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# Regulation of Cyclization for the Stereoselective Synthesis of Substituted Tetrahydrofurans and Tetrahydrooxepines

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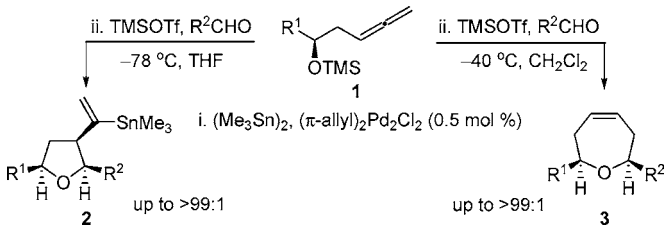
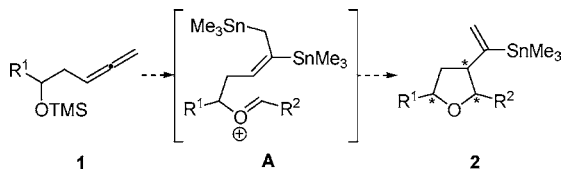
## ABSTRACT




**Dramatic solvent effect is observed during the cyclization of 1. Synthesis of 2 is achieved from the reaction of 1 with a hexamethylditin-catalyzed palladium complex followed by aldehydes in the presence of TMSOTf in THF, whereas 3 is formed in $CH_2Cl_2$. The method described herein is successful with various substrates 1 in good yields and high levels of diastereoselectivity.**

One of the recent goals of synthetic chemistry is the development of new reactions that allow for the efficient conversion of simple starting materials into complex products via transition metal catalysis.[1] In this regard, allene has been proved to be a useful substrate for a variety of transition metal catalytic reactions, particularly, for cyclizations in the construction of carbo- and heterocycles.[2] Recently, we have developed several cyclization methods using allenes as substrates or intermediates,[3] as part of a sequential allylic transfer strategy.[4] The characteristic features of this approach, in terms of the chemical efficiency of the stereoselective three-component assembly and the structural features of the products, have encouraged us to carry out further investigations to introduce other functionalities. As a consequence, we became quite interested in designing an intramolecular allylic transfer reaction from **1** to **2** with the generation of three stereogenic centers as depicted in Scheme 1.

**Scheme 1**




It was envisaged that the allylic transfer reaction starting from **1** with an aldehyde ($R^2CHO$) leading to the formation

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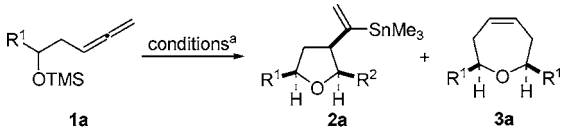
of **2** could be realized by the two-step sequence as described in Scheme 1. To provide direct access to the product **2**, we considered an oxonium **A** as a crucial intermediate. This transformation involves the distannylation of an allene, the formation of an oxonium species **A** with an aldehyde mediated by a Lewis acid and subsequent intramolecular allylic transfer reaction.

Substituted tetrahydrofurans are found in a wide range of useful biologically active molecules.[5] In general, these molecules contain various substituents and stereogenic centers around and adjacent to the tetrahydrofuran ring. Notable methods for the synthesis of tetrahydrofuran units have been developed in recent years to achieve stereoselectivity,[6] the useful strategy of which involves construction of the oxacyclic ring by carbon−carbon bond formation from an oxonium intermediate via electrophilic cyclization.[7] The realization of this method for the three-component assembly to achieve multiple stereoselectivity, illustrated in Scheme 1, should be valuable because synthetic application can be foreseen for the products. We report herein our discovery of a general and useful method in the construction of trisubstituted tetrahydrofurans **2** and disubstituted tetrahydrooxepines **3** from **1** in a single operation. During the investigations, the dramatic solvent effects to regulate reaction pathways for the formation of five- or seven-membered oxacycles were observed.

With this issue in mind, our investigations began with **1a** ($R^1$ = $PhCH_2CH_2$) as a model substrate. Reaction of **1a** (1 equiv) with hexamethylditin (1.2 equiv) in the presence of ($\pi$-allyl)$_2Pd_2Cl_2$ (0.5 mol %) at 0 °C in $CH_2Cl_2$ afforded a distannylated product within 3 h. The stage was thus set for the cyclization reaction with aldehydes mediated by a Lewis acid based on the conditions mainly developed by Marko and co-workers.[8] Attempts of a cyclization reaction, without separation of the distannylated intermediate, with hydrocinnamaldehyde indicated that the conversion to the corresponding **2** could not be satisfied with a variety of Lewis acids including $SnCl_4$, $TiCl_4$, and $EtAlCl_2$ under various reaction conditions. We observed the formation of only a trace of product except the decomposition of the intermediate. We found that $BF_3$·$OEt_2$ could be a promoter for this purpose. Initial experiments on the distannylation of **1a** followed by intramolecular allylic transfer with aldehyde in the presence of $BF_3$·$OEt_2$ (1.5 equiv) at −78 °C in $CH_2Cl_2$ afforded two products. Although **2a** was produced as a major component along with unexpected **3a** during the reaction, moderate selectivity (**2**:**3** = 73:27) and low chemical yield (13% combined) remained to be solved. We were surprised to find that the destannylated tetrahydrooxepine **3a** was formed.

Fortunately, we observed that the use of TMSOTf turned out to be the most effective promoter for this transformation, as can be seen in Table 1. After exploring numerous sets of conditions, we found that the choice of solvents led to the formation of **2a** or **3a** selectively. Reaction produced only **2a** in THF (entry 7), whereas **3a** was formed in $CH_2Cl_2$ (entry 12). We also observed inverse temperature effects for the formation of **3a**, but yields were decreased by increasing temperature (entries 12 and 13). We realized that the synthesis of seven-membered oxacycles is also important because the related structures are considerably distributed in nature and play a variety of biological roles.[9]

**Table 1.** Preliminary Investigations




**1a** **2a** **3a**

$R^1$ = $R^2$ = $PhCH_2CH_2$

| entry | Lewis acid (equiv) | solvent | **2a**:**3a**[b] | yield[c] (%) |
|---|---|---|---|---|
| 1 | $BF_3$·$OEt_2$ (1.5) | $CH_2Cl_2$ | 73:27 | 13 |
| 2 | $BF_3$·$OEt_2$ (1.5) | toluene | − | trace |
| 3 | $SnCl_4$ (1.5) | $CH_2Cl_2$ | − | trace |
| 4 | $TiCl_4$ (1.5) | $CH_2Cl_2$ | − | trace |
| 5 | $EtAlCl_2$ (1.5) | $CH_2Cl_2$ | − | trace |
| 6 | TMSOTf (1.1) | THF | **2a** only | 67 |
| 7 | TMSOTf (1.5) | THF | **2a** only | 83 |
| 8 | TMSOTf (1.5) | $CH_3CN$ | **2a** only | 23 |
| 9 | TMSOTf (1.5) | $Et_2O$ | **2a** only | 32 |
| 10 | TMSOTf (1.5) | $CH_2Cl_2$ | 9:91 | 73 |
| 11 | TMSOTf (1.5) | $CHCl_3$ | 8:92 | 65 |
| 12 | TMSOTf (1.5) | $CH_2Cl_2$[d] | 3:97 | 71 |
| 13 | TMSOTf (1.5) | $CH_2Cl_2$[e] | 2:98 | 42 |

[a] Reaction conditions: (i) $(Me_3Sn)_2$ (1.2 equiv), ($\pi$-allyl)$_2Pd_2Cl_2$ (0.5 mol %), 0 °C, 3 h; (ii) $R^2CHO$ (1.5 equiv), Lewis acid, −78 °C, 4 h, solvent. [b] Determined by $^1H$ NMR. [c] Refer to isolated product. [d] Performed at −40 °C. [e] Performed at −10 °C.

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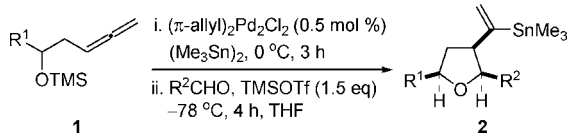
(9) For examples, see: (a) Blunt, J. W.; Copp, B. R.; Hu, W.-P.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep.* **2007**, *24*, 31−86. (b) Blunt, J. W.; Copp, B. R.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep.* **2006**, *23*, 26−78.

With the notion that this protocol might lead to a general and efficient method for the synthesis of **2**, we set out to determine the scope of the reaction with various **1** (Table 2). Upon optimal conditions, the reaction was conducted by a dropwise addition of a mixture of **1a** (1 equiv) and $Me_3SnSnMe_3$ (1.2 equiv) in THF to a solution of ($\pi$-allyl)$_2$PdCl$_2$ (0.5 mol %) at 0 °C in THF. After 3 h at 0 °C, the reaction mixture was cooled to −78 °C, and then aldehyde (1.5 equiv) and TMSOTf (1.5 equiv) were added. Reaction was usually complete within 4 h. Workup and chromatography on silica gel afforded **2a** in 83% yield as a diastereomerically pure form. Indeed, the method is successful with a variety of compounds **1** and affords products of high diastereomeric purity as it can be seen in Table 1. It is noteworthy that other diastereomers were not detected by analysis of $^1$H NMR. Stereochemical relationship was unambiguously deduced by a series of NMR experiments with **5** (see Supporting Information). Crucial evidence was the NOE enhancements between $H^2-H^3$ and $H^2-H^5$.

**Table 2.** Cyclization of **1** to **2** in THF

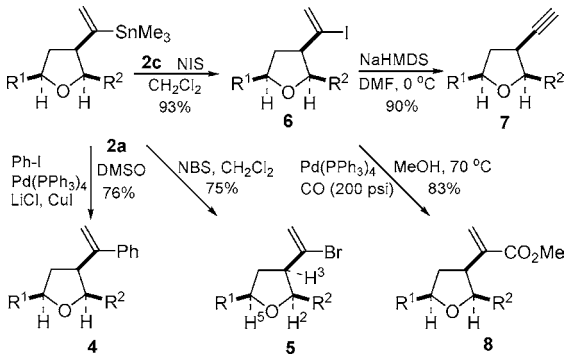



1 2

| entry | product | $R^1$ | $R^2$ | yield (%) |
|---|---|---|---|---|
| 1 | **2a** | $PhCH_2CH_2$ | $PhCH_2CH_2$ | 83 |
| 2 | **2b** | $PhCH_2CH_2$ | Me | 77 |
| 3 | **2c** | $n$-$C_5H_{11}$ | $PhCH_2CH_2$ | 75 |
| 4 | **2d** | $n$-$C_5H_{11}$ | Me | 71 |
| 5 | **2e** | $n$-$C_5H_{11}$ | $CH_2Cl$ | 69 |
| 6 | **2f** | Me | $PhCH_2CH_2$ | 87 |
| 7 | **2g** | $Me_2CH$ | $PhCH_2CH_2$ | 76 |
| 8 | **2h** | Ph | $PhCH_2CH_2$ | 67 |
| 9 | **2i** | Ph | $Me_2CH$ | 53 |

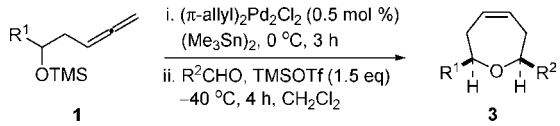
Product **2** is readily amenable for further conversion to synthetically useful compounds by functional group transformations of vinylstannane as depicted in Scheme 2. For example, compound **2a** was converted to **4** by the Stille coupling.[10] Elimination of **6** with NaHMDS in DMF yielded **7**. Carbonylation of **6** in the presence of Pd(0) under CO pressure in MeOH gave **8** in good yield.[11]

**Scheme 2**




In light of the above results for the synthesis of the tetrahydrofuran **2**, we next turned our attention to the application of this approach to extend to the synthesis of seven-membered oxacycles based on the preliminary investigations (Table 1, entry 12). Under similar conditions for the synthesis of **2a**, except the use of $CH_2Cl_2$ instead of THF as a solvent, **3a** was obtained as a single diastereomer in 71% yield. Indeed, the method is successful with various **1** and affords products of high purity as listed in Table 3. It is noteworthy that reaction produced less than 7% of five-membered oxacycles **2** according to the analysis of $^1$H NMR spectra of crude products. Stereochemical relationship of **3a** was proved by comparison of NMR data with literature.[12]

**Table 3.** Cyclization of **1** to **3** in $CH_2Cl_2$

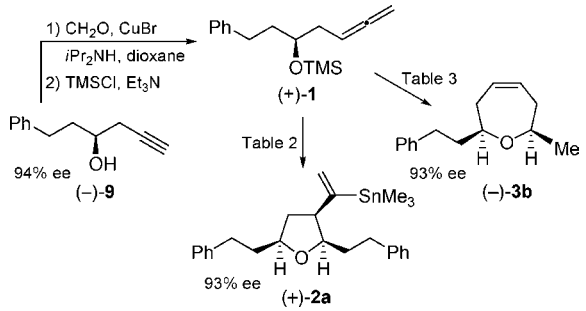



1 3

| entry | product | $R^1$ | $R^2$ | **3**:**2** | yield (%) |
|---|---|---|---|---|---|
| 1 | **3a** | $PhCH_2CH_2$ | $PhCH_2CH_2$ | 97:3 | 71 |
| 2 | **3b** | $PhCH_2CH_2$ | Me | 95:5 | 75 |
| 3 | **3c** | $PhCH_2CH_2$ | Ph | 98:2 | 67 |
| 4 | **3d** | $n$-$C_5H_{11}$ | $PhCH_2CH_2$ | 96:4 | 66 |
| 5 | **3e** | $n$-$C_5H_{11}$ | Ph | 98:2 | 61 |
| 6 | **3f** | $PhCH_2$ | $PhCH_2CH_2$ | 94:6 | 80 |
| 7 | **3g** | Me | $PhCH_2$ | 93:7 | 71 |
| 8 | **3h** | Ph | $PhCH_2$ | **3** only | 67 |
| 9 | **3i** | Ph | $Me_2CH$ | 99:1 | 64 |

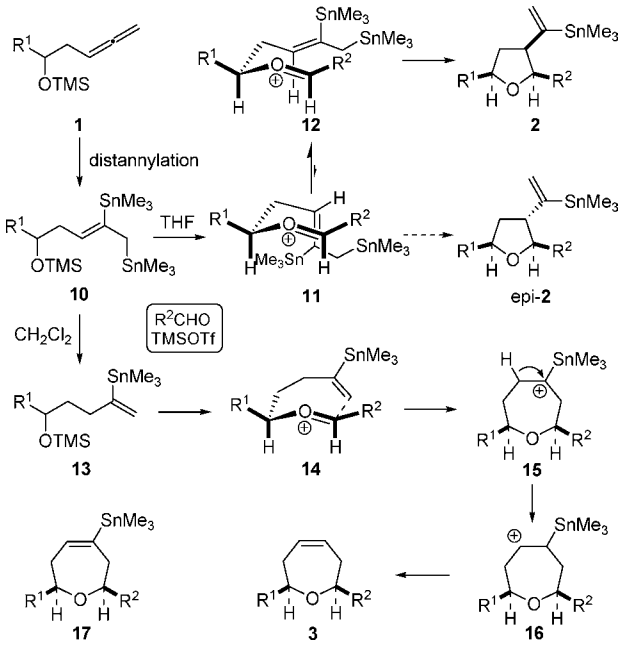
In order to prove retention of stereochemistry during the cyclizations, enantiomerically enriched (+)-**1a** was prepared from the corresponding propargyl alcohol.[13] As illustrated in Scheme 3, we demonstrated that the cyclizations of (+)-**1a**, both for five- and seven-membered oxacycles, proceeded with complete retention of stereochemistry as determined by chiral HPLC analysis.

**Scheme 3**



Although the exact mechanistic aspects of this transformation have not been rigorously elucidated, the following pathway is a probable stereochemical route on the basis of product formations and our observations as illustrated in Scheme 4. The exceptional stereoselectivity for tetrahydrofuran **2** from **1** can be predicted by comparison of stereochemical models **11** and **12**. The major reaction pathway could be dependent on the stability in the transition state under a kinetic control such as orientations and steric factors offered by existing substituents: geometrical preference of **12** for a minimum strain with existing components compared to **11** owing to a severe steric repulsion.

**Scheme 4**




However, the origin of the formation of seven-membered oxacycles **3** depending on solvent is not clear at this moment. There are two possibilities governing reaction pathways for the second allylic transfer reaction. First, we speculated that the formation of **3** could be explained by assuming that reaction produced **17** from **2** by α-addition through the 1,3-migration of allylic tin reagent followed by a destannylation to **2** under the reaction conditions or during a workup process. However, the experiments could not support this claim: a vinylstannyl group was stable under the same reaction conditions, and the addition of NBS before quenching the reaction did not afford a vinylbromide compound. Another possibility is a formation of **13** as a crucial intermediate. Subsequent cyclization of **13** and an aldehyde in the presence of TMSOTf could give rise to **3** as depicted in Scheme 4, a similar pathway described by Overman.[12a] The formation of **13** was confirmed by a control experiment. During the distannylation, we did not find any formation of **13**. After the introduction of TMSOTf, the formation of **13** was observed at −40 °C in $CH_2Cl_2$ for 1 h in more than 75% conversion as judged by NMR. However, we do not have the answer at this time, if this reaction pathway is plausible, why the route from **10** to **13** is faster than the route to **2** under the reaction conditions. We only know that the reaction of **1** in $CH_2Cl_2$ produced **3** as a major component.

In summary, this paper describes the synthesis of five- and seven-membered oxacycles selectively by simply changing the solvent. We also demonstrated that the reaction proceeded with a retention of stereochemistry. Studies are in progress to extend this protocol to other heterocycles containing nitrogen atoms.

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**Supporting Information Available:** General experimental procedure details and characterization data for all products. $^1H$ and $^{13}C$ NMR for all products and 2-D NMR spectra for **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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