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).

Keywords: Tomita Zipper cyclization, Microwave, Phosphine, Spirooxindole, Dicyanomethylideneoxindole

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 (Figure 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.

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 group⁵ and Fu group⁶ 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 Tomita⁵, Fu⁶, Lu,⁹ Shi,¹⁰ Ramachary,⁷ Kwon¹¹ 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.

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

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.^{17,18,19} 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).

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 minutes.

^b Yield was determined by ^1H NMR with CH_2Br_2 as internal standard.

^c Excellent diastereoselectivities (>20:1) was observed in all cases.

^d With 100 mg of 4Å MS.

^e Isolated yield.

^f Heated at 100 °C for 20 minutes by conventional heating.

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 spirocyclopentenones **3** were confirmed by X-ray structure analysis on compound **3n**.²¹

Table 2

Examination of Substrate Scope^{a,b}

^a Unless otherwise noted, reaction was performed with 0.2 mmol of **1**, 0.4 mmol of **2**, 60 mol% of PPh₃ and 30 mol% of BINOL in 1.0 mL of toluene under microwave irradiation at 100 °C for 20 minutes.

^b Isolated yields.

^c Performed at 100 °C for 25 minutes.

^d Performed with 30 mol% of PPh₃ and 10 mol% of BINOL at 70 °C for 90 minutes.

^e Performed with 30 mol% of PPh₃ and 10 mol% of BINOL at 70 °C for 120 minutes.

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 substituted ynone can also be applied in this process giving 65% yield (**3u**). Unfortunately, this method has its limitations. Corresponding product **3v** could not be obtained under the current system in the case of alkylated alkynyl ketone. Product **3w** could be obtained when ynone bearing longer chain was employed in this reaction, albeit with decreased yield. Ynone with phenyl group at γ -position failed to deliver spirocyclopenteneoxindole **3x** too.²² Complex mixture were observed instead of spirocyclopentene-oxindoles in the two cases of **3v** and **3x**.

Table 3

Examination of Substrate Scope^{a,b}

^a Unless otherwise noted, reaction was performed with 0.2 mmol of **1**, 0.4 mmol of **2**, 60 mol% of PPh_3 and 30 mol% of BINOL in 1.0 mL of toluene under microwave irradiation at 100°C for 20 minutes.

^b Isolated yields.

^c Not detected.

We proposed a possible mechanism for this reaction on the basis of our results and previous reports from other groups (Scheme 2).^{17,18} Attack of phosphine to hydrogen bonding activated ynone gives a zwitterionic intermediate **A** which would be subsequently transformed to intermediate **B** via intramolecular proton-transfer. α -Nucleophile **D** as a reactive resonance contributing structure undergoes Michael reaction giving carbanion species **E**. Further intramolecular addition, proton migration and elimination deliver the desired oxindole spirocyclopentene **3**. As intermediates **C** and **D** are more stable than intermediate **B**, α -addition is favored leading to excellent regioselectivities in all cases. BINOL as a hydrogen-bonding donor in this system can activate ynone **2**, stabilize enolate **D** and be beneficial for proton transformation. This may explain the improvement of yield by adding BINOL to reaction system.

Scheme 2. Proposed Catalytic Cycle

In conclusion, we have developed a microwave-assisted and phosphine-mediated construction of spirocyclopentene-oxindoles from simple dicyanomethylideneoxindoles and ynones. The reactions proceeded through a Tomita Zipper cyclization involving the *in situ* generation of α -nucleophile. Various functionalized spirooxindoles with five-membered carbocyclic ring can be obtained in moderate to good yields with moderate to excellent diastereoselectivities (up to 87% yield, > 20:1 dr). Application of this methodology in biomedical research is underway in our laboratory.

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19. For other optimization results, see supporting information.

20. See supporting information.

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