SHORT COMMUNICATION

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Tandem Nucleophilic Addition/Oxa-Michael Reaction for the Synthesis of *cis*-2,6-Disubstituted Tetrahydropyrans

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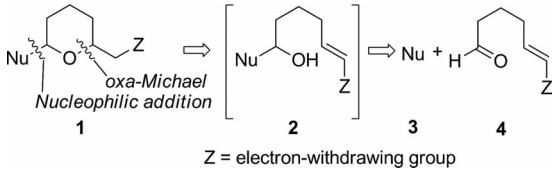
A Lewis acid catalyzed tandem nucleophilic addition/oxa-Michael reaction was developed for the synthesis of *cis*-2,6-disubstituted tetrahydropyran (THP) derivatives in good yields with excellent diastereoselectivities. The strategy was successfully used in the construction of THP derivatives with three stereocenters in a highly stereoselective fashion.

Introduction

Tetrahydropyrans (THPs) are omnipresent in nature and form common structural motifs of a vast number of biologically active molecules. Natural products such as marine toxins, acid ionophores, which are commonly known as polyether antibiotics, and pheromones possess a THP moiety in their molecular architecture.[1] Owing to their wide occurrence and biological activity, a variety of synthetic methods have been developed to assemble THPs.[2] Among the general methods developed for the synthesis of THP derivatives;[3] intramolecular oxa-Michael addition to enoates has been well studied and has been widely utilized in the synthesis of complex natural products.[4–7] Both the base-catalyzed as well as the Brønsted acid catalyzed intramolecular oxa-Michael addition is well established for the synthesis of THPs.[5,7,8] Interestingly, Lewis acid catalyzed intramolecular oxa-Michael additions for the stereoselective synthesis of THPs is relatively less explored. In the majority of cases, the synthesis of the precursors for this intramolecular oxa-Michael addition involves several steps, including the generation of the alcohol, protection of the alcohol, installation of the appropriate Michael acceptor, and deprotection of the alcohol followed by the Michael addition. A tandem reaction sequence that will obviate such a multistep synthesis thus looks very attractive.

Tandem reactions are highly desirable in present day synthesis because they enhance molecular complexity in a "single pot", which thereby minimizes the number of steps required and the quantities of chemicals and solvents used.[9] In this context, the synthesis of THPs by using tandem reactions has been the focus of some recent studies; the most notable among these are a tandem allylic oxidation/oxa-conjugate addition reaction, domino olefin cross-metathesis/intramolecular oxa-conjugate addition reaction, redox isomerization/oxa-conjugate addition reaction, and tandem Suzuki coupling/oxa-conjugate addition reaction.[6] Most recently, Zhao et al. reported the stereoselective synthesis of 2,6-*cis*-substituted tetrahydropyrans by using one-pot sequential catalysis involving a Henry reaction and an oxa-Michael reaction catalyzed by the addition of a Brønsted acid.[7a] In continuation of our efforts on developing strategies for the stereoselective synthesis of cyclic ethers,[10] particularly by using tandem reactions, herein we describe a Lewis acid catalyzed tandem nucleophilic addition/oxa-Michael reaction for the stereoselective synthesis of *cis*-2,6-disubstituted THPs.

We envisioned that 2,6-disubstituted THP derivatives **1** could be readily synthesized from alcohol **2** by intramolecular oxa-Michael addition. It was reasoned that if alcohol **2** was prepared by Lewis acid catalyzed addition of nucleophile **3** to the aldehyde functionality of **4**, which also bears an appropriately tethered Michael acceptor, it should lead to 2,6-disubstituted THP derivatives **1** by in situ oxa-Michael addition. This will obviate the need to isolate alcohol **2** (Scheme 1).



Scheme 1. Retrosynthesis of the 2,6-disubstituted THP derivatives.

Results and Discussion

To test the feasibility of the strategy, aldehyde **4a**, prepared by mono-Wittig olefination of glutaraldehyde with

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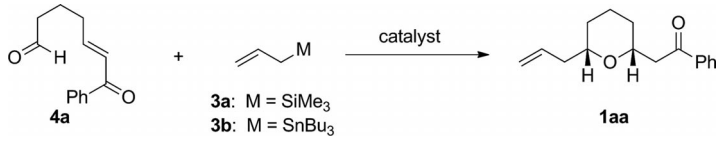
Table 1. Tandem nucleophilic addition/oxa-Michael reaction: screening of Lewis acids.



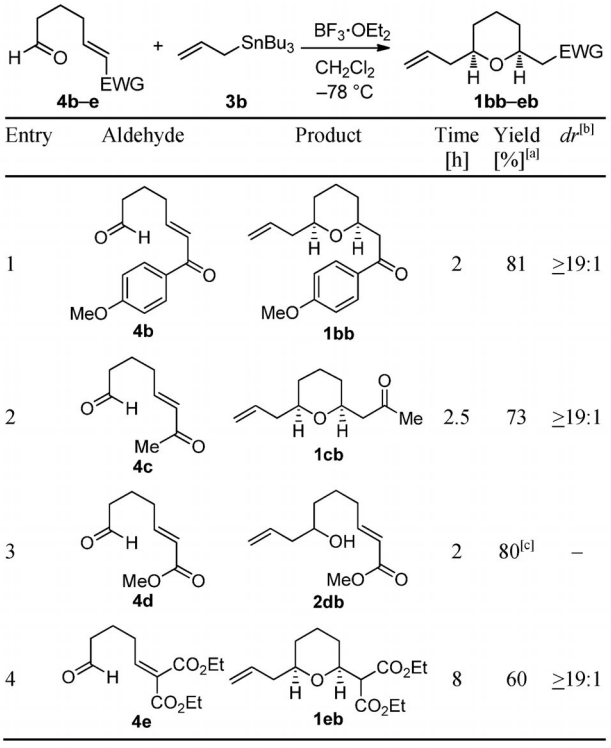
Entry	Nucleophile	Lewis Acid	Equiv.	Solvent	*T* [°C]	Time [h]	Yield [%][a]	*dr*[b]
1	**3a**	$BF_3{\cdot}OEt_2$	1.5	CH_2Cl_2	–78 to r.t.	4	66	≥19:1
2	**3a**	$TiCl_4$	1.5	CH_2Cl_2	0 to r.t.	0.5	13	≥19:1
3	**3a**	TMSOTf	1.5	CH_2Cl_2	–78 to r.t.	2.5	10	–
4	**3a**	$FeCl_3$	1.5	$MeNO_2$	r.t.	8.5	32	3:1
5	**3a**	$BiBr_3$	1.5	CH_2Cl_2	0 to r.t.	5	60	5:1
6	**3b**	$BF_3{\cdot}OEt_2$	1.5	CH_2Cl_2	–78 to r.t.	2.5	90	≥19:1
7	**3b**	$BF_3{\cdot}OEt_2$	0.1	CH_2Cl_2	–78 to r.t.	5.5	20[c]	≥19:1

[a] Yield of isolated product. [b] In all the cases, the diastereomeric ratio (*dr*) was determined by analysis of the crude reaction mixture by ^{1}H NMR spectroscopy. [c] Uncyclized alcohol was isolated in 33% yield.

[(phenylcarbonyl)methylene]triphenylphosphorane, was treated with allyl-organometallic reagents **3a** and **3b** in the presence of various Lewis acids, and the results are summarized in Table 1. Upon using $BF_3{\cdot}OEt_2$ (1.5 equiv.) as the Lewis acid along with allyltrimethylsilane (**3a**) as the nucleophile, desired *cis*-2,6-disubstituted THP derivative **1aa** was obtained in 66% yield with excellent diastereoselectivity (Table 1, entry 1). The stereochemistry of the 2,6-substituents was found to be *cis* on the basis of NOE experiments. Upon using more reactive allyltributylstannane (**3b**) as the nucleophile, *cis*-2,6-disubstituated THP **1aa** was obtained in 90% yield with excellent diastereoselectivity (Table 1, entry 6). The use of a catalytic amount (10 mol-%) of $BF_3{\cdot}OEt_2$ resulted in a poor yield (20%) of THP derivative **1aa**, along with uncyclized alcohol **2aa** in 33% yield (Table 1, entry 7). For other Lewis acids such as $TiCl_4$, trimethylsilyl trifluoromethanesulfonate (TMSOTf), $FeCl_3$, and $BiBr_3$, THP product **1aa** was formed in very poor yields with only moderate diastereoselectivities (Table 1, entries 2–5). Thus, $BF_3{\cdot}OEt_2$ was found to be the best Lewis acid in the tandem nucleophilic addition/oxa-Michael reaction for the synthesis of *cis*-2,6-disubstituated THP derivatives.

To study the scope of the tandem nucleophilic addition/oxa-Michael reaction for the stereoselective synthesis of *cis*-2,6-disubstituated THP derivatives, aldehydes **4b**–**e** bearing different Michael acceptors were prepared and subjected to the optimized reaction conditions. The results are summarized in Table 2. Treatment of aryl- and methyl-substituted enones **4b** and **4c** tethered to an aldehyde functionality with allyltributylstannane (**3b**) under the optimized reaction conditions gave corresponding THPs **1bb** and **1cb** in good yields with excellent diastereoselectivities (Table 2, entries 1 and 2). Interestingly, if an α,β-unsaturated ester was used as the Michael acceptor (cf. aldehyde **4d**), the second step of this tandem sequence, that is, the oxa-Michael addition, did not take place, and uncyclized alcohol **2db** was obtained in 80% yield (Table 2, entry 3). This was perhaps the result of the low reactivity of the α,β-unsaturated ester as the conjugate acceptor under the reaction conditions employed.[8,11,12] In contrast, aldehyde **4e**, bearing a more reactive alkylidine malonate as Michael acceptor, was found to work efficiently, and corresponding *cis*-THP derivative **1eb** was formed in good yield with good diastereoselectivity (Table 2, entry 4).

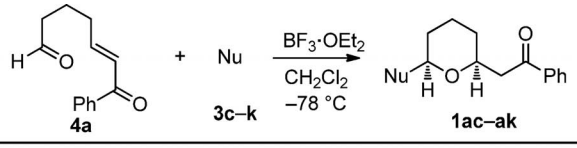
Table 2. Tandem nucleophilic addition/oxa-Michael reaction: substrate scope.

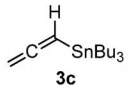
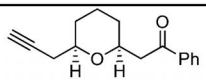
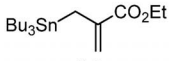
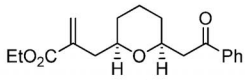
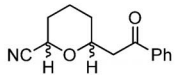
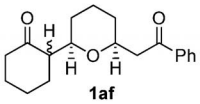
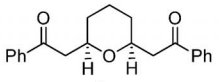
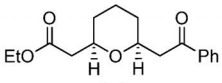
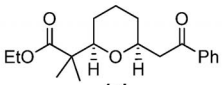
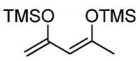
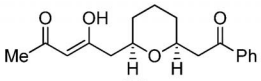
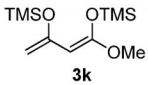
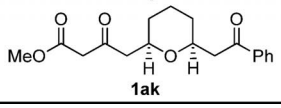


[a] Yield of isolated product. [b] In all cases, the *dr* was determined by analysis of the crude reaction mixtures by ^{1}H NMR spectroscopy. [c] The uncyclized alcohol was isolated.

To study the scope of the nucleophiles in the tandem nucleophilic addition/oxa-Michael reaction, aldehyde **4a** was treated with nucleophiles **3c**–**k**, and the results are summarized in Table 3. Tin-based reagents such as allenyltributyl-

Table 3. Tandem nucleophilic addition/oxa-Michael reaction: nucleophile scope.



Entry	Nucleophile	Product	Time [h]	Yield [%][a]	*dr*[b]
1	 **3c**	 **1ac**	10	75	≥19:1
2	 **3d**	 **1ad**	2	79	≥19:1
3	TMSCN (**3e**)	 **1ae**	3	63	1:1
4	 **3f**	 **1af**	3	66	1:1
5	 **3g**	 **1ag**	0.75	62	≥19:1
6	 **3h**	 **1ah**	2	70	≥19:1
7	 **3i**	 **1ai**	1	45	≥19:1
8	 **3j**	 **1aj**	10	64	≥19:1
9	 **3k**	 **1ak**	4.5	51	≥19:1

[a] Yield of isolated product. [b] In all the cases, the *dr* was determined by analysis of the crude reaction mixtures by ^{1}H NMR spectroscopy.

stannane (**3c**) and allyltin reagent **3d** added successfully to aldehyde **4a** to give THPs **1ac** and **1ad**, respectively, in good yields with excellent diastereoselectivities (Table 3, entries 1 and 2). If TMSCN (**3e**) was used as the nucleophile, 2,6-disubstituted THP derivative **1ae** was obtained in good yield but with 1:1 diastereoselectivity (Table 3, entry 3). Silyl enol ethers or silyl ketene acetals **3g**–**k** were found to be good nucleophiles, and products **1ag**–**ak** were obtained in good yields with good diastereoselectivities (Table 3, entries 5–9). Upon using the silyl enol ether of cyclohexanone **3f** as the nucleophile, product **1af** was obtained as a 1:1 mixture of diastereomers (Table 3, entry 4). It is pertinent to note that the diastereoselectivity of the first Mukaiyama aldol step was poor rather than that of the oxa-Michael addition step.

The stereochemical outcome of these reactions can be explained on the basis of transition-state structures **A** and **B** (Figure 1). In the first step, the nucleophile chemoselectively adds to aldehyde to generate an alcohol bound to the Lewis acid. During the second step, that is, the oxa-Michael addition, the bulky substituent (nucleophile) occupies the pseudoequatorial position to avoid 1,3-diaxial interactions. Because the incipient acylmethylene group is bulkier than hydrogen, it tends to adopt a pseudoequatorial orientation (**A** of Figure 1) rather than a pseudoaxial orientation (**B** of Figure 1) to avoid 1,3-diaxial interaction, which results in the *cis* product.[13]

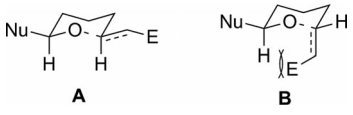
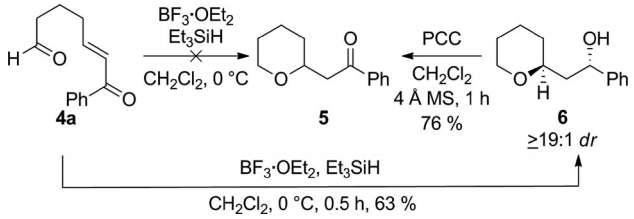


Figure 1. Explanation for stereochemical outcome of the reaction.

This transition-state structure also explains the poor selectivity in the case of THP derivative **1ae** in which CN was the nucleophile; in this case, because CN is small, it does not have any preference to be in the axial or equatorial position in comparison to hydrogen.

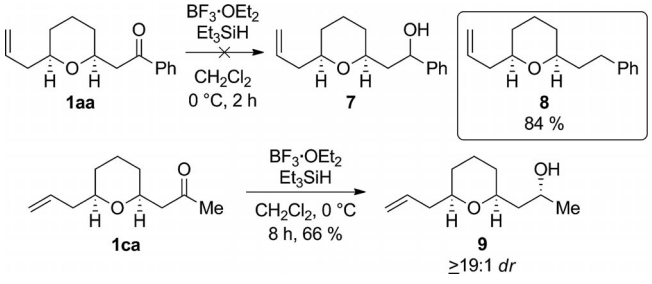
After successfully exploring the scope of the tandem nucleophilic addition/oxa-Michael reaction for the synthesis of 2,6-disubstituted THPs, it was decided to add hydride as a nucleophile. Thus, treatment of aldehyde **4a** with Et_3SiH in the presence of $BF_3{\cdot}OEt_2$ in dry CH_2Cl_2 resulted in the formation of THP **6** in 63% yield rather than ketone **5** (Scheme 2). THP **6** is clearly a product of over-reduction (reduction of the keto group) of intermediate ketone **5**.



Scheme 2. Tandem nucleophilic addition/oxa-Michael reaction: hydride as nucleophile; PCC = pyridinium chlorochromate, MS = molecular sieves.

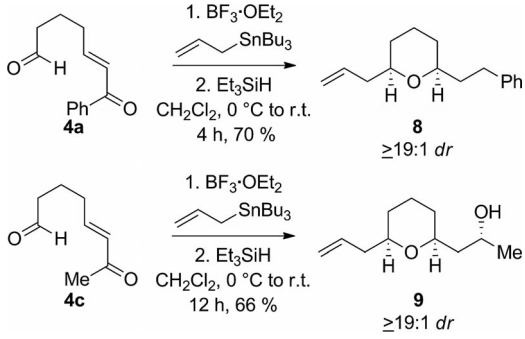
To ascertain the over-reduction of ketone with Et_3SiH under the ionic hydrogenation conditions, *cis*-2,6-disubstituted THP derivative **1aa** was subjected to the reaction with Et_3SiH in the presence of $BF_3{\cdot}OEt_2$. The reaction indeed led to the formation of alcohol **7**; however, it was only a minor product. The major product formed in this reaction was THP **8**, which was the outcome of the reduction of the benzylic hydroxy group under the ionic hydrogenation conditions employed.

Again, control of the reaction was found to be difficult; hence, the reaction was performed with an excess amount of Et_3SiH, which furnished THP **8** as the sole product in 84% yield (Scheme 3). In contrast, if 2,6-disubstituted THP derivative **1ca** bearing a methyl ketone rather than an aryl ketone was treated with Et_3SiH in the presence of $BF_3{\cdot}OEt_2$, alcohol **9** was obtained in 66% yield as a single diastereomer.[14]



Scheme 3. Reduction of THP ketones **1aa** and **1ca**.

It was then decided to study the "one-pot" allylation/oxa-Michael reaction/reduction sequence for the synthesis of 2,6-disubstituted THPs. Thus, aldehydes **4a** and **4c** were treated sequentially with allyltributylstannane (**3b**) and Et_3SiH in the presence of $BF_3{\cdot}OEt_2$ to furnish THP derivatives **8** and **9** in good yields with good diastereoselectivities (Scheme 4).



Scheme 4. Synthesis of THP derivatives: one-pot allylation/oxa-Michael addition/reduction sequence.

Conclusions

In conclusion, we developed a Lewis acid catalyzed tandem nucleophilic addition/oxa-Michael reaction for the synthesis of *cis*-2,6-disubstituted THP derivatives in good yields with excellent diastereoselectivities. The reaction worked well with good Michael acceptors. Various nucleophiles added successfully to the aldehydes to give rise to THP derivatives. The developed strategy was amenable to designing sequential reactions and was successfully used in the "one-pot" construction of THP derivatives bearing three stereocenters in a highly stereoselective fashion.

Supporting Information (see footnote on the first page of this article): Experimental procedures and characterization data along with copies of the ^1H NMR and ^{13}C NMR spectra for all new compounds.

Acknowledgments

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[14] The stereochemistry of the alcohol was tentatively assigned on the basis of NOE and NOESY experiments.

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