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Highly Stereoselective Metal-Mediated Entry to Functionalized Tetrahydrothiophenes by Barbier-Type Carbonyl-Addition Reactions

Benito Alcaide,*[a] Pedro Almendros,*[b] and Teresa Martínez del Campo[a]

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Reactions of tetrahydrothiophene-3-carbaldehydes with stabilized organometallic reagents were investigated in aqueous media. Tetrahydrothiophene-3-carbaldehydes and a variety of stabilized organic halides undergo stereocontrolled coupling under Barbier-type conditions in the presence of different metals (zinc, tin, indium) and additives [ammonium chloride, hydrobromic acid, hafnium(IV) chloride, bismuth(III) chloride]. The regiochemistry of the carbonyl addition processes, when applicable, was excellent.

Introduction

Functionalized tetrahydrothiophenes are important substrates for studies of biological activity,[1] and they are also useful synthetic intermediates for natural products and organocatalysts.[2] As a consequence, development of practical methods for their preparation is of interest. In contrast, the development of new carbon–carbon bond-forming reactions is of particular interest in organic synthesis. Among the most fundamental and important reactions for constructing carbon–carbon bonds are the allylation and the allenylation of aldehydes and ketones (carbonyls) with organometallic reagents. For example, Sakurai-, Grignard- and Barbier-type reactions have been widely utilized for the allylation[3] or allenylation/propargylation[4] of carbonyls, in which chemo- and regioselectivities of the desired alcohols are highly dependent on the nature of the metals employed. Although many efforts have been made in these fields into various types of carbonylic compounds, the addition reactions of stabilized organometallic reagents to tetrahydrothiophene carbonyls have not been reported yet.

The appealing properties of organometallic reactions in aqueous media include their synthetic advantages (many reactive functional groups, such as hydroxy, amine and carboxylic functionalities, do not require the protection–deprotection protocol in such reactions, and many water-soluble compounds do not need to be converted into their derivatives and can be used directly), its potential as an environmentally benign chemical process (the use of anhydrous flammable solvents can be avoided and the burden of solvent disposal may be reduced). Besides, a unique reactivity and selectivity that are not often attained under dry conditions (the performance of organic reactions in aqueous conditions might lead to different results in comparison to those obtained in purely organic solvents, regardless of whether the reactants are soluble or not in water), which makes them profitable in many cases.[5] Conversely, two general protocols are available for metal-promoted carbonyl addition with the use of organic halides: the stepwise Grignard procedure where the metal reagent is preformed and then added to the carbonyl compound, or the in situ Barbier procedure where the organometallic species is formed in the presence of the carbonyl moiety. Continuing with our work on the synthesis of heterocyclic compounds of biological interest,[6] we decided to pursue a convenient approach for the regiocontrolled incorporation of new substituents on the tetrahydrothiophene ring. In this context, we wish to report details of the manner in which tetrahydrothiophene carbaldehydes and a variety of stabilized organic halides undergo coupling under Barbier-type conditions in aqueous media.

Results and Discussion

Starting substrates, racemic tetrahydrothiophene-3-carbaldehydes **1a** and **1b**,[7] were prepared as single diastereomers by a proline-catalyzed Michael–aldol domino reaction.[8] A model reaction of tetrahydrothiophene-3-carbaldehyde **1a** was carried out by treatment of a THF/H_2O (1:1) solution of tetrahydrothiophene-3-carbaldehyde **1a** with allyl bromide in the presence of indium at room

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[a] Departamento de Química Orgánica I, Facultad de Química, Universidad Complutense de Madrid,
28040 Madrid, Spain
Fax: +34-91-3944103
E-mail: alcaideb@quim.ucm.es
[b] Instituto de Química Orgánica General, Consejo Superior de Investigaciones Científicas, CSIC
Juan de la Cierva 3, 28006 Madrid, Spain
Fax: +34-91-5644853
E-mail: Palmendros@iqog.csic.es

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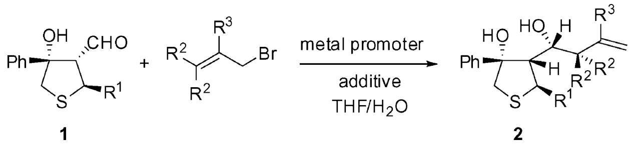
temperature to give regio- and diastereoselectively adduct **2a** in 65% yield (Table 1, Entry 1). Preliminary results encouraged us to screen other metals and conditions for the above reaction for better yield. The use of THF as cosolvent was necessary to increase the solubility of both starting material and product in every single addition reaction. The tin-promoted allylation also afforded homoallylic alcohol **2a**, but in poor 20% yield (Table 1, Entry 2). It was found that by using zinc under the above conditions gave **2a** as the sole isomer in 64% yield (Table 1, Entry 3). The addition of ammonium chloride to the aqueous medium did accelerate the process to an observable extent (Table 1, Entries 4–6). However, slightly lower yield was obtained in the allylindation reaction (Table 1, Entry 4). Fortunately, the ionic strength enhancement of the reaction solvent provided by ammonium chloride increased the yield of **2a** for the zinc- and tin-promoted reactions. Thus, the zinc-mediated coupling of allyl bromide and tetrahydrothiophene-3-carbaldehyde **1a** in THF/NH_4Cl (aq. satd.) medium, afforded adduct **2a** in a reasonable 74% yield (Table 1, Entry 6). Similar results were obtained in the metal-mediated allylation reaction by using tetrahydrothiophene-3-carbaldehyde **1b** or prenyl and methallyl bromides (Table 1, Entries 7–11).

Table 1. Allylation reaction of tetrahydrothiophene-3-carbaldehydes **1** in aqueous media.

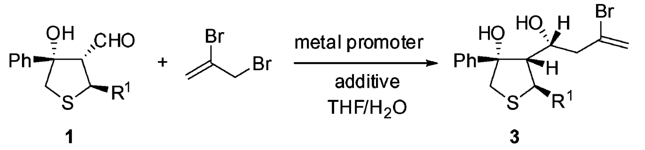


Entry	CHO	R^1, R^2, R^3	Metal	Additive	*t* [h][a]	Product[b]	Yield [%][c]
1	**1a**	Me, H, H	In	–	1	**2a**	65
2	**1a**	Me, H, H	Sn	–	40	**2a**	20
3	**1a**	Me, H, H	Zn	–	2.5	**2a**	64
4	**1a**	Me, H, H	In	NH_4Cl	0.5	**2a**	60
5	**1a**	Me, H, H	Sn	NH_4Cl	14	**2a**	30
6	**1a**	Me, H, H	Zn	NH_4Cl	0.75	**2a**	74
7	**1a**	Me, H, Me	Zn	NH_4Cl	1.5	**2b**	55
8	**1a**	Me, Me, H	Zn	NH_4Cl	2	**2c**	48
9	**1b**	*i*Pr, H, H	Zn	NH_4Cl	1.5	**2d**	62
10	**1b**	*i*Pr, H, Me	Zn	NH_4Cl	24	**2e**	51
11	**1b**	*i*Pr, Me, H	Zn	NH_4Cl	20	**2f**	51

[a] Reaction progress was followed by TLC. [b] Analysis of the ^1H NMR spectra (300 MHz) of the crude reaction mixtures revealed compounds **2** as the only detected isomer. [c] Yield of pure, isolated product with correct analytical and spectroscopic data.

In contrast to the reaction involving allylmetals, the analogous carbonyl–bromoallylation reaction has been scarcely investigated,[9] despite the fact that it can provide useful intermediates, such as the corresponding bromohomoallylic alcohols.[10] By taking into consideration the above allylation results, we decided to introduce the bromoalkenyl moiety onto the tetrahydrothiophene ring by zinc-promoted Barbier-type bromoallylation of tetrahydrothiophene-3-carbaldehydes in aqueous environment. Unfortunately, when the reaction of tetrahydrothiophene-3-carbaldehyde **1a** with 2,3-dibromopropene was conducted in the presence of zinc in aqueous tetrahydrofuran, the corresponding bromoallylated product **3a** was not formed, even after a reaction period of 4 d (Table 2, Entry 1). Next, we screened different metal mediators (indium, manganese and tin). Bromohomoallylic alcohol **3a** was achieved through tin-mediated bromoallylation in a low 20% yield (Table 2, Entry 4), but no coupling product was observed when indium and manganese were used. Because the incorporation of water-stable additives could improve both yield and conversion rate, we explored further the tin-promoted bromoallylation of tetrahydrothiophene-3-carbaldehyde **1a** in the presence of different additives. The addition of ammonium chloride to the aqueous medium containing tin, 2,3-dibromopropene and tetrahydrothiophene-3-carbaldehyde **1a** was effective, and bromohomoallylic alcohol **3a** was obtained in 35% yield after 2 d (Table 2, Entry 5). This encouraging observation prompted us to investigate different Lewis or protic acids as additives.[11] When the above reaction was mediated by tin and conducted in THF/H_2O (1:1) in the presence of hydrobromic acid, bromohomoallyl alcohol **3a** was obtained in moderate 39% yield after 2 d (Table 2, Entry 6). The addition of bismuth(III) chloride or hafnium(IV) chloride to the aqueous environment of the tin-promoted bromoallylation reaction of tetrahydrothiophene-3-carbaldehydes both shortened the reaction times and slightly increased the yields (Table 2, Entries 7–9). The effect of the amount of 2,3-dibromopropene on the conversion rate as well as on the yield was studied, and it was found that the efficiency of the process did increase on increasing the molar ratio between the allyl bromide and tin from 1:1 to 2:1.

Table 2. Bromoallylation reaction of tetrahydrothiophene-3-carbaldehydes **1** in aqueous media.



Entry	CHO	R^1	Metal	Additive	*t* [h][a]	Product[b]	Yield [%][c]
1	**1a**	Me	Zn		96	**3a**	
2	**1a**	Me	In		96	**3a**	
3	**1a**	Me	Mn		96	**3a**	
4	**1a**	Me	Sn		96	**3a**	20
5	**1a**	Me	Sn	NH_4Cl	48	**3a**	35
6	**1a**	Me	Sn	HBr	48	**3a**	39
7	**1a**	Me	Sn	$HfCl_4$	24	**3a**	52
8	**1a**	Me	Sn	$BiCl_3$	24	**3a**	55
9	**1b**	*i*Pr	Sn	$BiCl_3$	22	**3b**	49

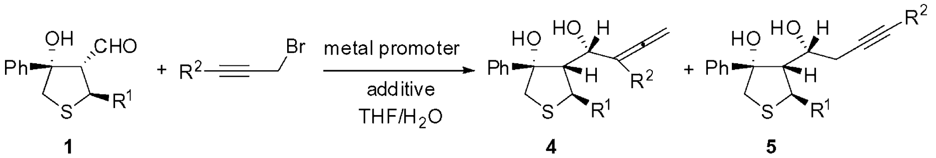
[a] Reaction progress was followed by TLC. [b] Analysis of the ^1H NMR spectra (300 MHz) of the crude reaction mixtures revealed compounds **3** as the only detected isomer. [c] Yield of pure, isolated product with correct analytical and spectroscopic data.

Once we had established the best reaction conditions to carry out the allylation and bromoallylation reactions, we envisioned the introduction of the propa-1,2-dienyl group at the C3 position of tetrahydrothiophene, because tetrahydrothiophene, which has this group, could be further functionalized through metal-catalyzed heterocyclization reactions to produce tetrahydrothiophenes possessing various five-membered rings at the C3 position. Our aim was to evaluate the feasibility of the metal-mediated Barbier-type allenylation reaction in tetrahydrothiophene-3-carbaldehydes by studying the regiochemistry of the connection. However, it is not easy to control selectivity between Barbier-type propargylation and allenylation with propargylic halides. The reaction of propargyl bromide with metals has been proposed to generate an equilibrium between the allenyl and propargyl organometallics. This metallotropic rearrangement often results in poor regioselection in the final organic product, because both organometallic species can react with the carbonyl compounds. By tuning the regioselectivity of the reaction of propargylmetals with carbonyl compounds towards the synthesis of either acetylenic or allenic products remains an important challenge in organic synthesis.[12] In this context, the preparation of homopropargylic and allenic alcohols from transient allenylindium reagents or propargylic stannanes, respectively, described by Marshall, and the regioselective synthesis of allenic and homopropargylic alcohols through the indium-mediated reaction of trialkylsilylpropargyl bromide with aldehydes reported by Loh are noteworthy.[13]

The aim of achieving full control of regiochemistry prompted us to seek an aqueous metal-induced allenylation reaction. For this purpose, the metal-mediated reaction between tetrahydrothiophene-3-carbaldehydes **1** and prop-2-ynyl bromides bearing substituents of varying steric demand at C3 were tested. Disappointingly, the coupling between tetrahydrothiophene-3-carbaldehyde **1a** and propargyl bromide under a broad variety of metals and reaction conditions in aqueous media did afford complicate mixtures. Next, we explored the carbonyl–allenylation reaction by using 3-substituted 2-propynyl bromides under different reaction conditions. Thus, the zinc-mediated reaction between tetrahydrothiophene-3-carbaldehyde **1a** and 1-bromobut-2-yne gave rise to desired α-allenol **4a**; however, the selectivity was low because regioisomeric homopropargylic alcohol **5a** was obtained in appreciable amount (**4a**/**5a**, 80:20) (Table 3, Entry 1). The corresponding tin-induced allenylation reaction proceeded reasonably, but the synthetic interest is diminished owing the poor regioselectivity (75:25) of the allenic/propargylic reaction site (Table 3, Entry 2). Contrary to the above results obtained in the indium-mediated propargylation reaction by using propargyl bromide itself, excellent regioselectivities can be obtained when the indium-promoted reactions were carried out in the presence of propargyl bromides bearing an aliphatic or an aromatic substituent at the terminal position. The indium-mediated reactions were found to proceed faster in the presence of ammonium chloride as additive (Table 3, compare Entries 3 and 4). Metal-promoted reactions of tetrahydrothiophene-3-carbaldehydes **1** with 1-bromobut-2-yne or 1-bromo-3-phenyl-2-propyne afforded α-allenols **4** as essentially regio- and diastereomerically pure products (Table 2, Entries 3–7). The results are summarized in Table 3.

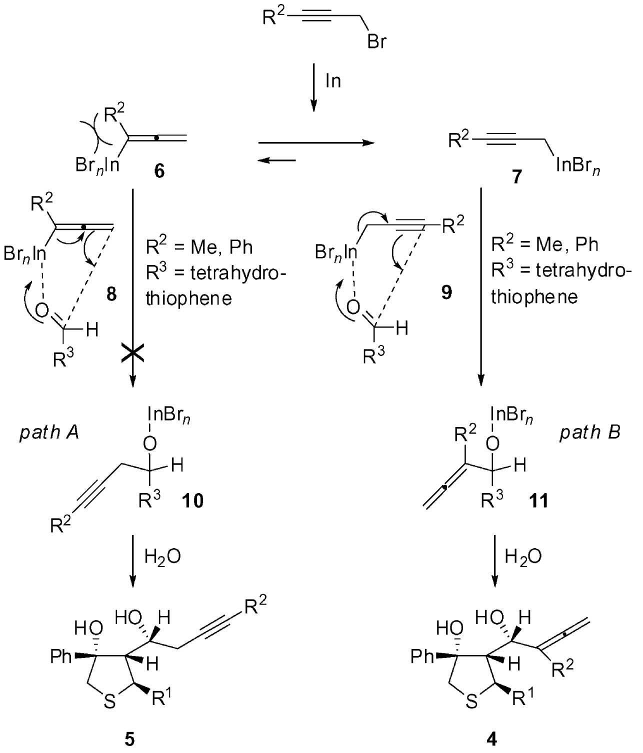
Although the mechanism for the indium-mediated carbonyl–allenylation of aldehydes by using propargyl bromides in aqueous media has not been fully established;[14] a possible reaction pathway is described in Scheme 1. It may be reasonable to postulate a metallotropic rearrangement between the propargyl- and allenylindium reagents, **6** and **7**, generated in situ from indium and 3-substituted 2-propynyl bromides. The reactions of **6** and **7** with tetrahydrothiophene-3-carbaldehydes have trouble with competing reactions. Thus, both intermediates from this equilibrium between **6** and **7** can react with tetrahydrothiophene-3-carbaldehydes **1** to produce α-allenic alcohols **4** or homopropargylic alcohols **5**. The formation of tetrahydrothiophenes **4** and **5** is consistent with participation of the six-membered cyclic transition structures **8** (*path A*) and **9** (*path B*), respectively. It seems feasible to suggest that the regiochemical preference observed for the indium-promoted reactions of 3-substituted 2-propynyl bromides with tetrahydrothiophene-3-carbaldehydes must be controlled by steric effects. The isomerization of propargylindium to allenylindium is presumably prohibited by the steric effect of both substituents (R^1 and $InBr_n$) in the bromopropyne. Thus, propargylindium reagent **7** undergoes nucleophilic addition to tetrahydrothiophene-3-carbaldehydes **1** to afford exclusively allenyl compounds **11**, which after hydrolysis provided α-allenols **4** through *path B* (Scheme 1).

Table 3. Regioselective allenylation reaction of tetrahydrothiophene-3-carbaldehydes **1** in aqueous media.



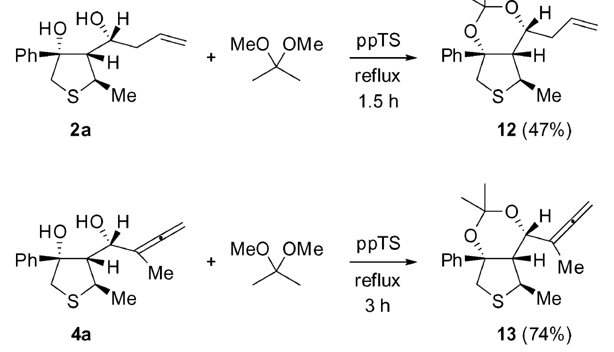
Entry	CHO	R^1, R^2	Metal	Additive	*t* [h][a]	**4/5** ratio[b]	Yield [%][c]
1	**1a**	Me, Me	Zn		10	**4a/5a** (80/20)	35
2	**1a**	Me, Me	Sn		48	**4a/5a** (75:25)	48
3	**1a**	Me, Me	In		6	**4a/5a** (100:0)	65
4	**1a**	Me, Me	In	NH_4Cl	0.5	**4a/5a** (100:0)	70
5	**1a**	Me, Ph	In	NH_4Cl	0.5	**4b/5b** (100:0)	76
6	**1b**	*i*Pr, Me	In	NH_4Cl	18	**4c/5c** (100:0)	63
7	**1b**	*i*Pr, Ph	In	NH_4Cl	20	**4d/5d** (100:0)	43

[a] Reaction progress was followed by TLC. [b] The ratio was determined by integration of well-resolved signals in the ^1H NMR spectra (300 MHz) of the crude reaction mixtures before purification. [c] Yield of pure, isolated product (or mixture of regioisomers, when applicable) with correct analytical and spectroscopic data.



Scheme 1. Plausible mechanism of addition of propargylindiums to tetrahydrothiophene-3-carbaldehydes.

Carbinolic adducts **2**–**4** were not crystalline. However, the observation of an NOE enhancement of the phenyl *ortho* protons on irradiation of the carbinolic hydrogen for 1,3-diol acetonides **12** and **13** indicated a *syn* stereochemistry for the 1,3-diol moiety, as shown in Scheme 2. Configuration at the carbinolic chiral centre for the rest of the tetrahydrothiophenes was identified by analogy.



Scheme 2. Preparation of diol acetonides **12** and **13**.

Two modes of stereocontrol determine which diastereomer is the major from the addition of a nucleophile to a β-alkoxyaldehyde. For the stereoselective addition of organometallic reagents to β-hydroxyaldehydes **1**, 1,3-metal chelation between the C4 hydroxy substituent and the aldehyde oxygen atom enforces a *syn*-periplanar relationship between the alcohol and aldehyde groups and should preferentially orient towards a 1,2-*anti* selectivity (chelation control). The lack of 1,3-chelation in tetrahydrothiophene-3-carbaldehydes **1a** and **1b** favours Cram–Felkin–Anh control,[15] which maximizes stereoelectronic interactions in the transition state and leads to 1,2-*syn* diastereomers **2**–**4** as the sole products (Figure 1).

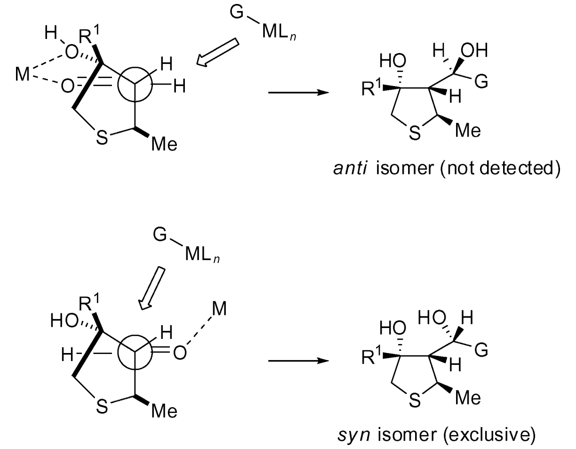
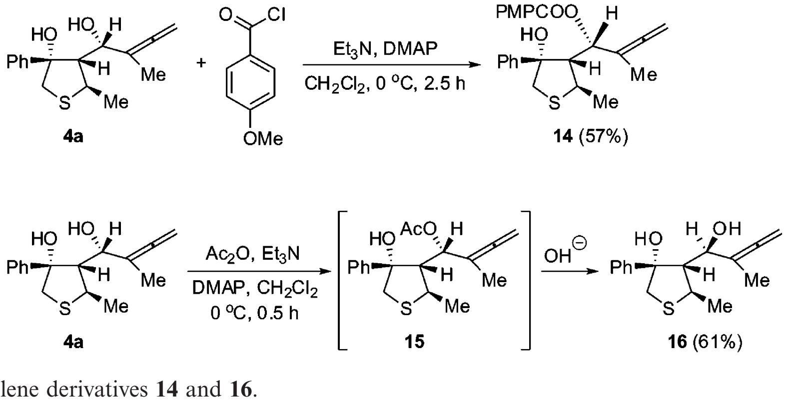


Figure 1. Model to explain the observed 1,2-*syn* stereochemistry.

As expected, diol **4a** might be selectively benzoylated, as a result of the differences in reactivities of both hydroxy groups (tertiary benzylic OH vs. secondary allenic OH), in the presence of 4-methoxybenzoyl chloride, triethylamine and 4-dimethylaminopyridine to provide 4-methoxybenzoate **14** (Scheme 3). More interesting was the regiospecific epimerization at the carbinolic stereocentre when allenol **4a** was intended to be acetylated; this shows the capacity of the method to prepare an array of tetrahydrothiophenes bearing stereochemical diversity. Previous to the epimeri-



Scheme 3. Preparation of allene derivatives **14** and **16**.

zation reaction, the secondary allenol group was probably acetylated to give intermediate **15**, which suffers displacement by hydroxide through a bimolecular nucleophilic substitution (S_N2) to afford **16** (Scheme 3).

Conclusions

We achieved efficient Barbier-type carbonylallylation, bromoallylation and allenylation reactions of tetrahydrothiophene-3-carbaldehydes in aqueous media, which proceeded with full regio- and diastereocontrol. The simple reaction protocol, which affords functionalized adducts and the chemically and biologically interesting tetrahydrothiophene moiety, is thus very appealing.

Experimental Section

General Methods: ^{1}H and ^{13}C NMR spectra were recorded with a Bruker Avance-300, Varian VRX-300S or Bruker AC-200 spectrometer. NMR spectra were recorded in $CDCl_3$ solutions, unless otherwise stated. Chemical shifts are given in ppm relative to TMS (^{1}H, 0.0 ppm), or $CDCl_3$ (^{13}C, 76.9 ppm). Low- and high-resolution mass spectra were recorded with a HP5989A spectrometer by using the electronic impact (EI) or electrospray modes (ES) unless otherwise stated. Specific rotation $[a]_D$ is given in $10^{-1}\,°\,cm^2\,g^{-1}$ at 20 °C, and the concentration (*c*) is expressed in g per 100 mL. All commercially available compounds were used without further purification.

General Procedure for the Synthesis of Homoallylic Alcohols 2 by the Zinc-Promoted Reaction of Allyl Bromides with Tetrahydrothiophene-3-carbaldehydes 1 in Aqueous Medium Containing NH_4Cl: The appropriate allyl bromide (1.0 mmol) was added to a well-stirred suspension of the corresponding tetrahydrothiophene-3-carbaldehyde **1** (0.5 mmol) and zinc powder (65 mg, 1.0 mmol) in aqueous saturated THF/NH_4Cl (1:5, 5 mL) at room temperature. The mixture was stirred at the same temperature until complete disappearance of the aldehyde (TLC). Saturated aqueous sodium hydrogen carbonate (2.5 mL) was added at 0 °C, and the mixture was warmed to room temperature before it was extracted with ethyl acetate (3×3 mL). The organic extract was washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (hexanes/ethyl acetate) of the residue gave analytically pure compounds **2**. Spectroscopic and analytical data for some representative forms of **2** follow.

Homoallylic Alcohol 2a: Tetrahydrothiophene-3-carbaldehyde **1a** (50 mg, 0.22 mmol) afforded compound **2a** (43 mg, 74%) as a colourless solid after purification by flash chromatography (hexanes/ethyl acetate, 8:1). M.p. 148–150 °C (hexanes/ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.42 (m, 5 H), 5.58 (m, 1 H), 5.03 (m, 2 H), 4.00 (dd, *J* = 8.5, 6.6 Hz, 1 H), 3.72 (ddd, *J* = 8.5, 6.1, 1.5 Hz, 1 H), 3.44 and 2.81 (d, *J* = 11.8 Hz, each 1 H), 2.30 (m, 2 H), 2.12 (td, *J* = 8.5, 1.5 Hz, 1 H), 1.60 (d, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 141.8, 134.5, 128.6, 127.5, 125.2, 118.0, 88.7, 68.9, 61.5, 46.3, 40.7, 39.1, 24.6 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3460 cm^{-1}. MS (ES): *m/z* (%) = 265 (100) $[M + H]^+$, 264 (15) $[M]^+$. $C_{15}H_{20}O_2S$ (264.4): calcd. C 68.14, H 7.62, S 12.13; found C 67.80, H 7.35, S 11.82.

General Procedure for the Synthesis of Bromohomoallylic Alcohols 3 by the Tin-Promoted Reaction of 2,3-Dibromopropene with Tetrahydrothiophene-3-carbaldehydes 1 in Aqueous Medium Containing $BiCl_3$: 2,3-Dibromopropene (300 mg, 1.5 mmol) was added to a well-stirred suspension of the corresponding tetrahydrothiophene-3-carbaldehyde **1** (0.5 mmol), tin powder (89 mg, 0.75 mmol) and bismuth(III) chloride (31 mg, 0.1 mmol) in aqueous saturated THF/NH_4Cl (1:5, 5 mL) at 5 °C. The mixture was stirred at room temperature until complete disappearance of the aldehyde (TLC). Saturated aqueous sodium hydrogen carbonate (2.5 mL) was added at 0 °C, and the mixture was warmed to room temperature and extracted with ethyl acetate (3×3 mL). The organic extract was washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (hexanes/ethyl acetate or ethyl acetate/dichloromethane) gave analytically pure compounds **3**. Spectroscopic and analytical data for some representative forms of **3** follow.

Bromohomoallylic Alcohol 3a: Tetrahydrothiophene-3-carbaldehyde **1a** (50 mg, 0.22 mmol) afforded compound **3a** (41 mg, 55%) as a colourless oil after purification by flash chromatography (hexanes/ethyl acetate, 12:1). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.41 (m, 5 H), 5.58 and 5.46 (d, *J* = 1.7 Hz, each 1 H), 4.02 (m, 2 H), 3.64 (s, 1 H), 3.48 and 2.82 (dd, *J* = 12.0 Hz, each 1 H), 3.19 (d, *J* = 2.0 Hz, 1 H), 2.54 (m, 2 H), 2.10 (dd, *J* = 8.5, 1.7 Hz, 1 H), 1.58 (d, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 141.2, 130.1, 128.6, 127.7, 125.2, 119.5, 88.7, 67.3, 61.5, 47.7, 46.2, 39.1, 24.6 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3464 cm^{-1}. MS (ES): *m/z* (%) = 344 (100) $[M + 2 + H]^+$, 342 (98) $[M + H]^+$.

General Procedure for the Synthesis of α-Allenic Alcohols 4 by the Indium-Promoted Reaction of 3-Substituted 2-Propynyl Bromides with Tetrahydrothiophene-3-carbaldehydes 1: The appropriate propargyl bromide (1.5 mmol) was added to a well-stirred suspension of the corresponding tetrahydrothiophene-3-carbaldehyde **1** (0.5 mmol) and indium powder (344 mg, 3.0 mmol) in THF/H_2O (1:1, 5 mL) at 5 °C. The mixture was stirred at room temperature until complete disappearance of the aldehyde (TLC). Saturated aqueous sodium hydrogen carbonate (2.5 mL) was added at 0 °C, and the mixture was warmed to room temperature and extracted with ethyl acetate (3×3 mL). The organic extract was washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography (hexanes/ethyl acetate) gave analytically pure compounds **4**. Spectroscopic and analytical data for some representative forms of **4** follow.

α-Allenic Alcohol 4a: Tetrahydrothiophene-3-carbaldehyde **1a** (50 mg, 0.22 mmol) afforded compound **4a** (43 mg, 70%) as a colourless solid after purification by flash chromatography (hexanes/ethyl acetate, 6:1). M.p. 120–121 °C (hexanes/ethyl acetate). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.48 (m, 5 H), 4.92 (m, 2 H), 4.26 (br. s, 1 H), 3.93 (m, 2 H), 3.40 and 2.89 (d, *J* = 11.6 Hz, each 1 H), 2.84 (br. s, 1 H), 2.32 (dd, *J* = 9.8, 1.5 Hz, 1 H), 1.56 (m, 3 H), 1.52 (d, *J* = 6.3 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 203.8, 142.7, 128.6, 127.4, 125.2, 101.9, 87.9, 79.5, 68.4, 59.1, 45.5, 39.2, 22.2, 15.4 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3462, 1940 cm^{-1}. MS (ES): *m/z* (%) = 277 (100) $[M + H]^+$, 276 (9) $[M]^+$. $C_{16}H_{20}O_2S$ (276.4): calcd. C 69.53, H 7.29, S 11.60; found C 69.20, H 7.01, S 11.88.

General Procedure for the Synthesis of 1,3-Diols Acetonides 12 and 13 by the Protection of Diols 2 and 4: A solution of the appropriate diol (0.5 mmol) and pyridinium *p*-toluenesulfonate (ppTS; 13 mg, 0.05 mmol) in 2,2-dimethoxypropane (4 mL) was stirred at reflux until complete disappearance of the diol (TLC). The reaction mixture was filtered, and the filtrate concentrated under reduced pressure. Chromatography (hexanes/ethyl acetate) gave analytically pure compounds **12** and **13**. Spectroscopic and analytical data for some representative forms of **12** and **13** follow.

1,3-Diol Acetonide 13: Allenol **4a** (65 mg, 0.27 mmol) afforded compound **13** (63 mg 74%) was obtained as a colourless oil after purification by flash chromatography (hexanes/ethyl acetate, 5:1). ^{1}H NMR (300 MHz, CDCl$_3$, 25 °C): δ = 7.36 (m, 5 H), 4.88 (m, 2 H), 4.44 (m, 1 H), 4.11 (td, J = 7.1, 2.0 Hz, 1 H), 2.99 (s, 2 H), 2.61 (dd, J = 8.3, 2.0 Hz, 1 H), 1.81 (dt, J = 2.4, 0.7 Hz, 3 H), 1.51 (d, J = 6.6 Hz, 3 H), 1.51 and 0.91 (s, each 3 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$, 25 °C): δ = 205.6, 143.0, 128.6, 125.4, 125.1, 100.5, 98.6, 87.7, 77.3, 66.5, 49.6, 47.3, 40.6, 30.7, 30.6, 23.9, 15.8 ppm. IR (CHCl$_3$): $\tilde{\nu}$ = 1942 cm^{-1}. MS (ES): m/z (%) = 317 (100) [M + H]$^+$, 316 (21) [M]$^+$.

Supporting Information (see also the footnote on the first page of this article): Complete characterization data and experimental procedures for compounds **2b**–**f**, **3b**, **4b**–**d**, **12**, **14** and **16**.

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