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Stereoselective Synthesis of Five-Membered Spirooxindoles through Tomita Zipper Cyclization

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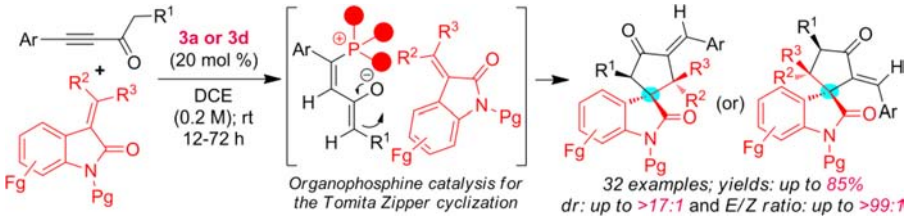
ABSTRACT



Functionalized five-membered spirooxindoles were furnished in good yields and excellent stereoselectivities by using an effective Tomita zipper cyclization (TZC) reaction through organophosphine catalysis.

Natural and unnatural compounds containing a spirooxindole as a core structure display vast biological activities.[1] Although many synthetic methods have been developed for the selective synthesis of spirooxindoles, but their high-yielding synthesis with multiple stereocenters and a spiro-quaternary carbon is a still demanding task.[2] Notably, existing stereoselective catalytic syntheses of substituted five-membered spirooxindoles from simple substrates and catalysts are very few.[3,4] Therefore, the development of a catalytic stereoselective protocol for the direct synthesis of functionalized five-membered spirooxindoles is a significant challenge.

In 2013, we have discovered an *aminoenyne* catalysis for the synthesis of six-membered spirooxindoles with a quaternary C-3 chiral center.[5a] Meanwhile, it was realized that substituted five-membered spirooxindoles also displayed in a number of biologically active natural products (Figure 1),[1] but their stereoselective synthesis with suitable functional groups remains a great challenge for synthetic chemists. Only a few reactions are known to achieve this goal.[3,4]

To attempt this synthetic goal, we aimed to design an organophosphine-catalyzed zipper cyclization that would involve a reaction between two simple starting materials. Providing the recent discovery of *in situ* generated (*Z*)-4-(tributylphosphonio)buta-1,3-dien-2-olate as a novel mild nucleophile in the intramolecular Tomita zipper cyclization (eq 1) and Fu cyclization reactions (eq 2) for the

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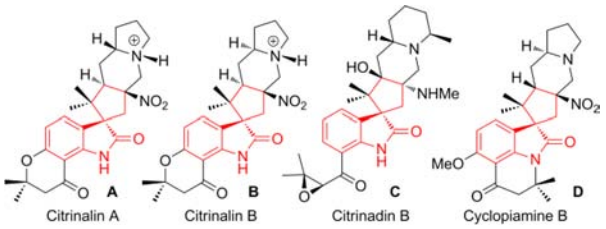
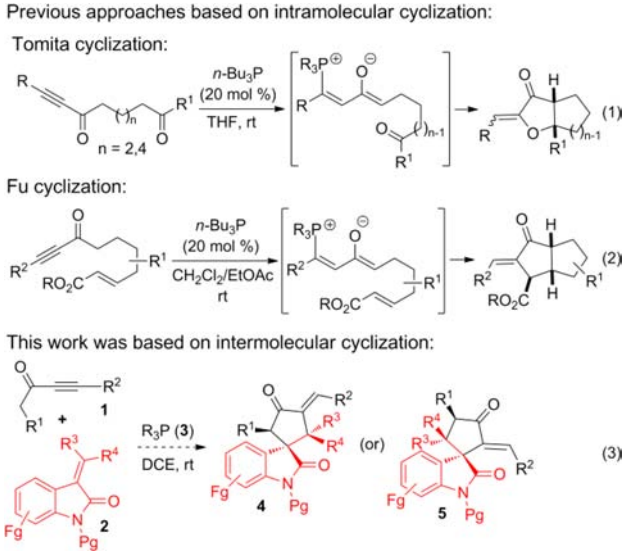


Figure 1. Bioactive natural products containing the spirooxindole core structure.

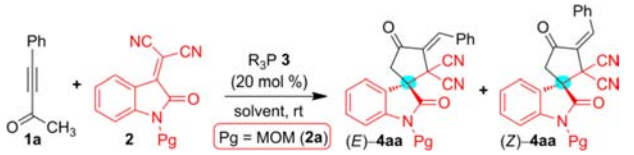
carbocycles synthesis,[6e,h] we realized that the intermolecular zipper cyclization between unmodified ynones **1** and 3-alkylideneindolin-2-ones **2** would yield the desired five-membered spirooxindoles in a highly stereoselective manner (eq 3, Scheme 1). As intermolecular Tomita zipper cyclization (TZC) is not known for carbocycle synthesis,[6] herein, we present the novel organocatalytic TZC between **1** and **2** that would provide the functionalized five-membered spirooxindole **4** or **5** in good yield with high selectivity (Scheme 1).

Scheme 1. Design for the Five-Membered Spirooxindoles Synthesis through Tomita Zipper Cyclization (TZC)



We commenced our studies by evaluating the TZC reaction between ynone **1a** and olefin **2a** using Ph_3P **3a** as the catalyst in DCE at 25 °C (Table 1, entry 1). We found that the reaction proceeded to furnish the (*E*)-**4aa** in 55% yield with >99% *E*-selectivity without formation of product **5aa**. Surprisingly, the same reaction with Ph_2EtP **3b** as the catalyst at 25 °C for 96 h furnished the spirooxindole (*E*)-**4aa** in only 40% yield, but there is no reaction with well-known *n*-Bu_3P **3c** as the catalyst at 25 °C for 72 h in THF (Table 1, entries 3−4). The same reaction with $(p\text{-}FC_6H_4)_3P$ **3d** as the catalyst at 25 °C for 24 h in DCE furnished (*E*)-**4aa** in 85% yield with a 17:1 *E*/*Z* ratio (Table 1, entry 5). After thorough investigation of the **3d**-catalyzed TZC reaction, we found that the solvent, catalyst loading, and temperature have a significant effect on the yields and *E*/*Z* ratio (Table 1, entries 6−12). Surprisingly, there is no TZC reaction observed under the catalysis of electron rich phosphine catalysts **3e** and **3f** (Table 1, entries 13−14). In the final optimization, TZC reaction of **1a** and **2a** through **3d** catalysis in DCE at 25 °C for 24 h furnished the spirooxindole (*E*)-**4aa** in 85% yield with 89% *E*-selectivity (Table 1, entry 5).

Table 1. Reaction Preliminary Optimization[a]



entry	solvent (0.2 M)	catalyst (mol %)	time (h)	yield (%)[b] (*E*)-**4aa**	yield (%)[b] (*Z*)-**4aa**
1	DCE	**3a**: Ph_3P	12	55	–
2[c]	DCE	**3a**	8	55	–
3	DCE	**3b**: Ph_2EtP	96	40	–
4	THF	**3c**: *n*-Bu_3P	72	–	–
5	**DCE**	**3d**: $(p\text{-}FC_6H_4)_3P$	**24**	**85**	**5**
6[d]	DCE	**3d**	36	75	5
7[e]	DCE	**3d**	60	75	5
8[f]	DCE	**3d**	16	55	5
9	DCM	**3d**	60	70	5
10	$CHCl_3$	**3d**	48	70	5
11	CH_3CN	**3d**	60	45	–
12	THF	**3d**	48	40	–
13	DCE	**3e**: $(p\text{-}OMeC_6H_4)_3P$	72	–	–
14	DCE	**3f**: HMPT	72	_	–

[a] Reactions were carried out in solvent (0.2 M) with 2 equiv of **1a** relative to the **2a** (0.2 mmol) in the presence of 20 mol % of catalyst **3**. [b] Yield refers to the column-purified product. [c] 3.0 equiv of **1a** were used. [d] Catalyst **3d** was taken as 10 mol %. [e] Catalyst **3d** was taken as 5 mol %. [f] Reaction performed at 60 °C.

Table 2. *N*-Substitution Effect on the TZC Reaction of **1a** with **2b**−**e** under the **3d** Catalysis in DCE at 25 °C

entry	Pg	time (h)	yield (%)[a] (*E*)-4	yield (%)[a] (*Z*)-4
1	**2b**: H	16	60 (*E*-**4ab**)	<5 (*Z*-**4ab**)
2	**2c**: Me	24	50 (*E*-**4ac**)	<5 (*Z*-**4ac**)
3	**2d**: $COCH_3$	16	50 (*E*-**4ad**)	– (*Z*-**4ad**)
4	**2e**: Boc	16	51 (*E*-**4ae**)	– (*Z*-**4ae**)

[a] Yield refers to the column-purified product.

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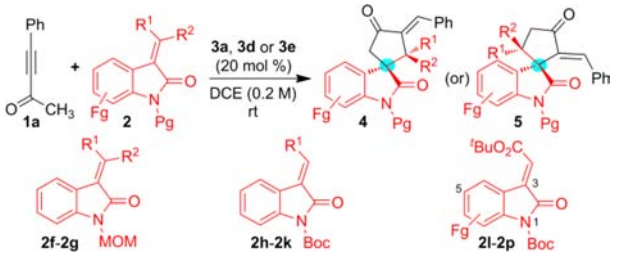
We further demonstrated the electronic factor of *N*-substitution of the designed TZC reaction (Table 2). Reaction of **1a** with *N*-H olefin **2b** under the catalysis of **3d** in DCE at 25 °C for 16 h furnished (*E*)-**4ab** in 60% yield with >85% *E*-selectivity (Table 2, entry 1). In a similar manner, TZC reaction of **1a** with *N*-Me olefin **2c** under **3d** catalysis for 24 h furnished (*E*)-**4ac** in 50% yield with >82% *E*-selectivity (Table 2, entry 2). Surprisingly, TZC reaction between **1a** and *N*-Ac or *N*-Boc olefins **2d**/**2e** under **3d** catalysis for 16 h furnished (*E*)-**4ad** and (*E*)-**4ae** in 50/51% yield with >99% *E*-selectivity, respectively (Table 2, entries 3–4). This result clearly shows that the single directional electrophilicity of olefin **2** is crucial to achieving high yields and selectivity in the designed TZC reaction.

To gain further insight into the electronic factors in TZC, we explored the treatment of different olefins **2f**–**p** with ynone **1a** under **3d** catalysis to furnish product **4** or **5** (Table 3). Reaction of olefin **2f** with **1a** under the **3d** or **3a** catalysis furnished the product **4af** in moderate yields and *E*/*Z* ratio, but the same reaction under **3e** catalysis gave **4af** in good yield with 2:1 *E*/*Z* ratio (Table 3, entries 1, 2). Olefin **2g** gave the product **4ag** in good yields with poor dr and a very good *E*/*Z* ratio under **3a** or **3d** catalysis (Table 3, entries 3, 4). Surprisingly, treatment of olefin **2h** with **1a** under **3a**, **3d**, or **3e** catalysis furnished the product **5ah** in poor yield, but the same reaction with olefin **2i** furnished the product (*E*)-**5ai** in 50% yield with 4:1 dr (Table 3, entries 5, 6). Reaction of **2j** with **1a** under **3d** or **3e** catalysis furnished the product **5aj** in poor yields, but the same reaction under **3a** catalysis gave the (*E*)-**5aj** in 70% yield with 6:1 dr (Table 3, entries 7, 8). In a similar manner, spirooxindoles (*E*)-**5ak**–**ap** were obtained in good yields and excellent dr's with a variety of olefins containing neutral and halogenated **2k**–**2p** from the TZC reaction (Table 3, entries 9–14).

After realizing the electronic factors of olefins, we further explored the scope of the **3d**-catalyzed TZC reaction by developing diversity-oriented stereoselective synthesis of spirooxindoles **4** through the reaction of ynones **1a**–**j** with olefins **2a** and **2q**–**u** (Table 4). The spirooxindoles **4** were obtained in good yields, excellent dr's, and *E*/*Z* ratios with a variety of olefins containing neutral and halogenated **2a**, **2q**–**u** and ynones containing a neutral, electron-donating, halogenated, α′-branched aliphatic group and heteroatom substituted **1a**–**1j** from the stereoselective TZC reaction (Table 4). In this work, treatment of the unmodified ynones **1a**–**j** with catalyst **3a** or **3d** gave the *in situ* catalytic species (*Z*)-4-(triarylphosphonio)buta-1,3-dien-2-olates as interesting mild nucleophiles, which are used in a TZC reaction to furnish the spirooxindoles **4ba**–**au** with up to >89% *E*-selectivity and 10:1 dr in good yields (Table 4). The structure and stereochemistry of the products **4** and **5** were confirmed by NMR analysis and also finally confirmed by X-ray structure analysis on **5an** and **4ar** as shown in Figures S1 and S2 (Supporting Information (SI)).[7]

With applications in mind, we explored the utilization of compounds **4** in the synthesis of functionalized spiranes **6**–**7** *via* simple cascade reductions. Reduction of

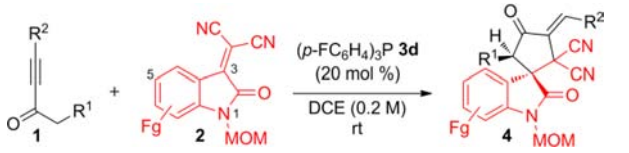
Table 3. Scope of the TZC Reaction with Other Olefins



entry	olefin **2**	catalyst **3**	time (h)	yield[a] (%)	dr[b,c]
1[d]	**2f**: R^1, R^2 = CO_2Et	**3a** or **3d**	72	40 (**4af**)	–
2[d]	**2f**: R^1, R^2 = CO_2Et	**3e**	72	60 (**4af**)	–
3	**2g**: R^1, R^2 = CN, CO_2Et	**3a**	24	60 (**4ag**)	1.3:1
4	**2g**: R^1, R^2 = CN, CO_2Et	**3d**	36	75 (**4ag**)	1.3:1
5	**2h**: R^1 = Ph	**3e**	72	<10 (**5ah**)	–
6	**2i**: R^1 = CO_2Me	**3a**	24	50 (**5ai**)	4:1
7	**2j**: R^1 = CO_2Et	**3a**	48	70 (**5aj**)	6:1
8	**2j**: R^1 = CO_2Et	**3d** or **3e**	72	<10 (**5aj**)	–
9	**2k**: R^1 = $CO_2{}^tBu$	**3a**	24	70 (**5ak**)	6:1
10	**2l**; Fg = 5-F	**3a**	24	60 (**5al**)	9:1
11	**2m**: Fg = 5-Cl	**3a**	12	55 (**5am**)	9:1
12	**2n**: Fg = 5-Br	**3a**	12	50 (**5an**)	17:1
13	**2o**: Fg = 5-I	**3a**	12	50 (**5ao**)	17:1
14	**2p**: Fg = 5,7-Me_2	**3a**	12	50 (**5ap**)	9:1

[a] Yield refers to the column-purified product. [b] dr determined by ^{1}H NMR analysis. [c] In all entries, <5% of *Z*-isomer is formed except in entries 1 and 2. [d] 2:1 ratio of *E*/*Z* isomers are formed.

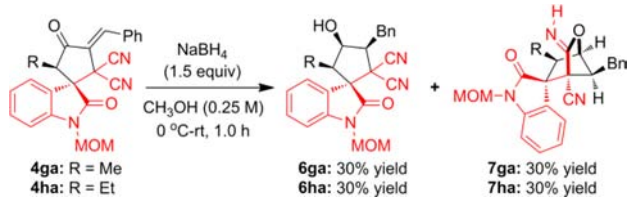
Table 4. Designed TZC Reaction with Other Ynones



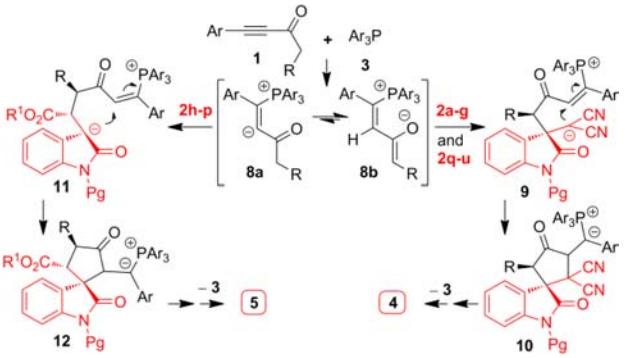
entry	ynone **1**	olefin **2**	*T* (h)	yield[a–c] (%)
1	**1b**: R^2, R^1 = 4-MeC_6H_4, H	**2a**: Fg = H	36	65 (**4ba**)
2	**1c**: R^2, R^1 = 4-$MeOC_6H_4$, H	**2a**	72	66 (**4ca**)
3	**1d**: R^2, R^1 = 4-$MOMOC_6H_4$, H	**2a**	48	60 (**4da**)
4	**1e**: R^2, R^1 = 4-FC_6H_4, H	**2a**	24	65 (**4ea**)
5	**1f**: R^2, R^1 = 4-ClC_6H_4, H	**2a**	36	65 (**4fa**)
6[d]	**1g**: R^2, R^1 = Ph, Me	**2a**	48	66 (**4ga**)[e]
7	**1h**: R^2, R^1 = Ph, Et	**2a**	48	78 (**4ha**)[f]
8[d]	**1i**: R^2, R^1 = 2-Thiophenyl, H	**2a**	48	64 (**4ia**)
9[g]	**1j**: R^2, R^1 = Ph, OMOM	**2a**	12	60 (**4ja**)[h]
10	**1a**: R^2, R^1 = Ph, H	**2q**: Fg = 5-F	24	60 (**4aq**)
11	**1a**	**2r**: Fg = 5-Cl	48	60 (**4ar**)
12	**1a**	**2s**: Fg = 5-Br	36	60 (**4as**)
13	**1a**	**2t**: Fg = 5-I	24	60 (**4at**)
14	**1a**	**2u**: Fg = 5,7-Me_2	36	80 (**4au**)

[a] Yield refers to the column-purified product. [b] dr determined by ^{1}H NMR analysis. [c] In all entries, <5% of *Z*-isomer is formed. [d] Reaction were carried out at 60 °C. [e] dr was 10:1. [f] dr was 8:1. [g] 3:1 ratio of *E*/*Z* isomers is formed. [h] dr was 2:1.

Scheme 2. Synthetic Applications of Spirooxindoles



Scheme 3. Reaction Mechanism



spirooxindoles (*E*)-**4ga** and (*E*)-**4ha** with 1.5 equiv of $NaBH_4$ in dry CH_3OH at 0−25 °C for 1.0 h furnished the double (olefin and carbonyl) reduced alcohols **6ga** and **6ha** in each 30% yield with >99:1 dr, accompanied by unexpected bicyclic imines **7ga** and **7ha** each in 30% yield with >99:1 dr, respectively (Scheme 2). Interestingly, diastereomerically pure alcohols **6** and bicyclic imines **7** were separated through column chromatography. The structure and stereochemistry of products **6** and **7** were confirmed by NMR analysis and also finally confirmed by X-ray structure analysis on **7ga** as shown in Figure S3 (SI).[7]

The most possible reaction pathway is shown in Scheme 3 based on the controlled experiments. A zwitterionic intermediate **8a** is produced by the Michael addition of the triarylphosphine catalyst **3** with ynones **1**, which further undergoes an intramolecular proton migration from the inner methylene to produce catalytic (*Z*)-4-(triarylphosphonio)buta-1,3-dien-2-olates **8b**.[6h] For the first time, the regioselective formation of zwitterionic intermediate **8a** was confirmed by ^{31}P NMR analysis and also online monitoring through HRMS analysis of the reaction between **1a** and **3a** (Scheme S1 and Figure S4, SI-I). Although supplementary studies are needed to securely elucidate the stereoselective formation of two kinds of cyclization products **4** and **5** from **2a**−**u** with **8b**, the reaction proceeds in a stepwise manner between *in situ* generated **8b** with olefins **2a**−**u** (Scheme 3). A nucleophilic attack of the resulting enolate **8b** to the olefins **2a**−**g** and **2q**−**u** produces carbanion species **9**, which further undergoes an intramolecular cyclization to furnish the phosphorane **10**. Charge migration followed by triarylphosphine **3** elimination of intermediate **10** produces the final product **4**. In a similar manner, products **5** are generated from the intermediates **11** and **12** through the treatment of *in situ* enolate **8b** with olefins **2h**−**p**. The reaction rate and diastereoselective product distribution of **4** and **5** through a TZC is completely based on the olefin π-electron distribution, which is controlled by the cyclic amide, *N*-substitution and olefin, aryl substitutions as shown in Tables 1−4. The reactivity of *in situ* generated species **8** from **1** with **3a** will be high compared to **3d** or **3e** due to their self-stabilization, which is reflected on the reaction with less reactive olefins **2i**−**p** (Table 3). Based on the control experiments and crystal structure studies, we can rationalize the observed high regio- and stereoselectivity of the TZC reaction is due to the *in situ* formation of (*Z*,*Z*)-enolate **8b** as the major isomer and also the strong electrostatic attraction, CH−π interactions between **8b** and **2**. Surprisingly, treatment of ynone **1a** with olefin **2a** under the diisopropylethylamine catalysis furnished the unexpected spiro[indoline-3,4′-pyran]-2-one **13aa** in 45% yield and product **4aa** in <5% yield, which highlights the importance of phosphine catalysis for the zipper cyclization (eq S1, SI-I).[8]

In summary, we have developed a versatile zipper cyclization protocol for the stereoselective synthesis of substituted five-membered spirooxindoles **4** and **5** from acyclic precursors by using a commanding but mostly less explored catalytic *in situ* generated species of (*Z*)-4-(triarylphosphonio) buta-1,3-dien-2-olates (**8b**) reactivity discovered by Tomita.[6h] The products of the TZC reaction **4** were transformed into the highly functionalized drug-like molecules **6**−**7** with >99:1 dr. Future studies from this group will continue to explore the scope of novel methods of catalytic **8b** reactivity furnished by chiral phosphines with unmodified ynones.

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Supporting Information Available. Experimental procedures, compound characterization, X-ray crystal structures, and analytical data (^1H NMR, ^{13}C NMR, and HRMS) for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(7) CCDC-949984 for **5an**, CCDC-949985 for **4ar**, and CCDC-949986 for **7ga** contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(8) For the treatment of ynones with secondary amines, see: (a) Ramachary, D. B.; Venkaiah, Ch.; Krishna, P. M. *Chem. Commun.* **2012**, *48*, 2252. (b) Silva, F.; Sawicki, M.; Gouverneur, V. *Org. Lett.* **2006**, *8*, 5417.

The authors declare no competing financial interest.