

0040-4039(95)01418-7

## Diastereoselective Reactions of $\delta$ -Siloxyallylzirconium Reagents with Aldehydes.

Andrew J. Clark\*, Ismail Kasujee, and Joanne L. Peacock

Department of Chemistry, University of Warwick, Coventry, CV4 7AL, UK

Abstract:  $\delta$ -Siloxyallylzirconium reagent (2) was produced by reaction of the TBDMS protected derivative (6) with zirconocene butene complex "Cp<sub>2</sub>Zr". Treatment of the  $\delta$ -siloxyallylzirconium reagent (2) with various aldehydes provided predominantly *anti*-homoallylic alcohols

The addition of allylic organometallic reagents to aldehydes and ketones has attracted a lot of attention in recent years<sup>1</sup>. The driving force for this research has been the need to develop highly diastereoselective and enantioselective methods for the controlled synthesis of acyclic systems. Particularly successful approaches have involved the addition of allylic boron<sup>1,2</sup>, allylic silicon<sup>1,3</sup> and allylic stannane<sup>1,4</sup> reagents to aldehydes, ketones, and imines. As part of an ongoing investigation using 1,4-butene-diol (1) as a cheap feedstock we have investigated the preparation and reactivity of  $\delta$ -siloxyallylzirconium reagents. Whereas the effect of heteroatoms at the  $\gamma$ -position in allylic metal reagents has been extensively studied<sup>1</sup>, much less work has been published of the effect of  $\delta$ -alkoxy substituents upon the selectivity of allylic metal additions to aldehydes<sup>1,4b,5</sup>. The effect of  $\gamma$ -heteroatom substituents on the diastereoselectivity of addition of allylic zirconium reagents to carbonyl compounds has been explored primarily by Yamamoto<sup>6</sup> and Taguchi<sup>7</sup>. Prompted by this work we wish to report the results of our recent investigations into the addition of the allylic zirconium derivative (2) to aldehydes (Scheme 1).



Taguchi has recently published a procedure for the facile generation of allylic zirconium compounds from allylic ethers by reaction with "ZrCp2"<sup>8</sup>. This procedure is thought to generate a zirconacyclopropane intermediate (3) that undergoes a  $\beta$ -elimination of the alkoxy group (OX) followed by metallotropic rearrangement to give the desired (E)-allyl zirconium species (5), (Scheme 2). NMR studies confirmed the (E)-geometry of (5). Taguchi has also demonstrated that the allylic zirconium compounds generated in this way add to aldehydes with high *anti* selectivity<sup>7</sup> with the best selectivity being reported when X = TBDMS.



Consequently, our initial investigations concentrated on the generation of the t-butyldimethylsilyloxy allylic zirconium (2) and its reaction with various aldehydes. The presence of the two bulky silicon substituents was expected to furnish the E-allylic zirconium preferentially by maximising any steric interaction between the  $\delta$ -alkoxy substituent and the bulky zirconium atom. Hence, the protected diol<sup>9</sup> (Z/E=95/5) (6) was reacted with 1.3 eq of "ZrCp2"<sup>8</sup> in THF followed by the addition of acetaldehyde at room temperature. Separation of the products by column chromatography followed by analysis by 400MHz <sup>1</sup>H NMR indicated that the desired *anti* (7) (R=Me)<sup>10</sup> and *syn* (8) (R=Me) homoallylic alcohols (d.e. 86%) had been formed along with a minor amount of an unexpected product (9) (R=Me)<sup>11, 12</sup>. A small amount of starting material was also recovered.



The structure of the major diastereomer (10) (R=Ph) was confirmed by chemical manipulation to the acetonide (11). Hence, desilylation of (10) with TBAF in THF followed by reaction of the diol with a catalytic amount of p-TSA in 2,2-dimethoxypropane furnished the cyclic product (11) in 93% overall yield for the two steps. NMR evidence ( $J_{H1-H2}=2.7Hz$ ,  $J_{H2-Hax}=2.9Hz$ ,  $J_{H2-Heq}=1.7Hz$ ) indicated that the major structure corresponded to the diastereomer shown<sup>13</sup>.



The scope of the reaction was determined by the addition of the allylic zirconium reagent (2) to various aldehydes, (table 1). Reactions were slow (18-24 hours) with varying proportions of unreacted starting material (6) being recovered<sup>14</sup>. Attempts to increase the yield of the reactions by forming the allylic zirconium (2) at higher temperatures (reflux) or by longer reaction times (48 hours) resulted in larger yields of

the by-product (9). The addition of Lewis acids to the reaction mixture had no beneficial effect on the yield and also eroded the diastereoselectivity.

Aldehyde (RCHO)	Yield <sup>a</sup> (7+8) %	Anti/syn (7/8) d.e.	product/byproduct ratio ([7+8]/9)	entry
РћСНО	51 (69)	91%	83:17	1
p-MeOC <sub>6</sub> H <sub>4</sub> CHO	68 (81)	88%	87:13	2
p-O2NC6H4CHO	58 (73)	>95%	100:0	3
o-BrC <sub>6</sub> H₄CHO	71 (78)	>95%	94:6	4
МеСНО	51 (58)	86%	89:11	5
i-PrCHO	31 (47)	>95%	84:16	6
(E)-PhCH=CHCHO	61 (73)	>95%	100:0	7
C <sub>6</sub> H <sub>13</sub> CHO	47 (53)	>95%	84:16	8

Table 1. Products from addition of (2) to aldehydes

a Yields in brackets are based upon recovered starting material and are unoptimised.

All the reactions proceeded with high diastereoselectivity with the lowest selectivity being obtained with acetaldehyde (entry 5). Exclusive 1,2 addition occurred with the  $\alpha$ , $\beta$ -unsaturated aldehyde, cinnamaldehyde (entry 7). Yields of (7+8) were in the range (31%-71%) with varying amounts of starting material being recovered.

In an attempt to increase the rate and yield of the reactions the alternative less sterically hindered monosubstituted alkene precursor (13) was prepared. Hence, rearrangement of cis-butene diol (1) followed by protection of the rearranged diol  $(12)^{15}$  using TBDMSOTf/2,6-lutidine furnished the desired precursor in 55% overall yield. Reaction with "ZrCp2" followed by addition of benzaldehyde furnished the two expected diastereomers (7) and (8) (R=Ph) in similar yield (55%) and in the same ratio as before (d.e.=91%). No increase in the rate of product formation was observed. Reaction of the triethylsilyl derivative under the same conditions was also examined however this gave a complex mixture of products.



A typical experimental procedure is as follows: To a solution of ZrCp<sub>2</sub>Cl<sub>2</sub> (1 eq) in THF at -78<sup>\*</sup>C under argon was added BuLi (2 eq). The mixture was stirred at this temperature for an hour and the substrate was added (0.75 eq). The mixture was allowed to warm to room temperature and then stirred for 6 hrs or until the solution turned red. The aldehyde (1.5 eq) was then added and the mixture stirred at room temperature overnight. The crude mixture was quenched with 10% HCl followed by extractive work up (diethyl ether). The residue was dissolved in 1/1 petroleum ether/ethyl acetate and added to a short silica plug. Eluting initially with petroleum ether followed by 1/1 petroleum ether/ethyl acetate allowed sequential isolation of unreacted starting material and the desired products.

## Acknowledgments

We wish to thank Dr. Alan Armstrong, Dr. Richard Whitby, and Prof. Tamotsu Takahashi for helpful discussions and suggestions and the University of Warwick for funding.

## References

- 1. Yamamoto, Y.; Asao, N. Chem Rev. 1993, 93, 2207-2293 and references therein.
- 2. a) Matteson, D. S. Synthesis, 1986, 973. b) Bubnov, Y. N. Pure Appl. Chem. 1987, 59, 895.
- a) Yamamoto. Y. Acc. Chem. Res. 1987, 20, 243. b) Fleming, I. In Comprehensive Organic Synthesis; Trost, B.M.; Fleming, I. Eds.; Pergamon Press; Oxford, 1991, Vol. 2, p 563. c) Fleming, I., Ed, Tetrahedron, 1988, 44, 3761-4292 (Symposium in Print)
- a) Thomas, E. J. ChemTracts Organic Chemistry, 1994, 207 b) Thomas. E. J. in Stereocontrolled Organic Synthesis, ed Trost, B. M.; Blackwell, 1994, p 235-258. c) Tetrahedron, 1989, 909-1230 (Symposium in print)
- 5. Naruta, Y.; Maruyama, K. J. Chem. Soc., Chem Commun, 1983, 1264.
- 6. Yamamoto, Y.; Saito, Y.; Maruyama, K. J. Organomet. Chem., 1985, 292, 311.
- a) Ito, H.; Taguchi, T.; Hanzawa, Y. Tetrahedron. 1995, 4507. b) Ito, H.; Taguchi, T.; Hanzawa, Y. Tetrahedron. Lett, 1992, 33, 7873. c) Ito, H.; Taguchi, T.; Hanzawa, Y. Tetrahedron. Lett, 1992, 33, 1295.
- 8. "ZrCp2" was prepared by the method of Negishi. Negishi, E.; Cederbaum, F. K.; Takahashi, T. Tetrahedron Letts., 1986, 27, 2829.
- 9. All compounds gave satisfactory spectral data.
- Selected data for major isomer of (7) (R=Me) <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) δ 5.82 (ddd, 1H, J=17.2, 10.5, 8.8Hz), 5.15 (dd, 1H, J=10.5, 2.0Hz), 5.07 (ddd, 1H, J=17.2, 2.0, 1.0Hz), 4.00 (dq, 1H, J=6.5, 3.5Hz), 3.77 (d, 2H, J=5.2Hz), 3.15 (brs, 1H, OH), 2.18 (m, 1H), 1.13 (d, 3H J=6.5Hz), 0.87 (s, 9H), 0.04 (s, 6H). <sup>13</sup>C NMR (100MHz, CDCl<sub>3</sub>) 135.1, 117.9, 69.9, 65.9, 51.3, 25.6, 20.1, 18.0, -5.8.
- Although the stereochemistry has yet to be defined the product exhibits only a single set of peaks in the <sup>13</sup>C NMR indicating that it is only one isomer. <sup>13</sup>C NMR (100MHz, CDCl<sub>3</sub>) 133.2, 126.8, 67.1, 42.4, 39.6, 34.5, 28.9, 22.4, 18.9, 11.3.
- (9) may arise from addition of acetaldehyde to the allylzirconium formed from the coupling of butadiene (arising from a second alkoxy elimination from the allylic zirconium complex (2)) to the zirconocene butene complex. See a) Yasuda, H.; Kajihara, Y.; Nagasuna, K.; Mashima, K.; Nakamura, A. Chem Letts, 1981, 719. b) Negishi, E-L; Miller, S. R; J. Org. Chem. 1989, 54, 6014. Experiments to verify this by NMR as well as to identify the geometry of the allylzirconium (2) are currently underway.
- (11) <sup>1</sup>H NMR (400MHz, CDCl<sub>3</sub>) δ 7.35-7.2 (m, 5H), 6.05 (ddd, 1H, J=17.5, 10.5, 9.0Hz), 5.20 (d, 1H, J=2.7Hz), 4.93 (dd, 1H, J=10.5, 2.0Hz), 4.82 (ddd, 1H, J=17.5, 2.0, 0.9Hz), 4.36 (dd, 1H, J=11.3, 2.9Hz), 3.86 (dd, 1H, J=11.3, 1.7Hz), 2.30 (m, 1H), 1.57 (s, 3H), 1.54 (s, 3H).
- 14. The Z/E ratio of the recovered starting material was 75/25.
- 15. Rao, A. V. R.; Bose, D. S.; Gurjar, M. K.; Ravindranathan, T. Tetrahedron, 1989, 45, 7031.