Asymmetric Catalysis

DOI: 10.1002/anie.201007351

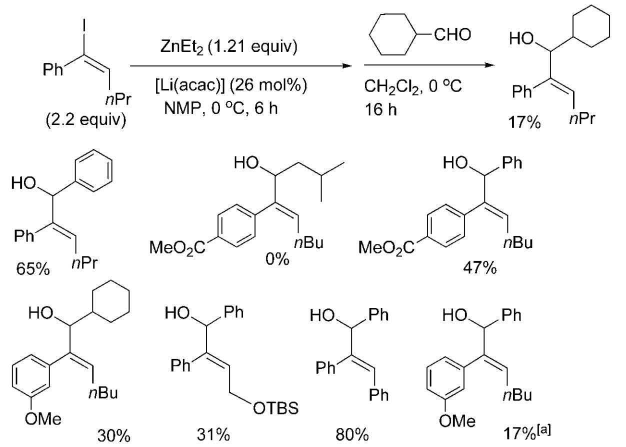
# Activation of Vinyl Iodides for the Highly Enantioselective Addition to Aldehydes**

*Albert M. DeBerardinis, Mark Turlington, and Lin Pu**

Grignard and organolithium reagents can be directly prepared from organohalides and are of great importance in organic synthesis. However, the high reactivity of these reagents makes it difficult to develop enantioselective catalysts for their nucleophilic addition to carbonyls to generate chiral alcohols.[1–3] In the past two decades, the use of organozinc reagents in asymmetric catalysis has been studied extensively.[4,5] Organozinc reagents are generally less reactive and more tolerant of functional groups than Grignard and organolithium reagents. These characteristics have allowed the rapid development of enantioselective catalysts for the asymmetric organozinc addition to carbonyls. Among these studies, several highly enantioselective catalysts were found for the asymmetric addition of vinylzinc compounds to carbonyls to generate chiral allylic alcohols.[6–9] In these reports, the vinylzinc reagents were prepared by using methods such as the hydrozirconation[6] or hydroboration[7] of alkynes with subsequent transmetallation, vinyl boronic acids or esters,[8] and the nickel-catalyzed addition of $ZnMe_2$ to alkynes.[9] The hydrozirconation and hydroboration of terminal alkynes generate alkenylzirconiums and alkenylboranes, respectively, which upon treatment with alkylzinc reagents can form the corresponding alkenylzinc reagents. These reagents in the presence of chiral ligands have been shown to be very useful for the asymmetric addition to carbonyls.[6,7]

However, the use of the hydrozirconation and hydroboration of terminal alkynes has limitations. For example, these methods cannot be applied to make cycloalkenylzinc reagents and only terminal alkynes are used in most cases. Preparation of vinylzinc reagents directly from vinyl halides would avoid these limitations. There is no report yet on the catalytic asymmetric reaction of carbonyl compounds with vinylzinc reagents that are prepared directly from vinyl halides without using the magnesium or lithium reagents, which are less tolerant of functional groups.[10] In 2004, Knochel and co-workers demonstrated that aryl iodides can be converted into arylzinc compounds by using Zn*i*$Pr_2$,[11] but it was not known whether this strategy was applicable to vinyl iodides. Herein, we report the discovery of a highly enantioselective catalyst for the reaction of vinyl iodides with aldehydes through the direct conversion of vinyl iodides into vinylzinc reagents in the presence of $ZnEt_2$. This method allows the synthesis of substituted and functionalized allylic alcohols with high enantiomeric purity under very mild reaction conditions.

We first examined the reaction of a vinyl iodide, (*E*)-1-iodo-1-phenyl-1-pentene, with *c*-$C_6H_{11}CHO$ in the presence of $ZnEt_2$ (Scheme 1). This led to the formation of the corresponding allylic alcohol in only a 17% yield. The reactions of other vinyl iodides with aldehydes were also tested and these reactions normally gave low yields of product except for a few cases. These results indicate that the vinylzinc reagents prepared directly from the vinyl iodides generally have low reactivity toward aldehydes.



***Scheme 1.*** Reaction of vinyl iodides with aldehydes in the presence of $ZnEt_2$. The reaction was carried out using method D in the Supporting Information without using a chiral ligand. The yields are of the isolated product. [a] Step 1 was performed at RT and run for 8 h. acac = acetylacetonate, NMP = *N*-methyl-2-pyrrolidone, TBS = *tert*-butyldimethylsilyl.

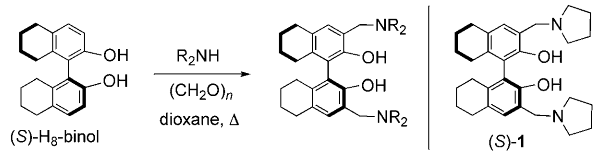
Recently, we reported a one-step synthesis of a class of amine-containing $H_8$-binol ligands by using the Mannich-type reaction of $H_8$-binol with secondary amines and paraformaldehyde (Scheme 2).[12] Among these compounds, (*S*)-**1** was found to catalyze the highly enantioselective arylzinc addition to aldehydes in a number of cases.[12] We investigated the use of (*S*)-**1** to promote the reaction of vinyl iodides with aldehydes in the presence of $ZnEt_2$. We were pleased to find that using 10 mol% of (*S*)-**1** can catalyze the reaction of

---

[*] Dr. A. M. DeBerardinis, M. Turlington, Prof. L. Pu
Department of Chemistry, University of Virginia
Charlottesville, VA 22904-4319 (USA)
Fax: (+1) 434-924-3710
E-mail: lp6n@virginia.edu

[**] The partial support of the US National Science Foundation (CHE-0717995 and ECCS-0708923) for this work is gratefully acknowledged.

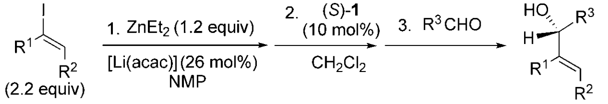
Supporting information (detailed synthesis and characterization data for the preparation of the vinyl iodides and allylic alcohols) for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201007351.

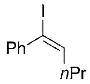
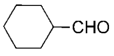
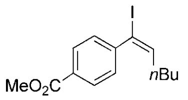
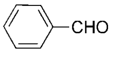
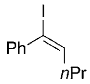
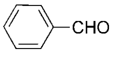
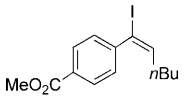
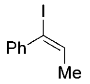
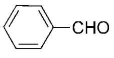
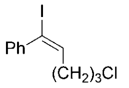
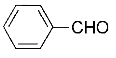
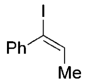
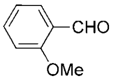
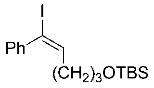
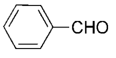
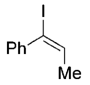
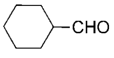
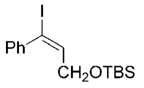
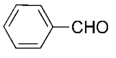
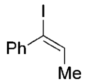
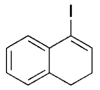
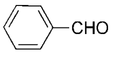
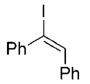
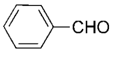
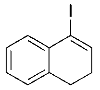
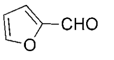
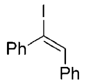
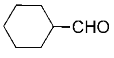
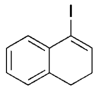
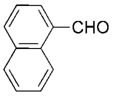
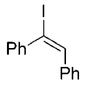
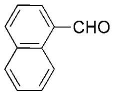
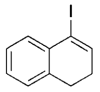
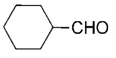
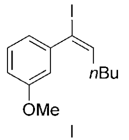
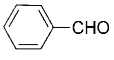
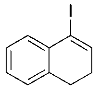
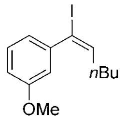
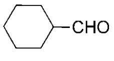


***Scheme 2.*** The general scheme for the synthesis of the amine-containing H$_8$-binol ligands such as (*S*)-**1**.

the vinylzinc reagent, generated by treatment of (*E*)-1-iodo-1-phenyl-1-pentene with ZnEt$_2$, with *c*-C$_6$H$_{11}$CHO to form the corresponding allylic alcohol in an 82% yield and 90% *ee* (entry 1, Table 1). Thus, (*S*)-**1** not only greatly enhances the reactivity of the vinylzinc reagent that is generated in situ but also provides excellent stereocontrol for the reaction. The stereochemistry of the original vinyl iodide is preserved in the product.

***Table 1:*** Catalytic asymmetric reaction of vinyl iodides with aldehydes in the presence of ZnEt$_2$ and (*S*)-**1**.[a]



| Entry | Vinyl iodide | Aldehyde | *t* [h] | | | Yield [%][b] | *ee* [%][c] | Entry | Vinyl iodide | Aldehyde | *t* [h] | | | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | step 1 | step 2 | step 3 | | | | | | step 1 | step 2 | step 3 | | |
| 1 |  |  | 6 | 1 | 16 | 82 | 90 | 12 |  |  | 6 | 1 | 16 | 81 | 97 |
| 2 |  |  | 6 | 1 | 16 | 68 | 97 | 13 |  | Me$_2$CHCH$_2$CHO | 6 | 1 | 16 | 74 | 96 |
| 3 |  |  | 3 | 1 | 12 | 79 | 97 | 14 |  |  | 6 | 1 | 16 | 86 | 98 |
| 4 |  |  | 3 | 1 | 12 | 60 | 90 | 15 |  |  | 6 | 1 | 16 | 84 | 94 |
| 5 |  |  | 3 | 1 | 12 | 84 | 97 | 16 |  |  | 6 | 1 | 16 | 72 | 98 |
| 6 |  | *n*-C$_7$H$_{15}$CHO | 3 | 1 | 12 | 68 | 90 | 17 |  |  | 3 | 1 | 12 | 88 | 93 |
| 7[d] |  |  | 5 | 1 | 12 | 90 | 97 | 18 |  |  | 3 | 1 | 12 | 79 | 96 |
| 8[d] |  |  | 5 | 1 | 12 | 75 | 94 | 19 |  |  | 3 | 1 | 12 | 90 | 91 |
| 9[d] |  |  | 5 | 1 | 8 | 90 | 97 | 20 |  |  | 3 | 1 | 12 | 84 | 96 |
| 10 |  |  | 6 | 1 | 16 | 73 | 98 | 21 |  | Me$_2$CHCH$_2$CHO | 3 | 1 | 12 | 61 | 91 |
| 11 |  |  | 6 | 1 | 16 | 60 | 97 | | | | | | | | |

[a] Reaction conditions for entries 1–16: vinyl iodide (2.2 equiv), ZnEt$_2$, (1.2 equiv), [Li(acac)] (26 mol%), NMP (1.0 mL in entries 1–6 and 10–16; 450 μL in entries 7–9), (*S*)-**1** (10 mol%), aldehyde (1.0 equiv), 0°C. Reaction conditions for entries 17–21: vinyl iodide (8.0 equiv), ZnEt$_2$ (4.0 equiv), [Li(acac)] (50 mol%), NMP (1.0 mL), (*S*)-**1** (10 mol%), aldehyde (1.0 equiv), 0°C. [b] Yield of the isolated product. [c] Determined by HPLC analysis (Chiralcel OD column or Chiralpak AD-H column). [d] Reactions carried out at RT.

We used (*S*)-**1** to catalyze the reaction of various aryl- and alkyl-substituted vinyl iodides with aromatic and aliphatic aldehydes. As the results summarized in Table 1 demonstrate, excellent enantioselectivity (90–98 % *ee*) and high yields (60–90 %) were achieved for the structurally diverse substrates that reacted at room temperature or 0 °C. In all the reactions, 10 mol % of (*S*)-**1** was used. These reactions can tolerate functional groups such as esters, chlorine, ethers, and silyl ethers on the substrates. The absolute configuration of the allylic alcohol product prepared in entry 15 of Table 1 was determined to be *R* by a $^1$H NMR study of its esters derived from (*R*)- and (*S*)-α-methoxy-α-phenylacetic acids (see the Supporting Information). By analogy, the other allylic alcohol products generated from the vinylzinc additions catalyzed by (*S*)-**1** are considered to have the same configuration as the product of entry 15 in Table 1. We also found that the 1-aryl substitution of the vinyl iodides was important for the reaction and no product could be obtained for the 1-alkyl-substituted vinyl iodides.

In summary, we have demonstrated that the vinylzinc reagents directly prepared from the reaction of a vinyl halide with $ZnEt_2$ can undergo highly enantioselective addition to aldehydes to generate structurally diverse allylic alcohols. The mild reaction conditions, the readily available catalyst, and the functional group tolerance make this process very practical.

Received: November 22, 2010

**Keywords:** aldehydes · allylic alcohols · asymmetric catalysis · enantioselectivity · vinyl iodides

---

[1] A review on the asymmetric addition of Grignard and organolithium reagents to carbonyl groups: M. R. Luderer, W. F. Bailey, M. R. Luderer, J. D. Fair, R. J. Dancer, M.-B. Sommer, *Tetrahedron: Asymmetry* **2009**, *20*, 981–998.

[2] a) J. T. Roberts in *Handbook of Grignard Reagents* (Eds.: G. S. Silvermn, P. E. Rakita), Marcel Dekker, New York, **1996**, pp. 557–565; b) *Topics in Organometallic Chemistry: Organolithiums in Enantioselective Synthesis* (Eds.: B. Goldfuss, D. M. Hodgson), Springer, **2003**, pp. 21–36.

[3] a) B. Weber, D. Seebach, *Angew. Chem.* **1992**, *104*, 96–97; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 84–86; b) Y. Muramatsu, T. Harada, *Angew. Chem.* **2008**, *120*, 1104–1106; *Angew. Chem. Int. Ed.* **2008**, *47*, 1088–1090; c) C.-S. Da, J.-R. Wang, X.-G. Yin, X.-Y. Fan, Y. Liu, S.-L. Yu, *Org. Lett.* **2009**, *11*, 5578–5581; d) B. Goldfuss, *Synthesis* **2005**, 2271–2280.

[4] K. Soai, S. Niwa, *Chem. Rev.* **1992**, *92*, 833–856.

[5] L. Pu, H. Yu, *Chem. Rev.* **2001**, *101*, 757–824.

[6] a) P. Wipf, S. Ribe, *J. Org. Chem.* **1998**, *63*, 6454–6455; b) P. Wipf, R. L. Nunes, *Tetrahedron* **2004**, *60*, 1269–1279; c) H. Li, P. J. Walsh, *J. Am. Chem. Soc.* **2005**, *127*, 8355–8361.

[7] a) M. Srebnik, *Tetrahedron Lett.* **1991**, *32*, 2449–2452; b) W. Oppolzer, R. N. Radinov, *Helv. Chim. Acta* **1992**, *75*, 170–173; c) Y. K. Chen, A. E. Lurain, P. J. Walsh, *J. Am. Chem. Soc.* **2002**, *124*, 12225–12231; d) J.-X. Ji, L.-Q. Qiu, C. W. Yip, A. S. C. Chan, *J. Org. Chem.* **2003**, *68*, 1589–1590; e) C. M. Sprout, M. L. Richmond, C. T. Seto, *J. Org. Chem.* **2004**, *69*, 6666–6673; f) Y. K. Chen, P. J. Walsh, *J. Am. Chem. Soc.* **2004**, *126*, 3702–3703; g) H.-L. Wu, P.-Y. Wu, B.-J. Uang, *J. Org. Chem.* **2007**, *72*, 5935–5937.

[8] a) F. Schmit, J. Rudolph, C. Bolm, *Synthesis* **2006**, 3625–3630; b) Z. Chai, X.-Y. Liu, J.-K. Zhang, G. Zhao, *Tetrahedron: Asymmetry* **2007**, *18*, 724–728.

[9] Y. Yang, S.-F. Zhu, Q.-L. Zhou, *J. Am. Chem. Soc.* **2008**, *130*, 14052–14053.

[10] A vinylzinc reagent was prepared for the asymmetric addition to aldehydes by treating a vinyl halide with Li followed by $ZnBr_2$: T. Shibata, K. Nakatsui, K. Soai, *Inorg. Chim. Acta* **1999**, *296*, 33–36.

[11] F. F. Kneisel, M. Dochnahl, P. Knochel, *Angew. Chem.* **2004**, *116*, 1032–1036; *Angew. Chem. Int. Ed.* **2004**, *43*, 1017–1021.

[12] A. M. DeBerardinis, M. Turlington, J. Ko, L. Sole, L. Pu, *J. Org. Chem.* **2010**, *75*, 2836–2850.