Stereoselective 1,2-Additions of α-Alkoxymethyllithiums to Aldehydes
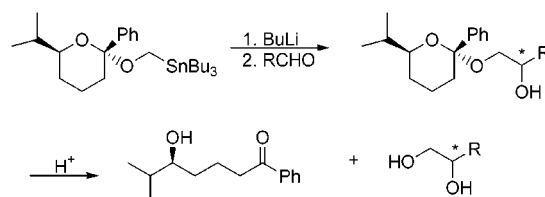
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ABSTRACT

A chiral derivative of tributylstannylmethanol, readily prepared from L-valine, undergoes Sn–Li exchange to provide an α-alkoxyorganolithium that adds to aldehydes with up to 91:9 dr. The diastereoselectivity depends on the solvent and alkyllithium used for transmetalation. Treatment of adducts with acid allowed recovery of the chiral auxiliary and diol with complete stereochemical integrity.

The asymmetric addition of organometallic reagents, particularly organozincs, to carbonyl compounds is now an important synthetic method.[1] However, these reactions are mostly restricted to unfunctionalized alkyl and aryl groups, and the stereoselective addition of heteroatom functionalized chiral organometallics[2] is a relatively unexplored area. With α-heteroatom substituted organometallics,[3] McGarvey has demonstrated high levels of asymmetric induction in the addition of α-substituted (i.e., 2°) α-alkoxyorganometallics

to aldehydes.[3a] As well, highly diastereoselective additions using diheteroatom-substituted organometallics (which are formyl anion equivalents) have been demonstrated.[4] In principle, diastereoselective addition of α-alkoxymethyl or α-aminomethyl (i.e., 1°) organometallics to aldehydes could be achieved by using a chiral auxiliary attached to the heteroatom (Scheme 1). This would constitute a new asymmetric

Scheme 1
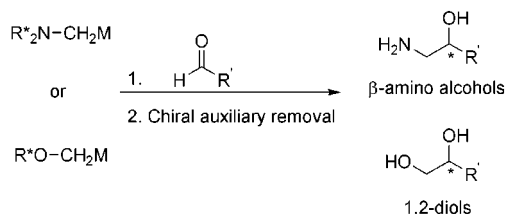
synthesis of β-amino alcohols and 1,2-diols, compounds of interest as biologically active materials or synthetic intermediates.[5]

(1) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757−824.

(2) Asymmetric γ-alkoxyallyl additions: (a) Brown, H. C.; Jadhav, P. K.; Bhat, K. S. *J. Am. Chem. Soc.* **1988**, *110*, 1535−1538. (b) Yamamoto, Y.; Kobayashi, K.; Okano, H.; Kadota, I. *J. Org. Chem.* **1992**, *57*, 7003−7005. (c) Roush, W. R.; VanNieuwenhze, M. S. *J. Am. Chem. Soc.* **1994**, *116*, 8536−8543. (d) Coleman, R. S.; Kong, J.-S.; Richardson, T. E. *J. Am. Chem. Soc.* **1999**, *121*, 9088−9095. Heteroatom functionalized chiral organozincs: (e) Eisenberg, C.; Knochel, P. *J. Org. Chem.* **1994**, *59*, 3760−3761. (f) Ostwlad, R.; Chavant, P.-Y.; Stadmüller, H.; Knochel, P. *J. Org. Chem.* **1994**, *59*, 4143−4153. (g) Lütjens, H.; Nowotny, S.; Knochel, P. *Tetrahedron: Asymmetry* **1995**, *6*, 2675−2678. Related organotitaniums: (h) Weber, B.; Seebach, D. *Tetrahedron* **1994**, *50*, 7473−7484.

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(4) (a) Gaul, C.; Seebach, D. *Org. Lett.* **2000**, *2*, 1501−1504. (b) Gawley, R. E.; Zhang, Q.; McPhail, A. T. *Tetrahedron: Asymmetry* **2000**, *11*, 2093−2106.

There are examples that demonstrate stereoselective addition of chiral α-aminomethyl[3g,6] or α-alkoxymethyl[7] carbanions to aldehydes. Thus by using proline[6] or menthol-based chiral directing groups,[7] diastereomeric ratios of up to 78:22 were obtained. However, the chiral groups used in these studies were not intended to be removed. We now report our efforts in developing the first method for the stereoselective addition of α-alkoxymethyl carbanions to aldehydes employing a removable chiral auxiliary.[8]

Our general strategy employs a cyclic chiral acetal containing a Bu_3SnCH_2O unit (**1**, Scheme 2). Sn−Li
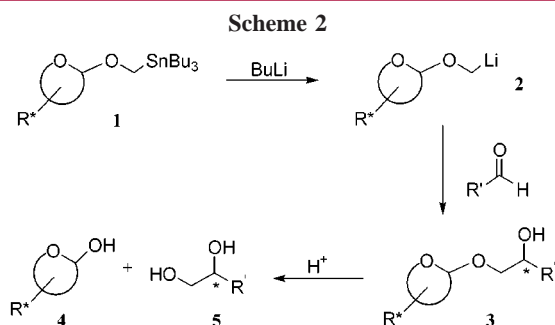
exchange[9] generates α-alkoxyorganolithium **2**, which is then trapped with an aldehyde to afford an addition adduct **3**. Exposure of **3** to acidic conditions should then allow recovery of the auxiliary **4** and enantiomerically enriched 1,2-diol product **5**.

Substituted tetrahydropyran **12** (Scheme 3) was chosen as

Scheme 3
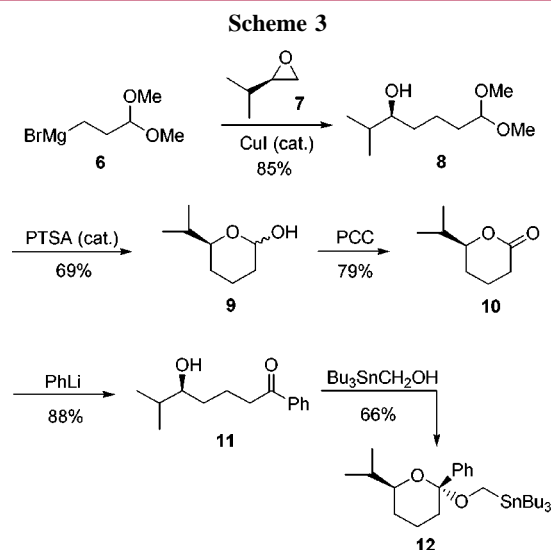
the chiral organolithium precursor for several reasons: (a) Enantiomerically pure material should be readily accessed

using chiral pool starting materials (L-valine). (b) The isopropyl and phenyl groups should help in biasing the conformation of the six-membered ring to a single chair. (c) The oxygen of the tetrahydropyran is expected to coordinate to the organolithium to decrease conformational mobility. (d) The phenyl group provides steric bulk to aid in enantiofacial discrimination with approaching aldehydes.

The synthesis of **12** involved only five steps from known epoxide **7**[10] (Scheme 3). A copper-catalyzed addition of Grignard reagent **6** gave alcohol **8**, which cyclized under acidic conditions to lactol **9**. PCC oxidation of **9** then furnished the lactone **10**, to which PhLi was added to afford keto alcohol **11**. Finally, treatment of **11** with Bu_3SnCH_2-OH in the presence of acid gave the desired ketal **12** as a single diastereomer. Formation of the α-anomer was expected on the basis of well-established precedence[11] and was verified using NOESY experiments.

Transmetalation/trapping studies on **12** were carried out using benzaldehyde as the electrophile under typical conditions (THF, −78 °C, Scheme 4). We were gratified to

Scheme 4
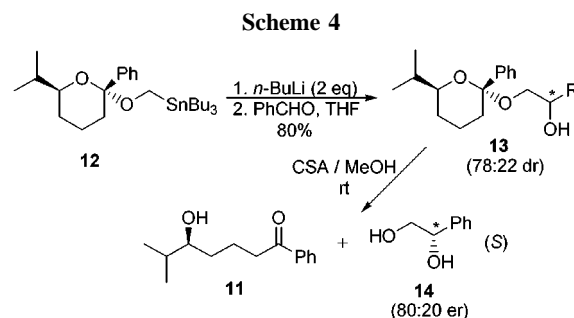
observe a reasonable level of diastereoselectivity (78:22 dr). In addition, treatment of the addition product **13** with CSA allowed for the recovery of auxiliary **11** and 1,2-diol **14** (80:20 er) with no detectable epimerization.

Since an excess (2 equiv) of *n*-BuLi was used to facilitate complete transmetalation, 1-phenyl-1-pentanol was also formed in this reaction. This alcohol proved to be inseparable from adduct **13**. Thus the reaction was repeated with 1 equiv of *n*-BuLi. Surprisingly, this resulted in a significant decrease in selectivity (Table 1). A larger excess (4 equiv) of *n*-BuLi gave a result similar to that observed with 2 equiv. Furthermore, other alkyllithiums gave selectivities different from those observed with *n*-BuLi. Thus it seems that the alkyllithium used is not simply involved in transmetalation and formation of a bystander tetraalkylstannane but also complexes with the alkoxymethyllithium generated.

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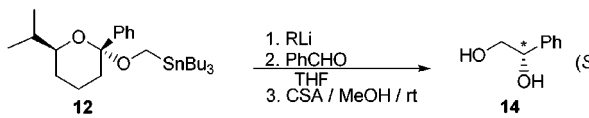(6) Coldham, I.; Holman, S.; Lang-Anderson, M. M. S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1481−1485.

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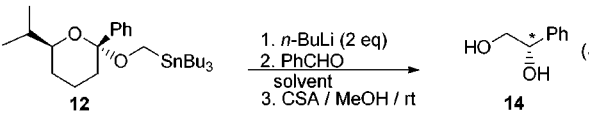
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Table 1. Effect of Alkyllithium on Selectivity

entry	RLi	equiv	yield (%)	er (*S:R*)
1	*n*-BuLi	2	85	80:20
2	*n*-BuLi	1	56	66:34
3	*n*-BuLi	4	90	80:20
4	*s*-BuLi	2	56	72:28
5	*t*-BuLi	2	21	73:27

Although 2 equiv of *n*-BuLi was usually used in these experiments, it should be noted that only 1 equiv is required for complete transmetalation. This was ascertained by experiments using 1 equiv of *n*-BuLi in which all of the alkoxystannane was consumed and >90% yields of Bu$_4$Sn were isolated. However, transmetalations did not always proceed to completion when only 1 equiv of *n*-BuLi was used; in these cases, no 1-phenylpentanol (i.e., PhCHO + *n*-BuLi product) was detected, suggesting that adventitious moisture was sometimes a problem. Thus excess *n*-BuLi was used initially primarily for practical reasons.

Other solvents and additives were also studied (Table 2).

Table 2. Effect of Solvents and Additives on Selectivity

entry	solvent	yield (%)	er (*S:R*)
1	THF	85	80:20
2	Et$_2$O	49	63:37
3	DME	97	69:31
4	15% THF/Et$_2$O	59	87:13
5	30% THF/Et$_2$O	91	88:12
6	0.9% THF/Et$_2$O	28	78:22
7	15% THF/TBME	52	85:15
8	15% Et$_3$N/Et$_2$O	26	53:47
9	15% TMEDA/Et$_2$O	18	72:28
10	15% THP/Et$_2$O	19	89:11
11	30% THP/Et$_2$O	24	91:9

Solvents less polar (Et$_2$O) and more polar (DME) than THF both gave significantly lower selectivities. However, use of 15% THF in either Et$_2$O or TBME resulted in higher selectivity over that observed in neat THF. These results suggest that THF plays an important coordinative role with the organolithiums involved in these reactions. Indeed, the amount of THF used had a dramatic influence on the selectivity observed. The use of tetrahydropyran (THP) gave similar selectivities (but lower yields due to incomplete transmetalation) to that observed with THF, but other additives (Et$_3$N, TMEDA) gave much lower selectivities.

Best results were obtained with 30% THF in Et$_2$O, which provided diol **14** in 91% yield with 88:12 er.

In all examples studied, (*S*)-**14** was the major product formed.[12] This may be explained by considering the model shown in Figure 1. This model incorporates an alkyllithium
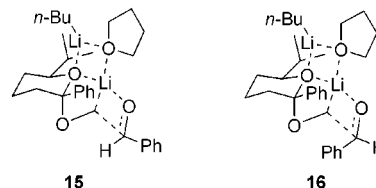
Figure 1. Possible approaches of PhCHO.

and THF/THP molecule such that the aldehyde approaches from the bottom face of the chiral auxiliary. The preferred orientation of the aldehyde would then be expected, for steric reasons, to be as shown in **15** [leading to (*S*)-**14**] as opposed to **16** [which leads to (*R*)-**14**]. While we have no spectroscopic evidence for this model, it is consistent with the known propensity of alkyllithiums to form aggregates[13] as well as the absolute configuration of **14** observed and the effects of alkyllithiums and solvents/additives observed.

Also, while there have been speculations that pentacoordinate stannylate ("ate") complexes might be responsible for the chemistry of organolithiums derived from Sn−Li exchange,[14] our results suggest that is not the case here. Stannylates have been detected spectroscopically in THF−HMPA[14] but were not observed when alkoxystannanes and alkyllithiums were admixed in THF.[15] Nonetheless, it is still possible that they are short-lived intermediates in the generation of α-alkoxyorganolithiums or are involved in reactions of these species. In our case, since the same stannylate would be formed from either 1 or 2 equiv of *n*-BuLi, one would not expect to observe different selectivities. Since the amount of *n*-BuLi does affect the selectivity, a discreet ate complex is not indicated. The present model is a simple way to explain the results observed. However, more complex scenarios involving aggregates of stannylates and alkyllithiums cannot be discounted completely.

In summary, it has been demonstrated for the first time that a chiral auxiliary directed stereoselective addition of an α-heteroatom methyl carbanion to aldehydes *along with* the subsequent recovery of the chiral auxiliary and enantiomeri-

(12) Determined by comparison of retention times on a chiral HPLC column (Chiralcel OD) using authentic commercial samples.

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cally enriched product can be accomplished. Furthermore the level of stereoselectivity observed (up to 91:9 dr) is considerably higher than what is currently in the literature for 1,2-additions of α-alkoxymethyl carbanions (64:36 dr).[7a] Finally, and perhaps most importantly, the observations that we have made regarding the effects of alkyllithiums and solvents/additives will be very useful in guiding future efforts in this area.

Supporting Information Available: Compound characterization data and experimental procedures for the preparation of compounds **6−14** and analytical procedures for determining the er and absolute configuration of **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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