

## Catalytic Asymmetric Allylation (CAA) Reactions. II. A New Enantioselective Allylation Procedure

Gary E. Keck,\* Leo S. Geraci

Department of Chemistry  
University of Utah  
Salt Lake City, Utah 84112

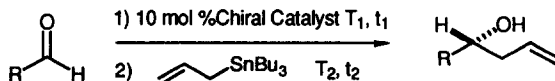
**Abstract:** A simplified and highly efficient new protocol is described for asymmetric allylation of aldehydes using allyltri-*n*-butylstannane and a chiral Lewis acid.

Recently, we described two new procedures for the enantioselective nucleophilic addition of allyl units to aldehydes.<sup>1</sup> Both procedures utilized allyltri-*n*-butylstannane and catalytic quantities of a chiral Lewis acid prepared from (R)- or (S)-BINOL, titanium tetraisopropoxide, and 4Å molecular sieves at either 1:1 or 2:1 stoichiometry (BINOL/Ti). Tagliavini and Umani-Ranchi have also recently described<sup>2</sup> a similar process using the Nakai<sup>3</sup> catalyst prepared from BINOL and TiCl<sub>2</sub>(*O*-*i*-Pr)<sub>2</sub>.<sup>4</sup>

The products produced by these procedures represent extremely versatile synthetic intermediates, particularly since they are easily converted, by simple oxidative cleavage of the vinyl moiety, to either aldehydes or carboxylic acids. Thus, these allylation procedures can be considered to afford very convenient access to the products of asymmetric aldol type condensations with enolates of acetaldehyde or acetic acid.

Since we expect that this methodology will see wide application,<sup>5</sup> we have been conducting studies to simplify the protocol employed in such reactions as much as possible. We record herein improvements in the protocol for reactions using the 2:1 BINOL/Ti catalytic system. Catalyst preparation can be accomplished *via* this new protocol under strictly homogeneous conditions, without the need for stirring, heating, or cooling.<sup>6</sup> In addition, the allyl addition reactions can be conducted at more convenient temperatures, with yields and enantiomeric excesses which rival those of our original report.<sup>1</sup> Representative experimental results are summarized in Table I.

In these cases, the catalyst solution was prepared by allowing a dichloromethane solution of (R)-BINOL and titanium tetraisopropoxide to stand at 23 °C for either 5 min or 1 h, or by heating the solution at reflux for 1 h. Reactions were 0.4 or 0.8 M in aldehyde (no difference was observed) with 0.10 equiv (10 mol %) of titanium tetraisopropoxide relative to aldehyde.



R	T <sub>1</sub> (°C), t <sub>1</sub>	T <sub>2</sub> (°C), t <sub>2</sub>	Yield (%)	% ee	Configuration <sup>a</sup>
Ph	23°, 5 min	0°, 3 h	71	93	R
	"	23°, 3 h	85	89	R
	23°, 1 h	-20°, 50 h	98	96	R

	"	0°, 3 h	94	95	R
	"	23°, 3 h	92	87	R
	reflux, 1 h	0°, 3 h	93	92	R
	"	23°, 3 h	87	92	R
PhCH=CH-	23°, 1 h	0°, 48 h	62	90	R
	"	23°, 43 h	77	85	R
C <sub>6</sub> H <sub>11</sub>	23°, 1 h	0°, 46 h	59	83	R
	"	23°, 22 h	58	71	R
PhCH <sub>2</sub> CH <sub>2</sub>	23°, 1 h	0°, 46 h	91	93	ND
	"	23°, 4 h	86	88	ND
furyl	23°, 1 h	0°, 3 h	82	92	ND
	"	23°, 1.5 h	84	90	ND

We believe that these results constitute a major advance in asymmetric synthesis. As in our original report, the BINOL ligand is easily recovered and recycled.

Further studies in this area are being actively pursued. A representative experimental procedure for the reactions summarized in Table I is detailed below for the specific case of reaction with benzaldehyde.<sup>7,8</sup>

**R-(+)-1-Phenyl-3-butene-1-ol:** A mixture of R-(+)-1,1-Bi-2-naphthol (22.5 mg, 0.078 mmol) and 1 M Ti(O-*i*-Pr)<sub>4</sub> in CH<sub>2</sub>Cl<sub>2</sub> (39  $\mu$ L, 0.039 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) was stirred at rt for 1 h. Benzaldehyde (41.2 mg, 0.394 mmol) was added to the red-brown solution, the contents were cooled to 0 °C and allyltri-*n*-butylstannane (144 mg, 0.435 mmol) was added. After 3 h at 0 °C, saturated NaHCO<sub>3</sub> (0.5 mL) was added and the contents stirred for 1 h, dried (Na<sub>2</sub>SO<sub>4</sub>) and filtered. The crude material was purified by chromatography over silica gel eluting with 19:1 (v/v) hexanes/acetone followed by 17:3 (v/v) hexanes/acetone to give R-(+)-1-phenyl-3-butene-1-ol as a clear oil (54.9 mg, 94% (95 % ee)).

### References:

1. Keck, G. E., Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 0000
2. Costa, A. L.; Piazza, M. G.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Am. Chem. Soc.* **1993**, *115*, 7001.
3. Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 3949.
4. In contrast to the observations of Tagliavini et al., with octanal<sup>2</sup> we find that stoichiometric amounts of TiCl<sub>2</sub> (O-*i*-Pr)<sub>2</sub> do promote the reaction of allyltri-*n*-butylstannane with a variety of simple aldehydes, even at -78 °C. In fact, this reaction was used by us to prepare racemic mixtures of allyl addition products (to develop analyses for enantiomeric excess) in connection with our earlier report
5. For example, the same bond construction *via* asymmetric aldol methodology is difficult with unsubstituted enolates. Note: Evans D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.
6. The implications of these observations for very large scale applications are considerable
7. Deletion of the 4Å MS from our original protocol using 1:1 stoichiometry<sup>1</sup> resulted in considerably decreased yields.
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