Indium-mediated allylation of aldehydes, ketones and sulfonimines with 2-(alkoxy)allyl bromides

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ABSTRACT

2-(Alkoxy)propenyl bromides are readily prepared from 1,3-dibromo-2-propanol in a two-step sequence involving hydroxyl protection and sodium hydride-induced dehydrobromination. Indium-mediated allylation of aldehydes, ketones, and sulfonimines with 2-(alkoxy)propenyl bromides furnishes the corresponding homoallylic alcohols and sulfonamines in good yields. The products can be easily transformed into β-hydroxy ketones and esters, as well as substituted dihydropyrans, and protected β-amino acids. Chiral 2-(alkoxy)propenyl halides, derived from (−)-menthol and D-glucal, furnish diastereomerically enriched products.

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1. Introduction

The indium-mediated allylation of aldehydes and ketones is a powerful and stereoselective method for carbon–carbon bond formation useful in organic synthesis.[1] The reaction takes place successfully in a variety of solvents including water, with allylindium(III) sesquihalide intermediates likely for processes occurring in organic solvents[2] and allylindium(I) species likely for processes occurring in aqueous media.[1e] The allylation reaction has been applied to the synthesis of a variety of complex products and tandem or sequential indium-mediated carbon–carbon bond-forming reactions have been shown to be especially useful in this regard.[3]

A variety of 2-substituted allyl halides have been employed with great utility in aldehyde and ketone allylation reactions. For example, it has been shown that 2-(carboxyalkyl)-substituted allyl halides are useful reagents for the indium-mediated synthesis of α-methylene-γ-butyrolactones.[4] Furthermore, 2-(trimethylsilylmethyl)allyl halides have been employed in the one-pot preparation of 2,6-disubstituted tetrahydropyrans[5] and oxa-bridged seven- and eight-membered carbocycles[6] via indium-mediated allylation of mono- and dicarbonyl compounds, respectively, in aqueous media. In this Letter we wish to report our studies on the preparation and indium-mediated reactions of 2-(alkoxy)allyl halides.

Horning has shown that 3-bromo-2-(tetrahydropyranyloxy)propene, prepared by sodium hydride-induced elimination of hydrogen bromide from 1,3-dibromo-2-(tetrahydropyran-2-y1oxy)propane, is a useful 'masked' acetonyl bromide equivalent, reacting with a variety of carbon nucleophiles to generate products containing new carbon–carbon bonds (Scheme 1).[7] We were interested not in

the electrophilic properties[8] of this reagent but rather in its potential to form an allyl nucleophile upon exposure to indium metal.[10] To test this hypothesis, we decided to prepare MEM derivative 3-bromo-2-((2-methoxyethoxy)methoxy)propene (3) and investigate its reactivity with aldehydes and ketones in the presence of indium metal.

Exposure of 1,3-dibromo-2-propanol to MEM-Cl[9] (1.5 equiv), i-Pr₂NEt (2 equiv), and TBAI (10 mol %) in CH₂Cl₂ for 36 h gave rise to 1,3-dibromo-2-((2-methoxyethoxy)methoxy)propane **2** in 60% yield. Addition of a DMF solution of **2** to NaH (2.2 equiv) in DMF at 0 °C, followed by warming to room temperature, furnished bromide **3** in 72% yield. This substance was not purified but used directly in allylation reactions. It was subsequently found that trace amounts of water in the DMF solvent employed for the preparation of **3** from **2** gave rise to allylic alcohol **4**, which proved difficult to separate from allylation products **5** (vide infra). The formation of this byproduct could be completely avoided by storing the DMF used for the dehydrobromination reaction over activated 4 Å molecular sieves for several days prior to use. It is worthy of note that 1,3-dibromo propanol derivatives bearing non-acetal-type protecting groups (e.g., methyl or menthyl ether) undergo dehydrobromination with NaH in only very poor yields (<10%) at room temperature.

The reaction of **3** with representative aldehydes and ketones in the presence of indium metal is presented in Table 1. The optimal solvent for the reaction was DMF; reactions performed in THF were slower, and as previously shown by Saicic,[10] mixtures of THF and water produced β-hydroxyketone **6** (Scheme 2) as the main product, presumably formed via hydrolysis of the enol ether functionality of **5** due to the rising acidity[5] of the reaction medium as the reaction progresses. Tetra-n-butylammonium iodide or sodium iodide (1 equiv) was found to be an important additive necessary for increasing the reactivity of **3** toward aldehydes and ketones,

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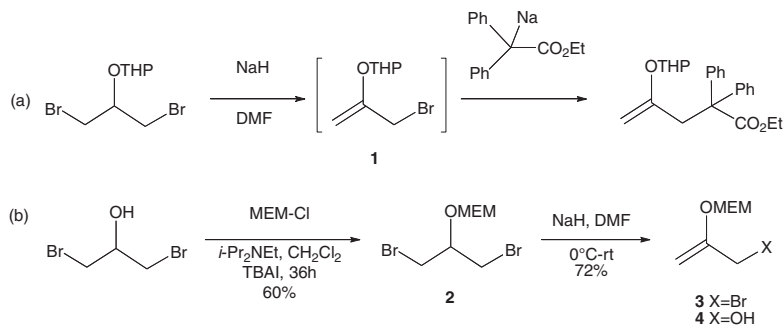
Scheme 1. (a) Horning's preparation of **1** and its utility as an electrophile. (b) Preparation of MEM derivative **3**.

Table 1
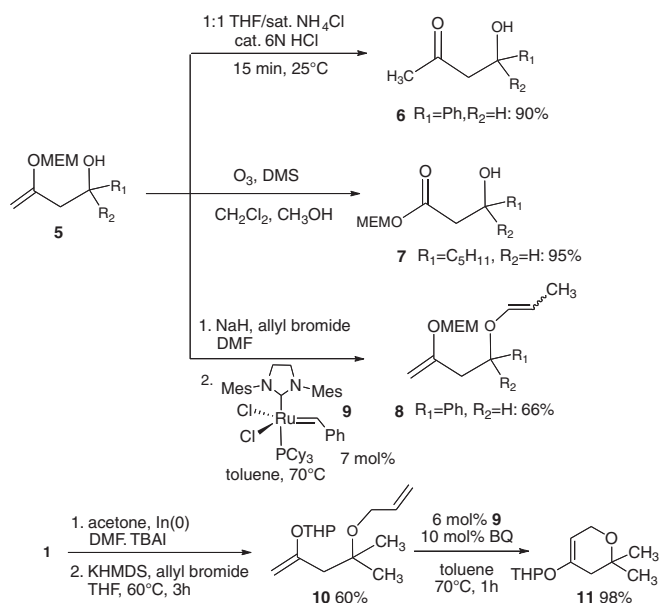Scope of indium-mediated allylation of aldehydes and ketones with **3**[a]

Entry	R$_1$	R$_2$	**5**	% Yield **5**
1	(phenyl)	H	a	87
2	(pentyl)	H	b	91
3	(cyclohexyl)	H	c	68
4	H$_3$C (propenyl)	H	d	61
5	C$_6$H$_5$ (styryl)	H	e	65
6	(dioxolane, H$_3$C, CH$_3$)	H	f	78[b]
7	CH$_3$	CH$_3$	g	92
8	CH$_3$	(phenyl)	h	89

[a] Reaction conditions: **3** (2 equiv) aldehyde or ketone (1 equiv), TBAI (1 equiv) and indium metal (1.5 equiv) combined in DMF (2 M) and stirred at room temperature for 4–6 h.
[b] *Anti/syn* diastereomer ratio = 5:1.

Scheme 2. Useful transformations of alcohol **5** and THP ether **10**.

leading to decreased reaction times (>24 h→5 h). The optimal conditions for the reaction involved combining the aldehyde or ketone (1 equiv) with **3** (2 equiv), indium metal (1.5 equiv), and TBAI or NaI (1 equiv) in DMF (2 M) at room temperature for 4–6 h. Allylation of glyceraldehyde acetonide (entry 6) led to the expected homoallylic alcohol as a 5:1 mixture of *trans/cis* diastereomers.[3]

Enol ethers **5** may be readily transformed into β-hydroxy ketones and esters. Stirring compound **5a** in a 1:1 THF/saturated NH$_4$Cl solution containing a drop of 6 N HCl for 15 min results in its conversion to ketone **6** in 90% isolated yield; bubbling ozone through a solution of **5b** in 1:1 CH$_2$Cl$_2$/CH$_3$OH at −78 °C for 30 min, followed by exposure to DMS and warming to room temperature, gives rise to MEM ester **7** in 95% yield (Scheme 2). Compound **5a** could be easily transformed into the corresponding allyl ether by treatment with NaH/allyl bromide in DMF; however, attempted ring-closing metathesis with Grubb's second-generation catalyst **9**[11] led only to the isomerized acyclic products **8**. Repetition of this reaction in the presence of the isomerization inhibitor benzoquinone (10 mol %) gave no reaction.[12] Since many examples of enol ether metathesis exist in the literature,[13] we surmised that the methoxyethoxymethyl ether moiety may be inhibiting ring-closing metathesis by coordination to ruthenium. Thus, we prepared allyl ether **10** from Horning's THP ether (**1**) and subjected it to ring closing metathesis. A 98% yield of dihydropyran **11** was

obtained after stirring **10** for 1 h at 70 °C in toluene in the presence of 6 mol % **9** and 10 mol % benzoquinone (BQ).

Toluenesulfonyl imine **12**[14] also underwent reaction with **1** (3 equiv) in the presence of indium metal (3 equiv) to produce homoallylic sulfonamide **13** as a 1:1 mixture of diastereomers in 90% yield (Scheme 3). Treatment of **13** with OsO$_4$/KIO$_4$ under Jin's conditions[15] cleanly gave rise to sulfonyl-protected β-amino acid **14** in 84% yield.

To explore the extension of this method beyond the use of an acetone enolate equivalent, we prepared MEM ether **16** from the known *cis,cis*-2,6-dibromocyclohexanol (**15**, Scheme 4).[16] Treatment of **16** with NaH in DMF, followed by exposure to benzaldehyde and indium metal in DMF overnight, led to the production of enol ether **17** in 45% yield as a 6:1 mixture of *syn/anti* diastereomers;[17] diene **18**,[18] formed competitively in *both* the dehydrobromination and allylation reactions, was also isolated in significant quantities.

Finally, we envisioned that chiral 3-bromo-2-alkoxypropenyl halides could be easily prepared by the protocols outlined above and participate in diastereoselective indium-mediated carbonyl allylation reactions. Menthyloxymethyl ether **20** was thus synthesized from 1,3-dibromo-2-propanol and symmetrical acetal **19**[19] (derived from (−)-menthol) under TMSOTf catalysis (Scheme 5). Dehydrobromination under standard conditions, followed by indium-mediated allylation of benzaldehyde, furnished homoallylic alcohol **21** in 80% yield. To assess the stereoselectivity of the reac-
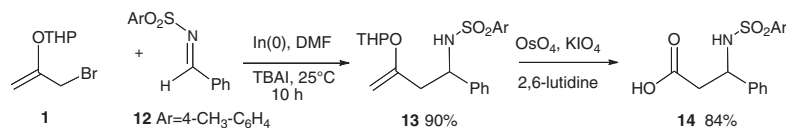
Scheme 3. Indium-mediated allylation of sulfonimine **12**.
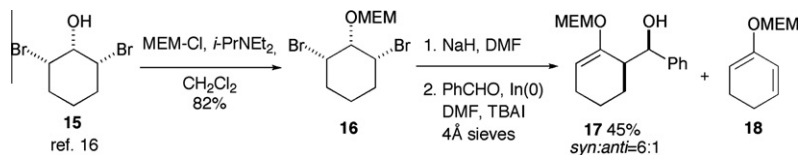
Scheme 4. Reactions of the allylindium reagent derived from dibromide **16**.
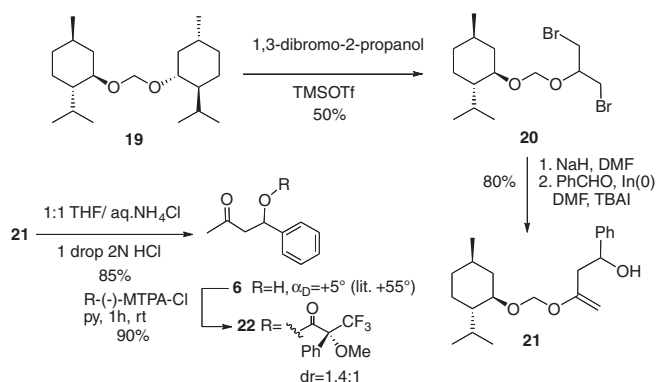
**Scheme 5.** Attempted use of the menthyloxymethyl ether as a chiral auxiliary in indium-mediated allylation.

tion, it was necessary to hydrolyze **21** to β-hydroxyl ketone **6** and prepare the corresponding Mosher ester[20] derivative. Analysis of the ^{1}H NMR spectrum of ester **22** revealed a disappointing 1.4:1 diastereomer ratio.

Given that tetrahydropyranyl ether **1** undergoes smooth indium-mediated carbon–carbon bond-forming reactions, we believed that the use of a carbohydrate auxiliary might give rise to enhanced diastereoselection in the allylation process. Thus, 3,4,6-tri-O-methyl-D-glucal[21] was treated with 1,3-dibromo-2-propanol

(1.5 equiv) and triphenylphosphine hydrobromide (5 mol %)[22] in CH$_2$Cl$_2$ at room temperature for 16 h to afford O-glycoside **23** in 80% yield as a 10:1 mixture of α/β diastereomers which could be easily separated by flash chromatography (Scheme 6). Dehydrobromination of the α-stereoisomer was carried out in DMF with NaH, and crude enol ether **24** (2 equiv) was reacted with benzaldehyde (1 equiv) and indium metal (1.5 equiv) in DMF overnight. The corresponding homoallylic alcohol **26** was obtained in 90% yield as 3:1 mixture of diastereomers. Repetition of the reaction in THF or dioxane furnished less than 10% of **26**; reaction in 4:1 THF/DMF provided **26** as a 3:1 mixture of diastereomers in 65% yield after 48 h. Treatment of intermediate allyl bromide **24** with NaI in acetone, isolation of iodide **25**, and stirring of crude **25** in THF with indium metal prior to the addition of benzaldehyde gave **26** in 55% yield, but again as a 3:1 mixture of diastereomers.

Aqueous acidic hydrolysis of the enol ether function of **26** gave β-hydroxy ketone **6**, whose sign of optical rotation indicated that the predominant enantiomer possessed the S-configuration.[23] The preferential formation of this stereoisomer may be rationalized based on a transition state assembly in which the pyran ether oxygen and the C.6 oxygen atom of the carbohydrate simultaneously coordinate the allylic indium species, as shown in Scheme 6.

In conclusion, we have demonstrated the synthetic utility of the indium reagents derived from 2-alkoxy-substituted allyl bromides. Studies directed toward improving the diastereoselectivity of this process, as well as explorations of the utility of this method in natural products synthesis, are currently under way and will be reported in due course.
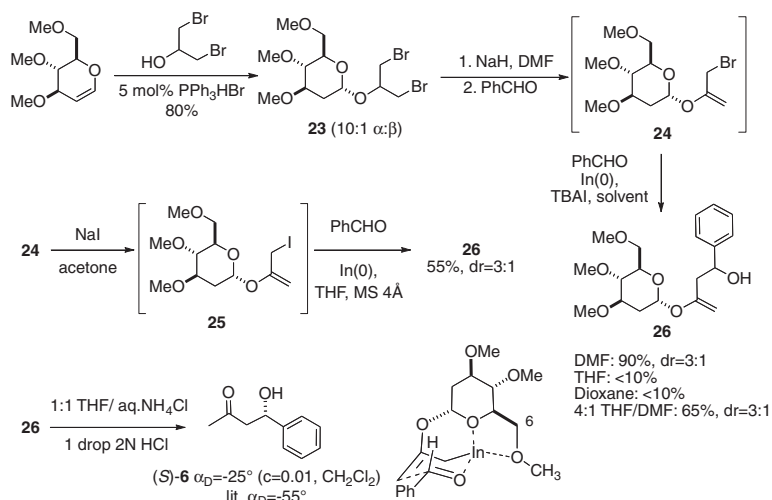
Scheme 6. Synthesis and indium-mediated allylation reactions of chiral allyl bromide **24**.

2. General procedure for the synthesis of homoallylic alcohols 5a–h from 2

A solution of **2** (603 mg, 2 mmol) in DMF (0.6 mL) was added rapidly to a 0 °C solution of NaH (400 mg, 10 mmol, 60% dispersion in mineral oil, washed 2× with dry pentane) in DMF (4 mL) and the resulting solution was allowed to warm to room temperature and stir for 30 min. The mixture was diluted with ether (20 mL) and quenched with saturated NaHCO$_3$ solution (10 mL). The layers were separated and the organic layer was washed with an additional portion of saturated NaHCO$_3$ solution (10 mL). The organic layer was dried over Na$_2$SO$_4$, filtered and concentrated in vacuo to provide **3** as a light yellow oil.

To a solution of crude **3** in DMF (0.5 mL) was added the appropriate aldehyde or ketone (1.0 mmol), indium metal (171 mg, 1.5 mmol), TBAI (369 mg, 1.0 mmol) and 4 Å molecular sieves (200 mg). The solution was allowed to stir overnight with protection from light. The reaction mixture was then diluted with 1:1 ether/ethyl acetate (10 mL) and saturated NaHCO$_3$ solution (10 mL) and the phases were separated. The aqueous phase was extracted again with ether (10 mL) and the combined organics were dried over anhydrous sodium sulfate. Filtration and concentration in vacuo furnished a crude yellow oil. Purification by flash chromatography provided homoallylic alcohols **5a–h**.

Acknowledgments

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.08.064.

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