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A Chiral Electrophilic Selenium Reagent To Promote the Kinetic Resolution of Racemic Allylic Alcohols

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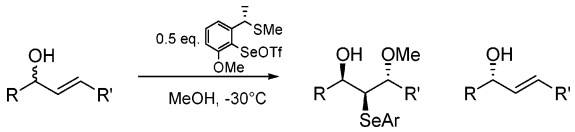
ABSTRACT



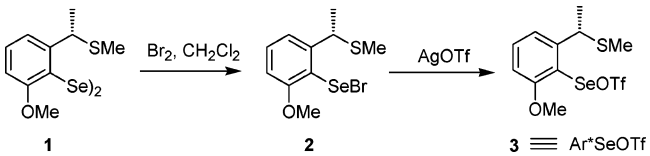
The first example of a kinetic resolution process promoted by electrophilic selenium reagents is reported. Racemic allylic alcohols react with half equivalents of a selenenylating agent in methanol leading to the regiospecific formation of the corresponding addition products with a very high level of facial selectivity (from 95:5 to 98:2 dr). The unreacted alcohols can be recovered in an optically enriched form (from 90 to 94% ee).

Chiral allylic alcohols have recently attracted great attention due to their stereodirecting propensity in diasteroselective reactions.[1] They can be considered valuable substrates to effect both synthetic[2] and mechanistic investigations.[3] The most common way to prepare chiral allylic alcohols involves asymmetric reductions,[4] elimination of iodo ketal,[5] and enzymatic,[6] as well as nonenzymatic,[7] kinetic resolutions. During the last 10 years, chiral nonracemic electrophilic selenium reagents were successfully employed in a number of enantioselectitive addition reactions with very high levels of facial selectivity.[8]

We now report that by combining the stereocontrol of the allylic hydroxy group with the facial selectivity of the chiral nonracemic selenium reagent it is possible to effect the kinetic resolution of racemic allylic alcohols. To the best of our knowledge, this is the first example of a kinetic resolution process promoted by an organoselenium reagent. This process allows a very common class of organic substrates to be obtained in an enantiomerically enriched form.

We have recently reported that the di-2-[methoxy-6-[(1*S*)-1-methylthio]ethyl]phenyl] diselenide **1** is a suitable precursor for the production of very efficient electrophilic reagents. As indicated in Scheme 1, the treatment of the diselenide **1** with bromine gives the aryl selenenyl bromide **2**. The triflate **3** can be prepared from **2** by reaction with AgOTf in CH_2Cl_2 at 0 °C.[9]

Scheme 1



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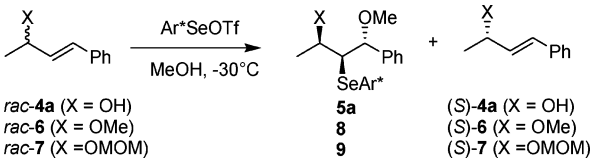
The kinetic resolution of racemic allylic derivatives could be obtained by effecting the methoxyselenenylation of the double bond using the electrophilic aryl selenenyl triflate **3** (Scheme 2).

Scheme 2



rac-**4a** (X = OH) *rac*-**6** (X = OMe) *rac*-**7** (X =OMOM) | **5a** **8** **9** | (*S*)-**4a** (X = OH) (*S*)-**6** (X = OMe) (*S*)-**7** (X =OMOM)

Preliminary experiments were carried out starting from the alcohol **4a**.

Two equivalents of the racemic allylic alcohol *rac*-**4a** reacted with 1 equiv of the selenenylating reagent **3** in a 10:1 mixture of CH_2Cl_2/MeOH at −30 °C afforded the addition product **5a** in a diasteroisomeric ratio of 98:2. A complete regioselectivity associated with a good facial selectivity (Table 1) was observed. The unreacted alcohol

Table 1. Preliminary Kinetic Resolution Results

racemate	reaction time (h)	addition products yield (%) (dr, %)	resolved products yield (%) (ee, %)
rac-**4a**	3	**5**, 46 (98:2)	(*S*)-**4a**, 45 (92)
rac-**6**	48	**8**, 40 (91:9)	(*S*)-**6**, 40 (82)
rac-**7**	20	**9**, 45 (97:3)	(*S*)-**7**, 40 (64)

(*S*)-**4a** could be obtained in an enantiomerically enriched form (92% ee) by column chromatography.

As reported in Scheme 2 and Table 1, the same procedure was also applied to the allylic ethers *rac*-**6** and *rac*-**7**. The best facial selectivity was obtained in the presence of the unprotected hydroxy group. These reaction conditions were therefore employed to effect the kinetic resolutions of a number of other allylic alcohols.

The results of these experiments are summarized in Table 2. It can be observed that, with only the exception of the cyclic allylic alcohol **4h**, all the reactions proceeded with complete regioselectivity. The Markovnicov addition products **5a**−**f** were obtained in the cases of the trans-disubstituted olefins **4a**−**f,** and the anti Markownicov adduct **5g** was formed in the case of the monosubstituted olefin **4g**.

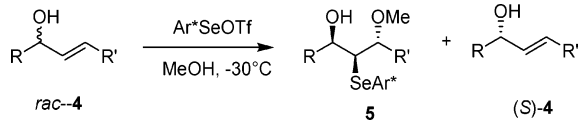
Table 2. Kinetic Resolution of Allylic Alcohols

	racemate **4**		adducts **5**		resolved **4**	
	R′	R	yield (%)	dr	yield (%)	ee (%) (*S* value)
a	Ph-	Me-	46	98:2	45	92 (0.83)
b	4-Br-C_6H_4	Me-	43	96:4	43	92 (0.79)
c	4-Cl-C_6H_4	Me-	36	96:4	35	94 (0.66)
d	4-Me-C_6H_4	Me-	40	95:5	42	90 (0.76)
e	2-Br-5-MeO-C_6H_3	Me-	47	97:3	48	94 (0.90)
f	Me-	Me-	35	85:15	25[a]	60[a] (0.30)
g	H-	n-Bu-	35	60:40	20	20 (0.08)
h	-$(CH_2)_3$-		35	mix isomers	15	20 (0.06)

[a] Not isolated. Yield and ee calculated by GC−MS.

The kinetic resolution process seems to be more efficient when the aryl-substituted olefins **4a**−**e** were employed. In these cases, in fact, two diasteroisomeric addition products **5a**−**e** were obtained in good chemical yields and with very high diasteroisomeric ratios (from 95:5 to 98:2). Moreover, the enantiomeric excess of the recovered allylic alcohols was similarly very good (from 90 to 94% ee). Only in the case of the cyclic allylic alcohol **4h** did the reaction afford a complex mixture of isomers, which could not be separated, and the unreacted alcohol showed a moderate enantiomeric excess. The diasteroisomeric ratios, as well as the enantiomeric excesses, were determined by NMR and in some cases confirmed by GC−MS. In no case could the two diastereoisomeric addition products **5** be separated (Scheme 3).

Scheme 3

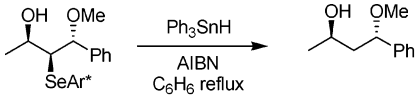


rac-**4** | **5** | (*S*)-**4**

The absolute configurations of the recovered alcohols (*S*)-**4a**−**d** and (*R*)-**4g** were assigned by comparison of the sign of the optical rotations with those reported in the literature.[6,10] By analogy with the alcohols (*S*)-**4a**−**d**, the *S* configuration was also assigned to **4e** and **4f**.

The selenium addition derivative **5a** was deselenenylated by treatment with Ph_3SnH and AIBN in refluxing benzene and afforded the (2*R*,4*S*)-4-methoxy-4-phenylbutan-2-ol **10** in 90% yield[11] (Scheme 4). Since the methoxyselenenylation

Scheme 4



5a | (-)-(*2R,4S*)-**10**

reaction is a stereospecific anti addition process, compound **5a** should have the 2*R*,3*S*,4*R* configuration. The same configuration can be assigned by analogy to the adducts **5b**−**f**.

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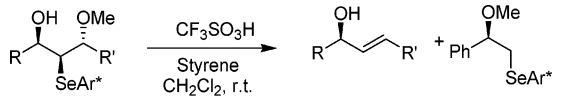
To effect a complete resolution process and to obtain the enantiomeric allylic alcohols also, the arylseleno and the methoxy groups must be eliminated from the addition products **5**. This elimination process was carried out in the cases of compounds **5a** and **5c**. The treatment of these compounds with a catalytic amount of CF_3SO_3H in the presence of 2 equiv of styrene afforded the corresponding (*R*)-allylic alcohols **4a** and **4c** in good yields and with an enantiomeric excess identical to the diasteroisomeric excess of the starting compounds (Scheme 5). The methoxyselenenylation product

Scheme 5



5a (d.e. 96%)
5c (d.e. 92%)

(*R*)-**4a** (e.e. 96%)
(*R*)-**4c** (e.e. 92%)

11

of styrene **11** was also obtained. This reaction can also be effected in the absence of styrene. In this case the deselenenylation process is slower, but it presents the considerable advantage that the arylseleno moiety is almost completely recovered as the diselenide **1**.

The syn relationship between the hydroxy and the arylseleneno groups in compounds **5** and the anti Markovnicov orientation observed in the methoxyselenenylation of the monosubstituted olefin **4g** is probably due to a stabilizing interaction between the allylic oxygen and the selenium atom (Figure 1). This interaction, as already observed in other selenium electrophilic addition reactions to allylic alcohols

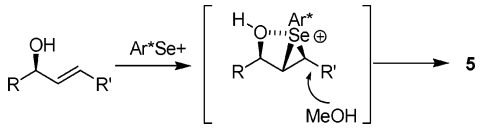


Figure 1. Stereocontrolling property of the hydroxy group.

and ethers, provides a very high regio- and stereoselectivity in the formation of the seleniranium intermediate.[12] In the case of the cyclic alkenol this participation is probably forbidden and this can explain the formation of a mixture of isomers.

In summary, we have described here a new method to effect the kinetic resolution of allylic alcohols using a methoxyselenenylation reaction promoted by an electrophilic chiral non racemic selenium reagent. The procedure has been optimized in order to obtain both enantiomers in an high enantiomerically enriched form and in very good chemical yields.

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Supporting Information Available: Physical and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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