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Cyclopropane Structural Units from Homoaldol Adducts

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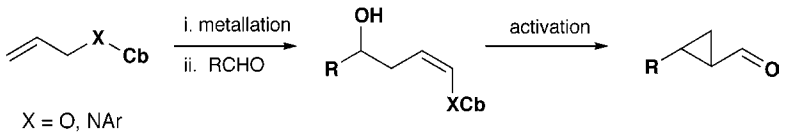
ABSTRACT

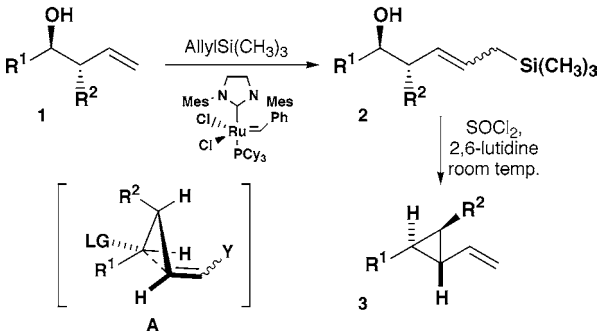


An efficient two-step homologation of aldehydes to cyclopropylaldehydes has been developed. Activation of homoaldol adducts derived from *O*-enecarbamates and *N*-enecarbamates provided high yields of cyclopropylaldehydes with good to excellent levels of *trans*/*cis* selectivity. Trapping of the intermediate oxonium ion and iminium ion intermediates has also been demonstrated, leading to direct isolation of cyclopropyl carbinol and cyclopropylamine products.

Progress in the area of diastereo- and enantioselective methods for cyclopropane construction[1] has been largely focused on the modification of allylic alcohols through intramolecular rhodium carbenoid intermediates[2] or intermolecular Simmons−Smith chemistry.[3] In contrast, our most recent report included a remarkably efficient route to nonracemic, diastereomerically pure 1,2,3-trisubstituted cyclopropanes in just two simple steps from readily available homoallylic alcohols, Scheme 1.[4] The stereochemistry of the cyclopropane product **3**, both absolute and relative, is controlled by the starting material **1** and the constraints imparted by transition state **A**. For our first generation approach we chose Y = CH_2SiR_3 to exploit the stabilization of the β-silicon effect. Herein we report an investigation of substrates that contain a heteroatom-substituted olefin, (Y = -OR, NR_2). The presence of an electron-rich olefin in the cyclization substrates should result in a faster ring closure and directly provide a cyclopropylaldehyde upon workup. More importantly, these substrates can be prepared in a single step from homoaldol addition reactions. The overall process represents an efficient two-step homologation of aldehydes to cyclopropylaldehydes.

Yamamoto has previously demonstrated high γ-selectivity of silyloxyallylbarium reagents with carbonyl compounds such as aldehydes and ketones.[5] A number of representative homoaldol adducts **5a**−**e** were prepared using a modified Yamamoto protocol, Scheme 2. At this point we envisioned that activation of the homoallylic alcohol would lead to

Scheme 1



(1) Donaldson, W. A. *Tetrahedron* **2001**, *57*, 8589.

(2) See: Doyle, M. P.; Austin, R. E.; Bailey, A. S.; Dwyer, M. P.; Dyatkin, A. B.; Kalinin, A. V.; Kwan, M. M. Y.; Liras, S.; Oalmann, C. J.; Pieters, R. J.; Protopopova, M. N.; Raab, C. E.; Roos, G. H. P.; Zhou, Q-.L.; Martin, S. F. *J. Am. Chem. Soc.* **1995**, *117*, 5763 and references therein.

(3) For a lead reference, see: Charette, A. B.; Lemay, J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1090.

(4) Taylor, R. E.; Engelhardt, F. C.; Schmitt, M. J.; Yuan, H. *J. Am. Chem. Soc.* **2001**, *123*, 2964.

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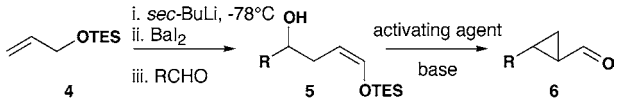
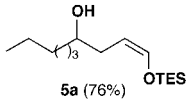
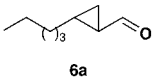
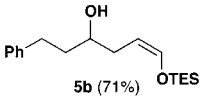
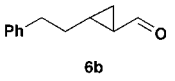
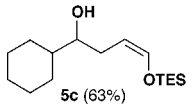
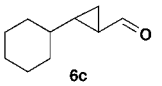
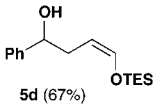
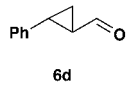
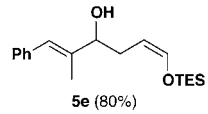
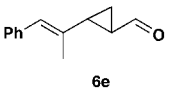
Scheme 2



cyclopropylaldehyde formation through an oxygen-stabilized cyclopropylcarbinyl cationic intermediate. Despite the electronic and steric differences between these substrates, high yields of cyclopropylaldehydes were obtained in each case, Table 1. Much to our surprise, however, the cyclopropane

Table 1. Cyclopropanes from Yamamoto Homoaldol Adducts

homoaldol adduct	cyclopropane	*(trans : cis)*
 **5a** (76%)	 **6a**	(68 : 32)
 **5b** (71%)	 **6b**	(74 : 26)
 **5c** (63%)	 **6c**	(84 : 16)
 **5d** (67%)	 **6d**	(55 : 45)
 **5e** (80%)	 **6e**	(89 : 11)

a; 89% (**5a**, **5b**); a; 84% (**5c**); b; 89% (**5d**); b; 86% (**5e**)

a) Tf_2O, 2,6-lutidine, -78° C; b) Ms_2O, iPr_2NEt, room temp.

products were obtained with varying *trans*/*cis* selectivity but always favoring the *trans*-isomer. The sterically encumbered cyclohexyl substrate **5c** is indeed more selective than the other aliphatic substrates **5a** and **5b**. The loss of selectivity observed in the phenyl substrate **5d** may be attributed to an increased rate of cyclization due to conjugation.

Previous studies in this area have shown that homoallylic participation proceeds with inversion of configuration.[6] Two transition states are possible: (1) **B-1**, which has a *trans* relationship between the C1 and C3 substituents, and (2) **B-2**, which has a *cis* relationship between C1 and C3 substituents, Figure 1.[7] It is important to note that we had not previously observed the formation of *cis*-1,2-disubstituted vinylcyclo-

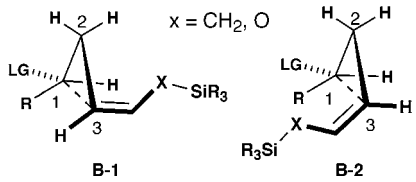
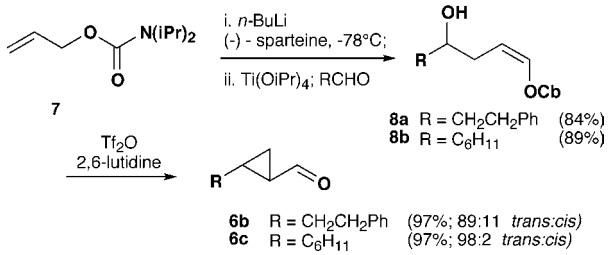


Figure 1. Transition state leading to cyclopropanes.

propanes in the allyltrimethylsilane system (X = CH_2). This suggests a significant energy difference ($\Delta\Delta G$) between **B-1** and **B-2** when X = CH_2.[8] In contrast, the isolation of *cis*-cyclopropyl aldehydes from the activation of homoallylic alcohols **5** suggests that when X is an oxygen atom **B-1** and **B-2** are significantly closer in energy. Although the steric volume of a methylene is greater than that of an oxygen atom, the *trans*/*cis* ratios in Table 1 are best explained by a combination of steric and electronic factors. It is clear that the increase in rate of cyclization has led to a decrease in diastereoselectivity.

We rationalized that the *trans*/*cis* selectivity could be improved by attenuating the reactivity of the enol ether functionality. We prepared *O*-enecarbamates using the method of Hoppe,[9] Scheme 3. Allyl carbamate **7** was lithiated

Scheme 3



with *n*-BuLi in the presence of (−)-sparteine and, after transmetalation with $Ti(OiPr)_4$, quenched with aldehydes to provide **8a** and **8b** in good yield. The *O*-enecarbamates **8** were subjected to triflic anhydride activating conditions, which yielded cyclopropylaldehydes **6b** and **6c** in excellent yield and high *trans*/*cis* selectivity. These results provide additional support for the importance of electronic factors for the control of *trans*/*cis* selectivity. Despite the use of (−)-sparteine in the lithiation step, the homoaldol adduct and thus the cyclopropylaldehyde was prepared without any significant degree of enantioselectivity.[10]

(5) Yanagisawa, A.; Yasue, K.; Yamamoto, H. *Synlett* **1993**, 686.

(6) (a) White, J. D.; Jensen, M. S. *J. Am. Chem. Soc.* **1993**, *115*, 2970. (b) Nagasawa, T.; Handa, Y.; Onoguchi, Y.; Ohba, S.; Suzuki, K. *Synlett* **1995**, 739. (c) Krief, A.; Provins, L. *Synlett* **1997**, 505. (d) Taylor, R. E.; Ameriks, M. K.; LaMarche, M. J. *Tetrahedron Lett.* **1997**, *38*, 2057. (e) Taylor, R. E.; Engelhardt, F. C.; Yuan, H. *Org. Lett.* **1999**, *1*, 1257. (f) Taylor, R. E.; Schmitt, M. J.; Yuan, H. *Org. Lett.* **2000**, *2*, 601. (g) See ref 4 of this manuscript.

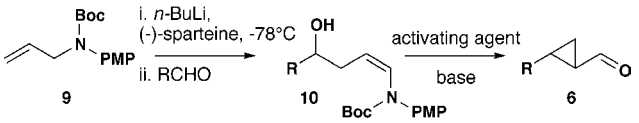
(7) Suzuki was the first to present transition states related to those depicted in Figure 1 (ref 6b).

(8) In systems more closely related to the allylsilane chemistry, White and Suzuki also observed, independently, exclusive *trans* cyclopropane formation. See: (a) White, J. D.; Jensen, M. S. *J. Am. Chem. Soc.* **1993**, *115*, 2970. (b) Nagasawa, T.; Handa, Y.; Onoguchi, Y.; Ohba, S.; Suzuki, K. *Synlett* **1995**, 739.

(9) For a lead reference, see: Prasad, K. R. K.; Hoppe, D. *Synlett* **2000**, 1067.

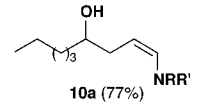
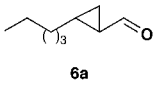
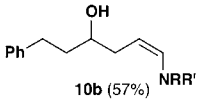
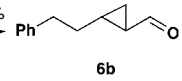
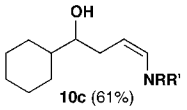
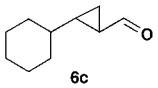
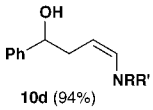
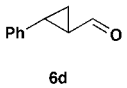
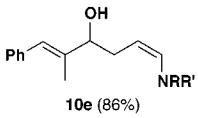
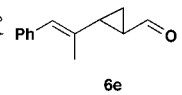
We also explored the use of *N*-enecarbamates prepared by a method developed by Beak.[11] *N*-Boc-*N*-(*p*-methoxyphenyl)-allylamine was metalated with *n*-BuLi/(−)-sparteine and then reacted directly with a variety of aldehydes to provide homoaldol products **10a**−**e**, Scheme 4. The enantioselectivity

Scheme 4



of the process was shown to be negligible, but inclusion of (−)-sparteine, as above, was shown to increase the efficiency of the deprotonation step. Each of these substrates was activated under our previously optimized conditions to provide cyclopropylaldydes **6a**−**e**.

Table 2. Cyclopropanes from Beak Homoaldol Adducts

homoaldol adduct (R = Boc, R' = PMP)		cyclopropane	*(trans : cis)*
	a; 88%		(98 : 2)
10a (77%)		**6a**	
	a; 90%		(93 : 7)
10b (57%)		**6b**	
	a; 86%		(98 : 2)
10c (61%)		**6c**	
	b; 72%		(98 : 2)
10d (94%)		**6d**	
	b; 90%		(95 : 5)
10e (86%)		**6e**	

a) Tf_2O, 2,6-lutidine, -78° C; b) Ms_2O, iPr_2NEt, room temp.

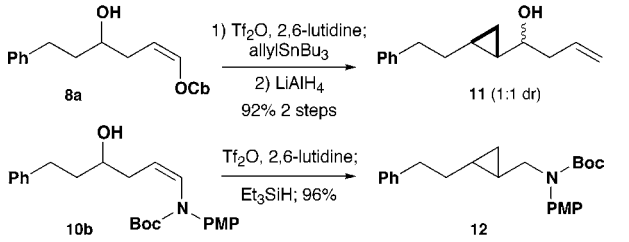
As is clear from these substrates the increased steric bulk and attenuated electronics associated with the cation-stabilizing carbamate leads to greater *trans/cis* selectivity in the ring-closure step and a highly efficient method for the preparation of cyclopropylaldehydes.

(10) The enantioselectivity of the ring closures were determined by Mosher ester analysis of cyclopropylcarbinols obtained by $NaBH_4$ reduction: Dale, J. S.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

(11) Weisenburger, G. A.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 12218. (b) Weisenburger, G. A.; Faibish, N. C.; Pippel, D. J.; Beak, P. *J. Am. Chem. Soc.* **1999**, *121*, 9522. (c) Whisler, M. C.; Vaillancourt, L.; Beak, P. *Org. Lett.* **2000**, *2*, 2655.

A key aspect of the ring-closure reaction presented here is the stabilization of the cyclopropylmethyl carbocation by heteroatom substitution. We have found that it is possible to trap the intermediate oxonium and acyliminium ions, with weak nucleophiles, to directly provide cyclopropyl carbinols and cyclopropylmethylamines, respectively. As shown in Scheme 5, *O*-enecarbamate **8a** underwent cyclization/

Scheme 5



allylation by activation under standard conditions, but in the presence allyltributylstannane. The allylated adduct **11** was isolated in 92% yield after reductive removal of the carbamate. In addition, cyclopropylamine **12** could be prepared efficiently from *N*-enecarbamate **10b** by in situ reduction of the intermediate acyliminium ion with triethylsilane. In each case, the cyclopropane product was isolated in higher yield and greater *trans* selectivity than when the reaction was performed without the in situ trapping reagent.

In summary, we have developed a method to homologate aldehydes to cyclopropylaldehydes in just two steps. The cyclizations are efficient and in many cases provide a high degree of *trans/cis* selectivity. The intermediate oxonium and iminium ions can be trapped with nucleophiles to directly provide cyclopropyl alcohols and amines. Hoppe[6] and Beak[7c] have already shown that γ-substituted allyl titanium and aluminum species can provide 3-substituted homoaldol adducts with high enantioselectivity. Activation of these substrates would then provide access to enantiopure 1,2,3-trisubstituted cyclopropanes. Efforts along these lines as well as additional enantioselective approaches are currently being explored in our laboratory and will be reported in due course.

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Supporting Information Available: Full experimental and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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