ORGANIC LETTERS

2011
Vol. 13, No. 9
2346–2349

Diasteroselective Preparation of Cyclopropanols Using Methylene Bis(iodozinc)

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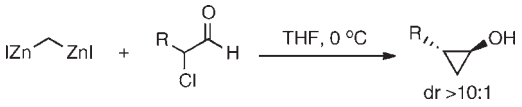
Received March 5, 2011

ABSTRACT



A diastereoselective synthesis of *trans*-2-substituted cyclopropanols is outlined. Bimetallic $CH_2(ZnI)_2$ was found to react with α-chloroaldehydes to give cyclopropanols in yields of 64−89% and dr's ≥ 10:1. The high *trans*-selectivity resulted from equilibration of the cyclopropoxide intermediates.

Cyclopropanes form an integral part of over 100 therapeutic agents[1−3] and exhibit a broad spectrum of biological properties.[1,4−6] They are frequently found in natural products, including pheromones, steroids, terpenes, fatty acid metabolites, and amino acids.[1,6] Their medicinal properties and synthetic utility have inspired numerous preparations.[1,4,7−12] One class of cyclopropanes that has received less attention is cyclopropanols.

Previous approaches to cyclopropanols include the Kulinkovich reaction using titanium tetraisopropoxide, Simmons−Smith cyclopropanation of silyl-enol ethers,[13] chromium(II) mediated cyclopropanation of α,β-unsaturated ketones,[14] and reaction of samarium with diiodomethane and ketones or esters.[15] Recently, there has been significant interest in the stereoselective synthesis of cyclopropyl boronates as precursors to cyclopropanols. Pietruszka and co-workers have studied diastereoselective cyclopropanation of vinyl boronates with stoichiometric chiral auxiliaries on boron[10] while the groups of Ito and Gevorgyan have both developed metal-catalyzed asymmetric methods.[11] Ito's method involves Cu(I) catalyzed reaction of bis(pinacolato)diboron with allylic carbonates and phosphates to form cyclopropyl boronates while Gevorgyan employs rhodium catalyzed hydroborations of cyclopropenes. We developed highly diastereoselective

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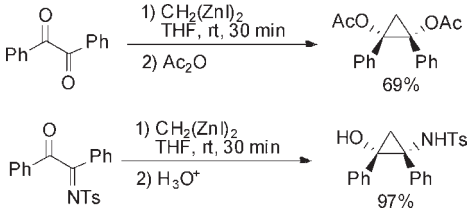
10.1021/ol200597h
Published on Web 04/04/2011

Scheme 1. Matsubara's Methylene Bis(iodozinc) Addition to α-Diketones and α-Ketoimines[19]



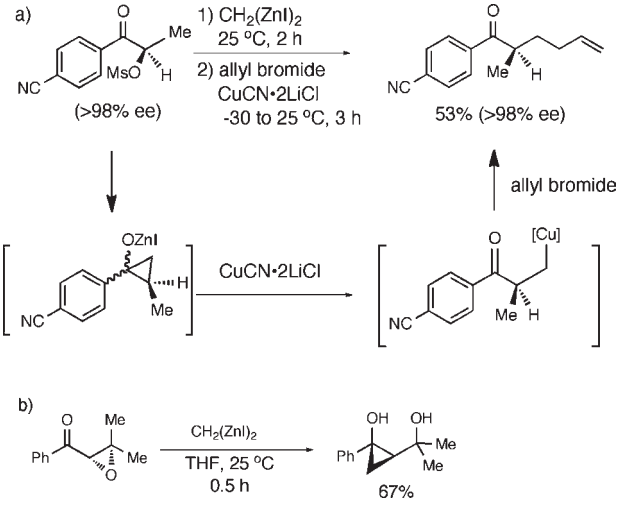
cyclopropanation of 2-B(pin)-substituted allylic alcohols and their oxidation to cyclopropanols.[16]

In this Letter, we describe a highly diastereoselective conversion of α-chloroaldehydes into *trans*-cyclopropanols using the readily prepared dizinc reagent $CH_2(ZnI)_2$. We demonstrate that the high *trans*-diastereoselectivity arises from equilibration of the *cis*- and *trans*-cyclopropoxide intermediates via a proposed transient homoenolate.

Methylene bis(iodozinc) derivatives have attracted attention,[17−22] because the two Zn−C bonds can be used to form two C−C bonds. Methylene bis(iodozinc) is conveniently prepared by mixing diiodomethane, zinc dust, and a catalytic amount of lead chloride.[23] Matsubara and co-workers have demonstrated that α-diketones and α-ketoimines react with $CH_2(ZnI)_2$ to form *cis*-cyclopropan-1,2-diols and *cis*-2-aminocyclopropanols, respectively (Scheme 1).[19]

The same group reported that treatment of enantioenriched α-sulfonyloxy ketones with $CH_2(ZnI)_2$ gave a zinc cyclopropoxide intermediate that furnished cyclopropanol with low dr on workup (dr = 76:24 to 67:33).[20] An important feature of cyclopropoxy zinc and copper complexes is their reversible ring opening to generate homoenolate intermediates. Thus, despite the low diastereoselectivity of cyclopropoxide formation in Scheme 2a, the addition of Cu(CN)•2LiCl allowed trapping of the homoenolate with allyl bromide. The ee of the sulfonyloxy ketone is conserved in the homoenolate formation and the subsequent reaction with electrophiles.[20b] In contrast, when $CH_2(ZnI)_2$ reacted with α,β-epoxyketones (Scheme 2b), formation of the cyclopropanol occurred with high diastereoselectivity. The authors proposed that initial attack on the ketone occurred with high diastereoselectivity by a chelation-controlled pathway.[21]

Scheme 2. Reaction of $CH_2(ZnI)_2$ with α-Sulfonyloxy Ketones[20] and α,β-Epoxy Ketones



Based on the reversible formation of homoenolates from cyclopropyl alkoxide derivatives,[24] we envisioned that *trans*-disubstituted cyclopropanols could be accessed with high diastereoselectivity by addition of $CH_2(ZnI)_2$ to α-haloaldehydes.

Racemic α-bromo- and α-chloroaldehydes were prepared according to the methods of Pagnoni[25] and Jørgensen and co-workers.[26] The optimization of the cyclopropanol formation was performed as outlined in Table 1. Initial studies were conducted with 2-bromooctanal. Reaction with 1 equiv of $CH_2(ZnI)_2$ at 0 °C

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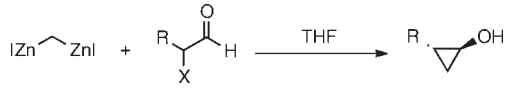
resulted in the formation of the desired cyclopropanol in 58% yield with a dr of 6:1 (entry 1). The initial assignment of the major diastereomer as the *trans* isomer was based on coupling constants in the ^{1}H NMR spectrum. Interestingly, lowering the temperature to −20 °C and doubling the amount of $CH_2(ZnI)_2$ resulted in no diastereoselectivity (entry 2). Initiating the reaction at 0 °C and allowing it to warm slowly to rt with 2.0 or 2.5 equiv of $CH_2(ZnI)_2$ resulted in an increase in the diastereoselectivity to >18:1 and yields reaching 71% (entries 3 and 4). Employing $CH_2(ZnBr)_2$ under similar conditions led to olefination product (^{1}H NMR, entry 5). Olefination products were not observed by ^{1}H NMR in the crude reaction mixtures throughout these studies when $CH_2(ZnI)_2$ was used. Maintaining the temperature at 0 °C with $CH_2(ZnI)_2$ resulted in an increase in the yield to 81% with high diastereoselectivity (16:1, entry 6).

We then chose to examine 2-chlorooctanal. The addition of 2 equiv $CH_2(ZnI)_2$ to the chloroaldehyde at 0 °C resulted in formation of the desired product with high diastereoselectivity (18:1) and 88% yield. Lowering the temperature again resulted in a significant drop in diastereoselectivity (entries 8 and 9). The reaction was also optimized with α-halodihydrocinnamaldehydes. Using the α-bromo derivative, the reaction with $CH_2(ZnI)_2$ gave the desired product with 74% yield and 13:1 dr (entry 10). The α-chloro analogue gave comparable results with $CH_2(ZnI)_2$. Based on the results in Table 1, we elected to pursue the chemistry with the more readily available α-chloroaldehydes.

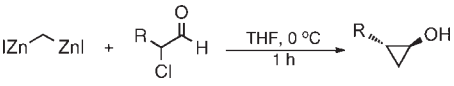
Table 1. Optimization of Reaction of $CH_2(ZnI)_2$ with α-Haloaldehydes

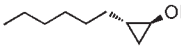
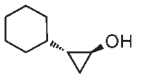
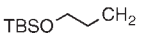
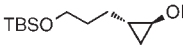
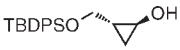
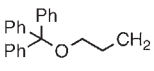
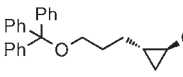
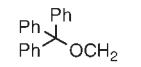
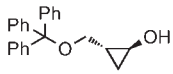
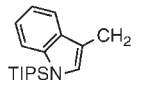
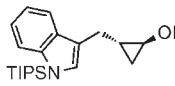


	R	X	dizinc:aldehyde	temp (°C)	time	yield (dr)
1	*n*-hexyl	Br	1:1	0	1 h	58% (6:1)
2		Br	2:1	−20	40 min	32% (1:1)
3		Br	2:1	0 to rt	8 h	64% (>20:1)
4		Br	2.5:1	0 to rt	8 h	71% (18:1)
5		Br	2.5:1	0 to rt	8 h	0%[a]
6		Br	2:1	0	1 h	81% (16:1)
7		Cl	2:1	0	1 h	88% (18:1)
8		Cl	2:1	−20	1.5 h	48% (2:1)
9		Cl	2:1	−40	1.5 h	24% (1:1)
10	benzyl	Br	2:1	0	1 h	74% (13:1)
11		Br	2:1	0 to rt	8 h	0%[a]
12		Cl	2:1	0	1 h	73% (12:1)

[a] Reactions employing $CH_2(ZnBr)_2$. ^{1}H NMR indicated mostly methylenation product.

Table 2. Diastereoselective Synthesis of *trans*-Cyclopropanols Using $CH_2(ZnI)_2$



	R =	product	yield (dr)[a]
1)	*n*-hexyl		88% (18:1)
2)	*n*-butyl		87% (11:1)
3)	allyl		65% (13:1)
4)	benzyl		73% (12:1)
5)	cyclohexyl		64% (16:1)
6)			83% (10:1)
7)			71% (12:1)
8)			89% (11:1)
9)			86% (13:1)
10)			61% (>19:1)
11)			66% (11:1)

[a] dr determined by ^{1}H NMR of the crude reaction mixture.

With suitable conditions in hand, we examined a variety of α-chloroaldehydes (Table 2). In addition to 2-chlorooctanal and 2-chlorodihydrocinnamaldehyde, other simple alkyl substituted chloroaldehydes were amenable to this method (entries 1−5). The dr's of the cyclopropanol products were ≥11:1, and yields ranged from 64 to 88%. The compound in entry 2 is previously known[27] and our NMR data matched the literature values, supporting the assignment of the *trans* stereochemistry. In addition, the cyclopropanols were independently synthesized as a mixture of diastereomers by Takai's method[28] to facilitate the NMR assignments and determination of dr (see Supporting Information (SI) for more details). 2-Chloroaldehydes with *β*- or *γ*-hydroxy

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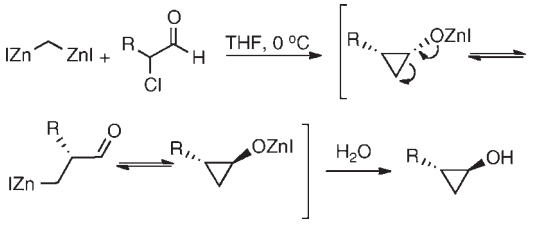
groups protected as silyl or trityl ethers gave cyclopropanols in good yields (61−89%) and with high diastereoselectivities (dr ≥ 10:1, entries 6−10). To further support the stereochemical assignment of the cyclopropanols, the structure of the product in entry 10 was confirmed by X-ray analysis (see SI). As shown in entry 11, the indole-containing substrate furnished the cyclopropanol with 11:1 dr in 66% yield. Reaction with α-bromoketones was largely unsuccessful as previously reported.[20b] Enantioenriched 2-chlorodihydrocinnamaldehyde[29] (95% ee) underwent reaction to give 2-benzylcyclopropanol of 95% ee.

Scheme 3. Proposed Mechanism for Equilibration of *cis*- and *trans*-Cyclopropoxides



We envisioned two possible mechanisms to explain the observed predominance of the *trans* diastereomer. The first involves diastereoselective carbonyl addition by the dizinc reagent. Addition must occur with chelation control to favor the *trans* product.[30] This seemes unlikely, because chelation of α-halo carbonyl groups is improbable, especially in THF.[31] A second mechanism involves addition of the dizinc reagent to α-haloaldehydes to generate mixtures of diastereomers (Scheme 3). Subsequent S_N2 displacement of the halide gives a mixture of the *cis*- and *trans*-cyclopropoxides. Ring opening generates a transient homoenolate[20,32] and allows equilibration of the diastereomers. The equilibrium favors the *trans*-cyclopropoxide on steric grounds.

To test the latter mechanism, a 3:1 mixture of *cis*- and *trans*-2-hexylcyclopropanol was treated with 1.0 equiv of $CH_2(ZnI)_2$ at 0 °C to form the corresponding zinc alkoxide. Upon quenching the reaction mixture, *trans* cyclopropanol was observed by ^{1}H NMR (16:1 *trans*/*cis* and 69% isolated yield). In a separate experiment, a 1:2 mixture of *cis*- and *trans*-2-hexylcyclopropanol was added to 2-chlorodihydrocinnamaldehyde and 2.0 equiv of dizinc reagent under conditions similar to those in Table 2. The ^{1}H NMR spectrum of the crude reaction mixture showed that the dr of the 2-hexylcyclopropanol had increased to 12:1. The dr of 2-benzylcyclopropanol was 8:1. We hypothesize that the low dr's in Table 1 (entries 2, 8, and 9) are due to the slow equilibration of the isomeric cyclopropoxides at low temperature and the high diastereoselectivity arises from equilibration of the cyclopropoxides, which favor the *trans*-isomer to minimize steric interactions.

In summary, a simple and highly diastereoselective route to *trans*-cyclopropanols was developed using $CH_2(ZnI)_2$ and α-chloro- and α-bromoaldehydes. Experimental observations indicate that the high diastereoselectivity arises from equilibration of the diastereomeric cyclopropoxides to the more stable *trans* isomer via a transient homoenolate intermediate.

Acknowledgment. We thank the NSF (CHE- 0848467) and NIH (National Institute of General Medical Sciences GM58101) for support of this work. Funds for instrumentation were provided by the NIH for a Waters LCTOF-Xe Premier ESI mass spectrometer (1S10RR023444) and NSF for an X-ray diffractometer (CHE-0840438). We thank Gretchen Stanton (University of Pennsylvania) for the preparation of some α-haloaldehyde substrates.

Supporting Information Available. Procedures and full characterization are available. This material is available free of charge via the Internet at http://pubs.acs.org.

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