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Enantioselective Synthesis of Spiropentanes from Hydroxymethylallenes

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Hydroxymethylallenes are efficiently converted to the corresponding spiropentanes in high yields and enantiomeric ratios upon treatment with $Zn(CH_2)_2$ and dioxaborolane ligand 1. The reaction also proceeds with complete diastereocontrol. The application of this methodology to the synthesis of spiropentaneacetic acid is also presented.

Spiropentanes, the simplest class of spirocyclic compounds,¹ have been the subject of numerous investigations to delineate their stability, optical properties² and overall reactivity toward ring opening processes due to their inherent ring strain. Recently, interest in the synthesis of such compounds has increased due to the recognition that one of the simplest members of this family displays interesting biological activity. Spiropentaneacetic acid (SPA) is a medium chain acyl-CoA dehydrogenase (MCAD) inhibitor that does not affect amino acid metabolism.³ Both enantiomers could effectively inactivate MCAD. Conversely, (*R*)-SPA-CoA is an irreversible inhibitor of short chain acyl-CoA dehydrogenase (SCAD) while (*S*)-SPA-CoA is a competitive inhibitor.⁴ Our interest in generating spiropentane-based pharma-

cophores led us to develop an efficient diastereo- and enantioselective method for their generation that would allow the synthesis of substituted spiropentanemethanol derivatives.



Precedents in the literature include formation of achiral spiropentanes,⁵ nonstereoselective reactions⁶ and reactions that exhibit modest diastereoselectivity.⁷ In one case, a highly diastereoselective reaction leading to a racemic spiropentane

⁽¹⁾ For review on oligospirocyclopropanes, see: de Meijere, A.; Kozhushkov, S. I. Chem. Rev. 2000, 100, 93.

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derivative was developed.⁸ Herein, we report that the chiral dioxaborolane ligand **1** is an effective chirality controller for the enantioselective zinc-mediated cyclopropanation of hydroxymethylallenes to form enantioenriched spiropentanes. We have previously shown ligand **1** to be an effective chiral additive for the enantioselective cyclopropanation of alcohols.⁹ We rationalized that if a similar degree of enantiofacial selectivity and chemoselectivity is observed in the delivery of the methylene unit at the allylic position of an allene, then the second methylene unit could be delivered through an alkyoxy-directed cyclopropanation that should lead to a major diastereomer (Scheme 1).¹⁰ This strategy should also



allow the elaboration of both stereogenic centers of a trisubstituted spiropentane framework in a single-pot reaction with a high degree of enantio- and diastereocontrol using only 1 equiv of the chiral additive. However, since most allenic alcohols are less hindered than the corresponding trisubstituted allylic alcohols, it is not clear whether the chiral dioxaborolane 1 will be an effective chiral controller for these reactions.

For our initial studies we have chosen achiral hydroxymethylallenes to facilitate analysis of the spiropentane products. The hydroxymethylallenes are readily available from the parent ketones according to a four-step protocol described in the literature.¹¹ The desired spiropentanes were obtained by the addition of dioxaborolane **1a** and hydroxymethylallene to the Zn(CH₂I)₂•DME complex. In most cases, conversion to the spiropentane proceeded in high yields and only one diastereomer was observed by ¹H NMR (Table 1).¹² Table 1. Formation of Spiropentanes^a

| _ | HO Zn(CH ₂ I) ₂ | Zn(CH ₂ I) ₂ •DME (3.0 equiv), | | но | |
|-------|---------------------------------------------------|------------------------------------------------------|-----------|---------------------------|--|
| R | | 1.2 equiv) | R// | Тн | |
| Entry | Allene | Product | Yield (%) | ee (% | |
| 1 | 2 (R = H) | 11 | 69 | 86 ^{b,c} | |
| 2 | 3 (R = Et) | 12 | 70 | 97 | |
| 3 | 4 (R = <i>n</i> -Pr) | 13 | 83 | 94 | |
| 4 | 5 (R = -(CH ₂) ₄ -) | 14 | 78 | 93 ^d | |
| 5 | 6 (R = -(CH ₂) ₅ -) | 15 | 65 | 96 ^d | |
| 6 | 7 (R = Cyclohexyl) | 16 | 57 | 91 ^{<i>e</i>, f} | |
| 7 | HO 8 | HO HO HO HO | 91 | 94 | |
| 8 | HO 9 | HO HO 18 | 55 | 95 | |
| 9 | HO Ph Ph Ph 10 | Ph Ph 19 | 7 | 92 ^g | |

^{*a*} Unless otherwise noted, the general procedure was used with ligand **1a** and the ee's were determined by GC on chiral stationary phases. ^{*b*}4 equiv of bis(iodomethyl)zinc•DME complex were required. ^{*c*}Determined by ¹³C NMR from amide derivative. ^{*d*}Ligand **1b** was used. ^{*e*}Substrate was submitted to reaction conditions twice. ^{*f*}Determined by ¹⁹F NMR of its Mosher ester derivative. ^{*g*}Determined by HPLC on chiral stationary phases.

Terminal hydroxymethylallene **2** provides the desired spiropentane with fair yield and good ee. Primary alkyl substrates whether acyclic (**3**, **4**) or cyclic (**5**, **6**) react to give good yields of the corresponding spiropentanes with excellent ee (\geq 92%). In the case of substrates bearing secondary alkyl substituents (such as **7**), a second treatment with bis-(iodomethyl)zinc reagent was required to obtain an acceptable yield and high ee of the desired spiropentane.¹³ In contrast, the sterically hindered but rigid adamantyl derivative **8** reacted in excellent yield and selectivity to give the desired spiropentane **17**. Highly hindered **9** provided exclusively the methylenecyclopropane **18** with excellent enantiocontrol. Diphenylhydroxymethylallene **10** proved to be a sluggish substrate giving only a poor yield of spiropentane **19**;

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⁽¹²⁾ The absolute stereochemistry has been established only in the case of entry 7 for which an X-ray crystal structure of the (*S*)-Mosher ester derivative has been obtained (see Supporting Information for details).

⁽¹³⁾ When reaction was stopped after the addition of only one treatment of zinc reagent. A lower yield and ee was observed (25% yield, 83% ee).

however, the enantiomeric excess was excellent. From these results, it is clear that the chiral controller is quite effective for the enantioselective cyclopropanation of hydroxymethylallenes. To determine the site of the first cyclopropanation, the reaction was carefully monitored by GC and the initial product formation was compared to authentic alkylidenecyclopropylmethanol derivatives of substrate **3** to **10**.¹⁴ GC analysis of the bis(cyclopropanation) reaction as a function of time unambiguously showed that the allylic position is the first site that is cyclopropanated. However, attempts to cyclopropanate the allylic position exclusively were unsuccessful. As noted by Lautens,¹⁵ this observation probably could be a consequence of the higher reactivity of the vinylcyclopropane intermediate compared to the allenic alkoxide.

A preliminary investigation into the bis(cyclopropanation) of chiral allene **20** was then carried out to see if double stereodifferentiation was possible (Table 2). When allene

| Tab | ble 2. Formation of Spiropentanes from Chiral Substrate ^{<i>a</i>} | | | | | |
|-----|------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|----------------|--|--|--|
| Me | Herrich H Hrrrie − 20 OH | $ \xrightarrow{Me} \xrightarrow{Me} H $ $H \xrightarrow{OF} 21 R = H $ $23 R = p \cdot NO_2C_6H_4 $ | | | | |
| | Entry | 21/22 | Conversion (%) | | | |
| | 1 ^{<i>b</i>} | 89/11 | 78% | | | |
| | 2 ^{<i>c</i>} | 56/44 | 58 | | | |
| | 3 ^d | 25/75 | >90% | | | |
| | 4 ^{<i>e</i>} | 96/4 | >90% | | | |

^{*a*} General procedure was used, presence and ytpe of ligand is specified. ^{*b*}(\pm)-**20** with no ligand. ^{*c*}(\pm)-**20** with ligand (*R*,*R*)-**1b**. ^{*d*}(\pm)-**20** with ligand (*R*,*R*)-**1a**. ^{*e*}(-)-**20** substrate with ligand (*S*,*S*)-**1a**.

(\pm)-20 was subjected to a ligand-free cyclopropanation reaction, two separable diastereomeric products 21 and 22 were formed in a 89:11 ratio (entry 1).^{15,16} When allene (\pm)-20 was subjected to the bis(cyclopropanation) conditions using dioxaborolane (*R*,*R*)-1a, the major product (21) was formed in only 12% de indicating that no kinetic resolution was possible in these reactions (entry 2).¹⁷ Conversely, when chiral, nonracemic (-)-20¹⁸ was treated with the zinc reagent

in the presence of both antipodes of the chiral additive, significantly different diastereoselectivities were observed (entry 3, 4). The matched pair involving (-)-20 and (S,S)-1a led to an excellent diastereoselectivity (entry 4) whereas the mismatched case led to an slight reversal of diastereoselectivity (entry 3). These observations are consistent with the transition structure that has been proposed for the cyclopropanation reaction involving ligand 1a.

The methodology was then applied to the synthesis of (+)-SPA. The synthetic route (Scheme 2) allows access to



 a (a) DME, Et₂Zn, CH₂I₂, **1a**, CH₂Cl₂, -10 °C to room temperature, 69%; (b) MsCl, Et₃N, CH₂Cl₂, 0 °C; 2. NaCN, DMSO, sealed tube, rt; 3. add HCl concentrated, 100 °C, 34%.

numerous optically enriched analogues of SPA.¹⁹ Spiropentane **11**, obtained in 86% ee after the cyclopropanation, was then mesylated (MsCl, Et₃N, CH₂Cl₂), and the mesylate was immediately treated with NaCN followed by nitrile hydrolysis to give enantioenriched (+)-SPA **24** in an overall yield of 23% from starting allene (**2**).

In summary, the present work provides the first enantioselective method to prepare chiral, nonracemic spiropentanes from achiral hydroxymethylallenes in high yield and excellent ee. Preliminary investigations of the diastereoselectivity of the ligand-assisted reaction with chiral hydroxymethylallenes demonstrates the possibility for matched and mismatched ligand/substrate pairs. Further studies on the diastereoselective cyclopropanation of chiral, nonracemic, hydroxymethylallenes along with the use of substituted spiropentane derivatives as pharmacophores will be reported in due course.

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Supporting Information Available: Experimental procedures, X-ray crystallographic orteps, characterization data, and spectra (¹H and ¹³C NMR) for the new compounds are available. This material is available free of charge via the Internet at http://pubs.acs.org.

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⁽¹⁶⁾ Unoptimized yield.

⁽¹⁷⁾ As observed previously, both enantiomers react at similar rates under the reaction conditions. For a related study using chiral allylic alcohols, see: Charette, A. B.; Lebel, H.; Gagnon, A. *Tetrahedron* **1999**, *55*, 8845.

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⁽¹⁹⁾ Application of the methodology to a homoallenic alcohol (3,4butadiene-1-ol) provided the desired spiropentane with only 47% ee.