## Zirconium-Mediated Diastereoselective Coupling Reactions of Chiral Aldimine: Remarkable Temperature-Dependence of Chiral Induction

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Abstract: Zr-Mediated coupling reactions of aldehyde with chiral aldimine which is derived from benzaldehyde and (R)-phenylglycinol methyl ether showed a remarkable temperature effect on the sense of chiral induction to yield amino alcohol derivatives with high diastereoselectivities.

For the past several years, zirconium-mediated coupling reactions of unsaturated compounds have attracted considerable attention from synthetic and mechanistic points of view.<sup>1</sup> Among the many zirconium-mediated carbon-carbon bond forming reactions, the coupling reactions of zirconaaziridine with unsaturated compounds are considered to be very attractive for preparations of amine derivatives. The generation of zirconaaziridine<sup>2</sup> has been carried out by treating chloro(methyl)zirconocene [Cp<sub>2</sub>Zr(Me)Cl], where Cp=cyclopentadienyl, with lithium dialkylamide followed by elimination of methane or reaction of aldimine with putative zirconocene ("Cp<sub>2</sub>Zr").<sup>3</sup> Recently, a chiral zirconium reagent was used to react aldimine with alkynes to give allylic amines in excellent enantiomeric excess by Buchwald et al.<sup>4</sup> We report herein the zirconium-mediated coupling reactions of chiral aldimine **1a**, derived from benzaldehyde and (R)-phenylglycinol methyl ether, with aldehydes and the remarkable temperature effect of chiral induction at newly formed chiral centers of coupled products **3**.<sup>5</sup>



Zirconaaziridine 2 was generated in situ by reaction of 1 with di-n-butylzirconocene  $[Cp_2Zr(nBu)_2]^3$  in tetrahydrofuran (THF) or toluene at the indicated temperature overnight and the following coupling reaction with aldehyde (2.5 eq) was carried out at ambient temperature for 5 h to give 3. The results are summarized in Table I. When the formation of 2a at 0 °C in THF and subsequent coupling reaction with benzaldehyde were conducted at room temperature, excellent chiral induction (R, R, R vs S, S, R = 94 : 6) in threo-3a<sup>6</sup> was noted (entry 1). To our surprise, on preparing 2a in THF at refluxing temperature followed by coupling with benzaldehyde at room temperature, the sense of chiral induction in threo-3a was found to have become

completely reversed (R, R, R vs S, S, R = 5 : 95) (entry 2). On changing the solvent from THF to toluene (entries 3 and 4) or adding an external ligand such as pyridine in the formation of zirconaaziridine 2a, no change was noted in either the threo/erythro ratio or temperature-dependence of chiral induction at the new chiral centers of 3a. The generation of zirconaaziridine 2b from 1b in THF at room temperature as in the case of 1a and coupling with benzaldehyde at room temperature resulted in high degree of chiral induction in threo- $3b^7$  (R, R, S vs S, S = 97 : 3) (entry 5), but the dramatic temperature-dependence of chiral induction at the new chiral centers, as in the case of 3a, could not be observed (THF reflux overnight for 2b followed by coupling with benzaldehyde at room temperature, R, R, S vs S, S = 64 : 36) (entry 6).

entry	imine	R of	temp (°C)	yield $(\%)^a$	ratio	threo/erythrob
		aldehyde		for 2	of threo-3	
1	1a	Ph	0 <i>c</i>	75	94/6d	6/1
2	<b>1</b> a	Ph	reflux <sup>C</sup>	84	5/95d	7/1
3	1a	Ph	23 <sup>e</sup>	83	88/12 <sup>d</sup>	6/1
4	1a	Ph	60 <i>e</i>	80	4/96d	10/1
5	1 b	Ph	23 <sup>c</sup>	70	97/3f	5/1
6	1 b	Ph	reflux <sup>C</sup>	77	64/36 <b>f</b>	3/1
7	1a	CH <sub>3</sub>	23 <sup>e</sup>	50	87/1 <i>38</i>	2/1
8	1a	CH <sub>3</sub>	60 <sup>e</sup>	35	5/958	2/1

Table I. Zirconium-Mediated Coupling Reactions of 1a,b with Aldehydes

<sup>a</sup> Isolated yield. <sup>b</sup> Determined by 400MHz-NMR. <sup>c</sup> Solvent; THF. <sup>d</sup> Ratio of threo-3a (R,R,R)/(S,S,R).

e Solvent; toluene. f Ratio of threo-3b (R,R,S/S,S,S). 8 Ratio of threo-3c (R,R,R/S,S,R).

In all cases as shown in Table I, threo-3 was the major isomer, as reported examples.<sup>2</sup> It should be pointed out that the coupling reaction of 1b with benzaldehyde in toluene at ambient temperature, in which there is no coordinative functionality with the zirconium metal of 2b, proceeded quite sluggishly to yield a complex mixture containing trace amount of 3b.<sup>8</sup> Participation of the internal ligand (MeO group) in zirconaaziridine 2 may thus be quite essential to the temperature-dependence of the sense of chiral induction in the products and reactivity of zirconaaziridine.<sup>9,10</sup> The same temperature-dependence of chiral induction was also noted in the coupling reaction of 1a with acetaldehyde (entries 6 and 7) and the formation of allylic amine 4 by reaction of 2a with trimethylsilylacetylene (Scheme II).

Scheme II



Since the insertion of an unsaturated compound was known to proceed with retention of configuration at the imine carbon atom of the zirconaaziridine,  $^{4,11}$  the ratios of the chiral induction in the products may possibly reflect the diastereoisomeric ratio of zirconaaziridine intermediate 2a.<sup>12</sup> Although the reactive zirconium species in the formation of zirconaaziridine by reaction of aldimine with Cp<sub>2</sub>Zr(nBu)<sub>2</sub> is not clear at present,  $^{1b,c}$  zirconaaziridine may possibly be formed by the addition of the reactive zirconium species to transimine from the less hindered site (Si-face)<sup>13</sup> (path a, Figure 1) followed by internal coordination of MeO group with zirconium to give 2A at room temperature or below (kinetic conditions). At higher temperature (60 °C) in preparing 2a, Re-facial adduct 2B (path b), coordinated with the internal MeO group becomes a dominant isomer through decomplexation of 2A and regeneration of 1a and the reactive zirconium species.  $^{5,14}$  Of the two possible diastereoisomers 2A, 2B, unfavourable 1,3-interaction between the phenyl group of the chiral auxiliary<sup>15</sup> and a Cp group in 2A is absent in 2B (Figure 1).<sup>16</sup> Adduct 2B thus accumulates through equilibrium by heating a solution of 2A (thermodynamic conditions). Further work is obviously necessary to verify this possibility. Through the results described herein, it may become possible to modify and create chiral ligand(s) for zirconium-mediated chiral coupling reactions.



Figure 1. Proposed formation of diastereomeric 2A and 2B

## **References and Notes**

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- 6. In the formation erythro-3a, the same temperature-dependence of chiral induction was also observed. The relative and absolute stereochemistries of 3a were unambiguously determined as follows. Full details of the results will be published in due course.





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- 10. Although the exact nature of the postulated intermediates 2A and/or 2B has not been established due to the failure of isolating 2A and/or 2B, a supporting evidence on the coordination of internal ligand has been observed in the preliminary <sup>1</sup>H-NMR experiment. In the <sup>1</sup>H-NMR spectrum of 2a generated at 60 °C in toluene, chemical shift of methyl group at 2.8 ppm was 0.35 ppm higher than that of 1a. Corresponding cyclopentadienyl signals of 2a were also observed at 5.45 and 5.60 ppm (1 : 1 ratio). We believe that these signals correspond to 2B. For 2a generated at 30 °C in toluene, methyl signals at 2.8 and 3.0 ppm and cyclopentadienyl signals at 5.40, 5.44, 5.45 and 5.60 ppm were also observed. The signals at 3.0, 5.40 and 5.44 corresponding to 2A were converted to the signals of 2B upon heating of the NMR sample at 60 °C for 2 h. Addition of benzaldehyde to both of the NMR solutions showed the formation of 3a. Unfortunately, we could not obtain an instructive spectrum to speculate the stereochemistry of intermediates.
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- 15. Changing the phenyl group of the chiral auxiliary to isopropyl group resulted in temperature effect (88: 12 at room temp, 4: 96 at 70 °C in toluene) on chiral induction similar to that of 1a, but the slow formation of zirconaaziridine and recovery of a large amount of starting chiral aldimine were observed.
- 16. The 1,3-interaction between two phenyl groups in 2B, which is a possible destabilizing factor for 2B, is considered much smaller than the 1,3-phenyl-Cp interaction in 2A by the inspection of space-filling molecular models.

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