (m, 5H), 7.13-7.11 (m, 3H), 6.98-6.94 (m, 1H), 6.78 (d, J = 8.0 Hz , 1H), 5.47 (dd, J_1 = 2.4 Hz, J_2 = 2.4 Hz, 1H), 4.43 (s, 1H), 4.15-4.07 (m, 1H), 4.00-3.92 (m, 2H), 3.79-3.73 (m, 1H), 3.62 (d, J = 14.8 Hz , 1H), 3.54-3.48 (m, 1H), 2.51(t, J = 12.4 Hz, 1H), 2.32 (s, 3H), 1.96 (dd, J_1 = 2.4 Hz, J_2 = 2.4 Hz, 1H), 1.25 (td, J_1 = 7.2 Hz, J_2 = 6.8 Hz, 3H), 1.17 (td, J_1 = 7.2 Hz, J_2 = 6.4 Hz, 3H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): 178.3, 139.2 (d, J = 7.1 Hz), 137.8, 137.6, 136.6, 135.4, 132.7 (d, J = 9.5 Hz) 130.7, 129.1, 128.9, 128.8, 128.6, 128.2, 128.0, 127.8, 127.0, 126.9, 126.2, 115.2, 77.4, 77.0, 76.7, 75.0, 73.3, 64.7 (d, J = 5.9 Hz), 64.1 (d, J = 5.5 Hz), 59.3, 54.7 (d, J = 5.7 Hz), 41.0, 21.2, 16.0 (d, J = 6.5 Hz), 15.9 (d, J = 7.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): -7.28; IR (ATR): 2995, 1737, 1602, 1465, 1298, 1127, 1026 cm^{-1}; MS (EI): 630 (M^+, 2), 419 (35), 212 (20), 195 (12), 194 (12), 91 (100), 65 (13), 44 (14); HRMS (EI-TOF): Exact mass calcd for $C_{35}H_{36}N_2O_5P^{35}Cl$ $[M]^+$: 630.2050, Found: 630.2045.

Spirocyclic oxindole-tetrahydro-1,2-oxazines 4o: White solid; 89.3 mg, 83% yield; ^{1}H NMR analysis revealed that the dr is 11.6:1. ^{1}H NMR (400 MHz, $CDCl_3$): 8.13-8.10 (m, 1H), 7.60 (dd, J_1 = 9.2 Hz, J_2 = 4.8 Hz, 1H), 7.34 (d, J = 8.0 Hz, 2H), 7.21-7.07 (m, 5H), 6.99 (td, J_1 = 9.2 Hz, J_2 = 2.8 Hz, 2H), 6.93 (s, 1H), 6.70-6.68 (m, 1H), 5.52 (dd, J_1 = 12.0 Hz, J_2 = 2.4 Hz, 1H), 4.19 (s, 1H), 4.14-4.06 (m, 1H), 3.99-3.91 (m, 1H), 3.76-3.70 (m, 1H), 3.52-3.45 (m, 1H), 2.53 (t, J = 13.2 Hz ,1H), 2.50 (s, 3H), 2.34 (s, 3H), 1.88 (dd, J_1 = 12.8 Hz, J_2 = 2.0 Hz, 1H), 1.24 (td, J_1 = 7.6 Hz, J_2 = 1.2 Hz, 3H), 1.15 (td, J_1 = 6.8 Hz, J_2 = 0.8 Hz, 3H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): 178.6, 159.2 (d, J = 240.2 Hz), 138.2, 136.6, 136.5 (dd, J_1 = 7.0 Hz, J_2 = 2.3 Hz), 135.6, 132.5 (t, J = 8.9 Hz), 130.6, 129.3, 128.0, 127.9, 127.7, 126.6, 115.1 (d, J = 8.9 Hz), 114.9 (d, J = 6.1 Hz), 114.6 (d, J = 25.0 Hz), 75.6, 75.6, 64.6 (d, J = 5.7 Hz), 63.9 (d, J = 5.6 Hz), 54.5 (dd, J_1 = 5.9 Hz, J_2 = 1.8 Hz), 44.6, 41.4, 21.2, 16.0 (d, J = 7.0 Hz), 15.9 (d, J = 7.8 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): -7.09; ^{19}F NMR (282 MHz, $CDCl_3$): -118.66.

Spirocyclic oxindole-tetrahydro-1,2-oxazines 4p: White solid; 100.2 mg, 85% yield; ^{1}H NMR (400 MHz, $CDCl_3$): 8.42 (s, 1H), 7.91 (s, 1H), 7.88-7.82 (m, 3H), 7.61-7.57 (m, 2H), 7.50-7.47 (m, 2H), 7.29 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H), 7.26-7.09 (m, 3H), 6.97 (s, br, 1H), 6.70 (s, br, 1H), 5.73 (dd, J_1 = 12.0 Hz, J_2 = 2.4 Hz, 1H), 4.25 (s, 1H), 4.14-4.06 (m, 1H), 4.00-3.90 (m, 1H), 3.77-3.69 (m, 1H),

3.54-3.44 (m, 1H), 2.62 (dd, J_1 = 12.8 Hz, J_2 = 12.0 Hz, 1H), 2.56 (s, 3H), 2.01 (dd, J_1 = 13.2 Hz, J_2 = 2.8 Hz, 1H), 1.24 (td, J_1 = 6.8 Hz, J_2 = 0.8 Hz, 3H), 1.16 (td, J_1 = 6.8 Hz, J_2 = 1.2 Hz, 3H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): 178.3, 139.2 (d, J = 7.0 Hz), 137.0, 135.5, 133.3, 133.3, 132.7 (d, J = 9.4 Hz), 130.6, 129.0, 128.7, 128.4, 128.2, 128.1, 128.0, 127. 8, 127.7, 127.0, 126.3, 126.2, 125.6, 124.4, 115.2, 75.8, 75.6, 64.7 (d, J = 5.7 Hz), 64.1 (d, J = 5.6 Hz), 54.5 (d, J = 5.8 Hz), 44.8, 41.4, 16.0 (d, J = 6.5 Hz), 15.9 (d, J = 7.3 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): -7.28.

General procedure for one-pot sequential [3+3] dipolar cycloaddition with ketone

To a Schlenk tube was sequentially added **5** (0.34 mmol), **2a** (0.30 mmol, 25.2 mg), 4 Å MS (100 mg) and K_2CO_3 (0.15 mmol, 20.7 mg), followed by the addition of anhydrous EtOH (1.0 mL), and the resulting solution was stirred at 50 ^oC for 4 h. After the complete formation of nitrone, EtOH was removed under reduced pressure. The residua was kept under vacuum for 1 h to remove EtOH thoroughly. Then $Sc(OTf)_3$ (9.8 mg, 0.02 mmol), spirocyclopropyl oxindole **3** (0.20 mmol) and ^{i}PrOAc were added. The reaction was kept stirring at 50 ^oC for 24 h. Then ^{i}PrOAc was removed under reduced pressure. The following work-up procedure to obtain product **6** was the same as mentioned for product **4**.

Spirocyclic oxindole-tetrahydro-1,2-oxazines 6a: White solid; 58.5 mg, 50% yield; ^{1}H NMR analysis showed the dr value is 3.9:1. ^{1}H NMR (400 MHz, $CDCl_3$): 8.53 (s, 1H), 7.41 (d, J = 8.8 Hz, 1H), 7.36 (d, J = 8.0 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 7.12 (dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz, 1H), 7.09 (s, br, 2H), 6.98 (s, 3H), 5.53 (dd, J_1 = 12.4 Hz, J_2 = 2.8 Hz, 1H), 4.10-3.98 (m, 2H), 3.96-3.94 (m, 2H), 2.66 (dd, J_1 = 13.6 Hz, J_2 = 12.4 Hz, 1H), 2.61 (s, 3H), 2.35 (s, 3H), 2.12 (s, 3H), 1.66 (dd, J_1 = 13.2 Hz, J_2 = 2.8 Hz, 1H), 1.35 (td, J_1 = 6.8 Hz, J_2 = 0.8 Hz, 3H), 1.24 (td, J_1 = 7.2 Hz, J_2 = 1.2 Hz, 3H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): 178.3, 140.7, 138.3 (d, J = 6.9 Hz), 138.2, 136.9, 133.9 (d, J = 9.6 Hz), 129.3, 128.6, 128.2, 128.0, 127.8, 126.9, 126.8, 126.6, 114.4, 74.8, 67.8, 64.5, 64.4, 56.7 (d, J = 5.5 Hz), 38.7, 38.0, 21.2, 16.1 (d, J = 7.2 Hz), 15.9 (d, J = 6.8 Hz), 10.0; ^{31}P NMR (162 MHz, $CDCl_3$): -6.85.

Spirocyclic oxindole-tetrahydro-1,2-oxazines 6b: White solid; 55.9 mg, 48% yield; ^{1}H NMR analysis showed the dr value is 4.2:1. ^{1}H NMR (400 MHz, $CDCl_3$): 8.54 (s, 1H), 7.42 (d, J = 8.8 Hz, 1H), 7.36 (d, J = 8.0 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 7.14 (dd, J_1 = 8.8 Hz, J_2 = 2.4 Hz, 1H), 6.97 (d, J = 7.6 Hz, 2H), 6.78 (d, J = 7.6 Hz, 2H), 5.53 (dd, J_1 = 12.4 Hz, J_2 = 2.8 Hz, 1H), 4.15-4.03 (m, 2H), 3.99-3.92 (m, 2H), 2.66 (dd, J_1 = 13.6 Hz, J_2 = 12.4 Hz, 1H), 2.59 (s, 3H), 2.35 (s, 3H), 2.14 (s, 3H), 2.10 (s, 3H), 1.65 (dd, J_1 = 13.6 Hz, J_2 = 2.8 Hz, 1H), 1.34 (td, J_1 = 6.8 Hz, J_2 = 1.2 Hz, 3H), 1.24 (td, J_1 = 7.2 Hz, J_2 = 1.2 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): 178.3, 138.3 (d, J = 6.7 Hz), 138.1, 137.7, 137.0, 136.3, 134.1 (d, J = 9.8 Hz), 129.3, 128.6, 128.2, 128.0, 127.7, 127.6, 126.6, 114.4, 74.8, 67.6, 64.5 (d, J = 4.0 Hz), 64.4 (d, J = 3.8 Hz), 56.8 (d, J = 5.6 Hz), 38.7, 38.1, 21.2, 21.2, 20.8, 16.0 (d, J = 7.5 Hz), 16.0 (d, J = 6.8 Hz), 10.1; ^{31}P NMR (162 MHz, $CDCl_3$): -6.88.

Spirocyclic oxindole-tetrahydro-1,2-oxazines 6c: White solid; 59.5 mg, 51% yield; m.p. 78-79 ^{o}C; ^{1}H NMR analysis showed the dr value is 4.5:1. ^{1}H NMR (400 MHz, $CDCl_3$): 8.54 (s, 1H), 7.44 (d, J = 8.4 Hz, 1H), 7.36 (d, J = 8.0 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 7.15 (dd, J_1 = 8.8 Hz, J_2 = 2.4 Hz, 1H), 7.00 (s, 2H), 6.50 (d, J = 8.4 Hz, 2H), 5.53 (dd, J_1 = 12.4 Hz, J_2 = 3.2 Hz, 1H), 4.11-4.05 (m, 2H), 3.99-3.93 (m, 2H), 3.65 (s, 3H), 2.65 (dd, J_1 = 13.6 Hz, J_2 = 12.4 Hz, 1H), 2.57 (s, 3H), 2.35 (s, 3H), 2.09 (s, 3H), 1.65 (dd, J_1 = 13.6 Hz, J_2 = 3.2 Hz, 1H), 1.34 (td, J_1 = 8.4 Hz, J_2 = 1.2 Hz, 3H), 1.23 (td, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): 178.3, 158.0, 138.4 (d, J = 6.7 Hz), 138.2, 136.9, 134.1 (d, J = 9.6 Hz), 132.6, 129.3, 129.0, 128.5, 128.2, 128.0, 126.6, 114.5, 112.2, 74.8, 67.3, 64.5, 56.8 (d, J = 5.4 Hz), 55.0, 38.6, 38.0, 21.2, 16.2 (d, J = 7.3 Hz), 16.0 (d, J = 7.1 Hz), 10.2; ^{31}P NMR (162 MHz, $CDCl_3$): -6.79; IR (ATR): 2914, 1736, 1511, 1465, 1314, 1182, 1023 cm^{-1}; MS (EI): 598 (M^+, 1), 419 (12), 163 (26), 162 (21), 148 (100), 133 (22), 105 (11), 91 (11); $[M+H]^+$; HRMS (EI-TOF): Exact mass calcd for $C_{31}H_{36}N_2O_6P^{35}Cl$ $[M]^+$: 598.2000, Found: 598.2007.

Spirocyclic oxindole-tetrahydro-1,2-oxazines 6d: White solid; 59.5 mg, 46% yield; ^{1}H NMR analysis showed the dr value is 2.3:1. ^{1}H NMR (400 MHz, $CDCl_3$): 8.50 (s, 1H), 7.40 (d, J = 8.8 Hz, 1H), 7.35 (d, J = 8.0 Hz, 2H), 7.20-7.16 (m, 3H), 7.12 (d, J = 8.0 Hz, 2H), 6.98 (s, 2H), 5.52 (dd, J_1 = 12.4 Hz, J_2 = 2.8 Hz, 1H), 4.12-4.06 (m, 2H), 3.98-3.94 (m, 2H), 2.65 (dd, J_1 = 13.6 Hz, J_2 = 12.4 Hz,

1H), 2.56 (s, 3H), 2.35 (s, 3H), 2.10 (s, 3H), 1.66 (dd, J_1 = 13.6 Hz, J_2 = 2.8 Hz, 1H), 1.33 (td, J_1 = 7.2 Hz, J_2 = 1.2 Hz, 3H), 1.26 (td, J_1 = 7.2 Hz, J_2 = 0.8 Hz, 3H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): 177.9, 139.8, 138.3, 138.2 (d, J = 6.9 Hz), 136.7, 133.5 (d, J = 9.5 Hz), 130.0, 129.6, 129.3, 128.5, 128.8, 128.3, 126.5, 121.0, 114.6, 74.8, 67.6, 64.6 (d, J = 5.5 Hz), 64.5 (d, J = 5.8 Hz), 56.5 (d, J = 5.7 Hz), 38.7 (d, J = 1.9 Hz), 37.7, 21.2 (d, J = 1.8 Hz), 16.1 (d, J = 7.1 Hz), 16.0 (d, J = 7.0 Hz), 9.9; ^{31}P NMR (162 MHz, $CDCl_3$): -6.96.

Spirocyclic oxindole-tetrahydro-1,2-oxazines 6e: White solid; 49.9 mg, 42% yield; m.p. 63-64 ^oC; ^{1}H NMR analysis showed the dr value is 5.3:1. ^{1}H NMR (400 MHz, $CDCl_3$): 8.50 (s, 1H), 7.47 (d, J = 8.8 Hz, 1H), 7.36 (dd, J_1 = 12.8 Hz, J_2 = 2.4 Hz, 1H), 7.33 (d, J = 8.0 Hz, 2H), 7.21-7.16 (m, 5H), 6.91 (dd, J_1 = 7.6 Hz, J_2 = 3.0 Hz, 2H), 6.45 (d, J = 12.4 Hz, 1H), 5.59 (d, J = 12.4 Hz, 1H), 5.42 (dd, J_1 = 12.4 Hz, J_2 = 2.8 Hz, 1H), 4.01-3.82 (m, 4H), 2.60 (dd, J_1 = 13.2 Hz, J_2 = 12.4 Hz, 1H), 2.56 (s, 3H), 2.35 (s, 3H), 1.84 (s, 3H), 1.64 (dd, J_1 = 13.6 Hz, J_2 = 2.8 Hz, 1H), 1.20 (td, J_1 = 7.2 Hz, J_2 = 1.2 Hz, 3H), 1.00 (td, J_1 = 6.8 Hz, J_2 = 1.2 Hz, 3H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): 178.0, 138.9 (d, J = 6.9 Hz), 138.2, 136.9, 134.0 (d, J = 9.6 Hz), 131.1, 130.6, 129.3, 128.8, 128.6, 128.5, 128.0, 127.8, 126.5, 126.3, 114.9, 75.5, 65.8 64.7 (d, J = 5.8 Hz), 64.2 (d, J = 5.5 Hz), 56.2 (d, J = 5.5 Hz), 38.8, 37.7, 21.2, 15.9 (d, J = 7.0 Hz), 15.8 (d, J = 9.2 Hz), 8.1; ^{31}P NMR (162 MHz, $CDCl_3$): -6.72; IR (ATR): 2985, 1749, 1464, 1372, 1280, 1157, 1021 cm^{-1}; MS (EI): 594 (M^+, 2), 419 (42), 316 (38), 159 (38), 158 (100), 144(65), 115 (33), 91 (36); $[M]^+$; HRMS (EI-TOF): Exact mass calcd for $C_{32}H_{36}N_2O_5P^{35}Cl$ $[M]^+$: 594.2055, Found: 594.2050.

Spirocyclic oxindole-tetrahydro-1,2-oxazines 6f: White solid; 61.3 mg, 50% yield; ^{1}H NMR analysis showed the dr value is 3.5:1. ^{1}H NMR (400 MHz, $CDCl_3$): 8.42 (d, J = 8.8 Hz, 1H), 7.70 (d, J = 2.0 Hz, 1H), 7.33 (d, J = 7.6 Hz, 2H), 7.29 (dd, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1H), 7.19 (d, J = 7.6 Hz, 2H), 7.08 (s, 2H), 6.99 (s, 3H), 5.53 (dd, J_1 = 12.0 Hz, J_2 = 2.8 Hz, 1H), 4.14-4.06 (m, 2H), 4.00-3.92 (m, 2H), 2.64 (dd, J_1 = 14.0 Hz, J_2 = 12.8 Hz, 1H), 2.59 (s, 3H), 2.35 (s, 3H), 2.13 (s, 3H), 1.63 (dd, J_1 = 14.0 Hz, J_2 = 2.8 Hz, 1H), 1.36 (t, J = 7.2 Hz, 3H), 1.25 (t, J = 6.8 Hz, 3H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): 178.4 140.9 (d, J = 6.4 Hz), 140.8, 138.2, 137.0, 131.2 (d, J = 9.5 Hz), 129.8, 129.3, 127.8,

126.9, 126.5, 125.7, 122.0, 116.7, 74.9, 67.7, 64.5 (d, J = 3.4 Hz), 64.5 (d, J = 3.2 Hz), 56.4 (d, J = 5.4 Hz), 38.7 (d, J = 2.0 Hz), 38.2, 21.2 (d, J = 2.2 Hz), 16.0 (d, J = 7.4 Hz), 16.0 (d, J = 6.9 Hz), 10.1; ^{31}P NMR (162 MHz, $CDCl_3$): -6.89.

Spirocyclic oxindole-tetrahydro-1,2-oxazines 6g: White solid; 55.7 mg, 49% yield; ^{1}H NMR analysis showed the dr value is 3.0:1. ^{1}H NMR (400 MHz, $CDCl_3$): 8.53 (s, 1H), 7.47 (d, J = 7.2 Hz, 2H), 7.43-7.37 (m, 3H), 7.34-7.31 (m, 1H), 7.13 (d, J= 8.8 Hz, 1H), 7.09 (s, br, 2H), 6.98 (s, 3H), 5.57 (dd, J_1 = 12.4 Hz, J_2 = 2.8 Hz, 1H), 4.14-4.07 (m, 2H), 3.99-3.95 (m, 2H), 2.69-2.66 (m, 1H), 2.63 (s, 3H), 2.13 (s, 3H), 1.69 (dd, J_1 = 13.6 Hz, J_2 = 3.2 Hz, 1H), 1.35 (t, J = 7.2 Hz, 3H), 1.25 (t, J = 7.2 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): 178.2, 140.6, 139.9, 138.3 (d, J = 6.9 Hz), 133.9 (d, J = 9.6 Hz), 128.6, 128.5, 128.3, 128.2, 128.0, 127.8, 126.9, 126.8, 126.5, 114.5, 74.9, 67.8, 64.5 (d, J = 1.6 Hz), 64.5 (d, J = 1.6 Hz), 56.7 (d, J = 5.5 Hz), 38.8 (d, J = 1.8Hz), 38.1, 16.1 (d, J = 7.4 Hz), 16.0 (d, J = 6.8 Hz), 10.04; ^{31}P NMR (162 MHz, $CDCl_3$): -6.85.

Spirocyclic oxindole-tetrahydro-1,2-oxazines 6h: White solid; 66.5 mg, 55% yield; ^{1}H NMR analysis showed the dr value is 3.0:1. ^{1}H NMR (400 MHz, $CDCl_3$): 8.60 (s, 1H), 7.90 (d, J = 9.6 Hz, 1H), 7.87-7.84 (m, 3H), 7.61 (dd, J_1 = 8.4 Hz, J_2 = 1.6 Hz, 1H), 7.50-7.48 (m, 2H), 7.44 (d, J = 8.4 Hz, 1H), 7.16-7.12 (m, 3H), 7.00 (s, 3H), 5.76 (dd, J_1 = 12.4 Hz, J_2 = 2.8 Hz, 1H), 4.14-4.06 (m, 2H), 4.02-3.94 (m, 2H), 2.78 (d, J = 12.8 Hz, 1H), 2.68 (s, 3H), 2.19 (s, 3H), 1.78 (dd, J_1 = 13.6 Hz, J_2 = 2.8 Hz, 1H), 1.36 (t, J = 6.8 Hz, 3H), 1.24 (t, J = 3.2 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): 178.2, 140.6, 138.3 (d, J = 6.9 Hz), 137.3, 133.9 (d, J = 9.6 Hz), 133.3, 133.3, 128.6, 128.4, 128.3, 128.1, 128.0, 127.7, 126.9, 126.8, 126.3, 126.2, 125.6, 124.3, 114.5, 75.0, 67.9, 64.5, 64.5, 56.7 (d, J = 5.6 Hz), 38.8 (d, J = 2.2 Hz), 38.1, 16.1 (d, J = 7.2 Hz), 16.0 (d, J = 6.8 Hz), 10.1; ^{31}P NMR (162 MHz, $CDCl_3$): -6.85.

Spirocyclic oxindole-tetrahydro-1,2-oxazines 6i: Nitrone preparation and cycloaddition reaction were conducted at 80 ^{o}C. White solid; 23.5 mg, 22% yield; m.p. 59-60 ^{o}C; ^{1}H NMR analysis showed the dr value is >20:1. ^{1}H NMR (400 MHz, $CDCl_3$): 8.38 (s, 1H), 7.84 (d, J = 8.4 Hz, 1H), 7.31 (dd, J_1 = 8.0 Hz, J_2 = 2.8 Hz, 1H), 7.25 (d, J = 6.8 Hz, 2H), 7.15 (d, J = 8.0 Hz, 2H), 5.28 (dd, J_1 = 12.0 Hz, J_2 =

2.8 Hz, 1H), 4.30-4.14 (m, 4H), 2.80 (dd, J_1 = 14.8 Hz, J_2 = 7.2 Hz, 1H), 2.55 (s, 3H), 2.49 (t, J = 12.8 Hz, 1H), 2.32 (s, 3H), 2.16-2.12 (m, 1H), 1.84-1.82 (m, 1H), 1.69-1.64 (m, 1H), 1.50-1.48 (m, 3H), 1.38-1.34 (m, 3H), 1.33-1.29 (m, 3H), 1.28-1.24 (m, 1H), 0.75-0.74 (m, 1H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$): 178.8, 139.6 (d, J = 7.0 Hz), 138.0, 137.1, 134.7 (d, J = 9.9 Hz), 129.2, 128.9, 128.2, 127.5, 126.5, 114.8, 75.4, 73.6, 64.8 (d, J = 6.1 Hz), 64.7 (d, J = 5.8 Hz), 56.6 (d, J = 5.3 Hz), 39.9, 38.0, 35.6, 27.1, 26.0, 24.0, 21.2, 16.1 (d, J = 3.4 Hz), 16.0 (d, J = 3.2 Hz); ^{31}P NMR (162 MHz, $CDCl_3$): -6.50; IR (ATR): 2955, 2918, 2872, 1738, 1463, 1313, 1277, 1020 cm^{-1}; MS (EI): 532 (M^+, 3), 316 (100), 260 (66), 180 (43), 119 (48), 114 (34), 91 (55), 68 (41); HRMS (EI-TOF): Exact mass calcd for $C_{27}H_{34}N_2O_5P^{35}Cl$ $[H]^+$: 532.1894, Found: 532.1890.

Catalytic asymmetric three-component [3+3] dipolar cycloaddition reaction

To a Schlenk tube was sequentially added $Ni(OTf)_2$ (10.7 mg, 0.030 mmol, 20 mol %) and **7** (11.8 mg, 0.033 mmol, 11 mol %), followed by the addition of anhydrous THF (1.0 mL), then the resulting solution was stirred at room temperature for 2 h.

To another Schlenk tube was sequentially added **1** (0.18 mmol), **2a** (0.15 mmol, 12.6 mg), 4 Å MS (80 mg) and K_2CO_3 (0.075 mmol, 10.3 mg), followed by the addition of anhydrous THF (1.0 mL). After the resulting solution was stirred at 50 ^oC for 1 h, the solvent of **7**/ $Ni(OTf)_2$ complex in 1.0 mL THF and oxindole **3a** (0.33 mmol, 138.3 mg) was added. The reaction was kept stirring at 50 ^oC for 24 h. Then THF was removed under reduced pressure. And the following work-up procedure to obtain enantioenriched **4** was the same as mentioned for product **4**.

Note: the chiral catalyst system is selected according to our previous report.[9]

Enantioenriched spirocyclic oxindole-tetrahydro-1,2-oxazines 4a: 65.3 mg, 74% yield; ^{1}H NMR analysis showed the dr value was 3.0:1. HPLC analysis (Chiralcel IC, ^{i}PrOH/hexane = 10/90, 1.0 mL/min, 230 nm; t_r (major) = 8.73 min, t_r (minor) = 11.27 min) gave the isomeric composition of the product: 97% ee.

Enantioenriched spirocyclic oxindole-tetrahydro-1,2-oxazines 4b: 49.9 mg, 60% yield; ^{1}H NMR analysis showed the dr value was 2.0:1. HPLC analysis (Chiralcel IC, ^{i}PrOH/hexane = 10/90, 1.0

mL/min, 230 nm; t_r (major) = 9.21 min, t_r (minor) = 10.75 min) gave the isomeric composition of the product: 95% ee.

Enantioenriched spirocyclic oxindole-tetrahydro-1,2-oxazines 4e: 57.1 mg, 67% yield; ^{1}H NMR analysis showed the dr value was 2.2:1. HPLC analysis (Chiralcel IC, ^{i}PrOH/hexane = 10/90, 1.0 mL/min, 230 nm; t_r (major) = 9.69 min, t_r (minor) = 11.10 min) gave the isomeric composition of the product: 96% ee.

Enantioenriched spirocyclic oxindole-tetrahydro-1,2-oxazines 4m: 59.2 mg, 68% yield; ^{1}H NMR analysis showed the dr value was 6.2:1. HPLC analysis (Chiralcel IC, ^{i}PrOH/hexane = 10/90, 1.0 mL/min, 230 nm; t_r (major) = 8.41 min, t_r (minor) = 10.47 min) gave the isomeric composition of the product: 96% ee, $[\alpha]^{25}_D$ = -49.1 (c = 1.0, $CHCl_3$).

General Procedure of the Biological Studies

Cell cultures: Human prostate cancer DU145 and PC3 cell lines were purchased from the Cell Bank of Type Culture Collection of Chinese Academy of Sciences (Shanghai, China). Human non-malignant prostate epithelial BPH1 cell line was kindly provided by Dr. Simon Hayward at the Vanderbilt University Medical Center, Nashville, TN, USA.[17] Cells were maintained in RPMI 1640 with 10% FBS (Life Technologies, Carlsbad, CA) at 37 ^{o}C in a humidified air atmosphere containing 5% CO_2.

MTT assay: Cells (3,000/well) were seeded into 96-well plates overnight, followed by the treatment with compounds for 48 h. Afterwards, the cells were incubated with 5 mg/mL 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT, Sigma-Aldrich, St. Louis, MO) for 2 h at 37 ^{o}C. Formazan was dissolved with DMSO and measured at 490 nm with a reference wavelength of 680 nm using a spectrophotometer.

Luciferase assay: 6xNFκB-Luc reporter plasmid contains six NFκB-binding sites, which could be activated by TNFα. DU145 cells (2.5 x10^4/well) were seeded into 24-well plates. Afterwards, the cells were transfected with 200 ng/well 6xNFκB-Luc plasmid by lipofectamine 3000 (Invitrogen). As for TNFα treatment assay, twenty-four hours after the transfection, the cells were pretreated with

compounds of interest for 4 h, followed by TNFα (10 ng/mL, R&D Systems, Minneapolis, MN) addition for 20 h and harvested. Luciferase activity was measured with the dual luciferase assay system (E1910, Promega). Cells were lysed in Passive Lysis Buffer (E1941, Promega) and harvested by centrifugation at 12,000 rpm to remove the cell debris. The protein concentration was measured with the Pierce™ BCA protein assay kit (23225, Thermo Fisher). The luciferase activities were calculated as a rate of firefly luciferase activity/total protein. The relative luciferase activity of vehicle control was set as 100%.

Statistical analysis: Each experiment was repeated three times. The mean values with standard deviations (SD) from the triplicates were plotted. The significant difference between control and experimental groups was analyzed using a Student *t*-test (*, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$).

Supporting Information Available: Copies of ^{1}H NMR, ^{19}F NMR, ^{31}P NMR, $^{13}C\{^{1}H\}$NMR and HPLC of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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References

(1) (a) Heathcock, C. L.; Graham, S. L.; Pirrung, M. C.; Plavac, F.; White, C. T. *The Total Synthesis of Natural Products* (Ed. ApSimon, J.), John Wiley & Sons, New York, **1983**, *5*, 264–313. (b) Smith, L. K.; Baxendale, I. R. Total Syntheses of Natural Products Containing Spirocarbocycles. *Org. Biomol. Chem.* **2015**, *13*, 9907–9933. (c) Undheim, K. Preparation and Structure Classification of Heteraspiro[m.n]alkanes. *Synthesis* **2014**, *46*, 1957–2006.

(2) Zheng, Y.; Tice, C. M.; Singh, S. B. The Use of Spirocyclic Scaffolds in Drug Discovery. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 3673–3682.

(3) For reviews: (a) Rios, R. Enantioselective Methodologies for the Synthesis of Spiro Compounds. *Chem. Soc. Rev.* **2012**, *41*, 1060–1074. (b) Franz, A. K.; Hanhan, N. V.; Ball-Jones, N. R. Asymmetric Catalysis for the Synthesis of Spirocyclic Compounds. *ACS Catal*. **2013**, *3*, 540−553. (c) D'yakonov, V. A.; Trapeznikova, O. A.; de Meijere, A.; Dzhemilev, U. M. Metal Complex Catalysis in the Synthesis of Spirocarbocycles. *Chem. Rev*. **2014**, *114*, 5775−5814. (d) Smith, L. K.; Baxendale, I. R. Total Syntheses of Natural Products Containing Spirocarbocycles. *Org. Biomol. Chem.* **2015**, *13*, 9907−9933. (e) Carreira, E. M.; Fessard, T. C. Four-Membered Ring-Containing Spirocycles: Synthetic Strategies and Opportunities. *Chem. Rev.* **2014**, *114*, 8257−8322. (f) Ding, A.; Meazza, M.; Guo, H.; Yang, J. W.; Rios R. New Development in the Enantioselective Synthesis of Spiro Compounds. *Chem. Soc. Rev.* **2018**, *47*, 5946-5996.

(4) Sharma, I.; Tan, D. S. Drug Discovery: Diversifying Complexity. *Nat. Chem.* **2013**, *5*, 157–158.

(5) (a) Kobayashi, J.; Watanabe, D.; Kawasaki, N.; Tsuda, M. Nakadomarin A, a Novel Hexacyclic Manzamine-Related Alkaloid from Amphimedon Sponge. *J. Org. Chem.* **1997**, *62*, 9236–9239. (b) Horii, Z.; Imanishi, T.; Yamauchi, M.; Hanaoka, M.; Parello, J.; Munavalli, S. Structure of Phyllantidine. *Tetrahedron Lett. Tetrahedron Lett.* **1972**, *13*, 1877–1880. (c) Parello, J.; Munavalli, S. Phyllantine et Phyllantidine Alcaloides du Phyllantus Discoides Muell Arg (Euphorbiacees). *C. R. Hebd. Seances Acad. Sci.* **1965**, *260*, 337–340. (d) Lajis, N. H.; Guan, O. B.; Sargent, M. V.; Skelton, B. W.; White, A. H. Viroallosecurinine and ent-Phyllanthidine from the Leaves of Breynia-Coronata (Euphorbiaceae). *Aust. J. Chem.* **1992**, *45*, 1893–1897. (e) Uchida, I.; Takase, S.; Kayakiri, H.; Kiyoto, S.; Hashimoto, M.; Tada, T.; Koda, S.; Morimoto, Y. Structure of FR 900482, a Novel Antitumor Antibiotic from a Streptomyces. *J. Am. Chem. Soc.* **1987**, *109*, 4108–4109. (f) Terano, H.; Takase, S.; Hosoda, J.; Kohsaka, M. A New Antitumor Antibiotic, FR-66979. *J. Antibiot.* **1989**, *42*, 145–148. (g) Naoe, Y.; Inami, M.; Kawamura, I.; Nishigaki, F.; Tsujimoto, S.; Matsumoto, S.; Manda, T.; Shimomura, K. Cytotoxic Mechanisms of FK317, a New Class of Bioreductive Agent with Potent Antitumor Activity. *Jpn. J. Cancer Res.* **1998**, *89*, 666–672. (h) Naoe, Y.; Inami, M.; Matsumoto, S.; Nishigaki, F.; Tsujimoto, S.; Kawamura, I.; Miyayasu, K.; Manda, T.; Shimomura, K. FK317: A Novel Substituted

Dihydrobenzoxazine with Potent Antitumor Activity Which Does Not Induce Vascular Leak Syndrome. *Cancer Chemother. Pharmacol.* **1998**, *42*, 31–36. (i) Masuda, K.; Nakamura, T.; Mizota, T.; Mori, J.; Shimomura, K. Antitumor Activity and Hematotoxicity of a New, Substituted Dihydrobenzoxazine, FK973, in Mice. *Cancer Res.* **1988**, *48*, 5172–5177.

(6) Young, I. S.; Kerr, M. A. A Homo [3 + 2] Dipolar Cycloaddition: The Reaction of Nitrones with Cyclopropanes. *Angew. Chem., Int. Ed.* **2003**, *42*, 3023–3026.

(7) (a) Sibi, M. P.; Ma, Z.; Jasperse, C. P. Enantioselective Addition of Nitrones to Activated Cyclopropanes. *J. Am. Chem. Soc.* **2005**, *127*, 5764–5765. (b) Kang, Y.-B.; Sun, X.-L.; Tang, Y. Highly Enantioselective and Diastereoselective Cycloaddition of Cyclopropanes with Nitrones and Its Application in the Kinetic Resolution of 2-Substituted Cyclopropane-1,1-dicarboxylates. *Angew. Chem., Int. Ed.* **2007**, *46,* 3918-3921.

(8) Spirocyclopropyl oxindoles could serve as monoactivated D-A cyclopropanes for reaction design. This is pioneered by Carreira et al in 1999, who successfully developed Lewis acid-catalyzed annulation of spirocyclopropyl oxindoles with imines, and applied this methodology for the total synthesis of natural products. See: (a) Alper, P. B.; Meyers, C.; Lerchner, A.; Siegel, D. R.; Carreira, E. M. Facile, Novel Methodology for the Synthesis of Spiro[pyrrolidin-3,3'-oxindoles]: Catalyzed Ring Expansion Reactions of Cyclopropanes by Aldimines. *Angew. Chem., Int. Ed.* **1999**, *38*, 3186−3189. (b) Lerchner, A.; Carreira, E. M. First Total Synthesis of (±)-Strychnofoline *via* a Highly Selective Ring-Expansion Reaction. *J. Am. Chem. Soc.* **2002**, *124*, 14826−14827. (c) Meyers, C.; Carreira, E. M. Total Synthesis of (-)-Spirotryprostatin B. *Angew. Chem., Int. Ed.* **2003**, *42*, 694−696. (d) Marti, C.; Carreira, E. M. Total Synthesis of (-)-Spirotryprostatin B: Synthesis and Related Studies. *J. Am. Chem. Soc.* **2005**, *127*, 11505−11515; For a review: (e) Marti, C.; Carreira, E. M. Construction of Spiro[pyrrolidine-3,3′-oxindoles]-Recent Applications to the Synthesis of Oxindole Alkaloids. *Eur. J. Org. Chem.* **2003**, 2209–2219.

(9) Xu, P.-W.; Liu, J.-K.; Shen, L.; Cao, Z.-Y.; Zhao, X.-L.; Yan, J.; Zhou, J. Diastereo- and Enantioselective [3 + 3] Cycloaddition of Spirocyclopropyl Oxindoles Using both Aldonitrones and Ketonitrones. *Nat. Commun.* **2017**, *8*, 1619.

(10) (a) Hong, L.; Wang, R. Recent Advances in Asymmetric Organocatalytic Construction of 3,3′-Spirocyclic Oxindoles. *Adv. Synth. Catal.* **2013**, *355*, 1023–1052. (b) Singh, G. S.; Desta, Z. Y. Isatins as Privileged Molecules in Design and Synthesis of Spiro Fused Cyclic Frameworks. *Chem. Rev.* **2012**, *112*, 6104−6155. (c) Cheng, D.; Ishihara, Y.; Tan, B.; Barbas III, C. F. Organocatalytic Asymmetric Assembly Reactions: Synthesis of Spirooxindoles *via* Organocascade Strategies. *ACS Catal.* **2014**, *4*, 743−762. (d) Lin, L.; Feng, X. Recent Progress in Enantioselective Synthesis of C3-Functionalized Oxindoles: Rare Earth Metals Take Action. *Chem. Sci.* **2012**, *3*, 327−334. (e) Zhou, F.; Liu, Y.-L.; Zhou, J. Catalytic Asymmetric Synthesis of Oxindoles Bearing a Tetrasubstituted Stereocenter at the C-3 Position. *Adv. Synth. Catal.* **2010**, *352*, 1381–1407. (f) Cao, Z.-Y.; Zhou, J. *Org. Chem. Front.* **2015**, *2*, 849–858.

(11) Young, I. S.; Kerr, M. A. Three-Component Homo 3 + 2 Dipolar Cycloaddition. A Diversity-Oriented Synthesis of Tetrahydro-1,2-oxazines and FR900482 Skeletal Congeners. *Org. Lett*. **2004**, *6*, 139–141.

(12) (a) Young, I. S.; Kerr, M. A. Total Synthesis of (+)-Nakadomarin A. *J. Am. Chem. Soc.* **2007**, *129*, 1465-1469. (b) Carson, C. A.; Kerr, M. A. Total Synthesis of (+)-Phyllantidine. *Angew. Chem., Int. Ed.* **2006**, *45*, 6560–6563. (c) Young, I. S.; Williams, J. L.; Kerr, M. A. Diastereoselective Synthesis of Pyrrolidines Using a Nitrone/Cyclopropane Cycloaddition: Synthesis of the Tetracyclic Core of Nakadomarin A. *Org. Lett*. **2005**, *7*, 953–955. (d) Dias, D. A.; Kerr, M. A. Domino Synthesis of Bridged Bicyclic Tetrahydro-1,2-oxazines: Access to Stereodefined 4-Aminocyclohexanols. *Org. Lett.* **2009**, *11*, 3694–3697. (e) Ganton, M. D.; Kerr, M. A. Magnesium Iodide Promoted Reactions of Nitrones with Cyclopropanes: A Synthesis of Tetrahydro-1,2-oxazines. *J. Org. Chem.* **2004**, *69*, 8554-8557.

(13) Review: (a) Cao, Z.-Y.; Zhou, F.; Zhou, J. Development of Synthetic Methodologies via Catalytic Enantiose-lective Synthesis of 3,3-Disubstituted Oxindoles. *Acc. Chem. Res.* **2018**, *51*, 1443–1454.

Researches: (b) Yu, J.-S.; Liao, F.-M.; Gao, W.-M.; Liao, K.; Zuo, R.-L.; Zhou, J. Michael Addition Catalyzed by Chiral Secondary Amine Phospho-ramide Using Fluorinated Silyl Enol Ethers: Formation of Quater-nary Carbon Stereocenters. *Angew. Chem., Int. Ed.* **2015**, *54*, 7381−7385. (c) Yin, X.-P.; Zeng, X.-P.; Liu, Y.-L.; Liao, F.-M.; Yu, J.-S.; Zhou, F.; Zhou, J. Asymmetric Triple Relay Catalysis: Enantioselective Synthesis of Spirocyclic Indolines through a One-Pot Process Featuring an Asymmetric 6π Electrocyclization. *Angew. Chem., Int. Ed.* **2014**, *53*, 13740−13745. (d) Cao, Z.-Y.; Wang, X.; Tan, C.; Zhao, X.-L.; Zhou, J.; Ding, K. Highly Stereoselective Olefin Cyclopropanation of Diazooxindoles Catalyzed by a C2□Symmetric Spiroketal Bisphosphine/Au(I) Com-plex. *J. Am. Chem. Soc.* **2013**, *135*, 8197−8200. (e) Zhou, F.; Tan, C.; Tang, J.; Zhang, Y.-Y.; Gao, W.-M; Wu, H.-H.; Yu, Y.-H.; Zhou, J. Asymmetric Copper(I)-Catalyzed Azide−Alkyne Cycloaddition to Quaternary Oxindoles. *J. Am. Chem. Soc.* **2013**, *135*, 10994−10997. (f) Cao, Z.-Y.; Zhou, F.; Yu, Y.-H.; Zhou, J. One-Pot Tandem Approach to Spirocyclic Oxindoles Featuring Adjacent Spiro-Stereocenters. *Org. Lett.* **2013**, *15*, 42−45. (g) Liu, Y.-L.; Wang, X.; Zhao, Y.-L.; Zhu, F.; Zeng, X.-P.; Chen, L.; Wang, C.; Zhao, X.-L.; Zhou, J. A Highly Diastereo- and Enantioselective Hg(II)-Catalyzed Cyclo-propanation of Diazooxindoles and Alkenes. *Angew. Chem., Int. Ed.* **2013**, *52*, 13735−13739.

(14) Pfeiffer, J. Y.; Beauchemin, A. M. Simple Reaction Conditions for the Formation of Ketonitrones from Ketones and Hydroxylamines. *J. Org. Chem.* **2009**, *74*, 8381–8383.

(15) (a) Aggarwal, B. B. Nuclear Factor-κB: The Enemy Within. *Cancer Cell* **2004**, *6*, 203−208. (b) Buchholz, T. A.; Garg, A. K.; Chakravarti, N.; Aggarwal, B. B.; Esteva, F. J.; Kuerer, H. M.; Singletary, S. E.; Hortobagyi, G. N.; Pusztai, L.; Cristofanilli, M.; Sahin, A. A. The Nuclear Transcription Factor KB/bcl-2 Pathway Correlates with Pathologic Complete Response to Doxorubicin-Based Neoadjuvant Chemotherapy in Human Breast Cancer. *Clin. Cancer Res.* **2005**, *11*, 8398−8402. (c) Liu, F.; Bardhan, K.; Yang, D.; Thangaraju, M.; Ganapathy, V.; Waller, J. L.; Liles, G. B.; Lee, J. R.; Liu, K. NF-B Directly Regulates Fas Transcription to Modulate Fas-Mediated Apoptosis and Tumor Suppression. *J. Biol. Chem.* **2012**, *287*, 25530–25540.

(16) (a) Kim, Y. R.; Kim, I. J.; Kang, T. W.; Choi, C.; Kim, K. K.; Kim, M. S.; Nam, K. I.; Jung, C. HOXB13 Downregulates Intracellular Zinc and Increases NF-kB Signaling to Promote Prostate Cancer Metastasis. *Oncogene* **2014**, *33*, 4558−4567. (b) Gannon, P. O.; Lessard, L.; Stevens, L. M.; Forest, V.; Bégin L. R.; Minner S.; Tennstedt, P.; Schlomm, T.; Mes-Masson, A. M.; Saad, F. Large-scale Independent Validation of the Nuclear Factor-Kappa B p65 Prognostic Biomarker in Prostate Cancer. *Eur. J. Cancer* **2013**, *49*, 2441-2448. (c) Jin, R.; Yamashita, H.; Yu, X.; Wang, J.; Franco, O. E.; Wang, Y.; Hayward, S. W.; Matusik, R. J. Inhibition of NF-Kappa B Signaling Restores Responsiveness of Castrate-Resistant Prostate Cancer Cells to Anti-Androgen Treat-ment by Decreasing Androgen Receptor-Variant Expression. *Oncogene* **2015**, *34*, 3700-3710. (d) Chang, C.; Zhao, W.; Xie, B.; Deng, Y.; Han, T.; Cui, Y.; Dai, Y.; Zhang, Z.; Gao, J.; Guo, H.; Yan, J. Pao Pereira Extract Suppresses Castration-Resistant Prostate Can-cer Cell Growth, Survival, and Invasion Through Inhibition of NFκB Signaling. *Integr. Cancer Ther*. **2014**, *13*, 249–258. (e) Palayoor, S. T.; Youmell, M. Y.; Calderwood, S. K.; Coleman, C. N.; Price, B. D. Constitutive Activation of IkB Kinase α and NF-kB in Prostate Can-cer Cells is Inhibited by Ibuprofen. *Oncogene* **1999**, *18*, 7389-7394.

(17) (a) Shin, H. M.; Kim, M. H.; Kim, B. H.; Jung, S. H.; Kim, Y. S.; Park, H. J.; Hong, J. T.; Min, K. R.; Kim, Y. Inhibitory action of novel aromatic diamine compound on lipopolysaccharide□induced nuclear translocation of NF□κB without affecting IκB degradation. *FEBS Lett*. **2004**, *571*, 50-54. (b) Koo, J. W.; Russo, S. J.; Ferguson, D.; Nestler, E. J.; Duman, R. S. Nuclear factor-κB is a critical mediator of stress-impaired neurogenesis and depressive behavior. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 2669-2674. (c) Kumar, A.; Negi, G.; Sharma, S. S. JSH□23 targets nuclear factor□kappa B and reverses various deficits in experimental diabetic neuropathy: effect on neuroinflammation and antioxidant defence. *Diabetes Obes. Metab.* **2011**, *13*, 750-758. (d) Ahmed, K. M.; Zhang, H.; Park, C. C. NF-κB Regulates Radioresistance Mediated By β1-Integrin in Three-Dimensional Culture of Breast Cancer Cells. *Cancer Res.* **2013**, *73,* 3737-3748. (e) Kesanakurti, D.; Chetty, C.; Rajasekhar Maddirela, D.; Gujrati, M.; Rao, J. S. Essential role of cooperative NF-κB and Stat3 recruitment to ICAM-1 intronic consensus elements in the regulation of radiation-induced invasion and migration in glioma. *Oncogene*

2013, *32*, 5144-5155. (f) Hayward, S. W.; Dahiya, R.; Cunha, G. R.; Bartek, J.; Deshpande, N.; Narayan, S. P. Establishment and Characterization of an Immortalized but Non-transformed Human Prostate Epithelial Cell Line: BPH-1. *In Vitro Cell. Dev. Biol.* **1995**, *31*, 14-24.