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A Simple Approach To Separate a Mixture of Homopropargylic and Allenic Alcohols

Fan Fu, Kim Le Mai Hoang, and Teck-Peng Loh*

Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore
teckpeng@ntu.edu.sg

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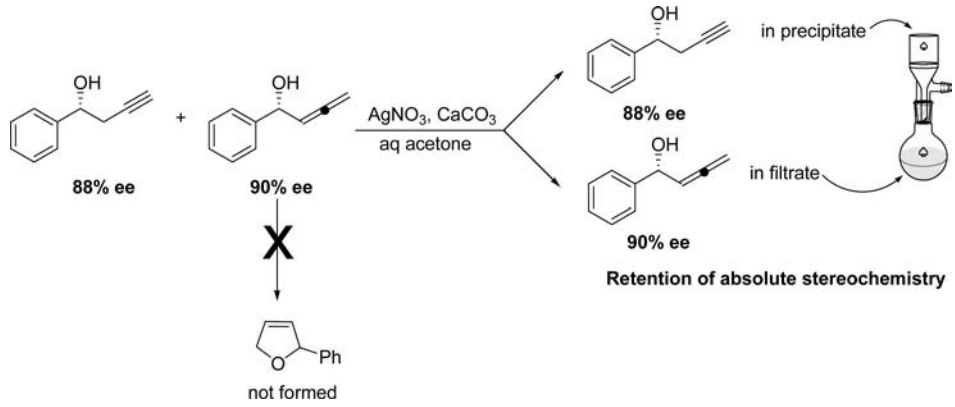
ABSTRACT



A simple and practical approach to separate homopropargylic alcohol from allenic alcohol has been developed. It involves the formation of an insoluble silver acetylide species between silver nitrate and homopropargylic alcohol in aqueous acetone which can be separated from the allenic alcohol through a simple filtration. The homopropargylic alcohol can subsequently be recovered by hydrolysis with 1 N HCl. This protocol has been applied to the separation of a mixture of chiral homopropargylic and allenic alcohols in excellent yields with retention of absolute stereochemistry.

The availability of efficient synthetic methods for achieving absolute stereoselectivity by catalytic processes in the production of optically active compounds is of considerable current interest because such products could be used as chiral building blocks for the synthesis of valuable chiral substances. Recent progress in organic synthesis suggests that the optically active homopropargylic and allenic alcohols[1] are versatile building blocks for the enantioselective synthesis of many biologically active compounds.[2] Hence, many methods have been developed for the enantioselective synthesis of this class of compounds.[3] The asymmetric addition of propargyl or allenyl metals to carbonyl compounds provides a practical method for the synthesis of these

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(2) (a) O'Malley, S. J.; Leighton, J. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 2915. (b) Yamamoto, H. In *Comprehensive Organic Synthesis, vol. 2*, Heathcock, C. H., Ed.; Pergamon Press: Oxford, 1991; Vol. 2, Chapter 1.3, pp 81−98. (c) Epsztein, R. In *Comprehensive Carbanion Chemistry*; BuncelE., Durst, T., Eds.; Elsevier: Amsterdam, 1984; part B, p 107. (d) Helal, C. J.; Magriotis, P. A.; Corey, E. J. *J. Am. Chem. Soc.* **1996**, *118*, 10938. (e) Matsummura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. J. *J. Am. Chem. Soc.* **1997**, *119*, 8738.

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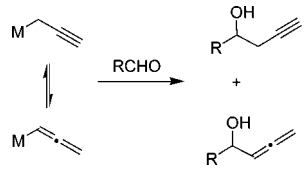
important intermediates.[4] However, this process often leads to both the homopropargylic and allenic alcohols at the same time due to the metallotropic rearrangement[5] between propargyl and allenylic metal species (Scheme 1).

Scheme 1. Metallotropic Rearrangement between Propargyl and Allenyl Species

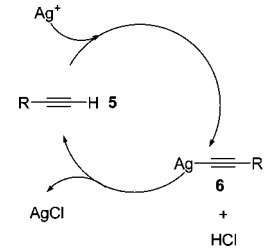


Recent work from our laboratory has demonstrated the successful application of the novel chiral (*S*,*S*)-iPr-pybox−In(III) complex and the chiral (*S*)-Binol−In(III) complex as efficent Lewis acid catalysts for the enantioselective propargylation and allenylation of aldehydes.[6] Although poor regioselectivity was observed due to metallotropic rearrangement, the addition of allenyltributyl stannane to a variety of aldehydes including aromatic, α,*β*-aromatic and aliphatic aldehyes catalyzed by the chiral complexes afforded the respective allenic and homopropargylic alcohols mixture in good yields and high enantioselectivities (up to 92% ee).

The enantiomeric enriched homopropargylic and allenic alcohols mixture are of little synthetic value if they are inseparable via the usual chromatographic separation. Previous work by Claesson et al.[7] reported the synthesis of 2,5-dihydrofurans via cyclization of allenic alcohols catalyzed by silver(I) nitrate. With an interest in this report, we attempt to convert the allenic alcohols in the mixture into 2,5-dihydrofurans with the homopropargylic alcohols remaining intact. The 2,5-dihydrofurans can be separated from homopropargylic alcohols via column chromatography as they have different R_f value.

In our initial study, we added a 1:1 ratio of 1-phenylbut-3-yn-1-ol **1a** and 1-phenylbuta-2,3-dien-1-ol **2a** (0.5 mmol) to a mixture of silver(I) nitrate (0.6 mmol) and calcium carbonate (0.6 mmol) in acetone/water (0.4 mL: 0.6 mL). The reaction mixture was stirred in the dark for 6 h, and a brown suspension was formed. The brown precipitate was removed via suction filtration, and the filtrate was dried with $MgSO_4$ before removal of excess solvent. Surprisingly, the heterocyclic-forming reaction did not proceed essentially as intended. The ^{1}H NMR spectrum showed no traces of the homopropargylic alcohol and the 2,5-dihydrofurans, only the allenic alcohol was isolated in the filtrate. However, when we proceeded to treat the brown precipitated isolated earlier with 1 M HCl, the homopropargylic alcohol was isolated cleanly after extraction with ether. It is noteworthy that the homopropargylic alcohol was trapped in the precipitate and can only be isolated by extraction with ether after treatment with 1 M HCl. The formation of a precipitate in the presence of alcoholic or ammoniacal silver nitrate has long been used as a diagnostic test and a method of analysis for compounds containing a terminal acetylenic group.[8] The mechanism probably involves the formation of a complex between silver nitrate and calcium carbonate which reacts with alkynes **5** to afford the corresponding silver acetylide **6** that precipitated (Scheme 2). This silver acetylide

Scheme 2. Mechanistic Hypothesis for Ag-Catalyzed Reaction with Alkynes



precipitate can be isolated by filtration. In the presence of a proton source such as HCl, the silver acetylide species would be hydrolyzed, generating back the alkynes species **5**.

Having optimized the separation protocol, we extended this procedure to a series of racemic aromatic, α,*β* unsaturated and aliphatic homopropargylic and allenic alcohols mixture. The results are shown in Table 1. The various aromatic, α,*β* unsaturated and aliphatic allenic alcohols were separated from the homopropargylic alcohols cleanly with excellent yields. Moreover, when the chiral mixture of (*R*)-1-phenylbut-3-yn-1-ol **7** and (*R*)-1-phenyl-buta-2,3-dien-1-ol **8** was subjected to the separation protocol, (*R*)-1-phenylbut-3-yn-1-ol **7** was separated from (*R*)-1-phenyl-buta-2,3-dien-1-ol **8** cleanly with excellent yields and retention of absolute stereochemistry.

In conclusion, a simple and practical approach to separate homopropargylic alcohol from allenic alcohol has been developed. It involves the formation of an insoluble silver acetylide species in aqueous acetone which can be separated from the allenic alcohol through a simple filtration. The homopropargylic alcohol can subsequently be recovered by hydrolysis with 1 N HCl. This approach is operationally simple and can separate a wide variety of homopropargylic

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(5) Normally, propargyl and allenyl metal compounds furnish allenyl and propargylic adducts, respectively, in S_E2'-type additions to carbonyl.

(6) Manuscript in preparation.

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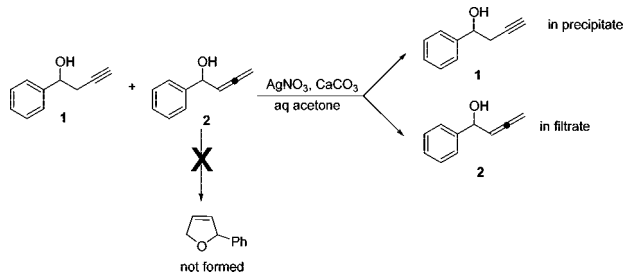
Table 1. Separation of Homopropargylic Alcohols and Allenic Alcohol Using $AgNO_3$ and $CaCO_3$



entry	R	product	yield[a](%)
1	Ph	**1a**:**2a**	81:93
2	4-ClC_6H_5	**1b**:**2b**	81:95
3	4-$OMeC_6H_5$	**1c**:**2c**	94:93
4	2-Napthyl	**1d**:**2d**	98:97
5	PhCHCH	**1e**:**2e**	80:96
6	$PhCH_2CH_2$	**1f**:**2f**	81:98
7	*n*-C_9H_{18}	**1g**:**2g**	92:95

[a] Yield is determined based on the amount of material recovered after the separation using $AgNO_3$ and $CaCO_3$.

and allenic alcohol mixtures in excellent yields with the retention of absolute stereochemistry. Hence, this catalytic procedure could be broadly applicable to many synthetic procedures.[9]

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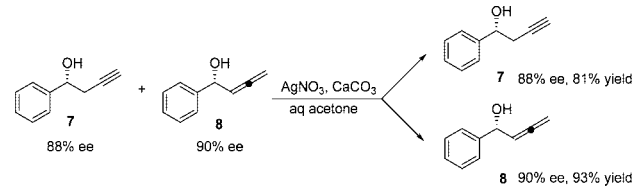
Scheme 3. Separation of Chiral Allenic and Homopropargylic Mixture



Supporting Information Available: Experimental details, characterization data, and stereochemical proofs. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) **Representative Procedure for Separation of Allenic and Propargylic Alcohol Mixture.** To a 8 mL sample vial equipped with a stirring bar were added $AgNO_3$ (1.2 equiv) and $CaCO_3$ (1.2 equiv) in acetone/water (0.6−0.4 mL). The homopropargylic and allenylic alcohol mixture (1 equiv) was added, and the mixture was stirred in the dark for 6 h to afford a brown precipitate in solution. The precipitate was separated via suction filtration, and the filtrate was dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to afford the pure allenic alcohol. The precipitate was treated with 1 M HCl (3 mL) and stirred vigorously for 5 min prior to extraction of the aqueous layer with diethyl ether (3 × 10 mL). The combined organic extracts was washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to afford the pure homopropargylic alcohol.