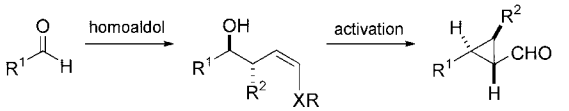
Cyclopropanes

Enantioselective Synthesis of Cyclopropanes by Aldehyde Homologation**

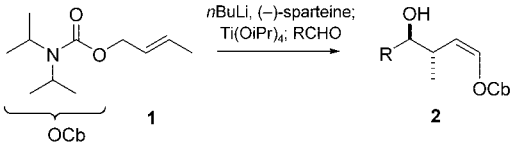
*Christina A. Risatti and Richard E. Taylor**

The prevalence of cyclopropane-containing compounds with biological activity, whether isolated from natural sources or rationally designed pharmaceutical agents, has inspired chemists to find novel and diverse approaches to their synthesis.[1] We recently reported an efficient two-step homoaldol/activation sequence that resulted in the isolation of racemic 1,2-disubstituted cyclopropyl aldehydes.[2] Herein we demonstrate the successful preparation of enantiomerically enriched and diastereomerically pure 1,2,3-trisubstituted cyclopropyl aldehydes by asymmetric metalation chemistry. In essence, this two-step procedure provides a three-carbon homologation of an aldehyde to give a nonracemic, stereochemically rich cyclopropyl aldehyde, [Eq. (1)].



(1)

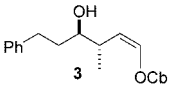
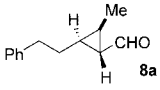
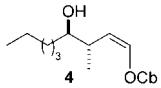
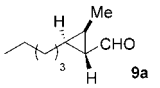
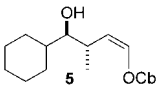
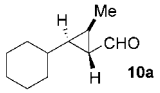
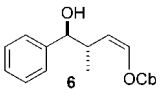
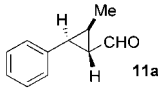
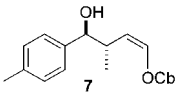
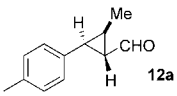
Hoppe et al. have elegantly demonstrated that homoaldol adducts are readily available from (*E*)-butenyl *N*,*N*-diisopropylcarbamates **1** through deprotonation with *n*BuLi/(−)-sparteine complex and transmetalation with $Ti(OiPr)_4$.[3] Condensation with an aldehyde was shown to provide *O*-enecarbamates **2** with high diastereoselectivity and good enantioselectivity [Eq. (2)].



(2)

Carbamate **1** is readily prepared through condensation of *N*,*N*-diisopropyl carbamyl chloride with crotyl alcohol in refluxing pyridine. A series of aldehydes were applied to the described homoaldol conditions using the crotyl substrate as a representative example. Aliphatic aldehydes, including sterically hindered substrates, resulted in high yields of (*Z*)-homoaldol adducts **3**–**5** with high *anti* selectivity as expected (Table 1). In addition aromatic aldehydes, including benzaldehyde and tolualdehyde, performed well in the coupling reaction to provide **6** and **7**, respectively (Table 1). In each case, the diastereoselectivity was >95:5 by crude ^{1}H NMR analysis.

Table 1: Trisubstituted cyclopropanes from *O*-enecarbamates.[a]

Homoaldol adduct	Yield [%]	Cyclopropane	Yield [%], e.r.
 **3**	92	 **8a**	91, 93:7
 **4**	85	 **9a**	82, 92:8
 **5**	84	 **10a**	96, 93:7
 **6**	87	 **11a**	92, 83:17
 **7**	89	 **12a**	73, 90:10[b]

[a] Reaction conditions: Tf_2O, 2,6-lutidine, toluene, −78 °C to −50 °C. [b] Two minor diastereomers were also observed in this case (5:1:1 ratio).

Exposure of homoaldol adducts **3**–**7** to triflic anhydride and 2,6-lutidine provided good to excellent yields of 1,2,3-trisubstituted cyclopropyl aldehydes **8a**–**12a** (Table 1). In contrast to our previous study[2] these cyclization substrates were more sensitive to the reaction conditions. When our standard activation conditions were employed, in CH_2Cl_2, multiple products were observed. However, when the reaction solvent was conducted in toluene, the inherent rate and alternative reaction pathways could be reduced such that the reaction was driven toward the formation of the desired cyclopropyl aldehyde products **8a**–**12a**. The enantiomeric purity of the cyclopropane derivatives was determined by reduction of the aldehyde with lithium aluminum hydride and analysis of the Mosher esters.[4] The observed enantiomer ratios corresponded well with expected enantioselectivity of the starting homoaldol adducts,[3] suggesting the cyclization step proceeds in a stereospecific manner.

The aliphatic systems provided high yields and diastereoselectivity for the cyclopropyl aldehyde products **8a**–**10a**. In each case, the ring closure takes place with inversion of configuration at the alcohol center.[5] In contrast, reduced diastereoselectivity was observed upon activation of homoaldol adduct **7**. The inductively donating methyl group appears to promote equilibration of the oxonium ion intermediate **13** through the homoallylic cation **14** [Eq. (3)]. Under these conditions no products resulting from elimination were observed.

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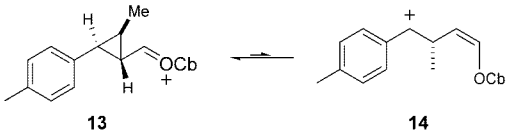
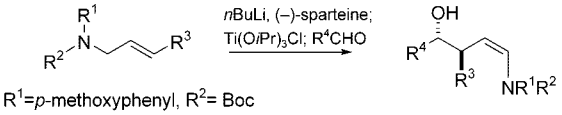


(3)

Ideally one would like access to both enantiomers of the cyclopropyl aldehyde products. In fact, Beak et al. have demonstrated that *N*-(*tert*-butoxycarbonyl)-*N*-(*p*-methoxyphenyl)cinnamyl amine **15** and *N*-(*tert*-butoxycarbonyl)-*N*-(*p*-methoxyphenyl)-3-cyclohexylallylamine **16** undergo asymmetric deprotonation by an *n*BuLi/(−)-sparteine complex [Eq. (4)].[6] However, in this case, transmetalation with $Ti(OiPr)_3Cl$ followed by quenching with an aldehyde furnished the enantiomeric, complementary homoaldol adducts.



(4)

R^1=*p*-methoxyphenyl, R^2= Boc

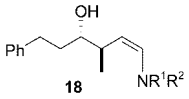
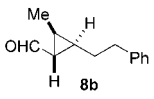
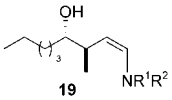
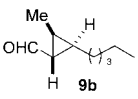
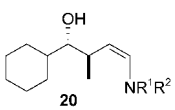
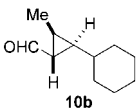
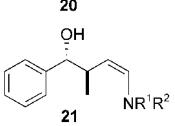
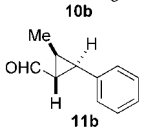
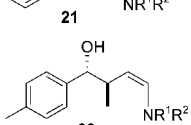
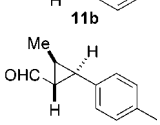
15 R^3=Ph

16 R^3=cyclohexyl

17 R^3=Me

The aldehydes used previously to generate the *O*-enecarbamates were subjected to the Beak homoaldol protocol. To complement the earlier work, the substrates were preformed with crotylamine **17**, and the yields and selectivities corresponded nicely with those observed by Beak for the cyclohexyl and cinnamyl systems. The (*Z*)-*N*-enecarbamates **18**–**22** were isolated with predominantly *anti* stereochemistry and the diastereoselectivity was >95:5 by crude ^{1}H NMR analysis (Table 2). Homoaldol adducts **18**–**22** were activated with triflic anhydride and 2,6-lutidine to provide aldehydes **8b**–**12b** in good to excellent yield. Again, the enantioselectivity of the cyclopropane products corresponded well with the expected enantiomer ratios from the homoaldol coupling, suggesting the cyclization step proceeds with complete stereospecificity.

Table 2: Trisubstituted cyclopropanes from *N*-enecarbamates.[a]

Homoaldol adduct	Yield [%]	Cyclopropane	Yield [%], e.r.
 **18**	69	 **8b**	91, 90:10
 **19**	66	 **9b**	70, 94:6
 **20**	73	 **10b**	86, 91:9
 **21**	67	 **11b**	96, 94:6
 **22**	68	 **12b**	70, 92:8

[a] Reaction conditions: Tf_2O, 2,6-lutidine, toluene, −78 °C to −50 °C. R^1 = *para*-methoxyphenyl, R^2 = *tert*-butoxycarbonyl.

In this system, cyclization of the aliphatic substrates **18**–**20** proceeded cleanly in CH_2Cl_2. However, care was taken with the activated aryl systems, and toluene was used as the reaction solvent. It is notable that, in contrast to *O*-enecarbamate substrate **7**, activation of *N*-enecarbamate **22** provided **12b** as a single diastereomer. The iminium ion intermediate, present in solution prior to quenching, is apparently more stable than the corresponding oxonium ion intermediate, and therefore, an equilibrium with its homoallylic cation is not relevant (Figure 1). Although the method has been applied to 1,2,3-trisubstituted cyclopropyl aldehydes containing a methyl substituent, alternative allylamine derivatives are expected to provide diversely substituted cyclopropanes and broaden the scope of this two-step three-carbon homologation procedure.

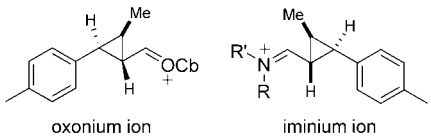


Figure 1.

In conclusion we have demonstrated the stereospecific cyclization of enantiomerically enriched homoaldol adducts. This chemistry is a remarkably efficient method for the homologation of readily available aldehydes to give nonracemic, stereochemically rich 1,2,3-trisubstituted cyclopropyl aldehydes.[7] Application of this method to the preparation of biologically relevant cyclopropanes is currently underway in our laboratories and will be reported in due course.

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Keywords: cations · cyclization · cyclopropanes · small ring systems · synthetic methods

[1] H. Lebel, J.-F. Marcoux, C. Molinaro, A. B. Charette, *Chem. Rev.* **2003**, *103*, 977.
[2] R. E. Taylor, C. A. Risatti, F. C. Engelhardt, M. J. Schmitt, *Org. Lett.* **2003**, *5*, 1377.
[3] For a lead reference, see: K. R. K. Prasad, D. Hoppe, *Synlett* **2000**, 1067.
[4] J. S. Dale, H. S. Mosher, *J. Am. Chem. Soc.* **1973**, *95*, 512.
[5] R. E. Taylor, F. C. Engelhardt, M. J. Schmitt, H. Yuan, *J. Am. Chem. Soc.* **2001**, *123*, 2964.
[6] a) M. C. Whisler, L. Vaillancourt, P. Beak, *Org. Lett.* **2000**, *2*, 2655; b) M. C. Whisler, P. Beak, *J. Org. Chem.* **2003**, *68*, 1207.
[7] During review of this manuscript we learnt of a similar investigation. See the preceding Communication in this issue: R. Kalkofen, S. Brandau, B. Wibbeling, D. Hoppe, *Angew. Chem.* **2004**, *116*, 6836; *Angew. Chem. Int. Ed.* **2004**, *43*, 6667.

