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An Anionic C_3–C_5 Ring Expansion of β-Ketocyclopropanes to Cyclopentenols

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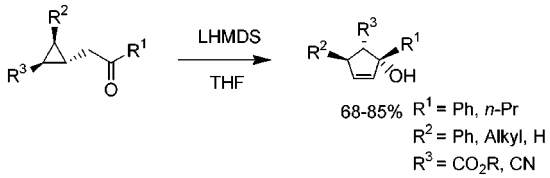
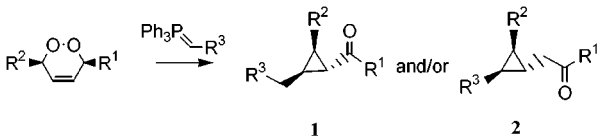
ABSTRACT



When treated with base, β-ketocyclopropylcarboxylates ring-open to initially afford either *cis* or *trans* α,β-unsaturated ketones. The *cis* isomer undergoes an intramolecular aldol reaction to afford allylic cyclopentenols in high yield and excellent diastereoselectivity. Choice of base is key to a successful outcome.

The cyclopropane to cyclopentene C_3-C_5 ring expansion has been used as a synthetic tool in the construction of a number of natural products.[1] The reaction usually utilizes vinyl cyclopropanes as precursors and requires high temperatures but may be promoted by transition metals,[1c] base[2] and light.[3] We have recently uncovered several new routes to diastereopure and optically active cyclopropanes of types **1** and **2** generated from 1,2-dioxines and stabilized phosphorus ylides, Scheme 1.[4−6] We report here optimized conditions for the

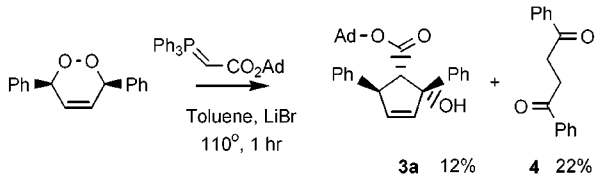
Scheme 1



base-catalyzed C_3-C_5 ring expansion of cyclopropanes of type **2** to cyclopentenols in high yield and excellent diastereoselectivity.

Cylopropanes of type **2** may be formed in preference to **1** by the use of bulky ylides, LiBr, and dilute conditions.[2] However, during our investigation we found that elevated temperatures yielded complex mixtures of product, with low yields of cyclopentenol **3a** and the known 1,4-diketone **4** being the only isolable products, Scheme 2.[5] Cyclopentenol

Scheme 2



3a was, however, of interest as analysis by 2D NMR and X-ray crystallography (Figure 1) revealed that **3a** contained three contiguous stereocenters.

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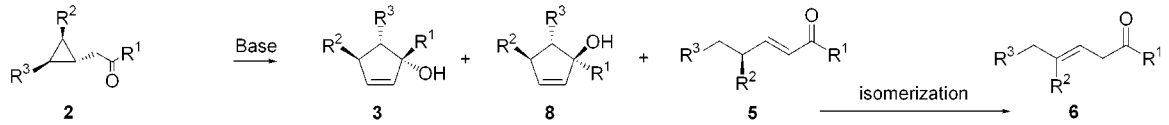
(1) For reviews on the C_3-C_5 ring expansion, see: (a) Salaun, J. Rearrangements involving the cyclopropyl group. In *The Chemistry of the cyclopropyl group*; Patai, S.Z. R., Ed.; Wiley: Toronto, 1987. (b) *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I. Eds.; Pergamon, Oxford, 1991; Vol. 5, 8.1, p 899. (c) Hudlicky, T.; Kutchan, T. M.; Naqvi, S. M. *Org. React.* **1985**, *33*, 247 and references therein.

(2) Danheiser, R. L.; Martinez-Davila, C.; Morin, J. M. *J. Org. Chem.* **1980**, *45*, 1340−1341. Danheiser, R. L.; Bronson, J. L.; Okano, K. *J. Am. Chem. Soc.* **1985**, *107*, 4579−4581.

(3) Jorgensen, M. J.; Heathcock, C. H. *J. Am. Chem. Soc.* **1965**, *87*, 5264.

Table 1. Reaction of β-Ketocyclopropanes with Base[a]



2 3 8 5 6

							yield, %[b]			
entry[a]	**2**	R^1	R^2	R^3	base	temp	**3**	**8**	**5**	**6**
1	**a**	Ph	Ph	$CO_2$1-Ad	NaH	rt	**a** 18 (23)		**a**	35 (77)
2[c]	**a**	Ph	Ph	$CO_2$1-Ad	LiOH	110	**a** 38		**a**	8
3	**a**	Ph	Ph	$CO_2$1-Ad	LHMDS	rt	**a** 83			
4[d]	**b**	Ph	Me	CO_2Bu^t	NaH	rt	**b** (23)		**b** (77)	
5[d]	**b**	Ph	Me	CO_2Bu^t	LHMDS	−78	**b** (6)		**b** (94)	
6	**b**	Ph	Me	CO-Bu^t	LHMDS	rt	**b** 78			
7	**c**	Ph	Ph	CO_2Bu^t	LHMDS	rt	**c** 80			
8	**d**	Ph	H	$CO_2$1-Ad	LHMDS	rt	**d** 85			
9	**e**	*n*-Pr	*n*-Pr	CO_2Bu^t	NaH	rt	**e**[d] (10)		**c** 59 (90)	
10	**e**	*n*-Pr	*n*-Pr	CO_2Bu^t	LHMDS	rt	**e** 84			
11	**f**	Ph	Ph	CN	LHMDS	rt	**f** 45			
12[e]	**b**	Ph	Me	CO_2Bu^t	KHMDS	rt	**b** 80 (86)	8(14)		

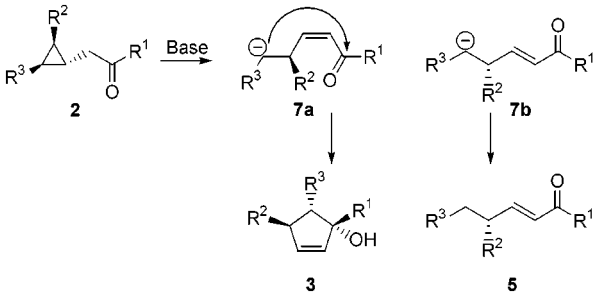
[a] Typically reactions were performed on a 50 mg scale by addition of a solution of cyclopropane in THF or ether to 1.5−2.0 equiv of base in THF and worked up after 15 min. [b] Yield refers to isolated product. Parentheses indicate product ratio determined by ^{1}H NMR. [c] Reaction time was 3 h. [d] Isolation not attempted. [e] Reaction performed in a 4:1 ether/toluene mixture (toluene was present from the solution of base).

Structural analysis of **3a** indicated that its likely genesis was from a base-catalyzed enolization of **2a** followed by either a ring-opening and then intramolecular aldol addition of the product ester enolate to the ketone or a concerted [1,3] sigmatropic shift.[3]

The first base tested with cyclopropanes of type **2** was sodium hydride (Table 1, entries 1, 4, and 9). Although a small amount of the ring-closed cyclopentenol **3** was found in each case, the major product was the *trans* ring-opened products **5** and **6**. When a mixture of **3a** and **5a** was allowed to react with an additional portion of sodium hydride, no increase in **3a** was observed. Instead, **5a** rearranged to the more thermodynamically stable styryl isomer **6**.

The isolation of the *trans* ring-opened products **5b** and **5c** indicated competitive *cis* and *trans* ring-opening. Of the two product enolates **7a** and **7b**, only *cis* **7a** could undergo an intramolecular aldol yielding the observed cyclopentenol, Scheme 3. Higher temperatures failed to cleanly afford cyclopentenol (entry 2) while changing counterions from sodium to lithium using lithium hydride gave a multicomponent reaction mixture.

Scheme 3



2 7a 7b 3 5

As two cyclopropyl keto-enolates are possible, it was thought that each enolate could lead to the formation of a specific ring-opened geometric isomer. Lithium hexamethyldisilazide (LHMDS) gives exclusively *Z*-keto-enolates at −72 °C.[4] The reaction of **2b** with LHMDS at −78 °C gave nearly exclusively *trans* ring-opening (entry 5); however, the addition of **2b** to 1.5 equiv of LHMDS in THF at 25 °C afforded cyclopentenol **3b** in 78% yield (entry 6). The order of addition was found to be important, as the dropwise addition of base to cyclopropane reduced the yield to only 17%.

This optimized methodology was then applied to a series of cyclopropanes with various substitution patterns (entries

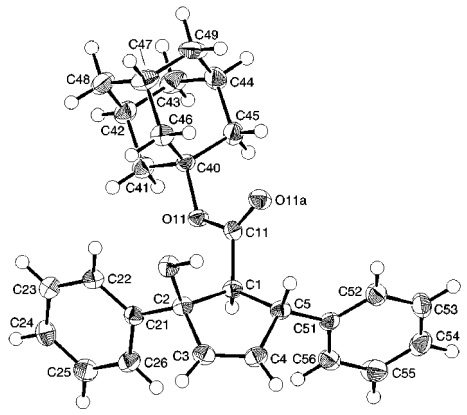


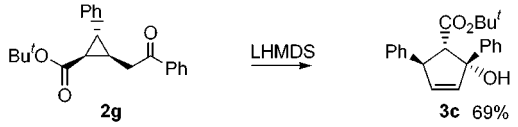
Figure 1. X-ray structure of cyclopentenol **3a**.

3, 6−8, and 10−12). All cyclopropanes with bulky ester groups afforded high yields of cyclopentenols, with most of the products being highly crystalline. Entry 11 demonstrates that the reaction is applicable with electron acceptors other than ester groups. Stereochemistry was assigned on the basis of the 2D ROESY NMR spectra, and all products were found to have *trans* stereochemistry between groups attached to C-1 and C-5 of the cyclopentenol ring. Further evidence for the conserved *syn* relationship between the group attached to C1 and the OH on C2 of the cyclopentene ring comes from the X-ray structure of cyclopentenol **3d**.[8]

The reaction of **2b** with potassium hexamethyldisilazide (KHMDS) in toluene/ether yielded two cyclopentenol products (entry 12) arising from competing transition states in the intramolecular aldol addition. The structure of the minor isomer **8** was deduced by 2D ^{1}H NMR. Attempts at increasing the yield of cyclopentenol **8** by performing the reaction in toluene were unsuccessful as the yield of cyclopentenol decreased in favor of the *trans* ring-opened product **5b**.

To ascertain whether the reaction was proceeding via a concerted [1,3] sigmatropic shift or stepwise aldol type addition, the effect of changing stereochemistry at C2 was examined, Scheme 4. The reaction of **2g** with base under

Scheme 4

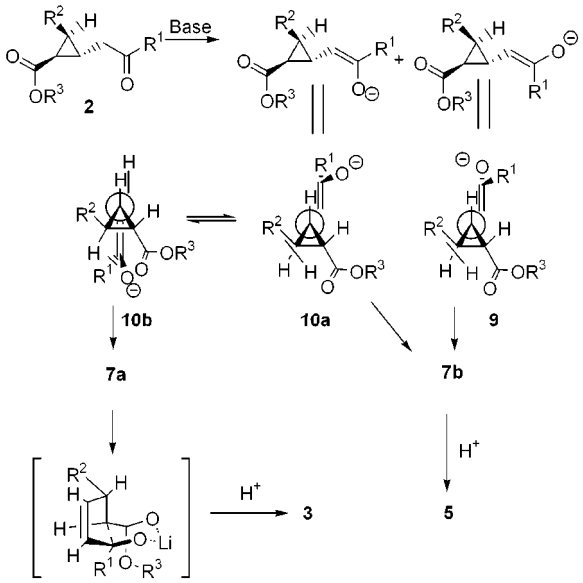


2g **3c** 69%

standard conditions afforded **3c** in good yield, establishing that the reaction is not concerted but has freely rotating intermediates.[9]

A mechanistic rationale for the ring opening and closing of the cyclopropyl esters is shown in Scheme 5. Deprotonation gives either the *E*- or *Z*-keto-enolate.[6] The *E* isomer **9** cannot adopt the conformation required for *cis* ring opening due to steric interactions between the R^1 group (for large R groups such as Ph, *n*-Pr) and the cyclopropane ring. The *Z*-keto-enolate is able to adopt both conformations **10a** and **10b**. The calculated barrier for rotation from **10a** to **10b** (4.3 kcal/mol) is similar to the energy required for ring opening from both **10a** (4.6 kcal/mol) and **10b** (4.7 kcal/mol) (for R^1 = R^2 = Me, R^3 = Bu^t).[10] The observed high selectivity

Scheme 5



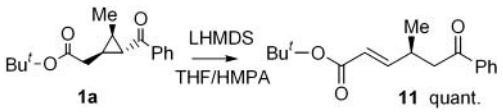
is therefore likely due to a faster ring opening for **10b**. Ring opening gives an ester enolate where two of the three original stereocenters have been destroyed.

The ester enolate undergoes an intramolecular aldol type addition, with product stereochemistry indicating an intermediate *Z*-ester enolate assuming a chairlike transition state.[11]

C_3−C_5 ring expansions not involving a concerted mechanism have previously been reported.[12] In particular, Larsen et al. have reported thio-cyclopentenes produced from 3,6-dihydro-2*H*-thiopyrans that involve the intermediacy of cyclopropyl thiolates.[13] In contrast to our proposed mechanism, both a concerted and intramolecular aldol-like mechanism were suggested. Hudlicky et al. have also reported similar allylic cyclopentenols generated under different conditions.[14]

Cyclopropyl series **1** was also treated with LHMDS (Scheme 6); however, none of the cyclopropanes tested gave

Scheme 6



1a **11** quant.

any *cis* olefinic ring-opened products. The procedure for generating *Z*-ester enolates in 23% HMPA/THF described by Ireland[15] also failed to give *cis* ring-opened products at

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(9) If the reaction occurred in a concerted manner, then an inversion of relative stereochemistry at C1 and C5 would be expected in the product cyclopentenol.

(10) Calculations were performed at the AM1 level of theory using the Spartan suite of programs. Wavefunction, Inc., 18401 Von Karman Ave., Suite 370, Irvine, CA 92715.

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room and subambient temperatures, preferring to form *trans* **11**. The greater reactivity of the ester enolate and the better electron affinity of the acceptor ketone are cited as reasons.

In conclusion, we report here a new method for the construction of allylic cyclopentenols with high diastereoselectivity. It is of interest as it involves a C_3-C_5 ring expansion which occurs at ambient temperatures not involving a concerted mechanism. The methodology should allow for the synthesis of cyclopentanoid natural products.

Acknowledgment. B.W.G. thanks the Faculty of Science for a scholarship. We also thank the Australian Research Council for funding.

Supporting Information Available: Full experimental details for compounds **2f**, **3a**−**f**, **5b**−**c**, **6**, **8**, and **11** as well as CIF data for **3a**. This material is available free of charge via the Internet at http://www.pubs.acs.org.

OL010246O

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