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Selective synthesis of optically active allenic and homopropargylic alcohols from propargyl chloride

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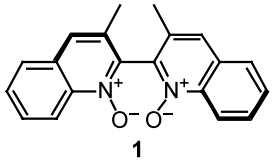
Abstract—Optically active allenic and homopropargylic alcohols were obtained selectively by a chiral *N*-oxide-catalyzed reaction of aldehydes with propargyltrichlorosilane and allenyltrichlorosilane, prepared in situ from propargyl chloride.

1. Introduction

Optically active allenic and homopropargylic alcohols are versatile building blocks that enjoy wide application in chemical synthesis.[1] Hence, the enantioselective addition of propargyl or allenyl metals to carbonyl compounds[2,3] provides a potentially practical method for the synthesis of these synthetically useful compounds. However, metallotropic rearrangement between propargyl and allenyl species results in poor chemoselectivity and a mixture of allenic and propargylic alcohols is often obtained. Recently, Kobayashi and co-workers reported that copper-catalyzed silylation of propargyl chloride with trichlorosilane produced propargyltrichlorosilane, whereas nickel-catalyzed silylation gave allenyltrichlorosilane selectively.[4] In order to avoid isomerization[5] during distillation, the silanes prepared were reacted directly with aldehydes in the presence of dimethylformamide as a Lewis base promoter, to afford homopropargylic alcohols from allenylsilane and allenic alcohols from propargylsilane. Shortly thereafter, the chemistry of propargyl- and allenyltrichlorosilanes was utilized for asymmetric allenylation or homopropargylation: Iseki and co-workers reported that chiral formamide-catalyzed addition of a mixture of propargyl- and allenyltrichlorosilane (3:1) to pivaldehyde afforded the corresponding allenic alcohol in 55% yield (−78°C, 2 weeks) with 95% e.e.[6] However, an asymmetric process for the selective synthesis of optically active allenic and propargylic alcohols from the same source (propargyl chloride) employing a chiral Lewis base is yet to be reported. We have previously reported the enantioselective allylation of aldehydes catalyzed by chiral *N*-oxides.[7–9] Herein, we describe the first example of the selective preparation of optically active homopropargylic and allenic alcohols from propargyl chloride.



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2. Results and discussion

We have recently reported a convenient one-pot method for the preparation of optically active homoallylic alcohols from allylic halides utilizing chiral *N*-oxide **1** as a Lewis base catalyst.[7b] We adopted this methodology to the selective formation of the homopropargylic and allenic alcohols. According to Kobayashi's procedure,[4] propargyl chloride was reacted with trichlorosilane in the presence of nickel bis(acetylacetate) as a catalyst to afford allenyltrichlorosilane preferentially (method A, **3**:**4** = >30:1). After switching the solvent from tetrahydrofuran to dichloromethane, benzaldehyde and chiral *N*-oxide **1** was added at −78°C. We were gratified to find that the reaction proceeded smoothly to afford homopropargylic alcohol (**5a**:**6a** = >30:1) with 52% e.e. (Table 1, entry 1).[10] Though the enantioselectivities are moderate, other aromatic and an aliphatic aldehydes (entries 2–4) also

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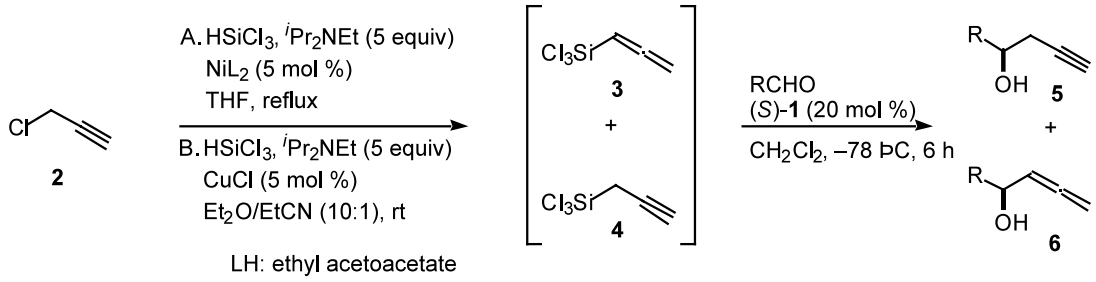
Table 1. Selective synthesis of optically active allenylic and homopropargylic alcohols



Entry	Method	Aldehyde	Adduct				
				Yield (%)[a]	**5**:**6**[b]	E.e. (%)[c,d]	Config.[e]
1	A	Ph	**5a**	65	>30:1	52	*R*
2		4-$MeOC_6H_4$	**5b**	62	>30:1	40	*R*
3		4-ClC_6H_4	**5c**	49	>30:1	46	*R*
4		$Ph(CH_2)_2$	**5d**	35	>30:1	23	*R*[f]
5	B	Ph	**6a**	72	1:15	54	*R*
6		4-$MeOC_6H_4$	**6b**	76	1:9	62	*R*[f]
7		4-ClC_6H_4	**6c**	48	1:9	49	*R*[f]
8		$Ph(CH_2)_2$	**6d**	44	1:10	22	*R*[f]

[a] Combined isolated yield.
[b] Determined by ^1H NMR.
[c] Enantiomeric excess of the major isomer.
[d] Determined by HPLC.
[e] Assigned by comparison with optical rotation and/or retention time on chiral HPLC in Refs. 2b, 3e, 6.
[f] Assigned by analogy.

afforded homopropargylic alcohols with high selectivity (>30:1) using method A. Lower reactivities and enantioselectivities were observed with the aliphatic aldehyde **5d** (entry 4). This trend is consistent with those seen in the allylation of aldehydes with allyltrichlorosilane catalyzed by chiral *N*-oxide **1**.[7a]

On the other hand, cuprous chloride-catalyzed silylation gave propargyltrichlorosilane preferentially (method B, **3**:**4** = 1:15), which reacted with benzaldehyde in the presence of chiral *N*-oxide **1** to afford allenic alcohol (**5a**:**6a** = 1:15) in 54% e.e. (entry 5).[10] 4-Methoxybenzaldehyde (entry 6) gave the best enantioselectivity of 62% e.e., while 4-chlorobenzaldehyde exhibited 49% e.e. (entry 7). Here again, lower reactivity and enantioselectivity were observed with hydrocinnamaldehyde (entry 8). Although the enantioselectivities are still modest, it is noteworthy that these data are the first example of enantioselective allenylation of aromatic aldehydes with propargylsilane catalyzed by Lewis base.

3. Conclusion

We have demonstrated that optically active allenic and homopropargylic alcohols can be obtained selectively by the chiral *N*-oxide-catalyzed reaction of aldehydes with propargyltrichlorosilane and allenyltrichlorosilane, prepared in situ from propargyl chloride. The present reaction provides the first example of enantioselective allenylation of aromatic aldehydes with propargylsilane catalyzed by Lewis base. Studies into design modifications of chiral *N*-oxides to further enhance enantioselectivity are currently in progress.

4. Experimental

4.1. General

All reactions were carried out under an Ar atmosphere with magnetic stirring in oven-dried glassware. HPLC analysis was performed on a JASCO PU-1580/UV-1575 (flow rate: 1.0 mL/min) using chiral column (Daicel CHIRALPAK AD, AS or CHIRALCEL OD). Optical rotations were taken with a JASCO DIP-370 digital polarimeter. ^1H NMR spectra were recorded at 270 MHz on a JEOL EX-270 spectrometer. The spectroscopic data of the adducts were compared with those in the literature.

4.2. Homopropargylation of aldehydes with allenyltrichlorosilane prepared in situ from propargyl chloride (method A)

4.2.1. 1-Phenyl-3-butyn-1-ol, 5a. Trichlorosilane (0.1 mL, 2.0 equiv.) was added to a stirred solution of propargyl chloride **2** (55 mg, 1.5 equiv.) and nickel bis(acetylacetate) (5 mg, 5 mol%) in tetrahydrofuran (5 mL) at rt under Ar atmosphere. After checking the ratio of **3** and **4** by ^1H NMR of the aliquot of the reaction mixture, the solvent was evaporated by rotary evaporator in vacuo. The residue was dissolved in

dichloromethane (2 mL) and cooled to −78°C. To this solution, a solution of benzaldehyde (50 mg) and (*S*)-**1** (15 mg) in dichloromethane (1 mL) was added via cannula and the whole was stirred for 6 h at the same temperature. The reaction was quenched with saturated $NaHCO_3$. The whole was extracted with ethyl acetate, and the organic extract was successively washed with brine and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product, which was purified by column chromatography on silica gel (15:1 hexane/EtOAc) to provide **5a**[3e] (45 mg, 65%, **5a**:**6a** = >30:1) as a colorless oil. $[\alpha]_D^{21}$ +27.2 (*c* 1.0 $CHCl_3$), t_R (AD, hex/2-propanol = 19:1), 14.5 min (major), 16.0 min (minor).

1-(4-Methoxyphenyl)-3-butyn-1-ol, 5b:[3e] t_R (AS, hex/2-propanol = 9:1), 15.0 min (major), 17.0 min (minor);
1-(4-Chlorophenyl)-3-butyn-1-ol, 5c:[3e] t_R (OD, hex/2-propanol = 39:1), 22.0 min (major), 24.0 min (minor);
1-Phenyl-5-hexyn-3-ol, 5d:[3e] t_R (AS, hex/2-propanol = 39:1), 13.0 min (major), 12.5 min (minor).

4.3. Allenylation of aldehydes with propargyltrichlorosilane prepared in situ from propargyl chloride (method B)

4.3.1. 1-Phenyl-2,3-butadien-1-ol, 6a. Trichlorosilane (0.1 mL, 2.0 equiv.) was added to a stirred solution of propargyl chloride **2** (55 mg, 1.5 equiv.) and cuprous chloride (3 mg, 5 mol%) in ether–propionitrile (10:1, 5 mL) at rt under an Ar atmosphere. After checking the ratio of **3** and **4** by ^1H NMR of the aliquot of the reaction mixture, the solvent was evaporated by rotary evaporator in vacuo. The residue was dissolved in dichloromethane (2 mL) and cooled to −78°C. To this solution, a solution of benzaldehyde (50 mg) and (*S*)-**1** (15 mg) in dichloromethane (1 mL) was added via cannula and the whole was stirred for 6 h at the same temperature. The reaction was quenched with saturated $NaHCO_3$. The whole was extracted with ethyl acetate, and the organic extract was successively washed with brine and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product, which was purified by column chromatography on silica gel (15:1 hexane/EtOAc) to provide a 1:15 mixture of **5a** and **6a**[6,11] (50 mg, 72%) as a colorless oil. $[\alpha]_D^{21}$ −41.0 (*c* 1 $CHCl_3$), t_R (AD, hex/2-propanol = 19:1), 21.5 min (major), 23.0 min (minor).

1-(4-Methoxyphenyl)-2,3-butadien-1-ol, 6b:[12] t_R (AS, hex/2-propanol = 9:1), 21.5 min (major), 23.0 min (minor);
1-(4-Chlorophenyl)-2,3-butadien-1-ol, 6c:[12] t_R (AS, hex/2-propanol = 49:1), 24.0 min (major), 26.5 min (minor);
1-Phenyl-4,5-hexadien-3-ol, 6d:[6] t_R (OD, hex/2-propanol = 9:1), 9.0 min (major), 12.5 min (minor).

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and allenic alcohols in 48 and 52% e.e., respectively. These results suggest that the presence of nickel bis(acetylacetate) and cuprous chloride have no detrimental influence on enantioselection in these reactions.

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