

# Zirconium-catalyzed asymmetric carboalumination (ZACA reaction) of 1,4-dienes

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This paper is dedicated to Professor Jack Halpern of the University of Chicago on the occasion of his 80th birthday

**Abstract**—Various substituted 1,4-dienes containing a terminal vinyl ( $H_2C=CH$ ) group, readily undergo the ZACA reaction with  $Me_3Al$  and higher alkylalanes in a 1:1 molar ratio in the presence of a catalytic amount (1–5 mol %) of bis[(1-neomenthyl)indenyl]zirconium dichloride in good yields and in good enantioselectivity (70–92% ee), thereby providing an efficient and convenient route to various alkene-containing chiral natural products. Only the reaction of the parent 1,4-pentadiene is accompanied by extensive racemization.

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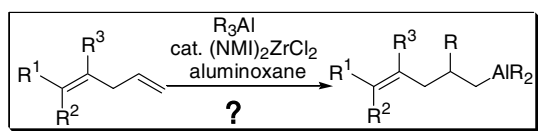
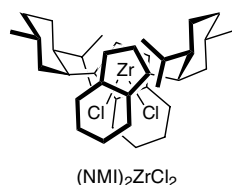
## 1. Introduction

The Zr-catalyzed asymmetric carboalumination of alkenes (ZACA hereafter) has provided a novel method for asymmetric carbon–carbon bond formation in an efficient and selective manner.<sup>1–4</sup> The ZACA reactions of 1-alkenes containing proximal  $\pi$ -bonds, such as those shown in [Scheme 1](#) are of potential interest and significance. At the same time, however, some of these reactions have proven to be capricious and problematic. Although the ZACA reaction of allylbenzene proceeds normally,<sup>1</sup> the corresponding reaction of styrenes was initially found to be very sluggish, albeit highly enantioselective (93–95%).<sup>1a</sup> However, this difficulty has since been nicely resolved through the use of aluminoxanes, such as MAO (methylaluminoxane),<sup>4</sup> which can be conveniently generated in situ by addition of water to  $Me_3Al$  or IBAO (*i*-butylaluminoxane) generated by treatment of  $tBu_3Al$  with water.<sup>2</sup> More recently, this reaction has provided an unprecedentedly efficient and selective, asymmetric route to various deoxypolypropionates.<sup>3d</sup> In marked contrast, the ZACA reaction of conjugated dienes has proven to be more problematic than that of styrene and has so far failed to yield synthetically useful results.<sup>5</sup> While these cases were still being investi-

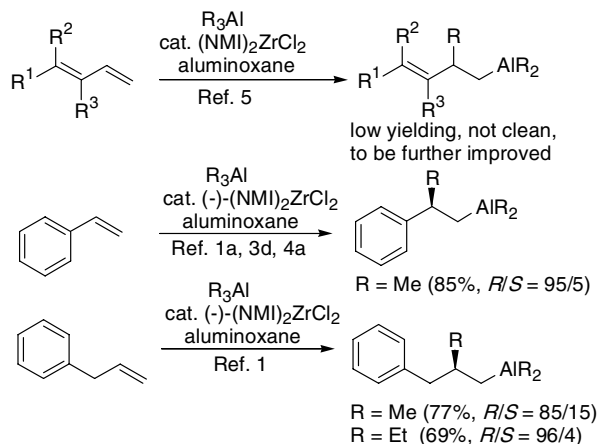
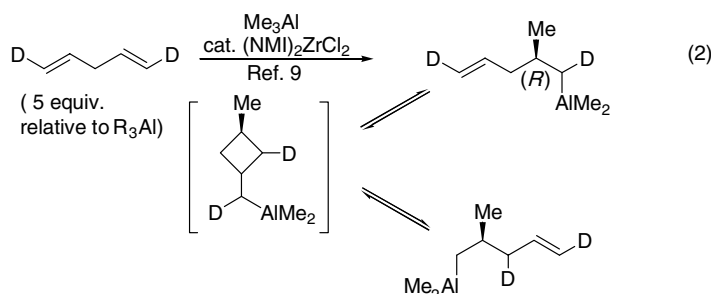
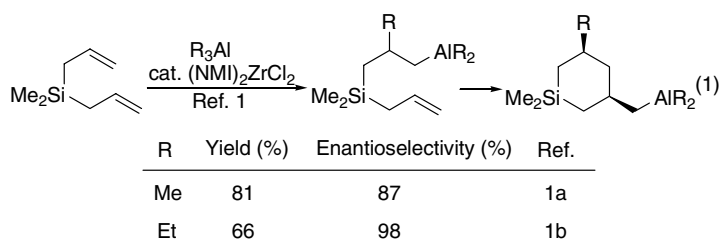
gated, our attention turned to 1,4-dienes and higher dienes. We briefly investigated the ZACA reaction of diallyldimethylsilane with  $Me_3Al$ <sup>1a</sup> and  $Et_3Al$ <sup>1b</sup> in the presence of a catalytic amount of (–)-(NMI)<sub>2</sub>ZrCl<sub>2</sub>,<sup>6</sup> and found that the ZACA reaction with  $Me_3Al$  and  $Et_3Al$  is accompanied by an intramolecular cyclic carboalumination to give (1*S*,5*S*)-5-methyl- and 5-ethyl-3-dimethylsilyl-1-cyclohexanemethanol, respectively, in good yields as well as in high enantio- and diastereoselectivity (Eq. 1 in [Scheme 2](#)).<sup>7,8</sup> In a recent study<sup>9</sup> on the ZACA reaction of 1,4-pentadiene (5 M equiv relative to  $Me_3Al$ ) with  $Me_3Al$  in the presence of 5 mol % of (–)-(NMI)<sub>2</sub>ZrCl<sub>2</sub>, the desired 2-methyl-4-penten-1-ol was obtained in 80% yield based on  $Me_3Al$  after oxidation with O<sub>2</sub>. To our surprise, however, the alcohol product was found to be completely racemic. This racemization has been shown to arise via cyclic carboalumination of the monocarboaluminated 2-methyl-4-pentenylalane intermediates (Eq. 2 in [Scheme 2](#)). Although very interesting, this reaction is synthetically unattractive. If, on the other hand, the unwanted cyclobutanation could be avoided, the ZACA reaction of 1,4-dienes should prove to be of considerable synthetic utility. The goals of this investigation have been twofold. One is to explore the scope of the ZACA reaction of 1,4-dienes that is accompanied by racemization, partial or full, from the basic chemical viewpoint. The other, that is complementary with the first, is to delineate the scope of the ZACA reaction of 1,4-dienes

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This work

R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> = H or C group. R = Alkyl.

Previous results

Scheme 1. ZACA reactions of proximally  $\pi$ -bond-substituted 1-alkenes.

Scheme 2. ZACA reactions of some dienes described in previous investigations.

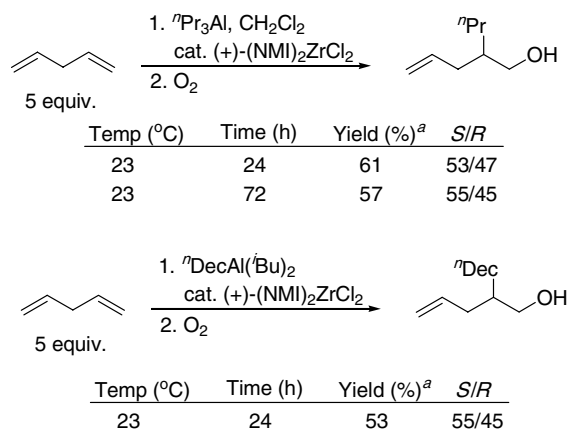
proceeding without significant loss of enantioselectivity attained in the initial asymmetric carboalumination step.

## 2. Results and discussion

### 2.1. ZACA reaction of the parent 1,4-pentadiene

The mechanism for racemization during the ZACA reaction of 1,4-pentadiene with Me<sub>3</sub>Al shown in Eq. 2 of Scheme 2 has been supported primarily by the results of D-labeling experiments. To further probe the nature and scope of the observed racemization, <sup>109</sup>Pr<sub>3</sub>Al and <sup>109</sup>DecAl(<sup>t</sup>Bu)<sub>2</sub> were used in place of Me<sub>3</sub>Al. The experimental results summarized in Scheme 3 indicate the following. Firstly, the observed enantioselectivities of 53–55% indicate that, despite the non-

negligible level of residual asymmetry, extensive racemization took place in these cases in accordance with the expectation based on the proposed mechanism. However, full racemization was not observed in these reactions. Attempts to force these reactions to reach the expected 0% enantioselectivity level by heating and/or prolonging the reaction time led only to extensive decomposition, which made accurate product analysis difficult. Nonetheless, it is sufficiently clear that the ZACA reaction of 1,4-pentadiene itself with various alkylalanes leads to full or extensive racemization most probably through thermodynamically unfavorable but kinetically accessible cyclobutane formation (Eq. 2 in Scheme 2). If this mechanism is indeed correct, it may also be predicted that the ZACA reaction of 1-monoenes with allylalanes should also undergo the same racemization. However, this prediction needs to be experimentally supported.



<sup>a</sup> Yields are based on alanes.

**Scheme 3.** ZACA reactions of 1,4-pentadiene with <sup>n</sup>Pr<sub>3</sub>Al and <sup>n</sup>DecAl(<sup>t</sup>Bu)<sub>2</sub>.

## 2.2. ZACA reactions of 4- and/or 5-substituted 1,4-dienes

Although interesting, the unwanted racemization observed with the parent 1,4-pentadiene casts a serious doubt about the synthetic usefulness of the ZACA reactions of 1,4-dienes in general. Fortunately, however, the ZACA reactions of all but two 4- and/or 5-substituted derivatives of 1,4-pentadiene that have so far been investigated have proceeded well. In a couple of exceptional cases of (4*Z*)-4,6-dimethyl-1,4-dienes, such as **1**, which

was chosen and prepared<sup>10</sup> as a potentially attractive intermediate for the synthesis of discodermolide,<sup>11</sup> the desired ZACA products were not obtained in any significant yields. The experimental results are summarized in Table 1.<sup>12</sup> These results indicate the following. First, it has been demonstrated that six out of the seven possible substitution patterns about the C=C double bond at C4 and C5 can be accommodated in the ZACA reaction. Only the pattern of full substitution, that is, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> ≠ H, was not examined. Even (4*Z*)-4-(*n*-butyl)-1,4-nonadiene reacted normally (entry 17). It may, therefore, be suggested that the difficulties encountered in the last two entries (entries 18 and 19) may be attributable more to the methyl-branched secondary alkyl groups incorporated as R<sup>3</sup>. In the case of entry 1, refluxing the reaction mixture in ClCH<sub>2</sub>CH<sub>2</sub>Cl at about 90 °C for 20 h led only to a decrease in yield by 25%, without any detectable change in enantioselectivity. We tentatively conclude that, at or below room temperature, the ZACA reaction of 1,4-dienes except the parent 1,4-diene proceeds without racemization and that the ZACA products are stable to racemization at room temperature.

## 3. Conclusions

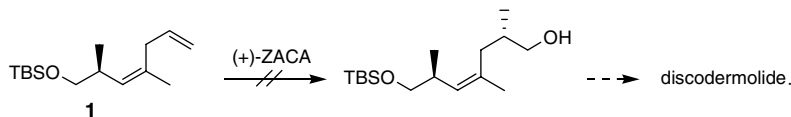
The ZACA reaction of the parent 1,4-pentadiene with various alkylalanes are accompanied by full or extensive racemization in accordance with the reversible cyclobut-

**Table 1.** ZACA reactions of 4- and/or 5-substituted 1,4-dienes

Entry	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R	(NMI) <sub>2</sub> ZrCl <sub>2</sub>	Yield (%) <sup>a</sup>	R/S
1	Me	H	H	Me	+	75	13/87
2	<sup>n</sup> Hex	H	H	Me	–	74	89/11
3	<sup>n</sup> Hex	H	H	Et	–	56	95/05
4	Ph	H	H	Me	–	75	90/10
5	Ph	H	H	Et	–	60	97/03
6	H	<sup>n</sup> Hex	H	Me	–	86	88/12
7	H	H	<sup>n</sup> Bu	Me	–	72	86/14
8	H	TBS	H	Me	–	72	85/15
9	H	TBS	H	Et	–	57	95/05
10	H	<sup>n</sup> Hex	Me	Me	–	79	89/11
11	H	Me <sub>2</sub> C=CHCH <sub>2</sub> CH <sub>2</sub> –	Me	Me	+	73	11/89
12	H	Me	Me <sub>2</sub> C=CHCH <sub>2</sub> CH <sub>2</sub> –	Me	+	68	10/90
13	H	<sup>n</sup> Hex	Cl	Me	–	73	90/10
14	H	<sup>n</sup> Hex	Cl	Et	–	69	96/04
15	Me	TBSO(CH <sub>2</sub> ) <sub>2</sub>	H	Me	–	75	92/08
16	Me <sub>3</sub> Si	<sup>n</sup> Bu	H	Me	–	69	87/13
17	<sup>n</sup> Bu	H	<sup>n</sup> Bu	Me	–	84	88/12
18	Me	H	( <i>S</i> )- <sup>n</sup> Bu	Me	–	<sup>c</sup>	
19		<b>1</b> <sup>b</sup>		Me	+	<sup>c</sup>	

<sup>a</sup> Isolated yield.

<sup>b</sup>



<sup>c</sup> No clean reaction was observed.

anation mechanism proposed recently.<sup>9</sup> This racemization process is practically shut out by any substitution of one of the two C=C bonds of 1,4-pentadiene at C4 and/or C5, and the ZACA reactions of variously substituted 1,4-dienes in the C4 and/or C5 positions can proceed normally in good yields, typically 70–85%, and in the normal range of enantioselectivity, that is, 70–92% ee. In these cases, the ZACA reaction promises to provide an efficient and enantioselective route to many naturally occurring and related proximally chiral alkenes. Despite the seemingly general applicability, there have been a couple of cases of failures as exemplified by the attempted ZACA reaction of **1**. Efforts are currently being made to further delineate the scope of the ZACA reactions of 1,4-dienes.

### Acknowledgements

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- (2*R*)-2-Methyl-4-<sup>n</sup>hexyl-4-penten-1-ol. Representative procedure: In a flame dried 25-mL round-bottomed flask under Ar was placed (–)-(NMI)<sub>2</sub>ZrCl<sub>2</sub> (35 mg, 0.05 mmol) and 3 mL of dichloromethane. Me<sub>3</sub>Al (0.2 mL, 2 mmol) was added through syringe followed by IBAO (1 M in CH<sub>2</sub>Cl<sub>2</sub>, 1.2 mL, 1.2 mmol), prepared by treating triisobutylalane with 1 equiv H<sub>2</sub>O in CH<sub>2</sub>Cl<sub>2</sub> at –40 °C for 15 min, then room temperature for 1 h. The mixture was placed in an ice water bath, and 2-<sup>n</sup>hexyl-1,4-pentadiene (152 mg, 1.0 mmol) was added. The reaction was monitored with GC. After stirring at 0 °C overnight, O<sub>2</sub> was vigorously bubbled through the reaction mixture for 30 min and the reaction mixture was kept under an O<sub>2</sub> atmosphere overnight. The reaction was quenched with 2 M NaOH and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The combined organic layers were washed with brine, dried over MgSO<sub>4</sub>, filtered, and concentrated. Flash column chromatography on silica gel (90:10 hexanes/ethyl acetate) gave 135 mg (74% yield) of the desired product: 77% ee; [ $\alpha$ ]<sub>D</sub><sup>23</sup> = +7.0 (c 2.1, CHCl<sub>3</sub>); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>)  $\delta$  0.8–0.9 (m, 6H), 1.2–1.45 (m, 8H), 1.7–2.15 (m, 6H), 3.3–3.5 (m, 2H), 4.65–4.75 (m, 2H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)  $\delta$  14.04, 16.66, 22.60, 27.64, 29.07, 31.74, 33.65, 35.64, 40.54, 68.29, 110.36, 148.42 ppm; MS (CI) *m/z* (%) 185 (100) [M<sup>+</sup>+1]; HRMS calcd for C<sub>12</sub>H<sub>24</sub>O [M<sup>+</sup>] 185.1905, found 185.1907; IR (neat) 3348, 3073, 2857, 1644, 1456, 1038 cm<sup>–1</sup>.