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Microwave-assisted organocatalysis: phosphine-mediated Tomita Zipper cyclization affording functionalized spirooxindole

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ABSTRACT

A microwave-assisted and phosphine-mediated Tomita Zipper cyclization of dicyanomethylideneoxindoles and ynones has been developed. Various functionalized spirooxindoles with five-membered carbocyclic ring can be obtained in moderate to good yields with moderate to excellent diastereoselectivities through in situ generation of α-nucleophile (up to 87% yield, >20:1 dr).

Spirooxindoles can be found in a large number of biologically active compounds and pharmaceuticals. Particularly, all-carbon five-membered spirooxindoles are featured in numerous natural products and synthetic bioactive compounds, such as Marcfortine B, Spirotryprostatin B, and Cyclopiamine B (Fig. 1).[1] Considering the intriguing molecular architecture and potent biological activities, various protocols have been developed to synthesize this class of molecules.[2,3] However, the diastereoselective synthesis of five-membered spirooxindole, especially functionalized all-carbon spirocyclopenteneoxindole containing two quaternary carbons, still remains a challenging task.

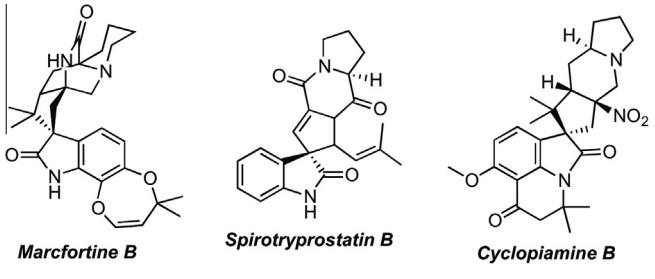
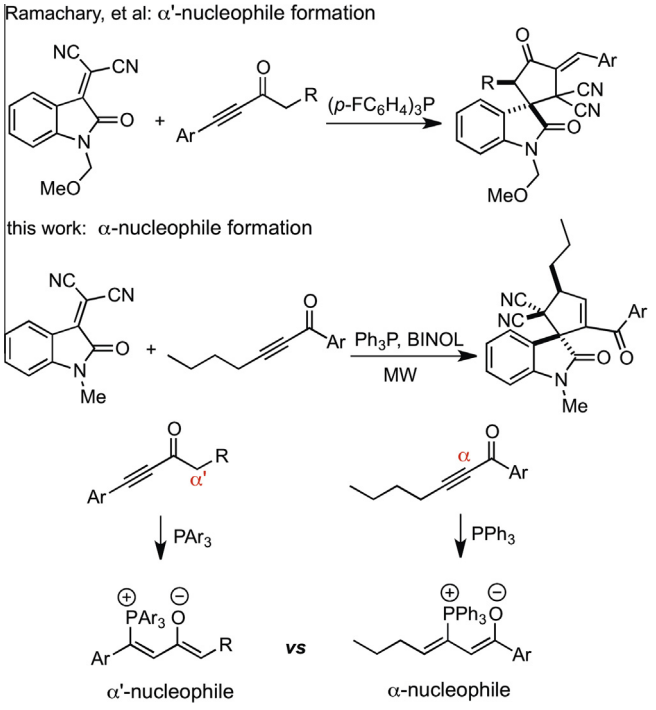


Figure 1. Natural products bearing all-carbon five-membered spirooxindole.



Scheme 1. Design for the synthesis of all-carbon five-membered spirooxindoles.

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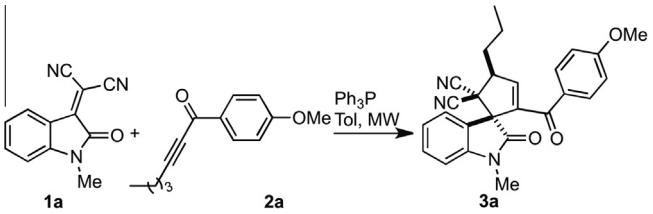
Table 1
Selected optimization studies[a,b,c]



Entry	Additive	Ratio (**1a**:**2a**:Ph_3P:Additive)	*T* (°C)	Yield (%)
1	—	1:1.2:0.3:0	150	24
2	BINOL	1:1.2:0.3:0.3	150	40
3[d]	BINOL	1:1.2:0.3:0.3	150	38
4	BINOL	1:1.2:0.6:0.3	150	43
5	BINOL	1:1.2:0.6:0.3	180	26
6	BINOL	1:1.2:0.6:0.3	100	63
7	BINOL	1:1.2:0.6:0.3	80	59
8	BINOL	1:2:0.6:0.3	100	79 (71)[e]
9	—	1:2:0.6:0	100	25
10[f]	BINOL	1:2:0.6:0.3	100	61

[a] Unless otherwise noted, reaction was performed with 0.2 mmol of **1a**, 0.24 mmol of **2a**, and 30 mol % of catalyst in 1.0 mL of toluene irradiated by microwave for 20 min.
[b] Yield was determined by ^1H NMR with CH_2Br_2 as internal standard.
[c] Excellent diastereoselectivities (>20:1) were observed in all cases.
[d] With 100 mg of 4 Å MS.
[e] Isolated yield.
[f] Heated at 100 °C for 20 min by conventional heating.

Recently, organocatalytic transformation of electron-deficient triple bonds has been emerging as a powerful method for the construction of carbocycles and heterocycles.[4] For instance, Tomita group[5] and Fu group[6] reported their strategies of phosphine-catalyzed synthesis of bicycles with alkynyl ketones. A novel α′-nucleophile, (*Z*)-4-(tributylphosphonio)buta-1,3-dien-2-olate, was formed in these intramolecular reactions. Ramachary and co-workers disclosed a phosphine-catalyzed stereoselective synthesis of functionalized five-membered spirooxindole through intermolecular Tomita Zipper Cyclization.[7] Xue group have also employed tributylphosphine for activation of alkynyl ketone to generate a nucleophile at the α-position. The in situ generated α-nucleophile could react with *N*-Tosylimines delivering pyrrolidines in good to excellent yields.[8] Inspired by these pioneering achievements of phosphine-catalyzed reactions by the groups of Tomita,[5] Fu,[6] Lu,[9] Shi,[10] Ramachary,[7] Kwon,[11] and others,[12,13] we hypothesized that phosphine-catalyzed transformation of alkynyl ketones could be applied in the construction of all-carbon five-membered spirooxindoles via a Tomita Zipper cyclization (Scheme 1).[14] α-Nucleophile would be generated when α′-blocked ynone is attacked by a nucleophilic catalyst and the subsequent tandem reactions would allow access to spirocyclopenteneoxindole.[15] Herein, we report our development of a microwave-assisted and phosphine-mediated synthesis of spirooxindoles with five-membered carbocyclic ring.

We began our study with olefin **1a** and ynone **2a** as model substrates in toluene to react with each other in the presence of 30 mol % of Ph_3P under irradiation of microwave.[16] Pleasingly, the desired all-carbon five-membered spirooxindole **3a** could be detected with a promising 24% NMR yield (Table 1, entry 1). With 30 mol % of BINOL as additive, an improved 40% yield could be observed (entry 2). Addition of 4 Å MS had no significant influence on yield (entry 3). Increase of catalyst loading led to a slightly improved yield (entry 4). Higher reaction temperature gave decreased yield, while lowering temperature afforded increased yield (entries 5–7). Improvement of yield was obtained when the reaction was performed with an excess amount of ynone (entry 8). However, the absence of BINOL resulted in a dramatically decreased yield (entry 9). We reasoned that the role of BINOL in this system is to activate ynone, stabilize enolate intermediate by hydrogen bonding, and facilitate proton transfer.[17–19] The reaction by conventional heating gave lower yield and was not as clean as that by microwave heating, showing the advantages of microwave energy for this reaction (entry 10).

With optimized conditions in hand, we then examined the substrate scope of olefins. As shown in Table 2, dicyanomethylideneoxindoles bearing methyl, methoxymethyl, propargyl, benzyl and phenyl groups at N1 position can be tolerated in this process, delivering corresponding spirocyclopenteneoxindoles in moderate to good yields (61–81%) and excellent diastereoselectivities (>20:1 in all cases). Lower catalyst loading and temperature can also afford desired products at the cost of prolonged reaction time when more reactive substrates were used (**3f** and **3g**). A drop in diastereoselectivity was observed in the cases of 4-substituted dicyanomethylideneoxindoles (**3h** and **3i**, 3.3:1–2.6:1 dr). Dicyanomethylideneoxindoles **1** with electron-withdrawing groups and electron-donating groups at 5 and 6 positions gave functionalized five-membered spirooxindoles in moderate to good yields (51–87%) with moderate to excellent diastereoselectivities (3.3:1–>20:1). Dicyano substituents were essential for this transformation, as methylideneoxindoles without dicyano substituents failed to deliver corresponding products.[20] The stereochemistry and structure of oxindole spirocyclopentenes **3** were confirmed by X-ray structure analysis on compound **3n**.[21]

Next, we explored the scope of alkynyl ketones under this catalytic system. As shown in Table 3, various aryl alkynyl ketones with phenyl ring or electron-deficient and electron-rich substituents on the phenyl ring delivered desired five-membered spirooxindoles in moderate to good yields (47–82%). Heteroaryl