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Control of up to Five Stereocenters in a Cascade Reaction: Synthesis of Highly Functionalized Five-Membered Rings

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Discovery of an efficient method to construct complex molecules with multiple stereogenic centers in excellent regio-, diastereo-, and enantioselectivity has been an important goal for both academic and industrial researchers.[1] In particular, asymmetric domino and cascade reactions which allow the formation of multiple C−C bonds and many stereogenic centers in a one-pot manner are useful for the synthesis of natural products and synthetic building blocks. These processes are usually cleaner as they generate less waste by minimizing isolation of intermediates in the multistep synthesis of complex molecular targets.[2,3] Accordingly, much effort has been focused on the development of new stereoselective cascade reactions, including the recent reports by Enders et al.[4] on an elegant asymmetric domino reaction for the construction of cyclohexane derivatives in excellent stereoselectivities. However, the development of a highly stereoselective domino reaction for the synthesis of cyclopentane derivatives remains difficult.[5,6]

Here we report the development of a highly regio-, diastereo-, and enantioselective domino Mukaiyama−Aldol−Prins (MAP) reaction for the synthesis of a highly substituted cyclopentyl system. This cascade reaction provides a powerful means to create a highly functionalized five-membered ring system in good to excellent yields with the generation of up to five new stereogenic centers in excellent regio- and diastereoselectivies with complete enantioselectivities.[7] In addition, variation of the substrates and simple manipulation of the products will allow the construction of diverse polyfunctionalized cyclopentane derivatives, which can serve as building blocks for the synthesis of complex molecules.

We envisage that the domino reactions involving the Mukaiyama−Aldol reaction of silyl enol ether **1** with acetal **2** will produce an oxocarbenium intermediate **4**,[8] which upon trapping by an alkene functionality in an intramolecular Prins cyclization fashion[9,10] may generate the cyclopentyl ring system **5** (Scheme 1).

In our initial studies, we reacted the monosubstituted acetal (Scheme 1, R_1 = Me, R_5 = Et) with silyl enol ether (Scheme 1, $R_{2,3}$ = Me, R_4 = TMS) in the presence of titanium tetrabromide. Unfortunately, the desired domino process did not take place. Only the Mukaiyama−Aldol reaction product **6** was obtained (Scheme 1). Next, we replaced the labile trimethyl silyl group with more robust silicon protecting groups, such as a triisopropylsilyl (TIPS) group. To our delight, the desired product **9** was obtained in very high yield with excellent diastereoselectivity (Table 1, entry 1). Using different silyl enol ethers (Table 1, entries 2 and 3), the domino process proceeded in the same manner to give the desired products in high yields with excellent diastereoselectivities. In all cases, a single isomer was obtained, and three new bonds and four new stereocenters were generated from this highly efficient cyclization process.

A noteworthy point in this study is the intriguing bromosubstituted silyl enol ether. In this case, five new chiral centers were formed contiguously in a one-pot reaction in high yield and excellent diastereoselectivity (Table 1, entry 4). The *E/Z* isomers (85/15) of the silyl enol ether which cannot be separated were retained in the product. This reaction further expanded the scope of this method. The MAP domino process can also proceed smoothly with $-CH_2OBn$-substituted acetal to afford the products in high yields and excellent diastereoselectivities. On the basis of X-ray analysis of a product (see Supporting Information), the relative configuration of the five-membered rings system was determined.

Of mechanistic interest is that no reaction was observed when the *E* isomer of the acetal was used in this reaction. On the basis of this information and the stereochemistries observed in the products, a plausible mechanism for the formation of the five-membered ring products was proposed as shown in Scheme 2. We believe that the steric repulsion between bulky OTIPS and R_3 in the *E* isomer disfavored pathway B.

Besides the acyclic acetal, we also looked into the cyclic acetal version (Scheme 3). Treatment of the TIPS silyl enol ether with

Scheme 1. Our Proposed Hypothesis

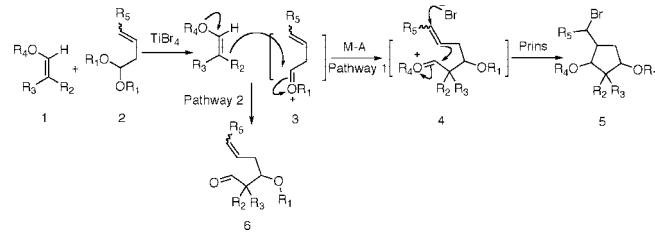
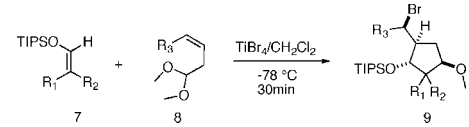


Table 1. MAP Reactions with Monosubstituted Acetal (*Z*)-**8**[a]



entry	R_1	R_2	R_3[b]	yield[c] (%)	dr[d]
1	CH_3	CH_3	Et	90	>99:1
2	CH_3CH_2	CH_3CH_2	Et	91	>99:1
3	$-(CH_2)_3-$		Et	86	>99:1
4	CH_3, Br		Et	80	>99:1
	(*Z*/*E* = 85:15)[e]			(87:13)	
5	CH_3	CH_3	CH_2OBn	81	>99:1
6	CH_3CH_2	CH_3CH_2	CH_2OBn	85	>99:1
7	$-(CH_2)_3-$		CH_2OBn	93	>99:1
8	$-(CH_2)_2-$		CH_2OBn	90	>99:1

[a] Mukaiyama−Aldol−Prins reactions were run with 2 equiv of $TiBr_4$, 1 equiv of acetal, and 1.2 equiv of silyl enol ether under N_2 atmosphere. [b] Monosubstituted acetals (*Z*)-**8** were prepared by Wittig reactions. MAP reaction cannot proceed using monosubstituted acetal (*E*)-**8**. [c] Isolated yield. [d] Diastereomeric ratios were based on ^1H and ^{13}C NMR analyses. [e] MAP reaction proceeds smoothly with (*Z*)- or (*E*)-silyl enol ether.

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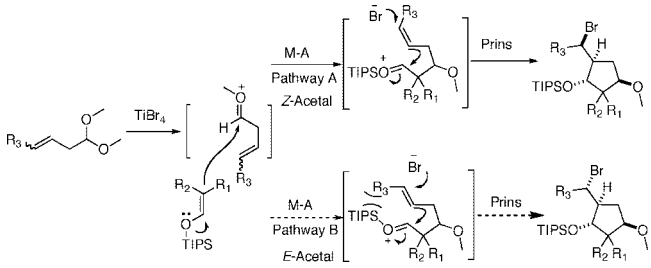
Scheme 2. Mechanism of Five-Membered Ring System Formation



Scheme 3. MAP Reactions Using Cyclic Acetal

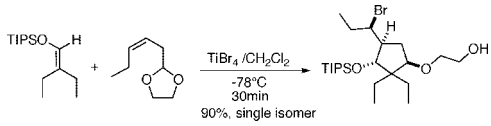
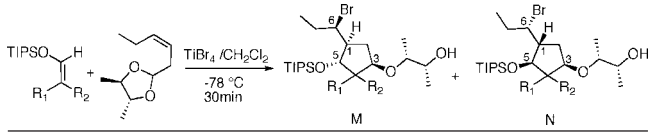


Table 2. MAP Reactions in Asymmetric Version for Five-Membered Rings[a,b]



entry	R_1	R_2	yield (%)	dr
1	CH_3	CH_3	93	90:10
2	CH_3CH_2	CH_3CH_2	94	89:11
3	$-(CH_2)_3-$	$-(CH_2)_3-$	90	92:8
4	CH_3Br (Z/E = 85:15)		80 (90:10)	99:1

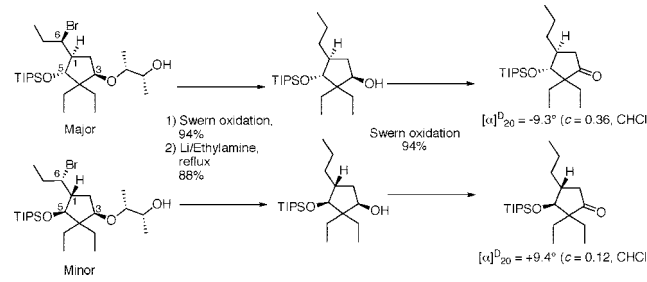
[a] Chiral pure cyclic acetals (*Z*) were prepared using (2*R*,3*R*)-(−)-butanediol. [b] M: Major; N: Minor.

cyclic acetal in the same reaction conditions obtained the desired product as a single isomer in excellent yield.

These encouraging results set the stage for carrying out asymmetric version of this methodology. Inspired by our research work on an intermolecular polyene cyclization initiated by a chiral acetal,[11] we decided to introduce an asymmetric element by using chiral pure cyclic acetal. In all cases, the cyclization reaction using cyclic monosubstituted acetal provided the desired products in high yields and excellent stereoselectivities (Table 2).

The absolute stereochemistry of the minor isomer was determined by X-ray crystallography analysis (see Supporting Information), while the relative configuration of the major isomer is assumed to be the same as the racemic product as shown in Table 1. We manage to confirm the absolute configuration of the major isomer as (1*S*, 3*R*,5*R*) after a series of synthetic manipulations (Scheme 4).[12]

Scheme 4. Determination of Absolute Stereochemistry of Major Products



In conclusion, we have developed a highly stereoselective domino reaction, accomplished with easily accessible starting materials. The novelty of this domino reaction is the ability to construct five-membered ring systems with up to five new chiral centers in a one-pot manner in high yields with excellent diastereo- and enantioselectivities. This new methodology provides a simple and practical method for the synthesis of polyfunctional cyclopentane building blocks.

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Supporting Information Available: Additional experimental procedures, chromatograms, cif file of crystallographic data, and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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