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Highly Enantio- and Diastereoselective Tandem Generation of Cyclopropyl Alcohols with up to Four Contiguous Stereocenters

Hun Young Kim, Alice E. Lurain, Patricia García-García, Patrick J. Carroll, and Patrick J. Walsh*

Department of Chemistry, P. Roy and Diana T. Vagelos Laboratories, University of Pennsylvania, 231 South 34th Street, Philadelphia, Pennsylvania 19104-6323

Received June 14, 2005; E-mail: pwalsh@sas.upenn.edu

Numerous natural and unnatural products containing cyclopropyl groups exhibit important biological activity.[1−3] As a result, substantial effort has been devoted to the asymmetric synthesis of these strained subunits.[4,5] While asymmetric cyclopropanation of olefins employing transition metal catalyzed decomposition of diazo compounds can provide cyclopropanes with high selectivity,[6] it has proven to be very difficult to control enantioselectivity in Simmons−Smith[7]-type cyclopropanations of olefins[8,9] and allylic alcohols.[4,10−12]

Given these limitations, we considered alternative strategies for the stereoselective synthesis of cyclopropanes from achiral reagents. We envisioned an enantioselective generation of an allylic zinc alkoxide intermediate followed by a diastereoselective cyclopropanation. Preforming these reactions in tandem enables formation of three C−C bonds and up to four stereocenters in a one-pot procedure with excellent stereoselectivity.

Scheme 1, pathway A, shows our first method wherein the key allylic zinc alkoxide intermediate is generated by asymmetric alkyl addition to α,β-unsaturated aldehydes in the presence of 4 mol % of Nugent's (−)-MIB (**1**).[13] Quenching this intermediate allows determination of the enantioselectivity in the first C−C bond-forming step (Table 1). In the one-pot addition/cyclopropanation procedure, the allylic alkoxide intermediate is treated with either $EtZnCH_2I$ or the more reactive $CF_3CH_2OZnCH_2I$[14] to furnish the cyclopropyl alcohols in 64−91% yield. The enantioselectivities in the addition of dimethylzinc, diethylzinc, and functionalized organozinc reagents were ≥89% with a range of enals. Furthermore, only a single diastereomer was detected in the crude ^1H NMR spectra in each case.

We next explored the addition of vinyl groups to saturated aldehydes in route to cyclopropyl alcohols (Scheme 1B). On the basis of Oppolzer's hydroboration/transmetalation[15] method, we generated vinylzinc reagents. In the presence of (−)-MIB, clean vinylation of the aldehyde proceeds to furnish the allylic alkoxide intermediates.

Unfortunately, directed cyclopropanation of this intermediate was complicated by low yields and diastereomeric ratios. We hypothesized that the triethylborane byproduct formed in the transmetalation step was reacting with the cyclopropanating reagent. To circumvent this problem, upon completion of the asymmetric addition, the volatile materials, including the excess triethylborane, were removed under reduced pressure. Diethylzinc and CH_2I_2 (5 equiv each) were added at 0 °C. After 24 h, the reactions were worked up to provide the cyclopropyl alcohols with 71−84% yield and enantiomeric excesses ≥93% (Table 2). Cyclopropanations of allylic alkoxides derived from vinyl additions to other aldehydes resulted in lower conversions and require further optimization.

The results in Tables 1 and 2 indicate that our tandem addition/cyclopropanation sequence gives similar diastereoselectivities to the cyclopropanation of isolated chiral allylic alcohols.[16,17] The tandem reaction is, however, more efficient.

Scheme 1. Two Tandem Asymmetric Addition/Diastereoselective Cyclopropanation Reactions

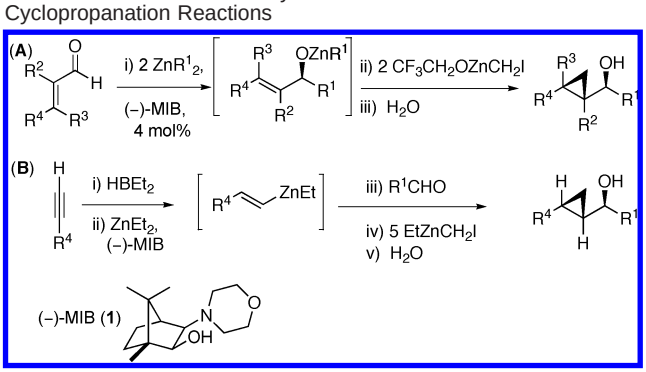
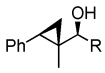
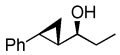
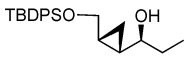
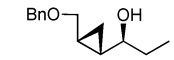


Table 1. Tandem Asymmetric Addition/Diastereoselective Cyclopropanation of Enals (Scheme 1A)

entry	ZnR_2	cyclopropyl alcohol	ee (%)	dr [a]	yield (%)
1	Et[b]		99	>20:1	90
2	-$(CH_2)_4$iPr[c]		97	>20:1	66
3	-$(CH_2)_5$OTBDPS[c]		98	>20:1	75
4	Me[c]		99	>20:1	76
5	Et		95	>20:1	78
6	-$(CH_2)_4$iPr[c]		96	>20:1	64
7	Me[c]		95	>20:1	85
8	Et		96	>20:1	90
9	Et		89	>20:1	87
10	Et		98	>20:1	80
11	Et		91	>20:1	91

[a] Determined by crude ^1H NMR analysis. [b] Stereochemistry assigned by X-ray analysis. See the Supporting Information. [c] With 5 equiv of $ZnEt_2$, 5 equiv of CF_3CH_2OH, and 5 equiv of CH_2I_2.

Wipf and co-workers reported a vinyl addition/cyclopropanation sequence with imines to afford racemic cyclopropylamines. Analogous reactions with aldehydes, however, were reported to be unsuccessful.[18]

Biologically active 1,2,3-substituted cyclopropanes are also found widely in natural products.[1,2] A modular approach to these chiral building blocks that allows flexibility for further elaboration of the cyclopropane ring is desirable. With this in mind, we targeted the stereoselective synthesis of iodocyclopropyl alcohols (eq 1). Despite their utility in cross-coupling[19] and metalation reactions,[20,21] few highly enantio- and diastereoselective syntheses of these valuable intermediates have been reported.[20] We explored the use of iodoform in place of diiodomethane in the cyclopropanation step of our tandem addition/cyclopropanation chemistry. This reagent

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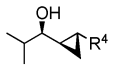
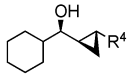
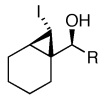
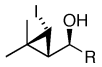
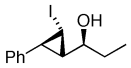
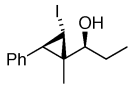
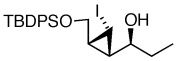
Table 2. Tandem Asymmetric Vinylation of Aldehydes: Diastereoselective Cyclopropanation (Scheme 1B)

entry	cyclopropyl alcohol	R^4	ee(%)	dr[a]	yield (%)
1		Ph	99	>20:1	75
2		nBu	92	>20:1	71
3		tBu	87	>20:1	78
4		Ph	99	>20:1	78
5		nBu	93	>20:1	84
6		tBu	96	>20:1	74
7		$(CH_2)_4Cl$[b]	94	>20:1	80
8		CH_2CH_2OTr	93	>20:1	73

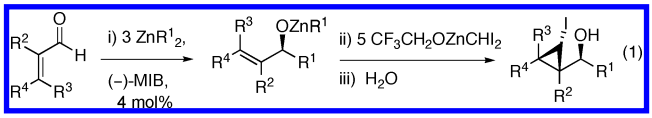
[a] Determined by crude ^{1}H NMR analysis [b] Stereochemistry assigned by X-ray analysis. See the Supporting Information.

Table 3. Tandem Asymmetric Addition/Iodocyclopropanation

entry	ZnR^1_2	cyclopropyl alcohol	ee (%)	dr [a]	yield (%)
1	Et[b]		99	>20:1	68
2	-$(CH_2)_5$OTBDPS		98	>20:1	70
3	Me		99	>20:1	78
4	Et[b]		95	>20:1	62
5	-$(CH_2)_4$iPr		96	>20:1	60
6	Et		89	>20:1	70
7	Et		96	>20:1	56
8	Et		98	>20:1	74

[a] Determined by ^{1}H NMR of the crude product. [b] Structure determined by X-ray analysis.

has been used in the synthesis of iodo-substituted cyclopropanes[22] and the generation of dizinc carbenoids.[23,24] Initially, we employed the carbenoid $EtZnCHI_2$, but the reactions were slow and stalled at about 50% conversion. It is known that electron-withdrawing groups on zinc carbenoids of the type $XZnCH_2I$ (X = O_2CCF_3,[25] OAr[26]) increase the reactivity. Thus, the intermediate allylic alkoxide formed upon alkyl addition to an enal was treated with a new reagent, $CF_3CH_2OZnCHI_2$. After standard workup, iodocyclopropyl alcohols were isolated in 56−80% yields with enantiomeric excesses ≥89%. The high diastereomeric ratio observed in the generation of the final three stereocenters attests to the ability of zinc to control stereoselectivity in this reaction. We anticipate that the iodides can be selectively substituted in C−C bond-forming reactions.



In summary, three expedient methods for the synthesis of cyclopropyl and iodocyclopropyl alcohols with up to four stereogenic centers have been presented. Beginning with achiral starting materials, initial enantioselective C−C bond formation is followed by diastereoselective cyclopropanation. The advantages of these methods are that (1) they circumvent the need to prepare and isolate either racemic or enantioenriched allylic alcohols, (2) the initial asymmetric C−C bond-forming step can be optimized by judicious choice of catalyst,[27] and (3) the enantio- and diastereoselectivities are very high for almost all substrate classes. Using our one-pot method, highly functionalized cyclopropanes are now easily accessible. We anticipate that the cyclopropyl alcohols outlined here will find widespread utility in enantioselective synthesis.[28]

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Supporting Information Available: Procedures and full characterization, stereochemical assignments, and X-ray determinations of new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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