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FACILE SYNTHESIS OF SPIROOXINDOLES VIA AN ENANTIOSELECTIVE ORGANOCATALYZED SEQUENTIAL REACTION OF OXINDOLES WITH YNONE

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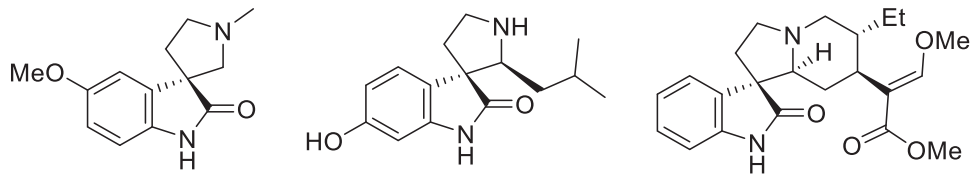
Abstract – The reaction of oxindole **1a** with phenylprop-2-yn-1-one (**2a**) was promoted by the chiral multifunctional phosphine catalyst **4a** derived from (*S*)-valine, giving spirooxindole **3a** in good yield and high enantioselectivity. The obtained spirooxindole forms a common scaffold of a vast number of natural products exhibiting various biological activities.

The introduction of spirocycle, defined as a structure consisting of two perpendicular rings connected through one atom, results in the formation of a rigid tetrahedral center. This rigidity of the spirocyclic framework is expected to minimize the number of possible conformations, leading to high activities in various therapeutic areas,[1] and achieving high stereoselectivities in asymmetric syntheses.[2] Due to these distinct advantages associated with the spirocyclic skeleton, the asymmetric construction of spirocycles poses an attractive synthetic challenge, contributing to the discovery of complex molecules and new catalysts.[3]



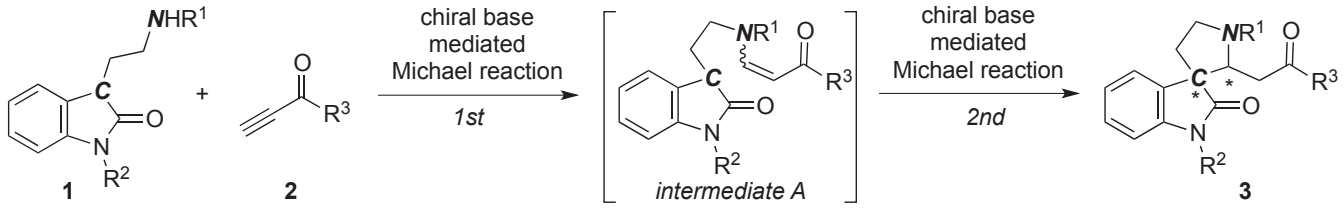
horsfiline (+)-elacomine rychnophyline

Figure 1. Natural products and biologically active molecules containing the spirooxindole motif

In recent years, spirooxindoles have attracted much attention in the area of antiviral drug discovery and development, owing to the high number of positive hits achieved by this scaffold.[1,4] In fact, spirooxindole motifs are found in numerous natural products and biologically active molecules such as horsfiline,

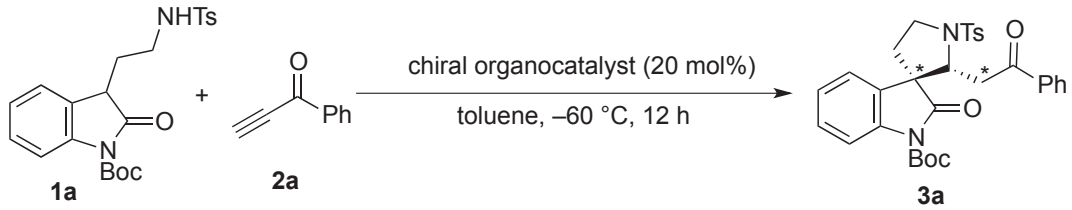
(+)-elacomine, and rychnophyline (Figure 1).[1,4] Although significant progress has been made in the asymmetric synthesis of diverse spirooxindoles, facile synthetic strategies capable of constructing multiple chiral centers from readily available substrates are still in high demand.[4]

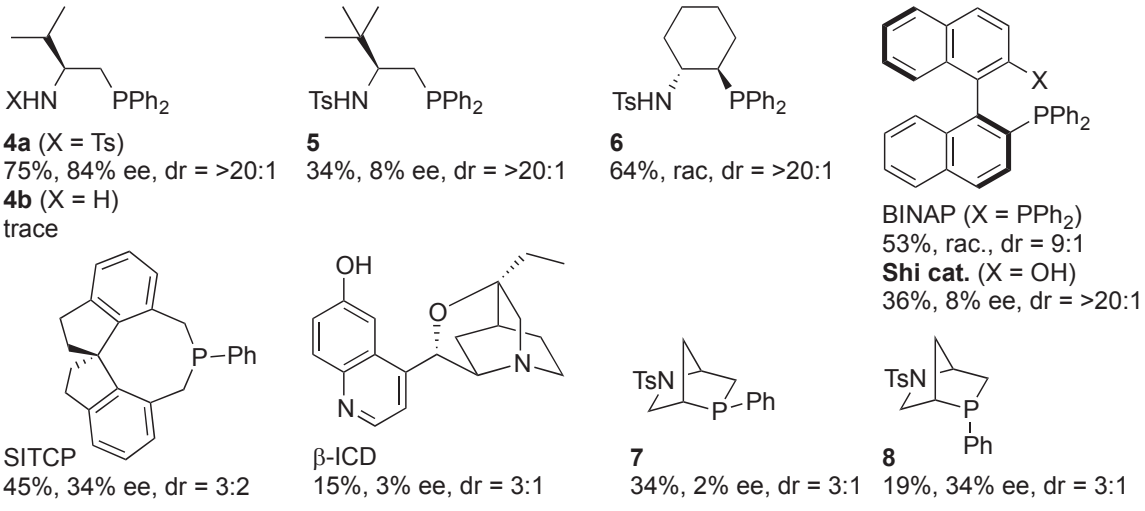
As part of our effort to explore enantioselective domino processes,[5] we were interested in designing sequential reactions to access chiral spirooxindole motifs. We envisioned that chiral spirooxindole **3** could be readily accessed by the reaction of the α-substituted oxindole **1**, bearing two potential nucleophilic units (***C*** and ***N*** as shown in Scheme 1), with ynone **2** via sequential additions to the ynone β-position. If ynone **2** could be used as a Michael acceptor, the generated *intermediate A* would possess one remaining degree of unsaturation, thereby enabling further incorporation of nucleophiles.



Scheme 1. Enantioselective organocatalyzed sequential reaction of **1** and **2** to produce spirooxindoles **3** with multiple chiral centers

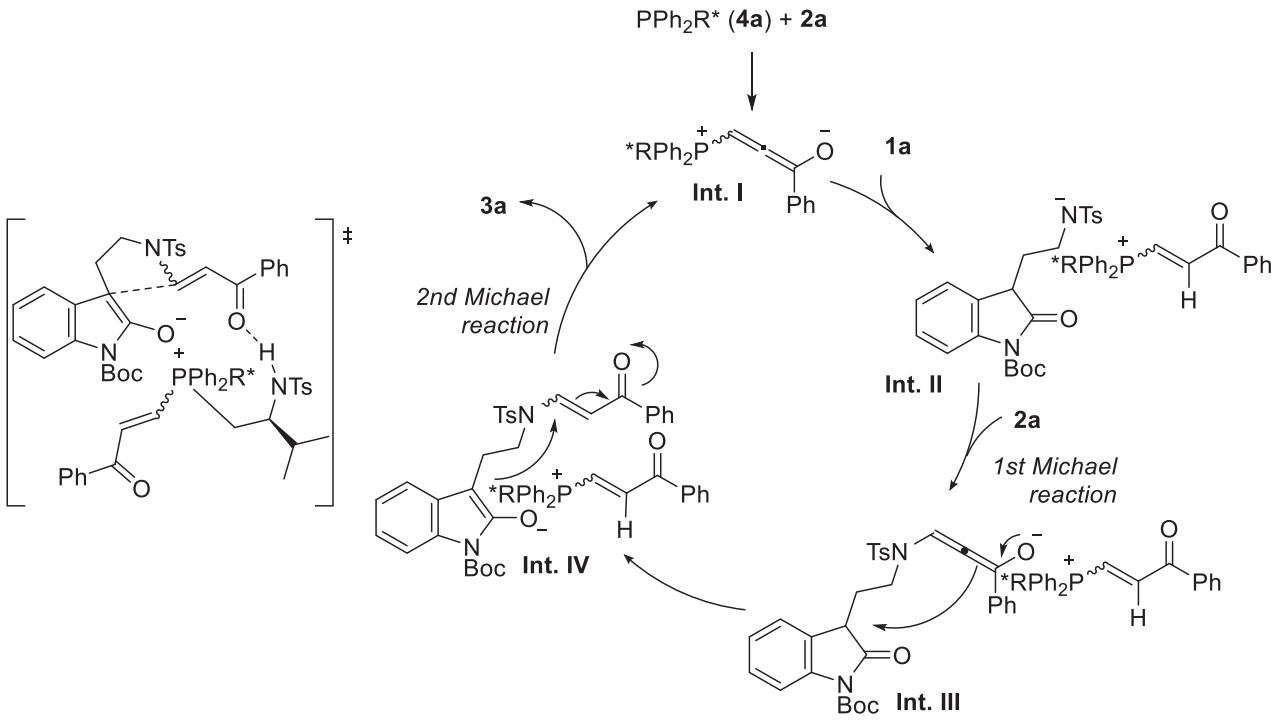
Table 1. Screening of organocatalysts for enantioselective sequential reaction





[a]Reaction conditions: **1a** (1.0 eq), **2a** (1.24 eq), and chiral organocatalyst (20 mol%) in toluene at –60 °C under N_2.

We initially tested the reaction of **1a**[6] (R^1 = Ts, R^2 = Boc), prepared from tryptamine, and commercially available **2a** (R^3 = Ph).[7] Among the reaction conditions screened (solvents,[8] temperature,[9] and chiral organocatalysts), the best performance was achieved at –60 °C in toluene using the multifunctional phosphine catalyst **4a**[10] derived from (*S*)-valine, furnishing the desired spirooxindole **3a**[11] in 75% yield and 84% ee (Table 1). In contrast, low catalytic activity was observed for the free-amine catalyst **4b**, *tert*-leucine-derived phosphine catalyst **5**,[10a] and cyclic organocatalyst **6**. β-ICD[12] bearing a Brønsted base unit, and other phosphines such as BINAP, Shi catalyst,[13] SITCP,[14] and catalysts **7**-**8** developed by Kwon,[15] some of which are known to mediate the enantioselective Morita–Baylis–Hillman (MBH) and Rauhut–Currier (RC) reactions,[16] also showed low enantioselectivities. These outcomes suggested that delicate steric interactions and/or hydrogen bonding between the substrates and the catalyst are important to promote the reaction with a high degree of enantiocontrol.



Scheme 2. Proposed mechanism of the enantioselective organocatalyzed sequential reaction

Although the reaction mechanisms have been controversial, our proposed mechanism, shown in Scheme 2, involves a 1,4-addition between phosphine **4a** as a precatalyst and **2a** to produce **Int. I**, which acts as a Brønsted base to deprotonate the pro-nucleophile **1a**, affording **Int. II**.[17] This allows the first intermolecular Michael reaction between **2a** and **Int. II** to afford **Int. III**, which then undergoes a proton transfer to produce **Int. IV**. Under the optimized conditions, the nucleophilic carbanion and the carbonyl groups in **Int. IV** would interact with the phosphonium ion and the toluenesulfonamide unit, which functions as a Brønsted acid in the real catalyst, through ion-pairing and hydrogen bonding to promote

asymmetric induction in the product.[18] Thus, **Int. IV** undergoes an enantioselective intramolecular Michael reaction, the following proton transfer produces compound **3a** and regenerate **Int. I**.

In summary, we have developed a highly enantioselective sequential reaction producing a single diastereomer of the natural product precursor **3a** with up to 84% ee. Further investigation of the reaction mechanism, scope, and applications to the synthesis of biologically active compounds is currently in progress.

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6. Synthesis of *tert*-butyl 3-(2-((4-methylphenyl)sulfonamido)ethyl)-2-oxoindoline-1-carboxylate (**1a**): Di-*tert*-butyl dicarbonate (1.5 mL, 6.7 mmol) was added to a solution of 4-methyl-*N*-(2-(2-oxoindolin-3-yl)ethyl)benzenesulfonamide[19] (2.0 g, 6.1 mmol**)** and Na_2CO_3 (780 mg, 7.3 mmol) in THF (35 mL) at 0 ºC. Then after the reaction was stirred under the reflux conditions for 1 h, 1 M HCl aq. was added. The aqueous layer was separated and extracted with EtOAc (three times). After the combined organic layer was dried over $MgSO_4$, The solvent was removed *in vacuo*. The residue was purified by silica gel column chromatography (eluent: hexane/EtOAc = 5/1) to obtain the title compound **1a** as a yellow solid (2.6 g, 75% yield). **1a**: IR (KBr): 3278, 2979, 2931, 1781, 1604, 1472, 1298, 1254, 1157, 1092, 822, 762, 671, 556 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.78 (d, J = 8.2 Hz, 1H), 7.72 (d, J = 8.2 Hz, 2H), 7.32-7.28 (m, 3H), 7.18-7.14 (m, 2H), 4.91 (t, J = 6.4 Hz, 1H), 3.63 (d, J = 8.2 Hz, 1H), 3.26-3.13 (m, 2H), 2.42 (s, 3H), 2.29-2.20 (m, 1H), 2.03-1.94 (m, 1H), 1.64 (s, 9H); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 176.19, 148.98, 143.46, 139.86, 136.67, 129.75, 128.41,

127.04, 126.90, 124.55, 123.56, 115.09, 84.62, 43.35, 40.24, 31.17, 28.06, 21.50; HRMS (ESI) *m*/*z* $[M+Na]^+$ calcd for $C_{22}H_{26}N_2O_5SNa$ 453.1455, found 453.1454.

7. When substrate **1b** (R^1 = Ts, R^2 = H) or ethyl alkynoate **2b** (R^3 = OEt) was applied for the reaction under the optimized conditions, no corresponding product **3** was obtained at all.
8. The reaction of **1a** with **2a** was performed at –60 ºC for 12 h in various solvents, see: In THF, **3a**: trace; in DCM, **3a**: 23% yield, 70% ee.
9. The reaction of **1a** with **2a** was performed in toluene for 12 h at various temperatures, see: at –40 ºC, **3a**: 51% yield, 83% ee; at –80 ºC, **3a**: 76% yield, 83% ee.
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11. Synthesis of *tert*-butyl 2-oxo-2'-(2-oxo-2-phenylethyl)-1'-tosylspiro[indoline-3,3'-pyrrolidine]-1-carboxylate (**3a**): Phenylprop-2-yn-1-one (**2a**) (4.05 mg, 0.031 mol) was added to a mixture of *tert*-butyl 3-(2-((4-methylphenyl)sulfonamido)ethyl)-2-oxoindoline-1-carboxylate (**1a**) (10.55 mg, 0.025 mmol) and (*S*)-*N*-(1-(diphenylphosphanyl)-3-methylbutan-2-yl)-4-methylbenzenesulfonamide (**4a**) (2.20 mg, 5.0 μmol) in toluene (0.13 mL) at –60 ºC under nitrogen atmosphere. After stirring at –60 ºC for 12 h, toluene (1.0 mL) was added to the mixture. Subsequently the diluted reaction mixture was filtrated with a pad of silica gel using EtOAc as an eluent, the filtrate was condensed *in vacuo*, the obtained residue was purified by PTLC (eluent: hexane/EtOAc = 4/1) to give the title compound (2'*R**,3*S**)-**3a** (10.51 mg, 75% yield, 84% ee) as a white solid. (2'*R**,3*S**)-**3a** (major): IR (KBr): 3058, 2977, 2931, 1775, 1730, 1682, 1603, 1474, 1349, 1158, 897, 837, 760, 660, 558 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.86 (d, *J* = 8.2 Hz, 2H), 7.72 (d, *J* = 8.2 Hz, 1H), 7.60 (dd, *J* = 7.8, 1.4 Hz, 2H), 7.47-7.40 (m, 3H), 7.31 (t, *J* = 7.8 Hz, 2H), 7.25 (d, *J* = 8.2 Hz, 1H), 7.14 (td, *J* = 7.8, 1.2 Hz, 1H), 7.02 (td, *J* = 7.8, 0.9 Hz, 1H), 4.54-4.50 (m, 1H), 3.99-3.93 (m, 1H), 3.86-3.79 (m, 1H), 3.73-3.68 (m, 1H), 3.39-3.31 (m, 1H), 2.47 (s, 3H), 1.90-1.84 (m, 1H), 1.79-1.76 (m, 1H), 1.66 (s, 9H); ^{13}C NMR ($CDCl_3$, 176 MHz) δ 197.35, 175.82, 149.14, 144.31, 139.57, 135.93, 133.05, 132.76, 130.08, 128.86, 128.26, 128.03, 127.85, 127.59, 124.06, 123.79, 115.69, 84.36, 63.77, 57.20, 48.55, 42.73, 37.36, 28.08, 21.68; HRMS (ESI) *m*/*z* $[M+Na]^+$ calcd for $C_{31}H_{32}N_2O_6SNa$ 583.1873, found 583.1872; Enantiomeric excess: 84%, determined by HPLC (Chiralpak AD-H, hexane/2-propanol = 9/1; flow rate 1.0 mL/min; 25 ºC; 220 nm) first peak: t_R = 15 min, second peak: t_R = 28 min; $[\alpha]_D^{26}$ +73.4 (*c* 1.0, THF) for 84% ee. (2'*S**,3*S**)-**3a** (minor): IR (KBr): 3060, 2976, 2927, 1758, 1726, 1685, 1601, 1476, 1341, 1165, 852, 809, 759, 661, 587 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.88 (d, *J* = 8.0 H, 2H), 7.81 (m, 2H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.43 (m, 4H), 7.20 (t, *J* = 7.6 Hz, 1H), 6.61 (t, *J* = 7.6 Hz, 1H), 5.62 (d, *J* = 7.6 Hz, 1H), 4.32 (dd, *J* = 10.2, 3.2 Hz, 1H), 4.04 (dd, *J* = 18.8, 10.2 Hz,

1H), 3.97 (dt, *J* = 8.0, 2.6 Hz), 3.84 (dd, *J* = 18.8, 3.2 Hz, 1H), 3.51 (dd, *J* = 8.0, 2.6 Hz, 1H), 2.54 (s, 3H), 2.60-2.46 (m, 1H), 1.92-1.76 (ddd, *J* = 12.0, 7.2, 3.2 Hz, 1H), 1.45 (s, 9H); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 198.93, 174.57, 148.89, 144.24, 138.56, 136.48, 133.17, 131.88, 130.15, 128.44, 128.35, 128.01, 127.97, 124.13, 121.51, 115.04, 84.09, 64.83, 55.45, 47.68, 42.78, 36.12, 27.85, 21.62; HRMS (ESI) *m*/*z* $[M+Na]^+$ calcd for $C_{31}H_{32}N_2O_6SNa$ 583.1873, found 583.1874.

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