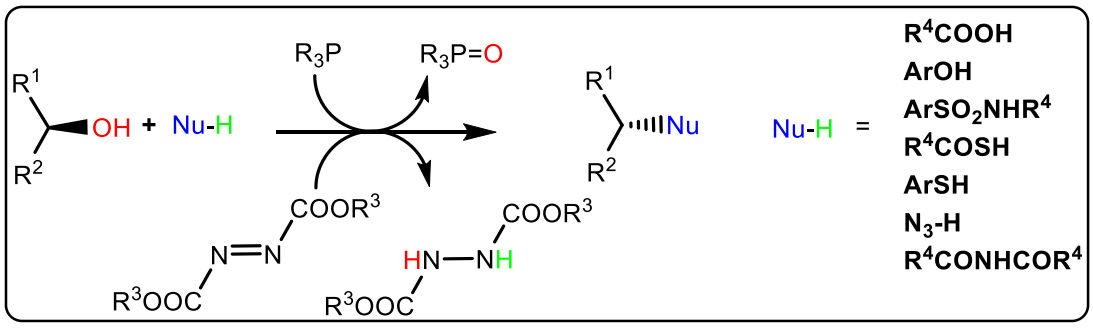
Chapter 3 Section-I

3.I.1 Mitsunobu Reaction

Mitsunobu reaction is mediated by the interaction between dialkylazodicarboxylate and a trialkyl or triarylphosphine pronucleophile of a primary or secondary alcohol (tertiary alcohols are sometimes used) dehydration coupling to (NuH) (**Scheme 1**). During the course of the reaction, azo species are reduced to hydrazine derivatives and phosphines are oxidized to phosphine oxides. The reaction is named after its discoverer, Taiyo Mitsunobu, who first reported this chemistry in 1967.[1,2] With chiral secondary alcohols, a complete reversal of stereochemistry is observed. Suitable pronucleophiles in traditional Mitsunobu reaction include (thio)carboxylic acids, (thio)phenols, imides, and sulfonamides, which promote the formation of C-O, C-S, and C-N bonds. Successful reactions with typical Mitsunobu reagents diethyl azodicarboxylate (DEAD; R3 in Scheme 1 = Et) or diisopropyl azodicarboxylate (DIAD; R3 in **Scheme 1** = iPr) require the presence of a pronucleophile. It is generally accepted that the pKa should be about 11 or less. This 'pKa standard' arises from the reaction mechanism whereby the betaine resulting from the reaction among DEAD and PPh_3 has a pKa of ~13 and can abstract an acidic proton from the nucleophile, otherwise, the alkylation of DEAD will occur. The Mitsunobu reaction yield under mild and neutral conditions, typically in ambient conditions. Standard solvents used in the reaction are THF, diethyl ether, dichloromethane, and toluene, although more polar solvents are sometimes used, including ethyl acetate, acetonitrile, and DMF.



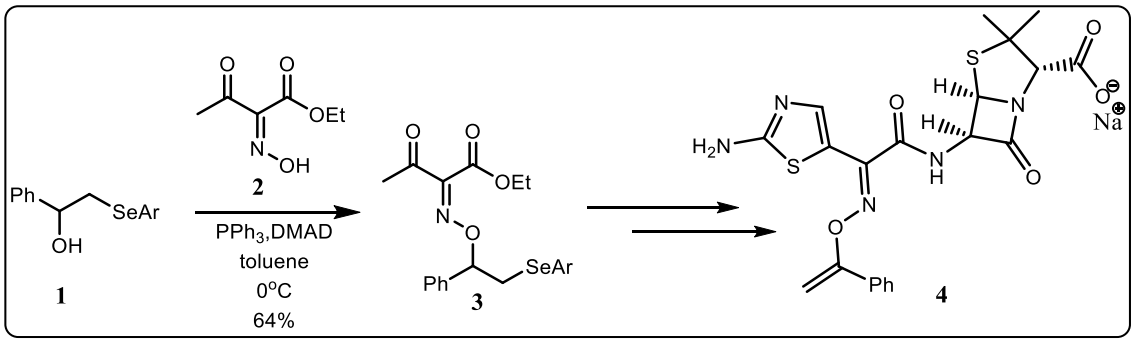
Scheme 1: The Mitsunobu Reaction

3.I.1.1 Oxygen pronucleophiles

The clean inversion of the stereogenic centres in secondary alcohols is arguably the most significant characteristic of the Mitsunobu reaction.[1–5] As a result, hydrolysis of the ester produced by the dehydrative pairing of a carboxylic acid and a secondary alcohol will typically result in the production of the inverted alcohol with a high degree of enantiomeric purity. Other oxygen pronucleophiles that have gained popularity as coupling partners in the Mitsunobu reaction alongside carboxylic acids include phenols and alcohols itself in intramolecular reactions. Here are a few more recent oxygen pronucleophiles that have been introduced for this reaction successfully.

3.I.1.1.1 Oximes

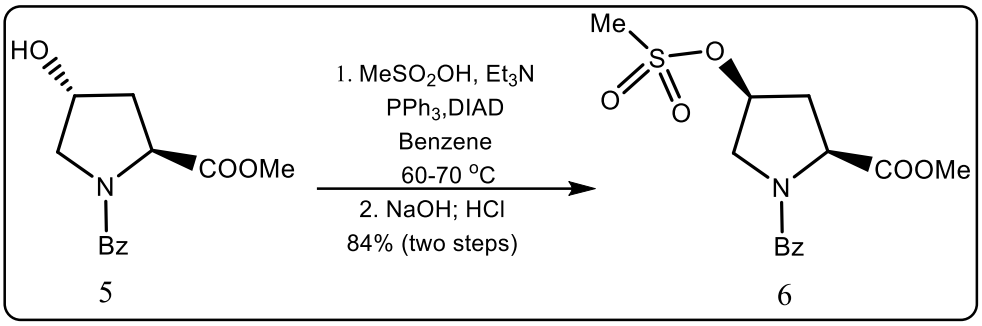
Stachulski at SmithKline Beecham showed that oximes work effectively as oxygen pronucleophiles en route to several O-vinyl penicillin derivatives, such as **4**. (**Scheme 2**).[6] Dimethyl acetylenedicarboxylate (DMAD) was utilised along with PPh_3 in place of the typical DEAD or DIAD. Similar to DIAD, DMAD can produce an activated betaine by a Michael-type reaction when combined with phosphines. Even though the yield of the Mitsunobu reaction was very moderate (64%), it is unknown if any efforts were taken to optimise the reaction.



Scheme 2: Oximes as oxygen nucleophiles in the Mitsunobu reaction.

3.I.1.1.2 Sulphonic acid

Sulfonic acids were demonstrated by a team at Bristol-Myers Squibb to be appropriate pronucleophiles in the Mitsunobu reaction.[7] The usual inversion of stereochemistry of secondary alcoholic substrates was seen, just like with carboxylic acids (**Scheme 3**). The chemistry is adaptable and functions equally well at high scales.



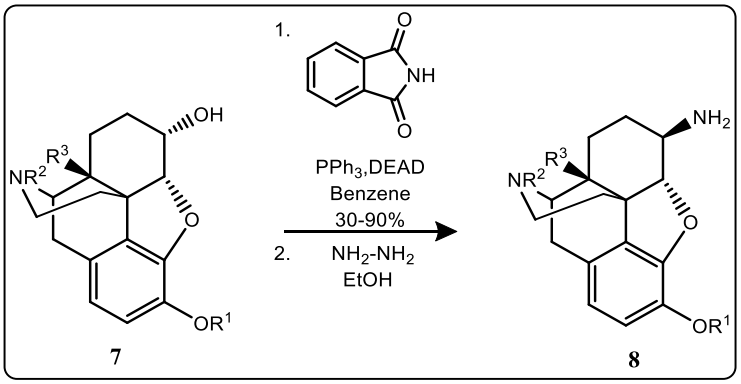
Scheme 3: Synthesis of a sulfonate ester employing a sulfonic acid as the Pronucleophile

3.I.1.2 Nitrogen pronucleophiles

Sulfonamides are good nucleophiles in the Mitsunobu reaction, with pKa values of around 10.[2–5] Azide can be delivered in a variety of ways, including as hydrazoic acid, metal azide, or diphenylphosphoryl azide. Azide is also an excellent nucleophile (DPPA).[2] However, caution must be exercised since too much PPh_3 could cause the organic azide to change into the equivalent iminophosphorane, which is the first step of the Staudinger reaction to produce primary amines.

3.I.1.2.1 Phthalimide: synthesis of primary amines.

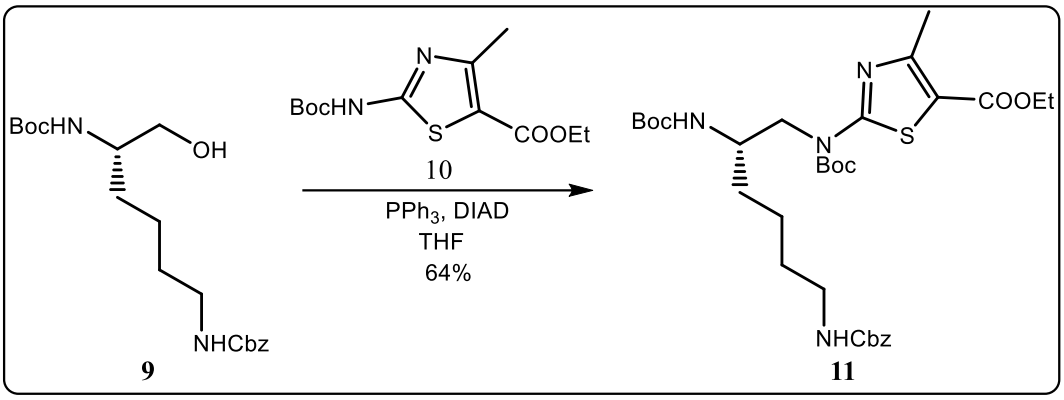
Alcohols can be converted into protected primary amines by utilising phthalimide as the nucleophile.[8] The resulting N-alkylated phthalimide is then subjected to hydrazinolysis, which is similar of the Gabriel synthesis, to release the free primary amine. This chemistry is demonstrated in **Scheme 4** where dihydrocodeine derivatives of β-naltrexamine were created.



Scheme 4: Phthalimide in the Mitsunobu reaction permits a two-step conversion of alcohols to primary amines.

3.I.1.2.2 Activated aminoazoles

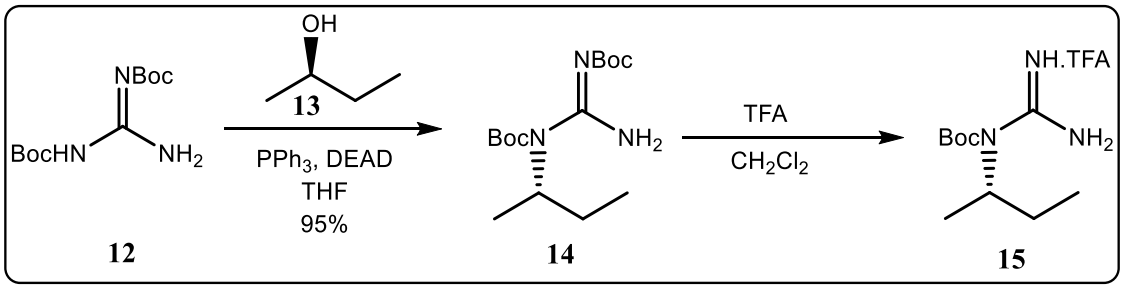
Molecumetics Ltd.'s Kim and Kahn have shown that Boc-protected 2-aminoazoles, such **10**, are sufficiently active to smoothly pass the Mitsunobu reaction to produce certain lysine and arginine analogues (Scheme 5).[9] Considering their high yields, it appears that the aliphatic Boc and Cbz carbamates did not interfere much, if at all, with the reaction, which is consistent with their higher pKa values of about.[16–18]



Scheme 5: Alkylation of a Boc-protected 2-aminoazole

3.I.1.2.3 Activated guanidines

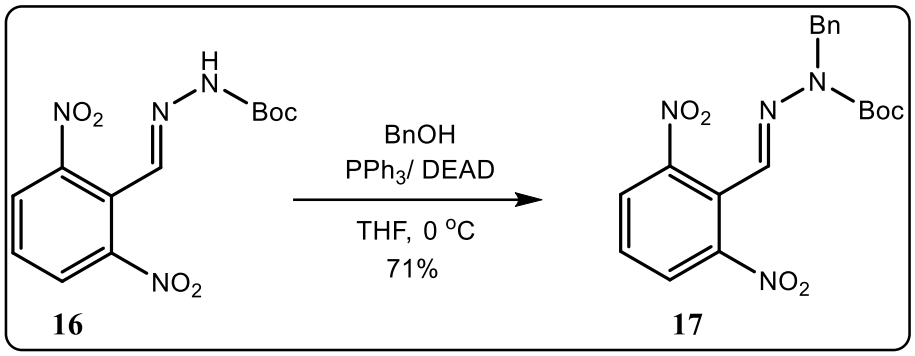
Kozikowski and Dodd demonstrated that bis-Boc-protected guanidine **12** linked to a range of alcohols in outstanding yields, resulting in the generation of mono-substituted guanidines, such as **15**, after deprotection (**Scheme 6**).[10] The reactions continued with inversion, as predicted.



Scheme 6: Synthesis of substituted guanidines exploiting the Boc protecting group as an activating group.

3.I.1.2.4 Activated hydrazones.

The reactivity of tosyl- and Boc-hydrazones in the Mitsunobu reaction was studied by chemists at Johnson and Johnson.[11] Tosyl hydrazones, which display an acidic NH group of the sulfonamide type, were ideal substrates because they coupled to primary, secondary, aliphatic, and benzylic alcohols in the majority of cases with very good to exceptional yields (**Scheme 7**). But at the other hand, without electron-withdrawing groups to reduce the pKa of the BocNH group, Boc hydrazones remained inert.



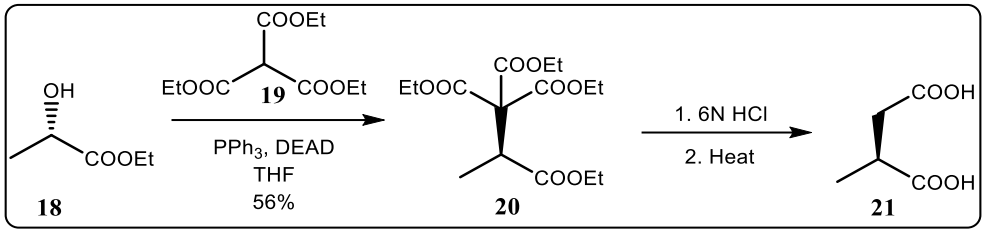
Scheme 7: Alkylation of Tosyl and Boc hydrazides

3.I.1.3 Carbon pronucleophiles

The synthesis of natural compounds and medicines depends heavily on processes that establish carbon-carbon bonds, and novel methods to create these links may represent a paradigm shift in conventional drug retrosynthesis.[12] The comparatively high pKa of carbon acids is partly to blame for the dearth of reports of using Mitsunobu chemistry to carry out such conversions.[13] The first to demonstrate that this chemical is feasible was Falck and Manna, who did so by utilising lithium cyanide to substitute an activated alcohol, delivering the matching organic nitrile as a result.[14] The Mitsunobu reaction has become more important in the creation of carbon-carbon bonds in recent times.

3.I.1.3.1 Triethyl methanetricarboxylate.

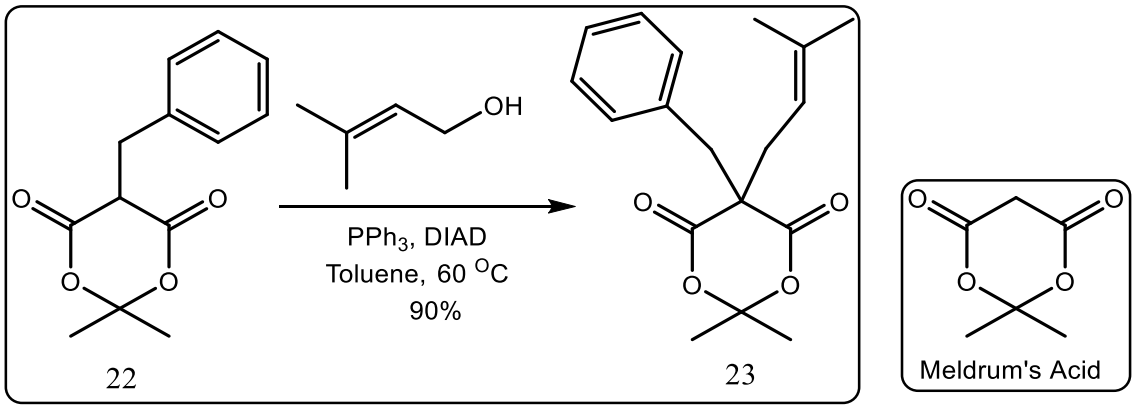
Triethyl methanetricarboxylate **19** is sufficiently acidic to link to alcohols under Mitsunobu conditions without eroding optical purity, according to research from Palmisano's team.[15] As an illustration, (S)-2-methylsuccinic acid **21** was created by alkylating (S)-ethyl lactate **18** and then undergoing acidic hydrolysis and decarboxylation (**Scheme 8**).



Scheme 8: Carbon–carbon bond formation in the Mitsunobu reaction with the triply -activated methine of triethyl methanetricarboxylate.

3.I.1.3.2 Meldrum's acid.

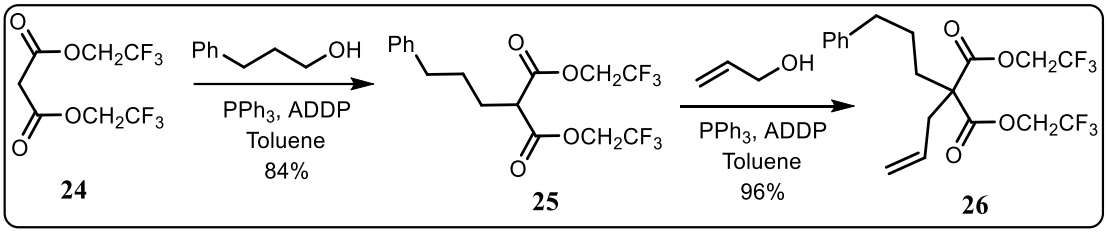
A useful synthon in organic synthesis is Meldrum's acid.[16] It was predicted that Meldrum's acid, which has "abnormally low" pKa of 4.97,[17] would be a useful pronucleophile in the Mitsunobu reaction. In particular, it can be challenging to manage the alkylation reaction when there are two acidic hydrogen atoms present.[18] Shing et al. demonstrated that C-alkylation of mono-substituted Meldrum's acids progresses in very good yields to produce the 5,5-disubstituted derivatives notwithstanding the failure of mono-C-alkylation of Meldrum's acid (**Scheme 9**).[18] Interestingly, isopropanol and 2-phenylethanol produced undesired products when combined with Meldrum's acid. The highly reactive primary allylic and arylmethyl alcohols required to be used in order for the reactions to be successful. A catalytic quantity of Pd(0) was needed in reactions with secondary allylic alcohols in order to encourage the regioselectivity of C- over O-alkylation.



Scheme 9: C-alkylation of C5 -mono-substituted Meldrum's acids

3.I.1.3.3 Bis(2,2,2-trifluoroethyl) malonates

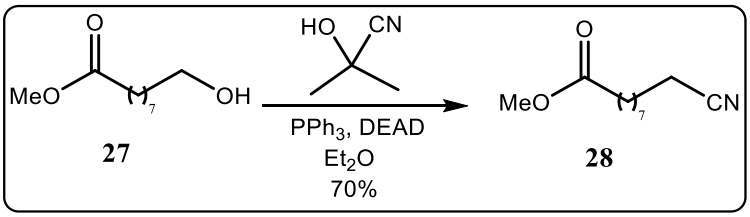
Malonic acid diesters resemble Meldrum's acid structurally, but they perform poorly as nucleophiles in the Mitsunobu reaction [13] because the active methylene protons have a much higher pKa of roughly.[13,19] Takacs reasoned that increasing the electron-withdrawing properties of the dialkyl malonate esters' alkyl components would result in a decrease in the pKa of the activated methylene bordered by the two carbonyls, activating it for further Mitsunobu chemistry.[20] In order to achieve this, his team created the bis(2,2,2-trifluoroethyl) malonate **24**, which was then C-alkylated with primary alcohols in good to exceptional yields (**Scheme 10**),[20] with no known O-alkylation. Secondary alcohols linked at best in a moderate yield. Takacs' discovery that monoalkylation might be regulated in addition to the observed regiocontrol is significant because it differs from the equivalent chemistry described with Meldrum's acid.[18]



Scheme 10: Activation of the malonate methylene function with greater electron -withdrawing 2,2,2-trifluoroethyl groups allows C-alkylation to proceed Smoothly

3.I.1.3.4 Acetone cyanohydrin.

Acetone cyanohydrin was used as the HCN equivalent to achieve the direct conversion of primary alcohols to nitriles (**Scheme 11**).[21]

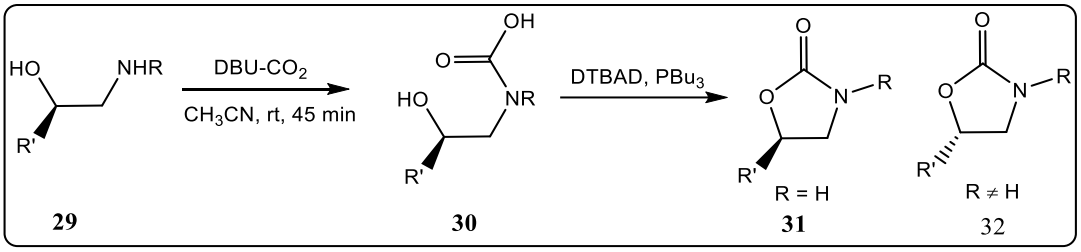


Scheme 11: Conversion of alcohols to nitriles with acetone cyanohydrin as a latent source of the pronucleophile HCN.

Szántay and colleagues demonstrated that, as long as the secondary alcohols were not sterically inhibited, this use of the Mitsunobu reaction was also compatible with them. This methodology for synthesising organic nitriles is particularly appealing because it does not use hazardous HCN or metal cyanide salts.

3.I.1.3.5 Carbamic acids.

The Mitsunobu reaction, where the alcohol could be intramolecular or intermolecular, has recently been employed to capture carbamic acids produced *in situ* as their carbamates.[22] It's interesting to note that the substitution of the nitrogen atom appears to affect the stereochemical course of the Mitsunobu step: when R was carbon, the predicted inversion was observed; while retention was found when R was hydrogen (**Scheme 12**).



Scheme 12: Synthesis of carbamates. Note the nature of the R group dictates the stereochemical course of the reaction.

3.I.1.4 New azodicarbonyl species

Due to identical R_f values, DEAD and/or its hydrazine byproduct DEAD-H_2 can frequently contaminate the Mitsunobu product. Many of the novel DEAD analogues that have been reported in recent years, particularly those that make it easier to purify the reaction mixture, are shown in Figure 1. Most of them are readily available commercially , but they can also be made by reacting hydrazine with the right chloroformate, then oxidising it to the desired azo species.

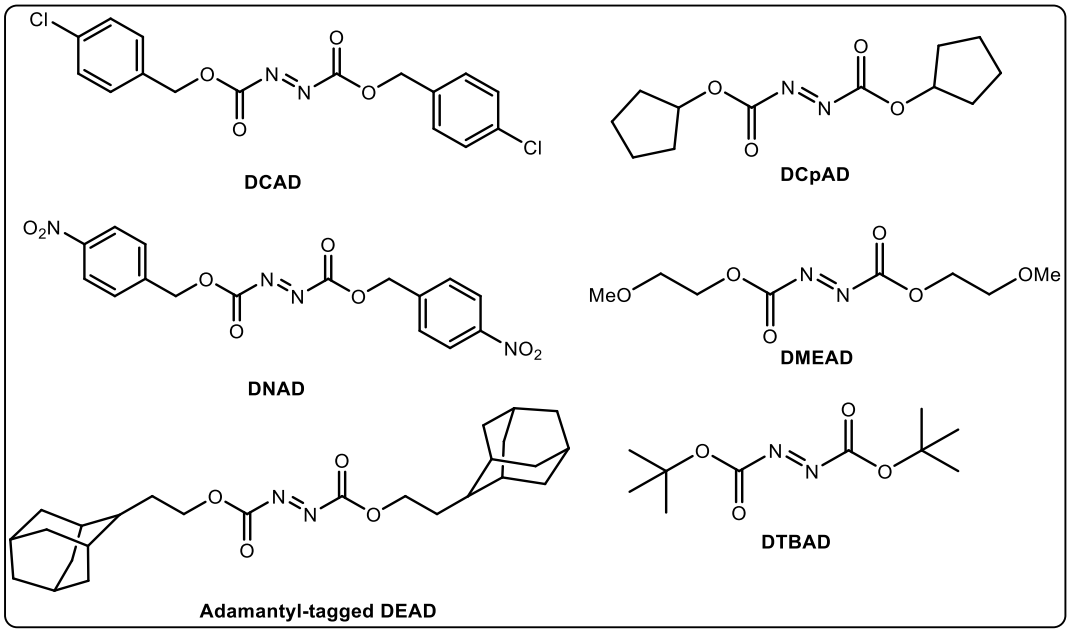


Figure 1: DEAD/DIAD alternatives that facilitate reaction mixture purification.

3.I.1.4.1 Di-4-chlorobenzyl azodicarboxylate (DCAD).

The orange solid DCAD, which is easier to handle than the liquids DEAD and DIAD, can be stored at ambient temperature, and is almost as potent, is produced by replacing the ethyl groups of DEAD with 4-chlorobenzyl groups.[23] The majority of the hydrazine byproduct of DCAD produced in the Mitsunobu reaction can be eliminated by precipitation from dichloromethane, and purification by column chromatography may be aided because it has a different polarity from the hydrazine by-product of DIAD.

3.I.1.4.2 Di-4-nitrobenzyl azodicarboxylate (DNAD).

As a newer substitute for DEAD and DIAD, Dai and colleagues have created DNAD.[24] DNAD is a stable crystalline solid at ambient temperature, just like DCAD. The hydrazine by-product of DNAD is substantially less soluble in CH_2Cl_2 and THF than that of DIAD, which allows it to precipitate from such solvents despite the fact that it is at least as effective as DIAD.

3.I.1.4.3 Di-cyclopentyl azodicarboxylate (DCpAD).

Another variation of DEAD and DIAD is DCpAD.[25] Similarly, DCpAD is a solid orange substance that can be kept at room temperature. According to the Mitsunobu reaction, DCpAD looks to be just as effective as DEAD.

3.I.1.4.4 Di-2-methoxyethyl azodicarboxylate (DMEAD).

In the form of DMEAD, which has 2-methoxyethyl moieties in place of the isopropyl groups, Japanese chemists created yet another counterpart of DEAD.[26] Regarding Mitsunobu reactions, DMEAD is roughly as effective as DIAD. The reduced hydrazine by-product can, however, be eliminated in an aqueous work-up, which is significant. We can also extract more DMEAD into the aqueous phase. Filtration can fully eliminate the need for column chromatography because Ph_3PO can be eliminated. Now that DMEAD is on the market, even if it costs a little more than DIAD, the time and money saved by avoiding chromatography make this new azodicarbonyl economical.

3.I.1.4.5 Di-tert-butyl azodicarboxylate (DTBAD).

DTBAD's "strength" is derived from its fundamental reactivity to acid, which causes its conversion to gaseous by-products, in contrast to the other DIAD forms.[27] In addition to decomposing DTBAD (and its hydrazine by-product), work-up with acid also extracts the phosphine (and its oxide) into the aqueous, suggesting that column chromatography may not even be necessary when DTBAD is combined with diphenyl(2-pyridyl)phosphine (Ph_2PPy). DTBAD is also marketed, just like DCAD and DMEAD.

3.I.1.4.6 Adamantyl-tagged derivatives of DEAD

Two DEAD analogues were created by Curran and colleagues containing adamantly-based groups in place of the ethyl groups.[28] Due to the host-guest interaction between the adamantyl tags (guests) and the cyclodextrin, the azo parents and hydrazine by-products, respectively, have higher retention durations on cyclodextrin-bonded silica gel than do DEAD and DEAD-H_2 (hosts). Purification of the Mitsunobu products is facilitated by the various retention times.

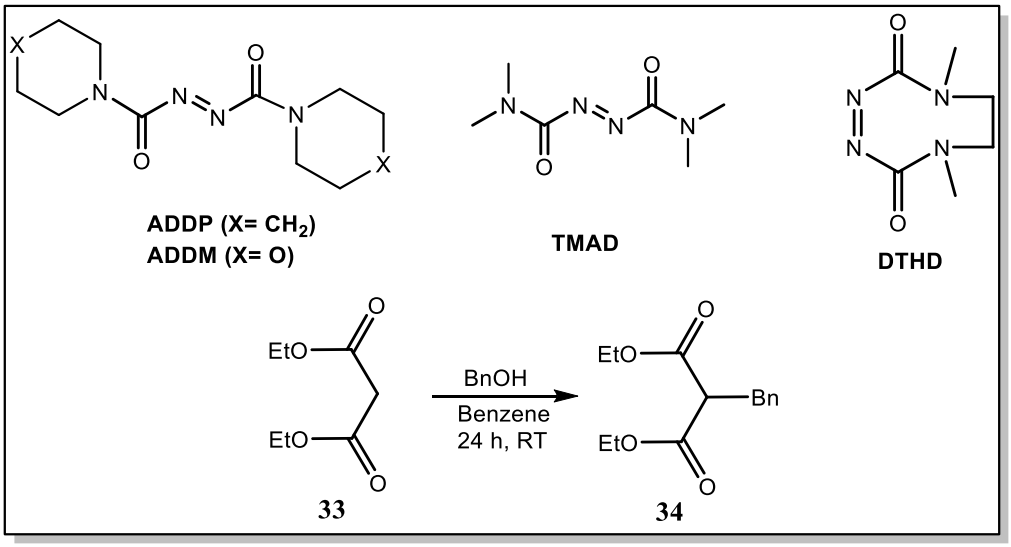
3.I.1.4.7 N,N,N′,N′-Tetramethyldicarboxamide (TMAD), 1,1′-(azodicarbonyl)dipiperidine (ADDP) and 4,7-dimethyl-3,5,7-hexahydro-1,2,4,7-tetrazocin-3,8-dione (DHTD)

More effective coupling agents [29] are produced by converting the azodicarboxylates' esters to amides; in the reaction with phosphines, the resulting betaine intermediates are highly basic and can deprotonate pronucleophiles with pKa values higher than 11. The superiority of these compounds over DEAD is illustrated by an excellent example of C-

alkylation of diethyl malonate using 1,1′-(azodicarbonyl)dipiperidine (ADDP), N,N,N′,N′- tetramethyldicarboxamide (TMAD), and 4,7-dimethyl-3,5,7- hexahydro-1,2,4,7-tetrazocin-3,8-dione (DHTD).[30] A noteworthy fact of ADDP is that it can be precipitated out by adding hexanes or ether, as well as from THF reaction media.

3.I.1.4.8 Azodicarbonyl dimorpholide (ADDM).

According to literature, azodicarbonyl dimorpholide (ADDM; **Scheme 13**), a morpholine counterpart of ADDP, is likewise a potent azo species for the Mitsunobu reaction.[31] The fact that ADDM and its hydrazine by-product can both be entirely eliminated from the reaction mixture by an aqueous work-up marks a significant contrast between ADDM and ADDP. Furthermore, it is established that the Mitsunobu reaction produced by the combination of PPh_3 on resin and ADDM was chromatography-free.



DEAD-PPh_3	ADDP-PBu_3	TMAD-PBu_3	DHTD-PBu_3
2%	**56%**	**66%**	**75%**

Scheme 13: Comparison of the efficiencies of Mitsunobu co-reagents in the C -alkylation of diethyl malonate. Percentages are yields of product **34**.

3.I.1.5 New phosphine species

The main obstacle to the Mitsunobu reaction, is triphenylphosphine or triphenylphosphine oxide contamination of reaction products. Since excess phosphine may be eliminated via evaporation and the tributylphosphine oxide is extractable into

water during aqueous work-up, replacing triphenylphosphine with tributylphosphine was one of the first methods to simplify the purification of the reaction mixture. Tributylphosphine should not be used on a wide scale because it is pyrophoric, even though moving from triphenylphosphine to it seems to have no impact on product outcome. Another substitute for PPh_3 is 1,2-bis(diphenylphosphino)ethane (DPPE). Because of its higher polarity, the resultant bis-oxide precipitates from the reaction medium and may thus be eliminated by straightforward filtration before chromatography.[32] Finally, additional solution phase phosphine species have been produced (Figure 2,3), which will be addressed below, in addition to several reports of triphenylphosphine on resin as a way to simplify the purification of Mitsunobu reactions.

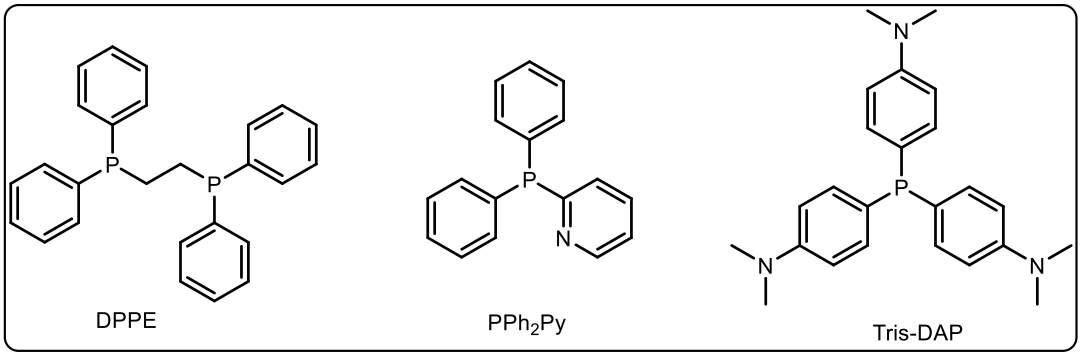


Figure 2: PPh_3 alternatives that simplify purification of the Mitsunobu reaction.

3.I.1.5.1 2-Pyridyl-diphenylphosphine (PPh_2Py).

The yield of the conversion is tolerated when one of the phenyl rings in PPh_3 is replaced with a pyridine ring to produce 2-pyridyl-diphenylphosphine (PPh_2Py).[33] However, the addition of a basic nitrogen significantly enhances reaction mixture purification by enabling the elimination of extra PPh_2Py and its oxide byproduct into an acidic aqueous layer throughout reaction work-up.

3.I.1.5.2 Tris(dimethylamino)phosphine (Tris-DAP).

Tris(dimethylamino)phosphine, often known as Tris-DAP,[34] is produced by inserting dimethylamino groups into the para locations of each of the phenyl rings of PPh_3. Similar to Ph_2PPy, a straightforward acidic aqueous work-up can likewise remove Tris-DAP and its phosphine oxide by-product.

3.I.1.5.3 Phosphoranes/ylides.

Tsunoda and colleagues successfully synthesized cyanomethylenephosphorane (CMMP) and cyanomethylenetributylphosphorane (CMBP) (Figure 3). CMMP and CMBP act as both the azotype reagent and the phosphine.[35,36] The pronucleophile is deprotonated by the neutral phosphorane in order to produce a positively charged phosphonium ion, which converts the alcohol into a useful leaving group. These phosphoranes have the unique ability to deprotonate pronucleophiles, which are typically insufficiently acidic for the Mitsunobu reaction. However, there are a few limitations, such as their low commercial availability and the requirement for reaction temperatures over the boiling points of the solvents, which necessitates re-sealable reaction containers.

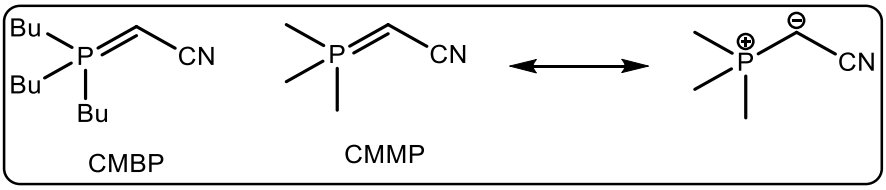
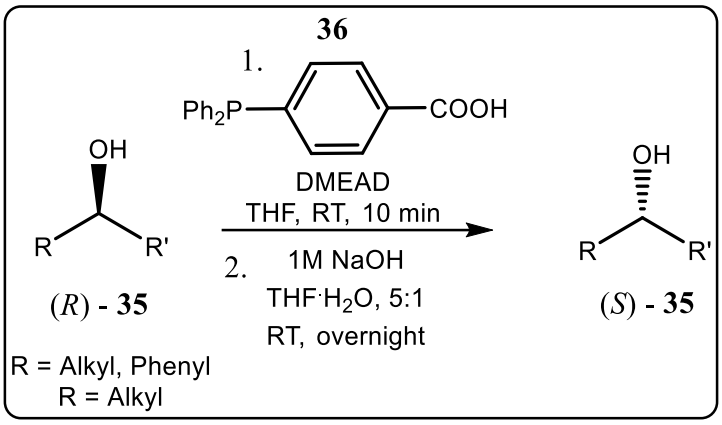


Figure 3: Phosphoranes/ylides that function as combined equivalents of phosphines And azodicarbonyls.

3.I.1.5.4 4-(Diphenylphosphino)benzoic acid.

Recently 4-(diphenylphosphino)benzoic acid **36**, is developed commercially which is a combination of a reducing agent and a pronucleophile.[37] This phosphine was linked with secondary alcohol in the vicinity of DMEAD, as shown in **Scheme 14**, to produce, following saponification, the matching inverted secondary alcohols. Due to the extractability of DMEAD/DMEAD-H_2 and 4-(diphenylphosphoryl)benzoic acid into the water layer during work-up, the compounds not only displayed high stereochemical purities but were also sufficiently chemically pure.



Scheme 14: Built-in phosphine: inversion of a secondary alcohol with a carboxylic acid that also carries the requisite triarylphosphine functionality.

3.I.2 Result and Discussion

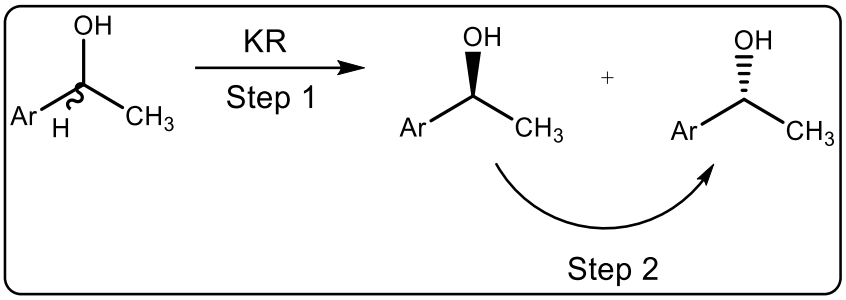
Many different types of enzymes' stereoselectivity is used to produce optically active molecules.[38] Particularly crucial are the lipase-catalyzed kinetic resolutions of carboxylic acid derivatives and racemic alcohols through acylation in organic solvents (**Scheme 1**). One of the enantiomers is isolated as a free alcohol and the other is obtained as a (or unreactive) ester derivative simultaneously with high enantiomeric purities when the value of the enantiomeric ratio (E; the ratio of the specificity coefficients of the enantiomers) [39] for such a reaction is high sufficiently.

Chromatographic processes can be time-consuming when separating these resolution products. A more significant flaw of conventional resolutions (chemical or enzymatic) is that for some uses, 50% of the initial material has the opposite absolute configuration. Our goal has been to present a one-pot method that can be employed to get the necessary enantiorner with a theoretical yield of 100% when computed using the racemic starting material while avoiding the above-mentioned drawbacks of lipase-catalyzed resolution. Racemization of the isomer *in situ* during the reaction or subsequent resolution after the unwanted enantiomer has been separated from the resolved mixture have both been used as methods of recycling unwanted enantiomers as a method of accomplishing this.[40-42] An inversion at the stereogenic centre has been suggested as another method for producing the correct stereochemistry.[43-50] As a reasonable option for the enantioconvergent S_N2 step in one-pot synthesis, we reverted to this method and used resolution followed by the Mitsunobu reaction [51] of a free alcohol enantiomer using redox couple of diethyl azodicarboxylate (DEAD)-triphenylphosphine (PPh3) and a

carboxylic acid (**Scheme 1**). The chemically produced and original optically active esters become configurationally identical when the RCOOH of the S_N^2 step matches to the acid constituent of the ester in the resolved mixture, increasing the chemical yield of the ester enantiomer to 100% in principle.

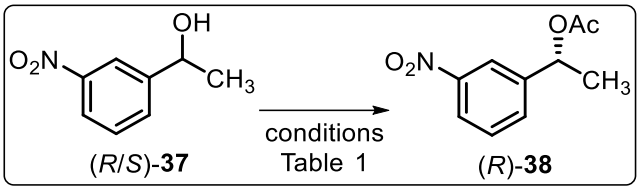
3.I.3.0 One pot Kinetic Resolution-Mitsunobu Reaction

In this chapter we shall discuss our approach to use a one-pot strategy of combining enzyme mediated KR and Mitsunobu esterification. In the present reaction we chose to use metal acetates as source of nucleophile. The acetate ion is more readily available in the salt of acetic acid due to its enhanced ionic character. Conversion of less reactive isomer of alcohol to the acetate by inversion of configuration by Mitsunobu reaction is done with acetic acid as the source of acetate ion.



Scheme 15: Separation of isomers by KR.

The nucleophilicity of acetate ions in the metal salt of AcOH will be appreciably more and will favor the displacement procedure. With this aim we have screened number of metal acetates for the Mitsunobu step in the one-pot sequence of this reaction. The standard reaction was performed on 1-(3-nitrophenyl)ethan-1-ol (*R*/*S*-**37**), where the first step of KR was done with suitable immobilized bio-catalyst and with vinylacetate as source for acetylation. After standardizing conditions for this step, we performed parallel set of example, where the reaction mixture was immediately subjected to Mitsunobu conditions with metal acetates to convert unreacted alcohol to acetate (**Scheme 16**).



Scheme 16: One-pot KR-Mitsunobu with MOAc as nucleophile

The first step of KR was performed using Novozyme-435 as the immobilized enzyme and vinyl acetate as the acetylating agent. The conditions of using excess vinyl acetate (10 eq.), diethyl ether as solvent, with the beads of Novozyme-435 (50 % w/w) as biocatalyst and performing the reaction at room temperature was optimized after several experiments. After the KR is achieved, the reaction mixture was filtered to remove the solid matrix of immobilized enzyme and the reaction mixture was treated with metal acetate, DEAD and Ph_3P for the Mitsunobu reaction step (Table 1). The reaction with AgOAc was smooth at room temperature and high conversion to acetate **38** was achieved. The product was isolated and its optical purity measured by HPLC analysis on chiral column. The overall reaction furnished the desired acetate in excellent chemical yield and optical purity.

Table-1 Screening of different MOAc for one-pot KR-Mitsunobureaction[a]

No	MOAc	Acetate (*R*)-38	
		Yield (%)	e.e. (%)b
1	AgOAc	94	96.2
2	$Hg(OAc)_2$	81	91.4
3	$Pb(OAc)_2$	70	76.2
4	$Cu(OAc)_2$	84	84.9
5	$Mn(OAc)_2$	78	86.2
6	$Mg(OAc)_2$	82	73.9
7	$Co(OAc)_2$	76	66.9
8	$Ni(OAc)_2$	80	83.3

*[a]For (R/S)-**37** (0.30 g); vinyl acetate (10.0 eq.); Novozyme-435 (0.15 g; 50 % w/w); dry Et_2O (10 mL); r.t. (24 h for KR step-1 & 24 h for Mitsunobu step-2); For step-2: dry CH_3CN (15 mL); DEAD (2.0 eq.); Ph_3P (2.0 eq.); MOAc (2.0 eq.). Reaction for step 2 required reflux conditions, except for entry 1. [b]Determined by HPLC analysis (Amylose, IPA (5.0%) in hexane; 18.42 min for (R)-**37** and 22.37 min for (S)-**37**). For experimental procedure see ESI.*

good conversion and purity; however, the reaction mixture was needed to be held at reflux temperature. We extended the study to compare efficacy of different

metal acetates as source of acetate ion for the second step of this one-pot sequence. In most of the cases moderate yields were obtained, though good selectivity was observed. The other metal acetates have stronger M-OAc bonds and were not as effective; however, their lower cost and other considerations may offer some advantage.

Another experiment was conducted where the reagents for Mitsunobu step were introduced without removing the biocatalyst. With (*R*/*S*)-**37**, the acetate (*R*)-**38** was isolated in comparable parameters (89 % Y and 92 % ee).

3.I.3.1 Generation of *in situ* CH_3COOAg by mixing $AgNO_3$ and metalacetates

In the effort to improve the conditions with lesser reactive metal acetates, we explored the scope of addition of readily available silver nitrate in the one-pot reaction.

Table-2 Use of sub-stoichiometric amount of **$AgNO_3$** to activate less reactive **$Co(OAc)_2$** and **NaOAc.**[a]

No	Conditions (eq.)		Acetate (*R*)-38	
	$AgNO_3$	**$Co(OAc)_2$**	**Yield (%)**	**e.e. (%)[b]**
1	--	2.00	76	66.9
2	0.25	1.75	81	87.8
3	0.50	1.50	88	88.0
	$AgNO_3$	**NaOAc**	**Yield (%)**	**e.e. (%)[b]**
4	--	2.00	81	83.6
5	0.25	1.75	87	85.2
6	0.50	1.50	94	90.1

[a]*For (R/S)-**37** (0.30 g); vinyl acetate (10.0 eq.); Novozyme-435 (0.15 g; 50 % w/w); Et_2O (10 mL); r.t. 24 h for KR step-1 &reflux conditions, 24 h for Mitsunobu step-2; For step-2: Dry THF (15 mL); DEAD (2.0 eq.); Ph_3P (2.0 eq.);Rest of the conditions same as Table-1. For experimental procedure see ESI.*

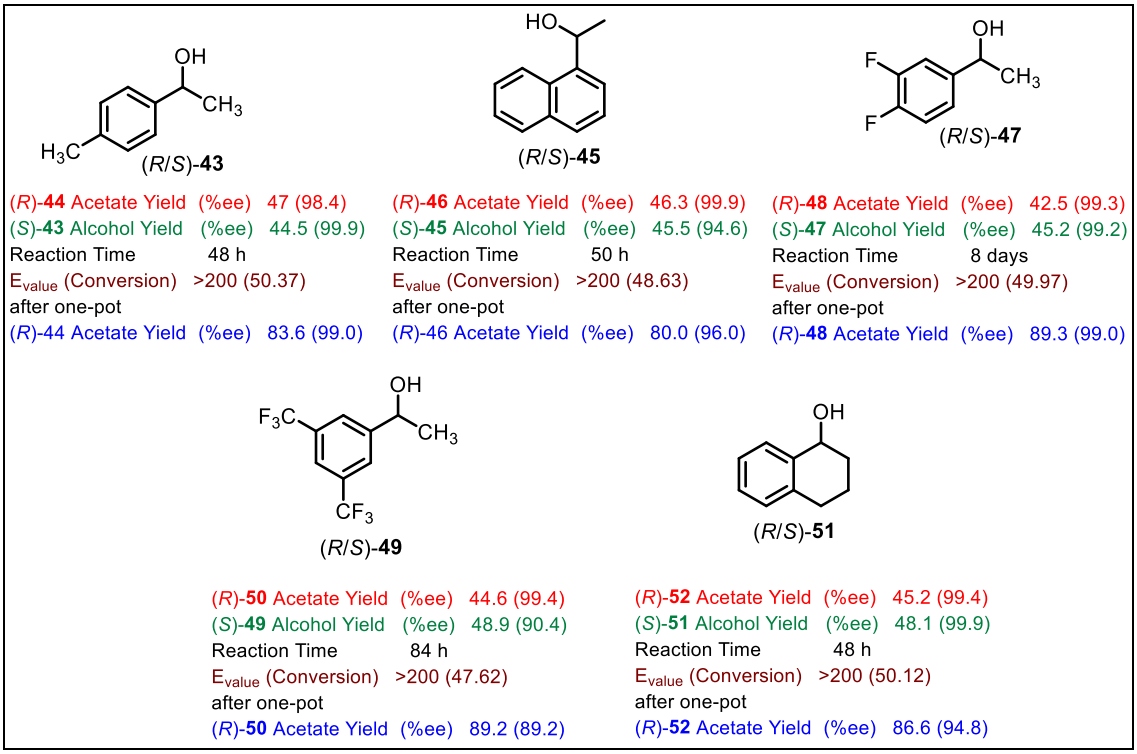
We envisaged the *in situ* exchange between acetate salt and silver nitrate leading to the formation of AgOAc, which is more effective in the Mitsunobu inversion step, results are presented in Table 2. Although the cost of both silver salts don't differ much, the availability of $AgNO_3$ is more widespread, also the protocol can be extended with any derivatives of carboxylic acids.

3.I.3.2 Substrate Screening for One pot KR – Mistunobu Protocol

In the initial part of this study the conditions for KR were established and then extended for one-pot methodology. In most of the cases we found that Novozyme-435 was found to be suitable biocatalyst to bring about highly selective KR, except 3,5-difluoro derivative (*R*/*S*)-**47**, for which Steapsin lipase was more efficient. In all the cases the inversion of configuration was completely controlled under the Mitsunobu conditions. This also enabled us to compare the two operations and establish the effective stereochemical control in the inversion step. The standard conditions developed for (*R*)-**38** could be extended for other examples, in few cases slightly better optical purity of acetate was observed in one-pot method. Having established suitable conditions with AgOAc for synthesis of optically pure (*R*)-**38**, by one-pot combination of KR and Mitsunobu reaction, the method was then extended for number of examples (Table 3). This study confirms the generality of this method to access the acetates in high chemical yield and in optical purity.

.**Table 3.** Examples of comparison of KR and one-pot KR-Mitsunobu reaction as shown in **Scheme 15**[a]

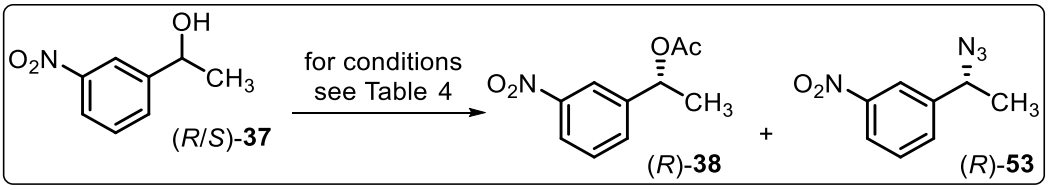
(*R*/*S*)-**37**	(*R*/*S*)-**39**	(*R*/*S*)-**41**
(*R*)-**38** Acetate Yield (%ee) 49 (98.3) (*S*)-**37** Alcohol Yield (%ee) 48 (99.7) Reaction Time 24 h E_{value} (Conversion) >200 (50.55) after one-pot (*R*)-**38** Acetate Yield (%ee) 94.2 (96.1)	(*R*)-**40** Acetate Yield (%ee) 48.3 (97.8) (*S*)-**39** Alcohol Yield (%ee) 46.1 (99.9) Reaction Time 24 h E_{value} (Conversion) >200 (50.53) after one-pot (*R*)-**40** Acetate Yield (%ee) 85.5 (99.0)	(*R*)-**42** Acetate Yield (%ee) 48.6 (94.7) (*S*)-**41** Alcohol Yield (%ee) 45.8 (99.9) Reaction Time 16 h E_{value} (Conversion) >194 (51.33) after one-pot (*R*)-44 Acetate Yield (%ee) 82.3 (96.3)



[a]*General conditions as per Table 1. Reaction Time is for KR step 1 of the one-pot procedure, and 24 h for Mitsunobu step 2 E is enantiomeric ratio and c is conversion; Optical purity was determined by converting to alcohols by HCl mediated hydrolysis; Steapsin lipase (300 % w/w); dry THF.*

3.I.3.3 One pot KR-Mitsunobu by Sodium Azide

The chiral secondary azides are important precursors for accessing optically pure amines. Our process was then extended with azide as second nucleophile in Mitsunobu step.[52-56] The standard one-pot reaction with (*R*/*S*)-**37**, was performed with NaN_3 (**Scheme 17**). The acetate (*R*)-**38** was isolated in the same way, but the azide (*R*)-**53** was obtained in poor chemical yield (Table-4).This probably was due to low reactivity of NaN_3 in Mitsunobu step, which prompted us to explore the use of $AgNO_3$ to enhance activity of azide. Suitable



Scheme 17: Introduction of azide as other nucleophile in this methodology

The reaction conditions were optimized and summarized in Table 4.

Table-4 Use of $NaN_3$and $AgNO_3$in the Mitsunobu step.[a]

No	Conditions (eq.)	Acetate (*R*)-38		Azide (*R*)-53[b]	
	NaN_3 [$AgNO_3$]	Yield (%)	e.e. (%)	Yield (%)	e.e. (%)
1	2.00 [--]	44	91.4	12	88.8
2	1.75 [0.25]	45	91.1	24	91.9
3	1.50 [0.50]	46	91.4	36	98.9
4	1.25 [0.75]	45	92.1	39	99.9
5	2.00 [0.75]	45	91.9	41	99.7

[a]*Conditions for KR and characterization of* ***38*** *are same as Table-1.* [b]*Determined by HPLC analysis (Chiralcel OD-H, IPA (1.0%) in hexane; 17.55 min for (S)-****53*** *and 18.42 min for (R)-****53****. For experimental procedure see ESI.*

This modification can generate two useful chiral compounds in a single, easy operation in high selectivity.

3.I.3.4 Conclusion

Thus in this approach we have developed an efficient one-pot combination of enzyme mediated KR and Mitsunobu reaction to efficiently access chirally pure arylalkylcarbinols in high, more than 50%, yield, excellent atom economy and optical purity. The use of catalytic amount of readily available silver nitrate increased the efficiency of acetate for this reaction. The process of using catalytic quantity of silver nitrate is used to introduce azide as another nucleophile to produce two different chiral compounds in good chemical and optical yield.

3.I. 3.5 Experimental Section

Chemicals and solvents received from commercial sources were used without further purification. All solvents were purified as per the standard protocol. Thin layer chromatography was performed on F_{254} aluminium coated plates. All the compounds were purified by column chromatography using silica gel (60-120 mesh). ^{1}H NMR spectra were recorded on a 400 MHz spectrometer (100 MHz for ^{13}C NMR) in $CDCl_3$ as solvent and TMS as internal standard.

General procedure for the enzymatic resolution.

To the oven dried flask racemic alcohol **37** (0.3 g, 1.8 mmol) was taken in dry diethyether (10 mL) and lipase (Novozyme-435) (0.150 g, 50% w/w), vinyl acetate (0.49 mL, 5.4 mmol) were added and stirred at room temperature. The reaction was followed by TLC. The material was filtered and the filtrate was concentrated in vacuo. Separation was carried out by column chromatography over silica gel using petroleum ether and ethyl acetate as the eluent. The acetate *(R)*-**38** was isolated with ethyl acetate - petroleum ether (2:98) and alcohol (*S*)-**37** in ethyl acetate - petroleum ether (5:95).

Procedure for one-pot enzymatic KR followed by Mitsunobu reaction.

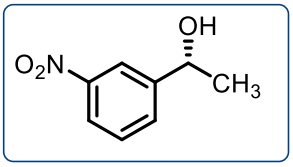
The KR was set up as per the above process. After this step (tlc), the enzyme matrix was filtered off. To the filtrate,metal acetates (0.3 g, 1.80 mmol) and triphenyl phosphine (0.71 g, 1.80 mmol) were added under nitrogen atmosphere followed by the slow addtion of solution of DEAD (0.49 mL, 1.80 mmol) in dry CH_3CN (10 mL) at 0^oC. The reaction mixture was stirredat ambient conditions for AgOAc and at reflux temperature for other acetates (24h), the solvent was removed under reduced pressure and the crude product was purified by silica-gel column chromatography withethyl acetate- petroleum ether (2:98). Colourless liquid was obtained.

General procedure for hydrolysis of acetates

The acetates were converted to alcohols for HPLC analysis to determine the optical purity.

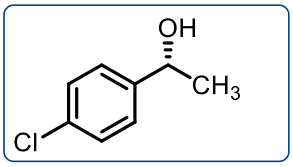
To a solution of (*R*)-**38** (0.368 g, 1.75 mmol) in methanol (5 mL), HCl (0.05 mL, 3.50 mmol, 36 %) was added. The reaction mixture was refluxed (3 h). After on completion of the reaction (tlc), MeOH was evaporated under reduce pressure. The residue was taken in ethyl acetate and washed with water, brine. The organic layer was dried over sodium sulphate and concentrated to afford (*R*)-**37** (0.28 g, 94%).

***(R)*-1-(3-Nitrophenyl)ethan-1-ol (37)**



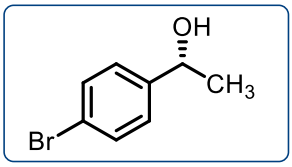
$[\alpha]^D$ = 16 (c = 1.0 $CHCl_3$) (lit. $[\alpha]^D$ = 14 (c = 0.88 $CHCl_3$)[57] **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 8.27 (t, *J* = 1.2 Hz, 1H), 8.15 (m, *J* =1.2Hz,1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.54 (t, *J* = 8.0 Hz,1H), 5.05 (q, *J* = 6.4 Hz, 1H), 2.12 (s, 1H), 1.55 (d, *J* = 6.4 Hz, 3H).

***(R)* 1-(4-Chlorophenyl)ethan-1-ol (39)**



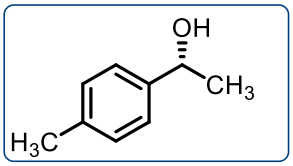
$[\alpha]^D$ = 40.86 (c = 1.0 $CHCl_3$) (lit. $[\alpha]^D$ = 42.5 (c = 1.85 $CHCl_3$)[58] **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 7.32 (m, 4H), 4.89 (q, *J* = 6.4 Hz, 1H), 1.48 (d, *J* = 6.4 Hz, 3H).

***(R)* 1-(4-Bromophenyl)ethan-1-ol (41)**



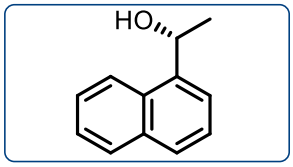
$[\alpha]^D$ = 32.20 (c = 1.0 $CHCl_3$) (lit. $[\alpha]^D$ = 35.3 (c = 0.9 $CHCl_3$)[59] **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 7.47 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 4.85 (q, *J* = 6.4 Hz, 1H), 1.49 (d, *J* = 6.4 Hz, 3H).

***(R)* 1-(4-Methylphenyl)ethan-1-ol (43)**



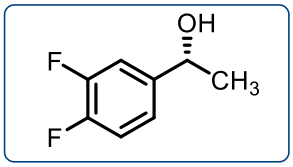
$[\alpha]^D$ = 41.96 (c = 1.0 $CHCl_3$) (lit. $[\alpha]^D$ = 42.1 (c = 2.94 $CHCl_3$)[60] **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 7.29 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 4.88 (q, *J* = 6.4 Hz, 1H), 2.37 (s, 3H), 1.51 (d, *J* = 6.4 Hz, 3H).

***(R)*1-(Naphthalen-2-yl)ethan-1-ol (45)**



$[\alpha]^D$ = 59.76 (c = 1.0 $CHCl_3$) (lit.$[\alpha]^D$ = 68.8 (c = 1.0 $CHCl_3$)[61] **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 8.15 (d, *J* = 8.0 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.60 (m, 3H), 5.72 (q, *J* = 6.4 Hz, 1H), 1.70 (d, *J* = 6.4 Hz, 3H).

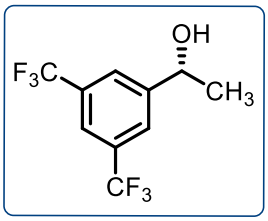
***(R)* 1-(3,4-Difluorophenyl)ethan-1-ol (47)**



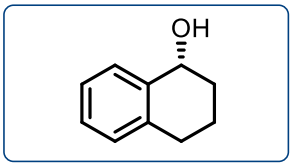
$[\alpha]^D$ = 25.36 (c = 1.0 CH_2Cl_2) (lit. $[\alpha]^D$ = -25.36 (c = 1.0 CH_2Cl_2)[62] **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 7.10 (m, 3H), 4.82 (q, *J* = 6.4 Hz, 1H), 1.43 (d, *J* = 6.4 Hz, 3H).

***(R)*1-(3,5-Bis(trifluoromethyl)phenyl)ethan-1-ol (49)**

$[\alpha]^D$ = 24.1 (c = 1.0 $CHCl_3$) (lit. $[\alpha]^D$ = -24.1 (c = 1.0 $CHCl_3$)[63] **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 7.87 (s, 2H), 7.81 (s, 1H), 5.08 (q, *J* = 6.4 Hz, 1H), 2.01 (s, 1H), 1.57 (d, *J* = 6.4 Hz, 3H).

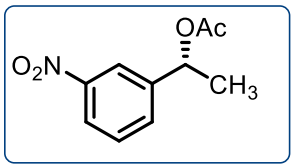


***(R)* 1,2,3,4-Tetrahydronaphthalen-1-ol (51)**



$[\alpha]^D$ = 23.48 (c = 2.0 MeOH) (lit. $[\alpha]^D$ = 28.1 (c = 2.0 MeOH)[64] **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 7.45 (m, 1H), 7.26 (m, 2H), 7.13 (m, *J* = 4.0 Hz, 1H), 4.81 (t, *J* = 4.0 Hz, 1H), 2.83 (m, 1H), 2.76 (m, 1H), 1.98 (m, 3H), 1.81 (m, 3H).

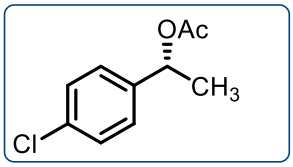
***(R)*1-(3-Nitrophenyl)ethyl acetate (38)**



$[\alpha]^D$= +69.45 (c = 1.0 in $CHCl_3$).

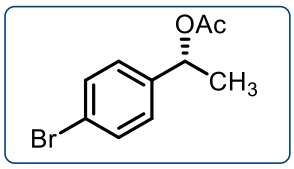
^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.23 (t, *J* = 1.2 Hz, 1H), 8.15 (m, *J* = 1.2 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.53 (t, *J* = 8.0 Hz, 1H), 5.93 (q, *J* = 6.4 Hz, 1H), 2.11 (s, 1H), 1.57 (d, *J* = 6.4 Hz, 3H).

(*R*)1-(4-Chlorophenyl)ethyl acetate (40)



$[\alpha]^D$ = +66.5 (c = 1.0 $CHCl_3$) (lit. $[\alpha]^D$ = + 68.8(c = 1.0 $CHCl_3$)[65] **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 7.32 (m, 4H), 5.86 (q, *J* = 6.4 Hz, 1H), 2.09 (s, 1H), 1.53 (d, *J* = 6.4 Hz, 3H).

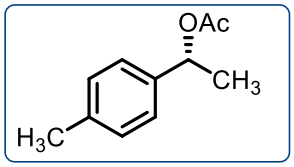
(*R*)1-(4-Bromophenyl)ethyl acetate (42)



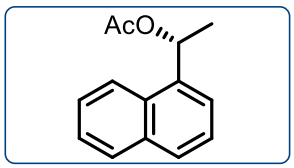
$[\alpha]^D$ = +90.12 (c = 1.0 $CHCl_3$) (lit. $[\alpha]^D$= +91.2(c = 1.1 $CHCl_3$)[65] **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 7.49 (d, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 5.83 (q, *J* = 6.4 Hz, 1H), 1.53 (d, *J* = 6.4 Hz, 3H), 2.09 (s, 1H).

(*R*)1-(4-Methylphenyl)ethyl acetate (44)

$[\alpha]^D$ = +112.32 (c = 1.0 $CHCl_3$) (lit. $[\alpha]^D$ = +115.8 (c = 1.1 $CHCl_3$)[65] **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 7.28 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 5.87 (q, *J* = 6.4 Hz, 1H), 2.37 (s, 3H), 2.08 (s, 1H), 1.55 (d, J = 6.4 Hz, 3H).

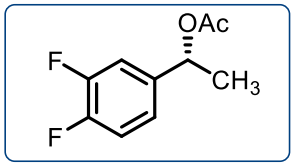


(*R*)1-(Naphthalen-2-yl)ethyl acetate (46)



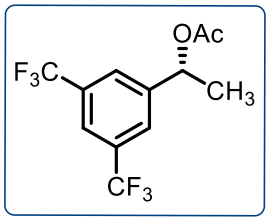
$[\alpha]^D$ = +44.32 (c = 1.0 $CHCl_3$) (lit. $[\alpha]^D$ = -49.5 (c = 1.0 $CHCl_3$)[64] **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 8.08 (d, *J* = 8.0 Hz, 1H), 7.86 (m, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.52 (m, 4H), 2.11 (s, 3 H), 6.65 (t, *J* = 6.0 Hz, 1H), 1.70 (d, *J* = 6.0 Hz, 3H).

(*R*)1-(3,4-Difluorophenyl)ethyl acetate (48)



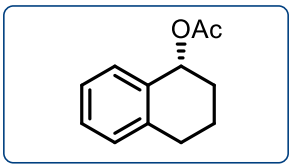
$[\alpha]^D$ +85.40 (*c* = 1.0, CH_2Cl_2)(lit. $[\alpha]^D$ = +85.40 (c = 1.0 $CHCl_3$)[62] **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 7.14 (m, 3H), 5.83 (q, *J* = 6.4 Hz, 1H), 2.09 (s, 3H), 1.52 (d, *J* = 6.4 Hz, 3H).

***(R)*1-(3,5-Bis(trifluoromethyl)phenyl)ethyl acetate (50)**



$[\alpha]^D$ = +54.1 (c = 1.0. MeOH) (lit.66 $[\alpha]^D$ = +57 (c = 1.0.MeOH)[63] **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 7.82 (m, 3H), 5.97 (q, *J* = 6.4 Hz, 1H), 2.14 (s, 3H), 1.60 (d, *J* = 6.4 Hz, 3H).

***(R)* 1,2,3,4-Tetrahydronaphthalen-1-yl acetate (52)**

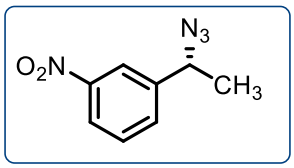


$[\alpha]^D$ = +105 (c = 2.0. $CHCl_3$) (lit.66 $[\alpha]^D$112 (c = 2.0. $CHCl_3$)[64] **^{1}H-NMR (400 MHz, $CDCl_3$)** δ 7.30 (m, 1H), 7.24 (m, 2H), 7.16 (d, *J* = 8.0 Hz, 1H), 6.03 (m, 1H), 2.79 (m, 1H), 1.89 (m, 3H), 2.11 (s, 3H), 1.83 (m, 1H).

Procedure for enzymatic reaction followed by Mitsunobu reaction with NaN_3 (Entry 5, Table 4)

After enzymatic resolution as per the above procedure, the enzyme matrix was filtered off. To the filtrate NaN_3 (0.3gm, 1.80 mmol) and $AgNO_3$ (0.14 g, 0.67 mmol)triphenyl phosphine (0.71 g, 1.80 mmol) were added under nitrogen atmosphere followed by the slow addtion of solution of DEAD (0.49 mL, 1.80 mmol) in dry THF (10 mL) at 0^{o}C. The reaction mixture was stirred for 24h. The solvent was removed under reduced pressure and the crude product was purified by silica-gel column chromatography with ethyl acetate- petroleum ether (2:98). Colourless liquid was obtained. The azide **53** was converted to amine with Ph_3P in aqueous toluene, (reflux 3h) and the crude amine was subjected to acetylation with Ac_2O/Et_3N in dicloromethane (r.t.; 2 h).[66a] The optical purity and absolute configuration of this amide was established by HPLC analysis on chiral stationary phase column (Chiralcel-IC) and compared with the reported data.[66b]

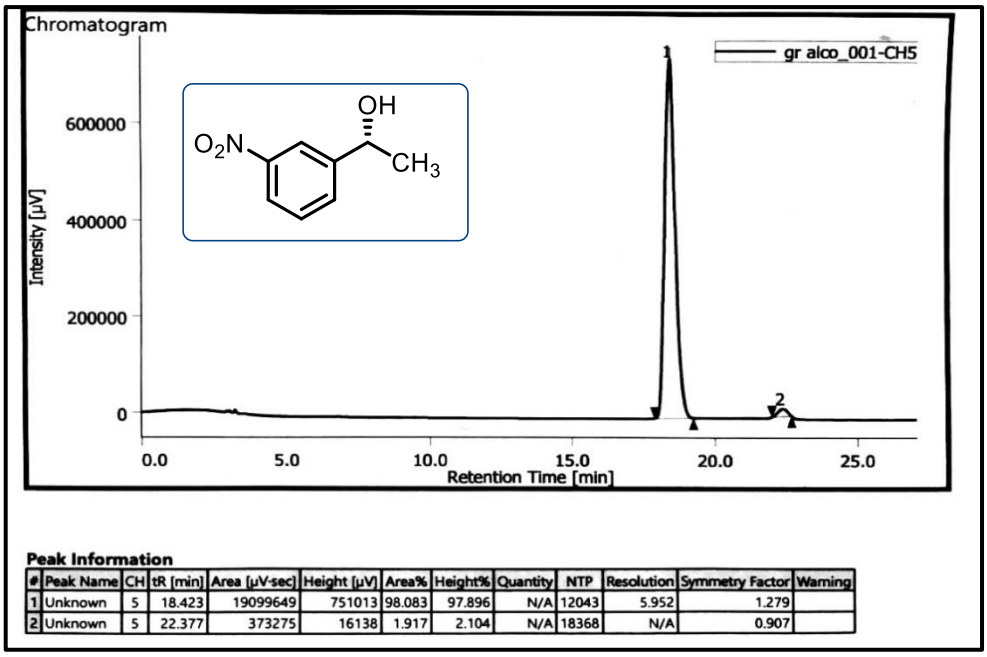
***(R)* 1-(1-azidoethyl)-3-nitrobenzene (53)**[52]



$[\alpha]^{D}$ = +62.8 (c = 1.0 $CHCl_3$)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.21 (m, 2H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.59 (t, *J* = 8.0 Hz, 1H), 4.78 (q, *J* = 6.8 Hz, 1H), 1.64 (d, *J* = 6.8 Hz, 3H). **IR(KBr)** υ 3089, 2924, 2870, 2854, 2090, 1689, 1527, 1350, 1095, 1072, 902, 810 $cm.^{-1}$

3.I.3.6 Spectral Data

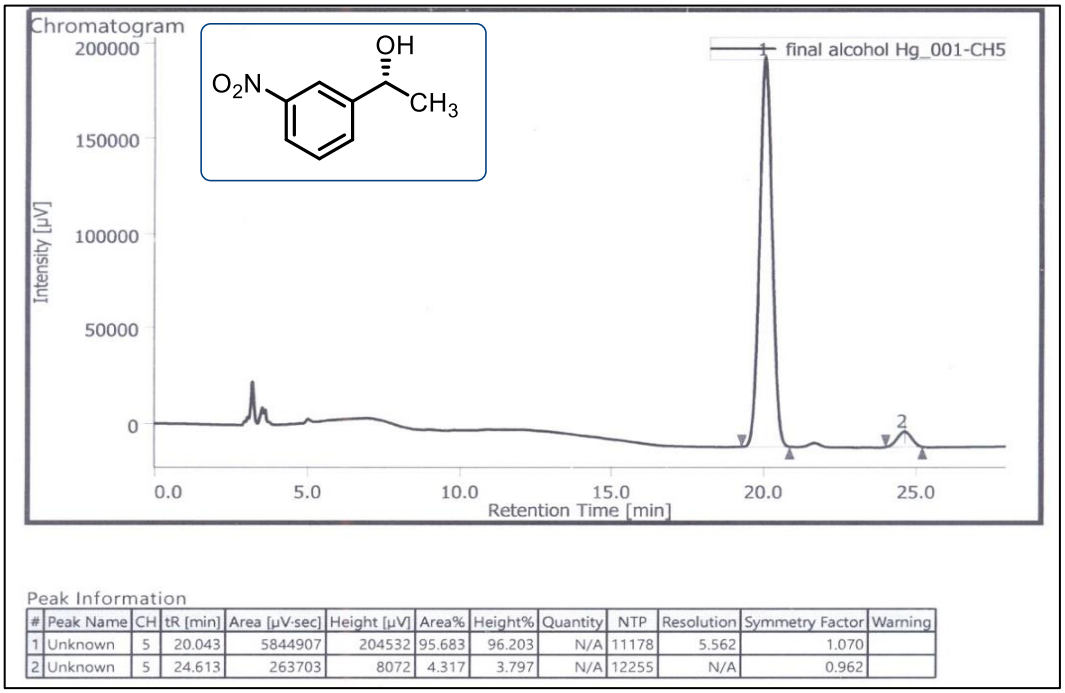


Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	18.423	19099649	751013	98.083	97.896	N/A	12043	5.952	1.279	
2	Unknown	5	22.377	373275	16138	1.917	2.104	N/A	18368	N/A	0.907	

HPLC chromatogram of *(R)* 1-(3-nitrophenyl)ethan-1-ol for CH_3COOAg

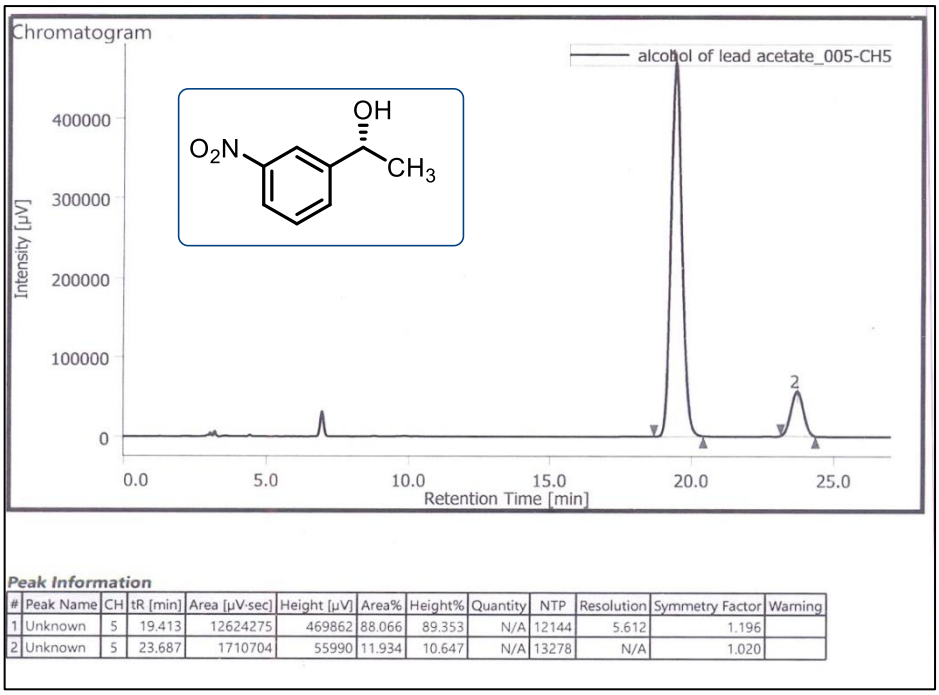
HPLC Condition for compound 1-(3-nitrophenyl)ethan-1-ol [b] *Determined by HPLC analysis (chiral column Amylose, 1ml/min IPA (5.0%) in hexane; 18.42 min for (R)-**37** and 22.37 min for (S)-**37**)*



Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	20.043	5844907	204532	95.683	96.203	N/A	11178	5.562	1.070	
2	Unknown	5	24.613	263703	8072	4.317	3.797	N/A	12255	N/A	0.962	

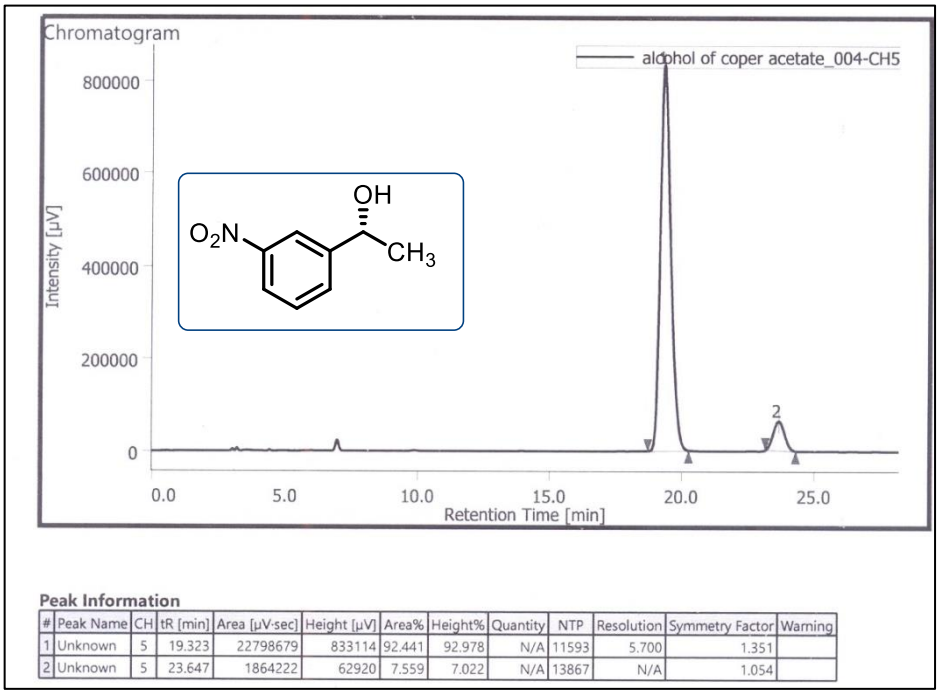
HPLC chromatogram of *(R)* 1-(3-nitrophenyl)ethan-1-ol for $Hg(OAc)_2$



Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	19.413	12624275	469862	88.066	89.353	N/A	12144	5.612	1.196	
2	Unknown	5	23.687	1710704	55990	11.934	10.647	N/A	13278	N/A	1.020	

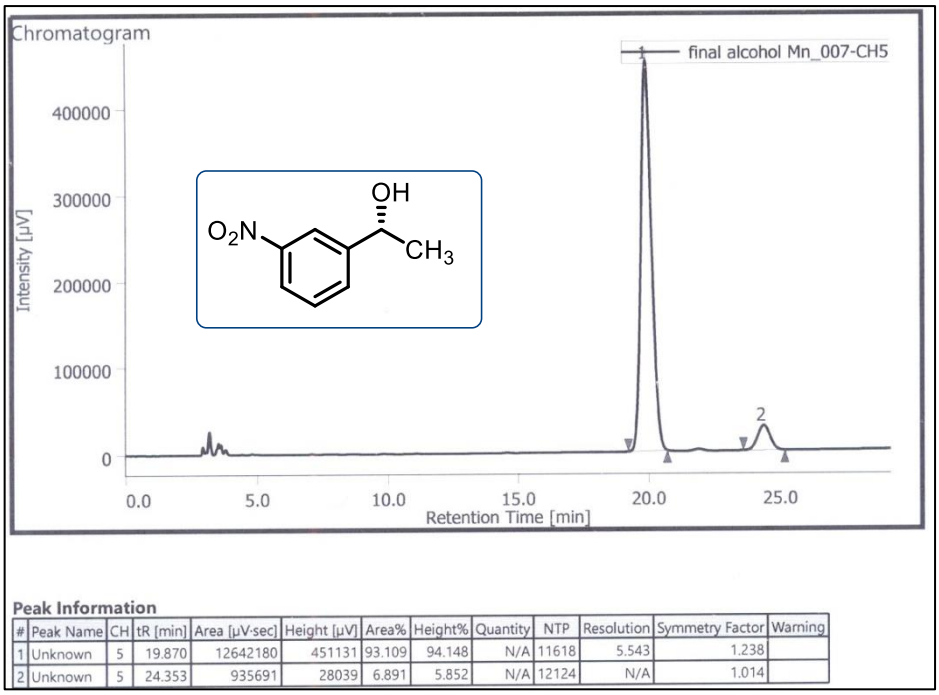
HPLC chromatogram of *(R)* 1-(3-nitrophenyl)ethan-1-ol for $Pb(OAc)_2$



Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	19.323	22798679	833114	92.441	92.978	N/A	11593	5.700	1.351	
2	Unknown	5	23.647	1864222	62920	7.559	7.022	N/A	13867	N/A	1.054	

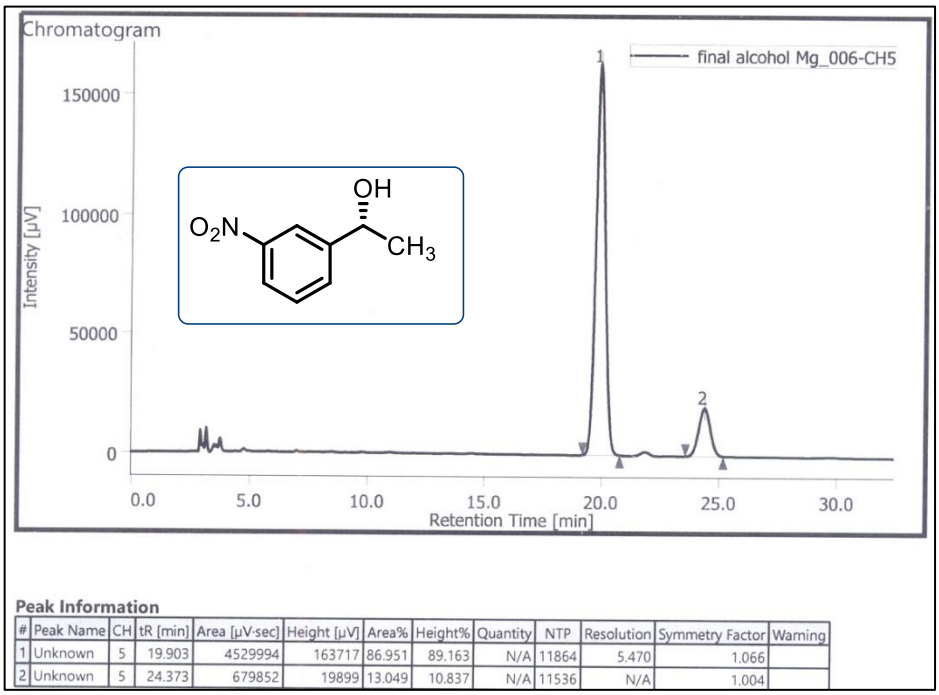
HPLC chromatogram of *(R)* 1-(3-nitrophenyl)ethan-1-ol for Cu(OAc)



Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	19.870	12642180	451131	93.109	94.148	N/A	11618	5.543	1.238	
2	Unknown	5	24.353	935691	28039	6.891	5.852	N/A	12124	N/A	1.014	

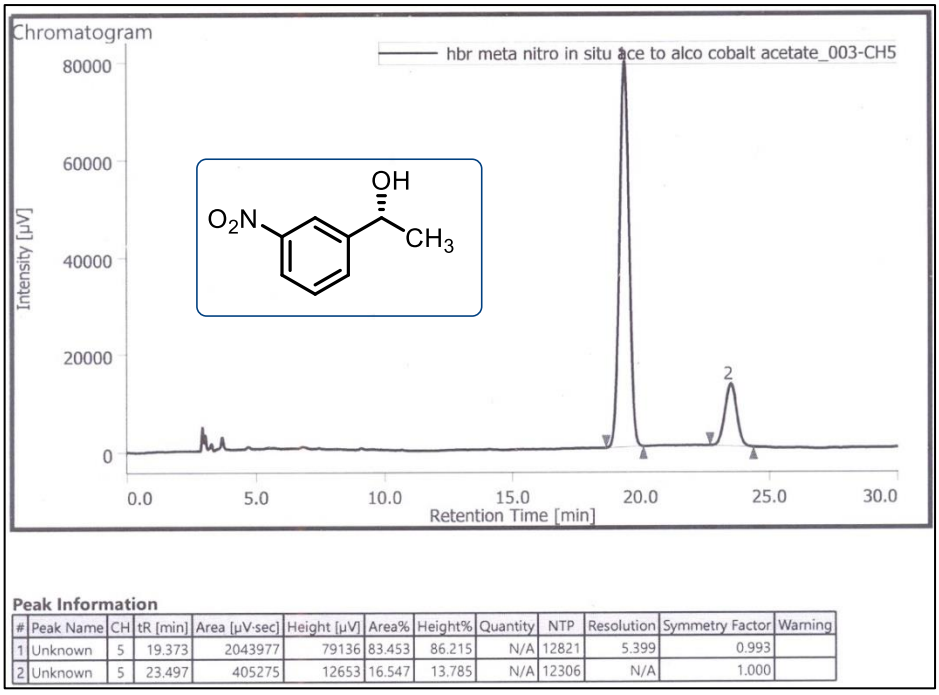
HPLC chromatogram of *(R)* 1-(3-nitrophenyl)ethan-1-ol for $Mn(OAc)_2$



Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	19.903	4529994	163717	86.951	89.163	N/A	11864	5.470	1.066	
2	Unknown	5	24.373	679852	19899	13.049	10.837	N/A	11536	N/A	1.004	

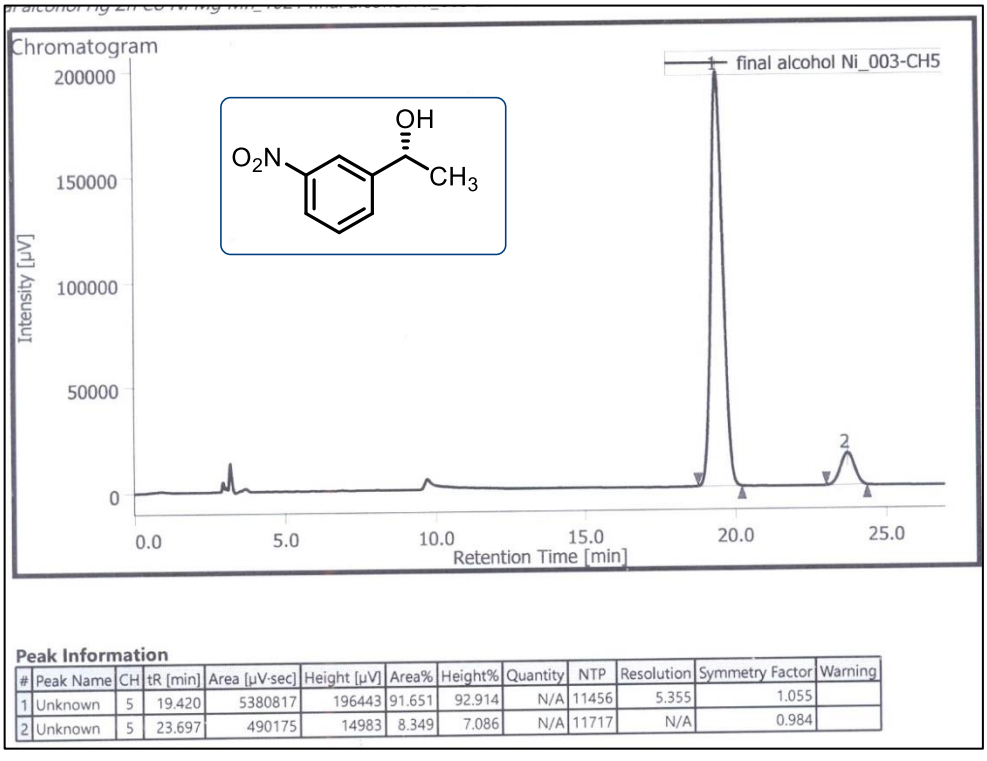
HPLC chromatogram of *(R)* 1-(3-nitrophenyl)ethan-1-ol for $Mg(OAc)_2$



Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	19.373	2043977	79136	83.453	86.215	N/A	12821	5.399	0.993	
2	Unknown	5	23.497	405275	12653	16.547	13.785	N/A	12306	N/A	1.000	

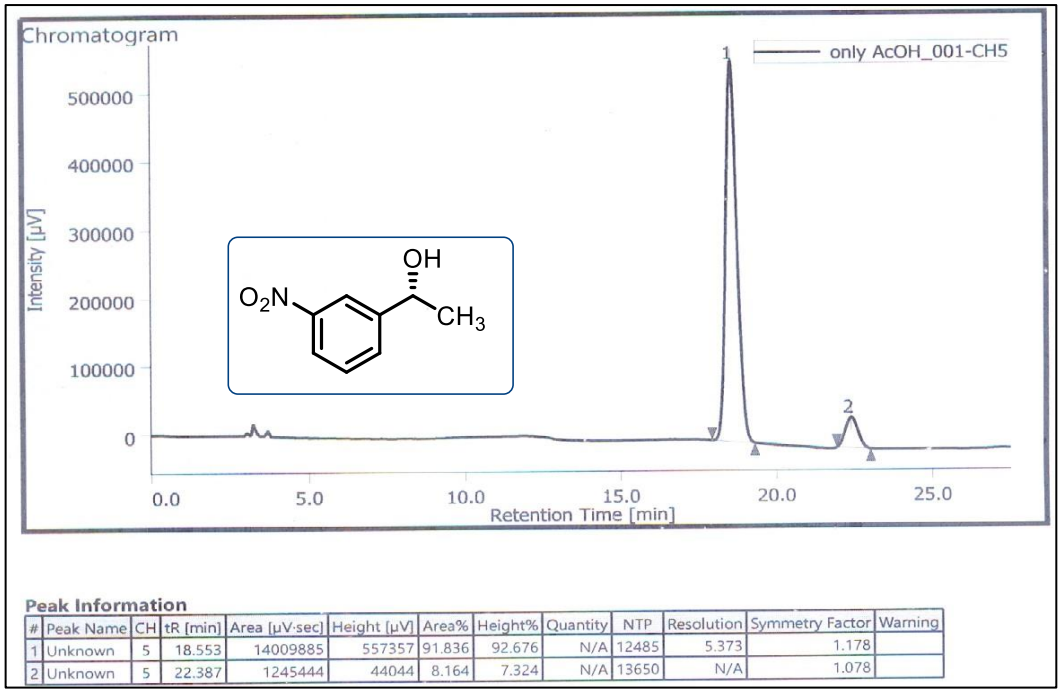
HPLC chromatogram of *(R)* 1-(3-nitrophenyl)ethan-1-ol for $Co(OAc)_2$



Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	19.420	5380817	196443	91.651	92.914	N/A	11456	5.355	1.055	
2	Unknown	5	23.697	490175	14983	8.349	7.086	N/A	11717	N/A	0.984	

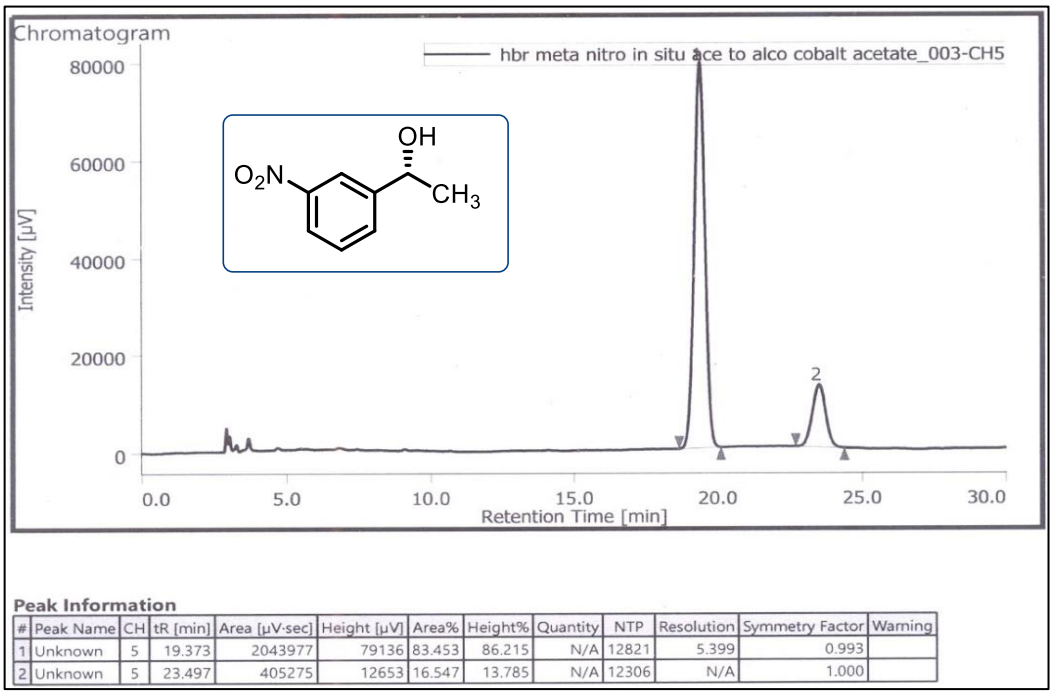
HPLC chromatogram of *(R)* 1-(3-nitrophenyl)ethan-1-ol for $Ni(OAc)_2$



Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	18.553	14009885	557357	91.836	92.676	N/A	12485	5.373	1.178	
2	Unknown	5	22.387	1245444	44044	8.164	7.324	N/A	13650	N/A	1.078	

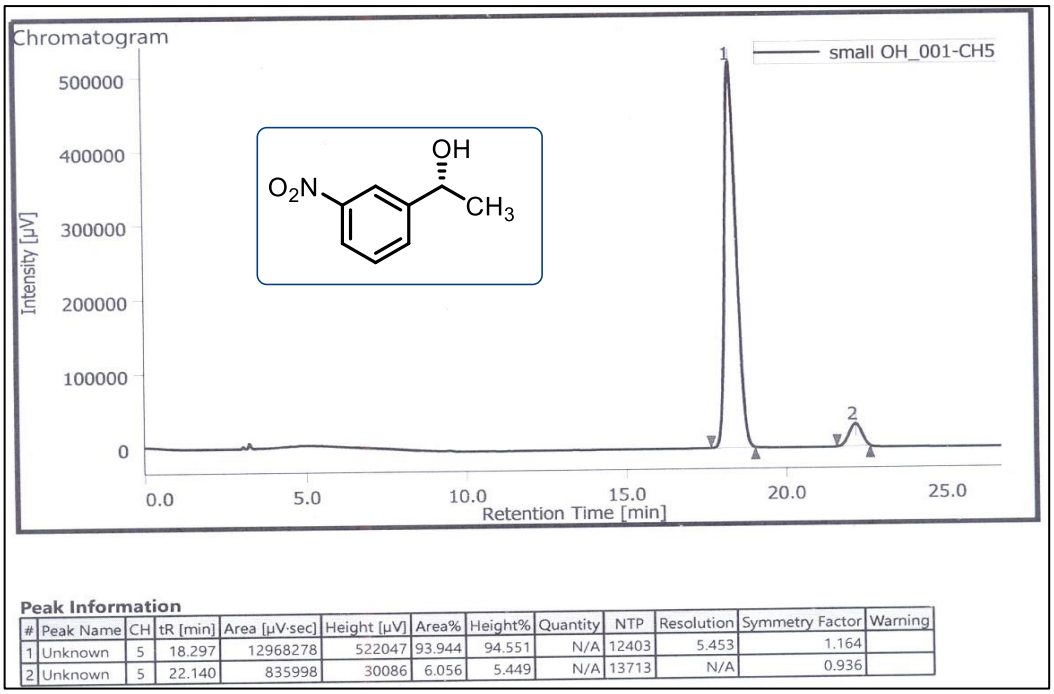
HPLC chromatogram of *(R)* 1-(3-nitrophenyl)ethan-1-ol for CH_3COONa



Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	19.373	2043977	79136	83.453	86.215	N/A	12821	5.399	0.993	
2	Unknown	5	23.497	405275	12653	16.547	13.785	N/A	12306	N/A	1.000	

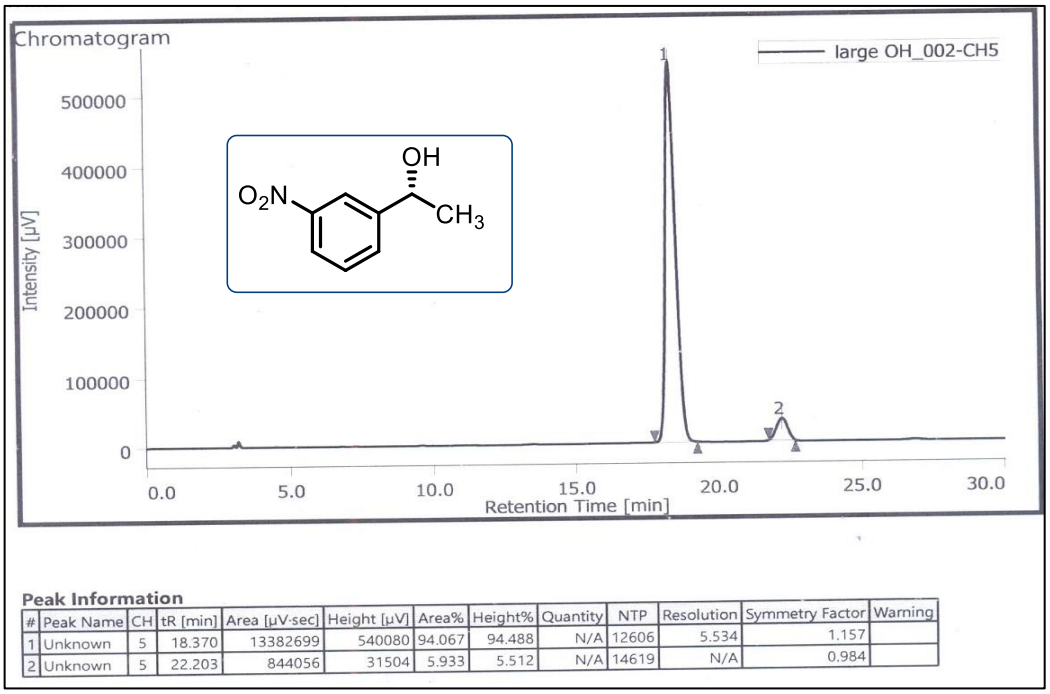
HPLC chromatogram of *(R)* 1-(3-nitrophenyl)ethan-1-ol(Co(OAc)2/AgNO3:2.0/0.0)



Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	18.297	12968278	522047	93.944	94.551	N/A	12403	5.453	1.164	
2	Unknown	5	22.140	835998	30086	6.056	5.449	N/A	13713	N/A	0.936	

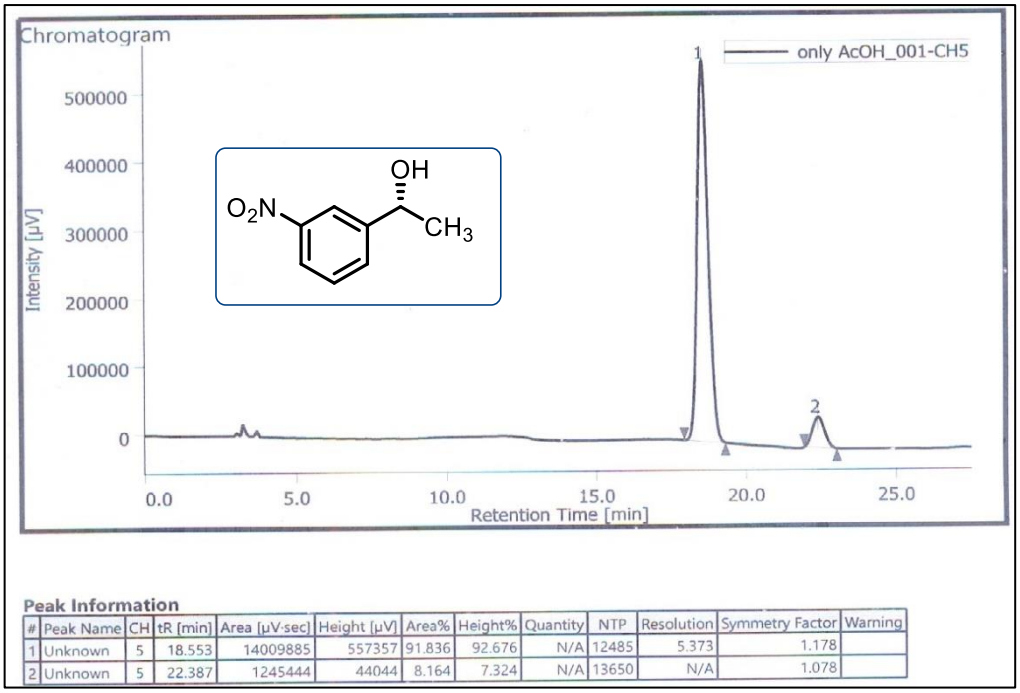
HPLC chromatogram of *(R)* 1-(3-nitrophenyl)ethan-1-ol
(Co(OAc)2/AgNO3:1.75/0.25)



Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	18.370	13382699	540080	94.067	94.488	N/A	12606	5.534	1.157	
2	Unknown	5	22.203	844056	31504	5.933	5.512	N/A	14619	N/A	0.984	

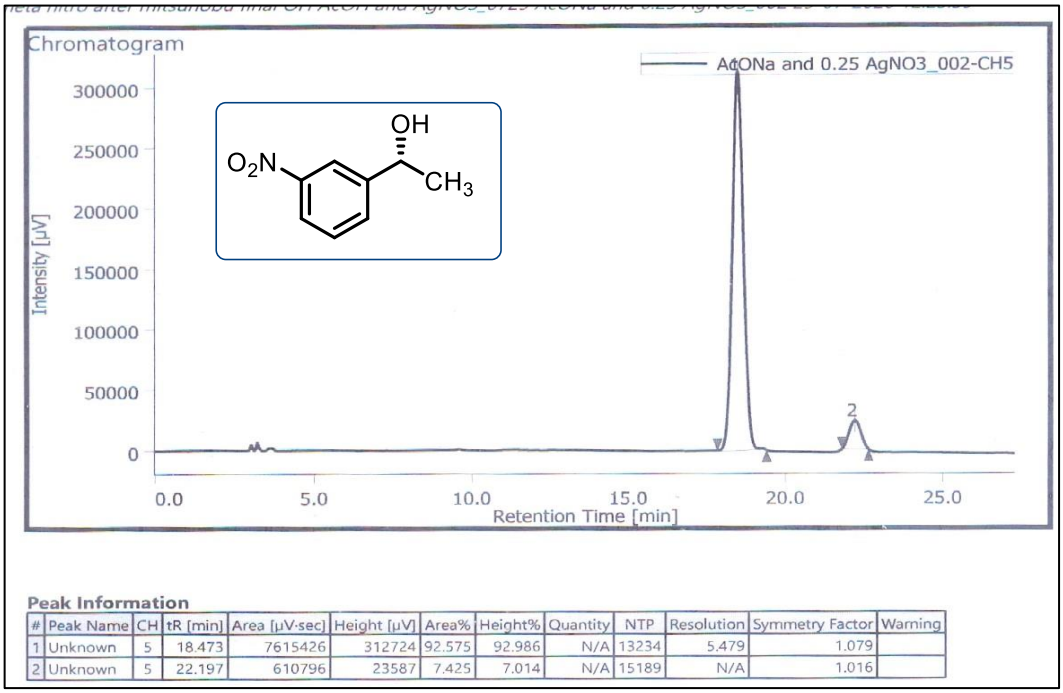
HPLC chromatogram of *(R)* 1-(3-nitrophenyl)ethan-1-ol
(Co(OAc)2/AgNO3:1.50/0.50)



Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	18.553	14009885	557357	91.836	92.676	N/A	12485	5.373	1.178	
2	Unknown	5	22.387	1245444	44044	8.164	7.324	N/A	13650	N/A	1.078	

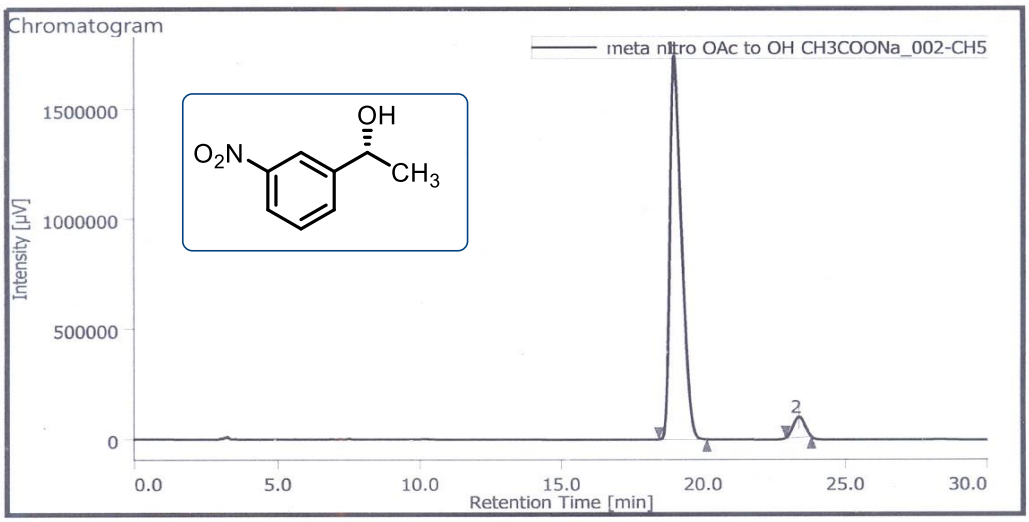
HPLC chromatogram of *(R)* 1-(3-nitrophenyl)ethan-1-ol(CH3COONa/AgNO3:2.0/0.0)



Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	18.473	7615426	312724	92.575	92.986	N/A	13234	5.479	1.079	
2	Unknown	5	22.197	610796	23587	7.425	7.014	N/A	15189	N/A	1.016	

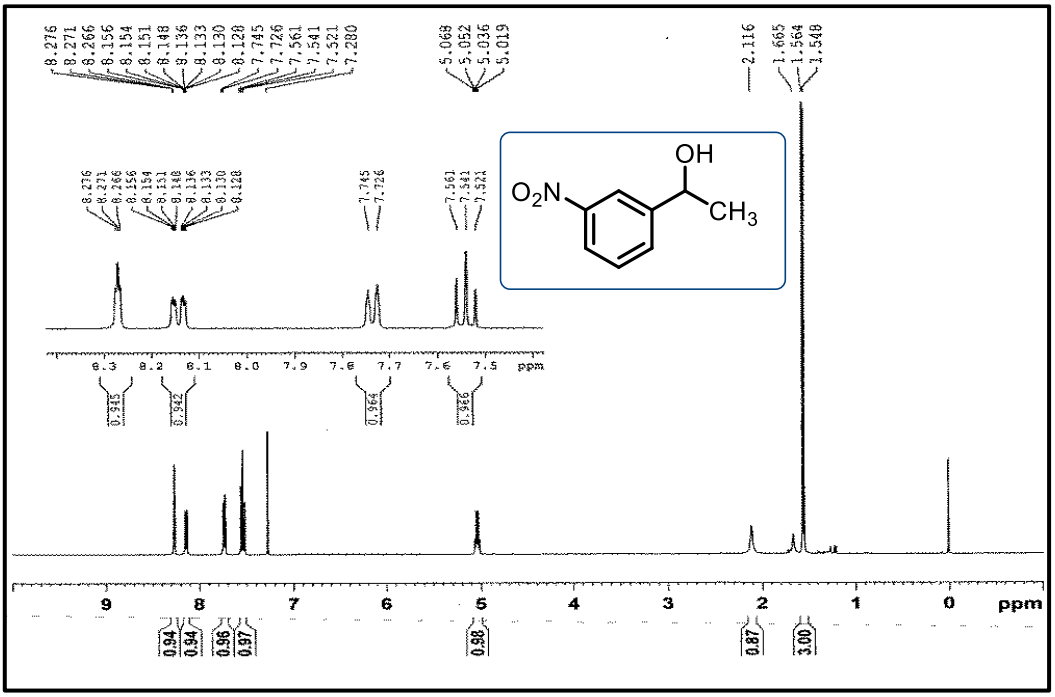
HPLC chromatogram of *(R)* 1-(3-nitrophenyl)ethan-1-ol(CH3COONa/AgNO3:1.75/0.25)



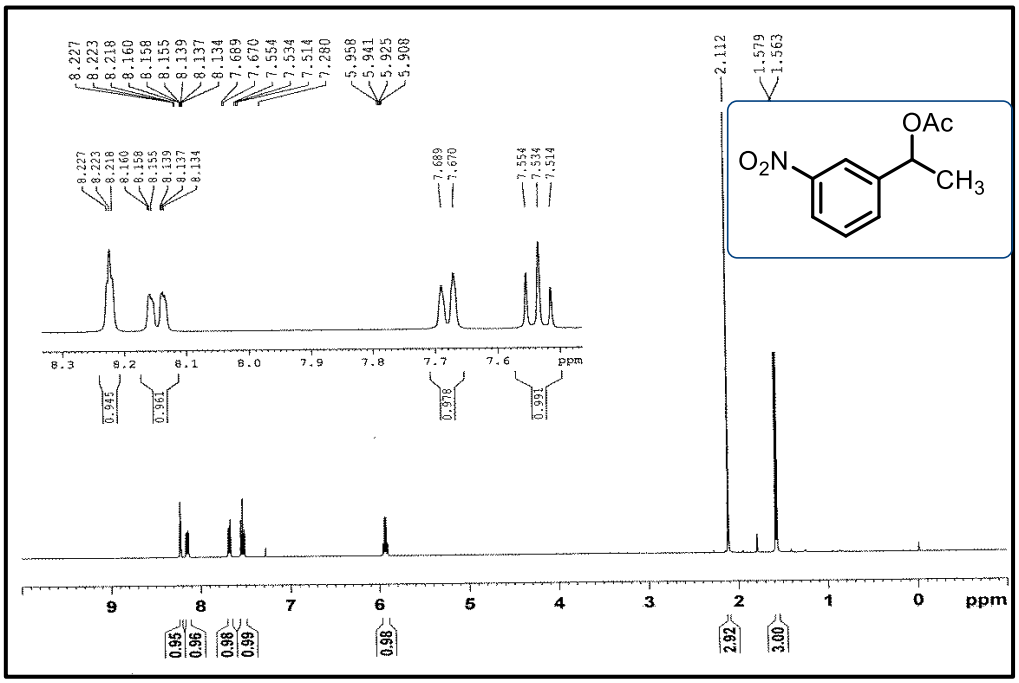
Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	18.973	49362935	1739983	95.074	94.987	N/A	10273	5.764	1.529	
2	Unknown	5	23.357	2557572	91823	4.926	5.013	N/A	14490	N/A	0.977	

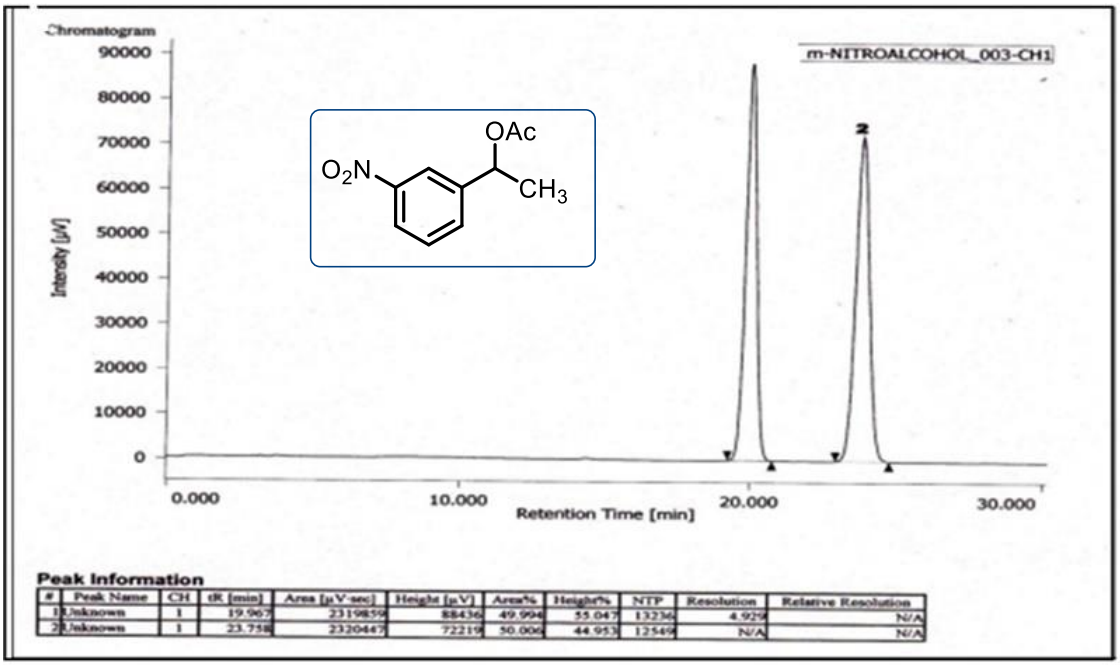
HPLC chromatogram of *(R)* 1-(3-nitrophenyl)ethan-1-ol(CH_3COONa/AgNO3:1.50/0.50)



^{1}H NMR of *(R)* 1-(3-nitrophenyl)ethan-1-ol **37**

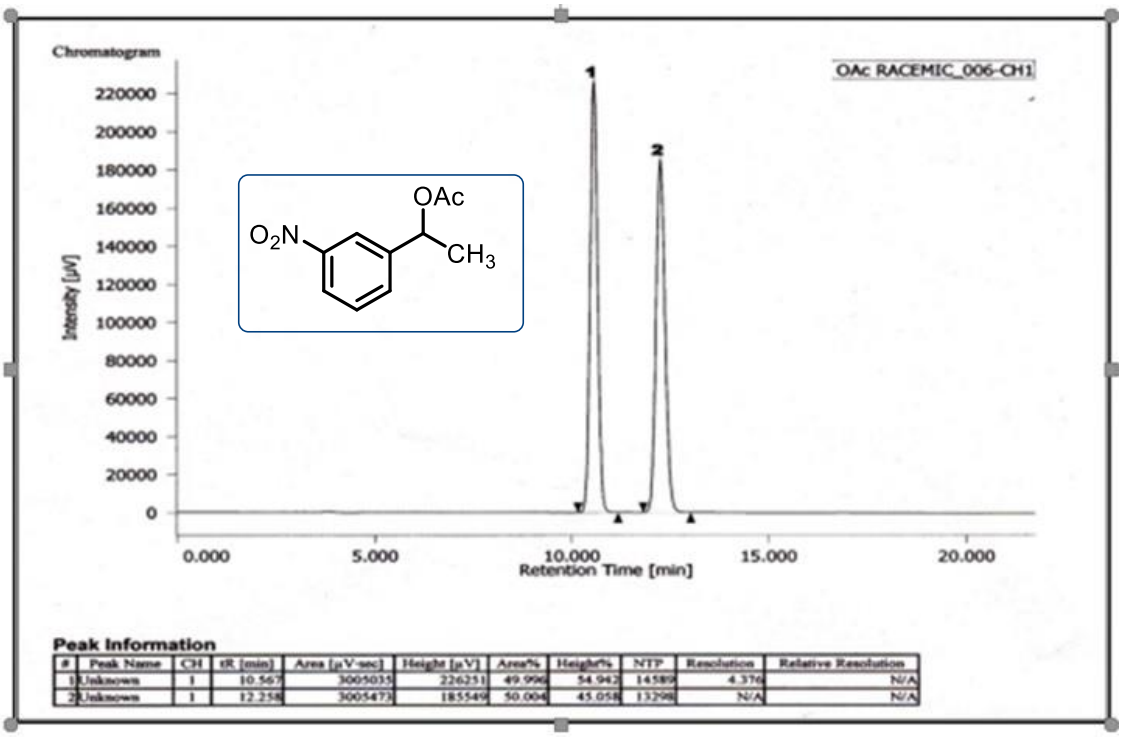


^{1}H NMR of 1-(3-nitrophenyl)ethyl acetate **38**



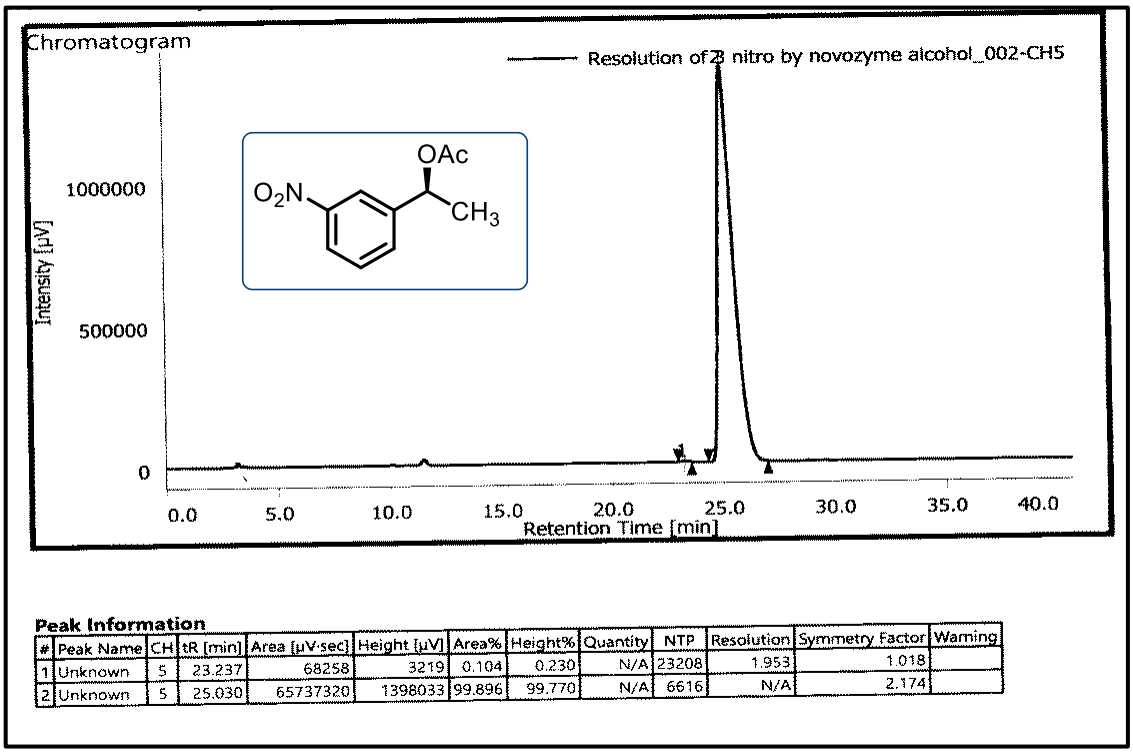
HPLC chromatogram of Racemic 1-(3-nitrophenyl)ethan-1-ol **37**

HPLC Condition for compound 1-(3-nitrophenyl)ethan-1-ol [b]*Determined by HPLC analysis (chiral column Amylose, 1ml/min IPA (5.0%) in hexane; 18.42 min for (R)-**37** and 22.37 min for (S)-**37**)*



#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	Height%	NTP	Resolution	Relative Resolution
1	Unknown	1	10.567	3005035	226251	49.996	54.942	14589	4.376	N/A
2	Unknown	1	12.258	3005473	185549	50.004	45.058	13298	N/A	N/A

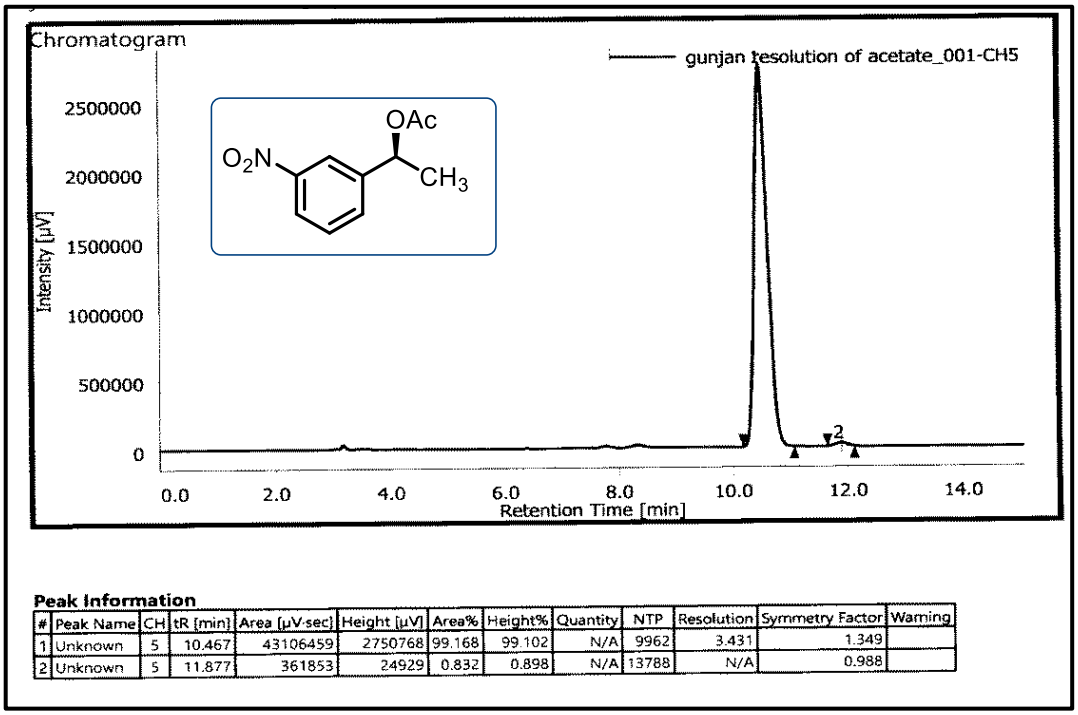
HPLC chromatogram of Racemic 1-(3-nitrophenyl)ethan-1-ol **38**



#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	23.237	68258	3219	0.104	0.230	N/A	23208	1.953	1.018	
2	Unknown	5	25.030	65737320	1398033	99.896	99.770	N/A	6616	N/A	2.174	

HPLC chromatogram of (*S*) 1-(3-nitrophenyl)ethyl acetate **38**

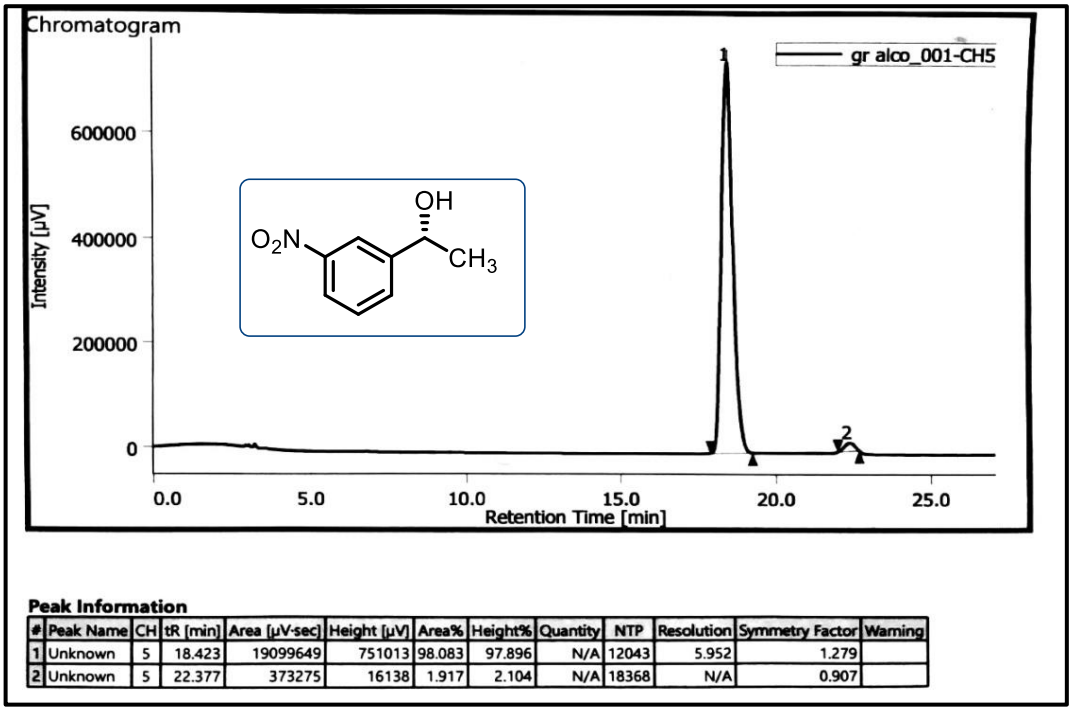
HPLC Condition for compound 1-(3-nitrophenyl)ethyl acetate Determined by HPLC analysis (chiral column Amylose, 1ml/min IPA (5.0%) in hexane; 11.23 min for (*R*)-**38** and 12.67 min for (*S*)-**38**)



Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	10.467	43106459	2750768	99.168	99.102	N/A	9962	3.431	1.349	
2	Unknown	5	11.877	361853	24929	0.832	0.898	N/A	13788	N/A	0.988	

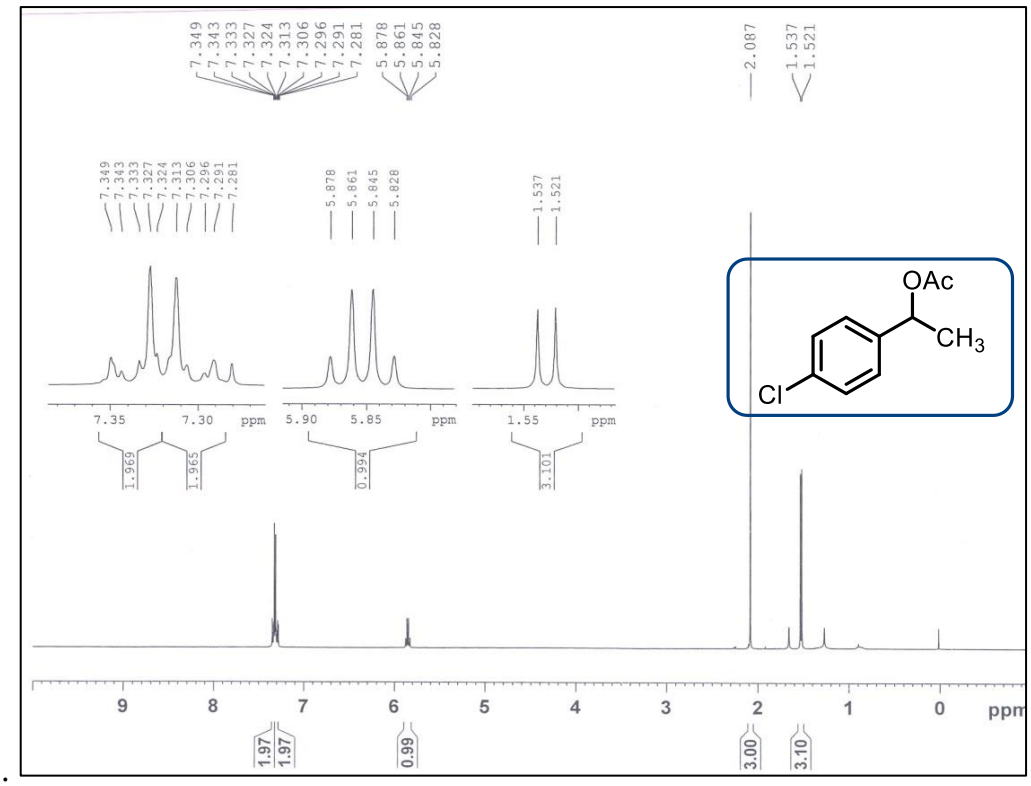
HPLC chromatogram of (*S*) 1-(3-nitrophenyl)ethyl acetate **38**



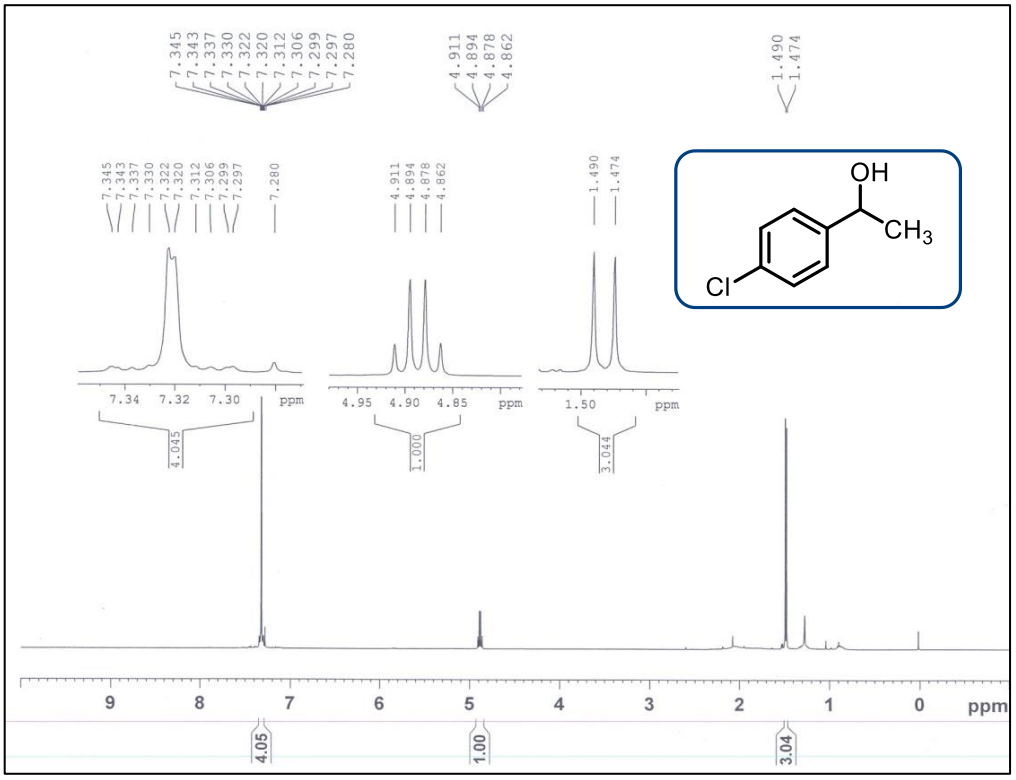
Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	18.423	19099649	751013	98.083	97.896	N/A	12043	5.952	1.279	
2	Unknown	5	22.377	373275	16138	1.917	2.104	N/A	18368	N/A	0.907	

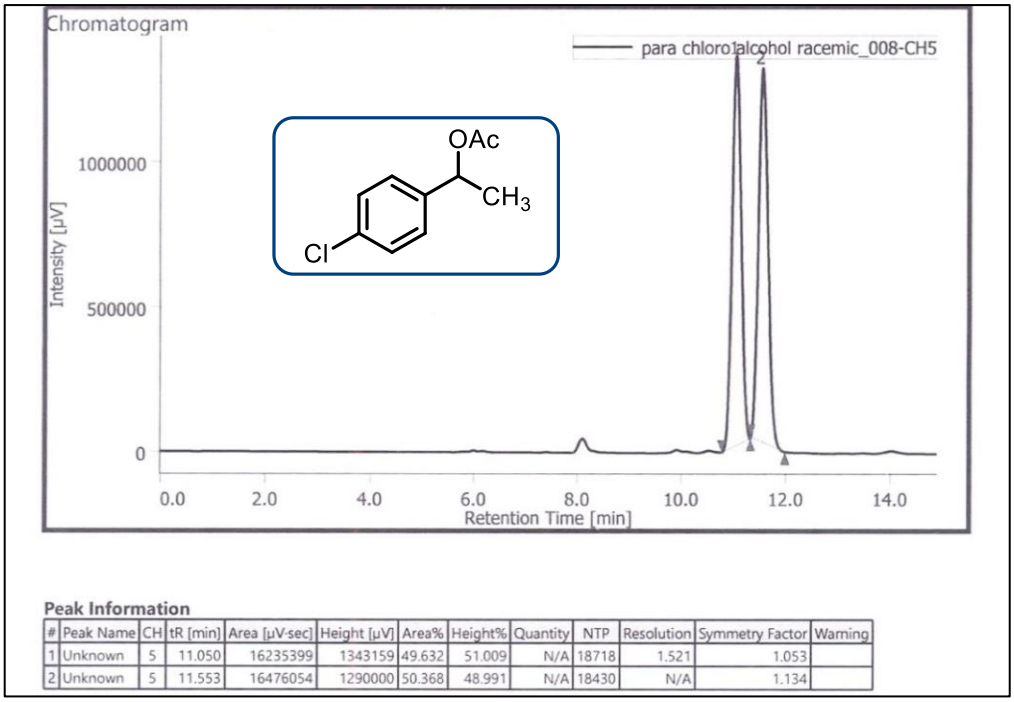
HPLC chromatogram of *(R)* 1-(3-nitrophenyl)ethan-1-ol **37** after Mitsunobu reaction



^{1}H NMR of 1-(4-chlorophenyl)ethyl acetate **40**



^{1}H NMR of 1-(4-chlorophenyl)ethan-1-ol **39**

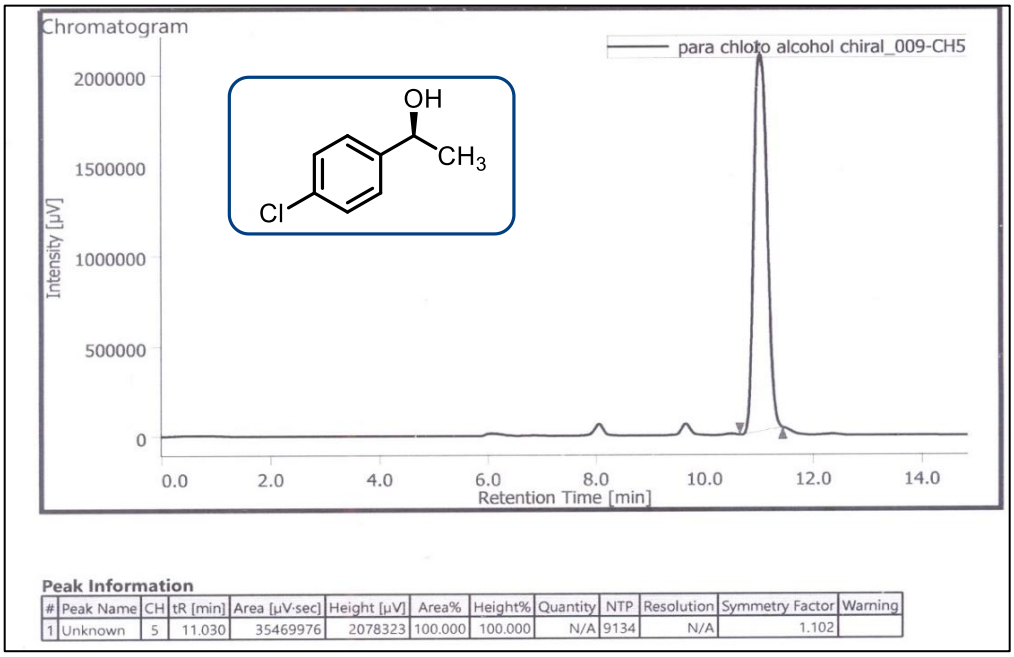


Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	11.050	16235399	1343159	49.632	51.009	N/A	18718	1.521	1.053	
2	Unknown	5	11.553	16476054	1290000	50.368	48.991	N/A	18430	N/A	1.134	

HPLC chromatogram of racemic 1-(4-chlorophenyl)ethan-1-ol **39**

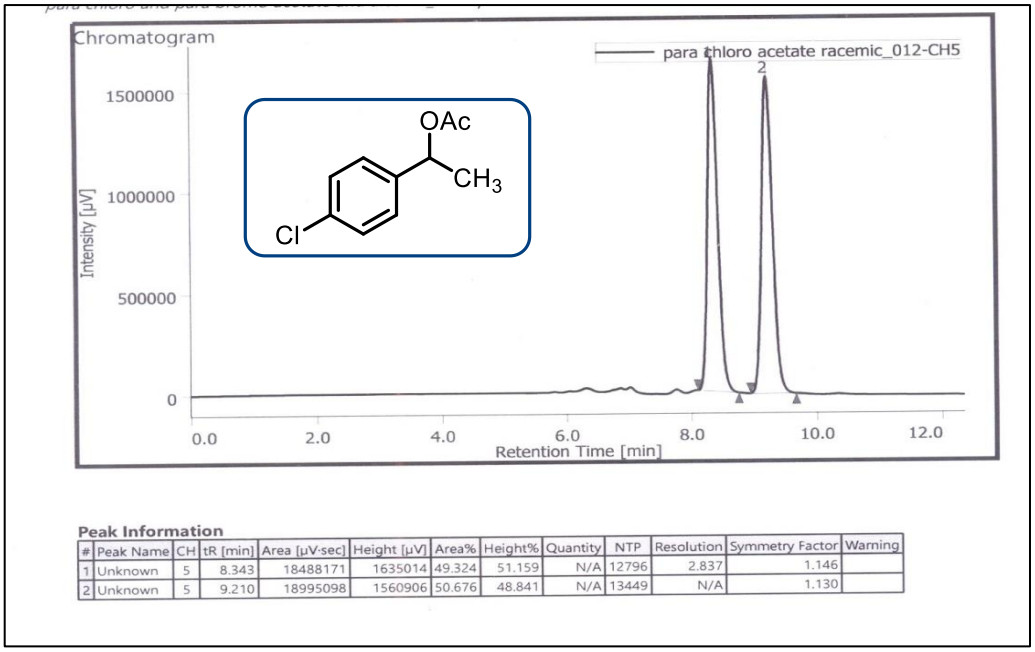
*HPLC Condition for compound 1-(4-chlorophenyl)ethan-1-ol Determined by HPLC analysis (chiral column OD-H, 0.5ml/min IPA (10.0%) in hexane 11.05 min for (R)-**39** and 11.53 min for (S)-**39**)*



Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	11.030	35469976	2078323	100.000	100.000	N/A	9134	N/A	1.102	

HPLC chromatogram of (*S*) 1-(4-chlorophenyl)ethan-1-ol **39**

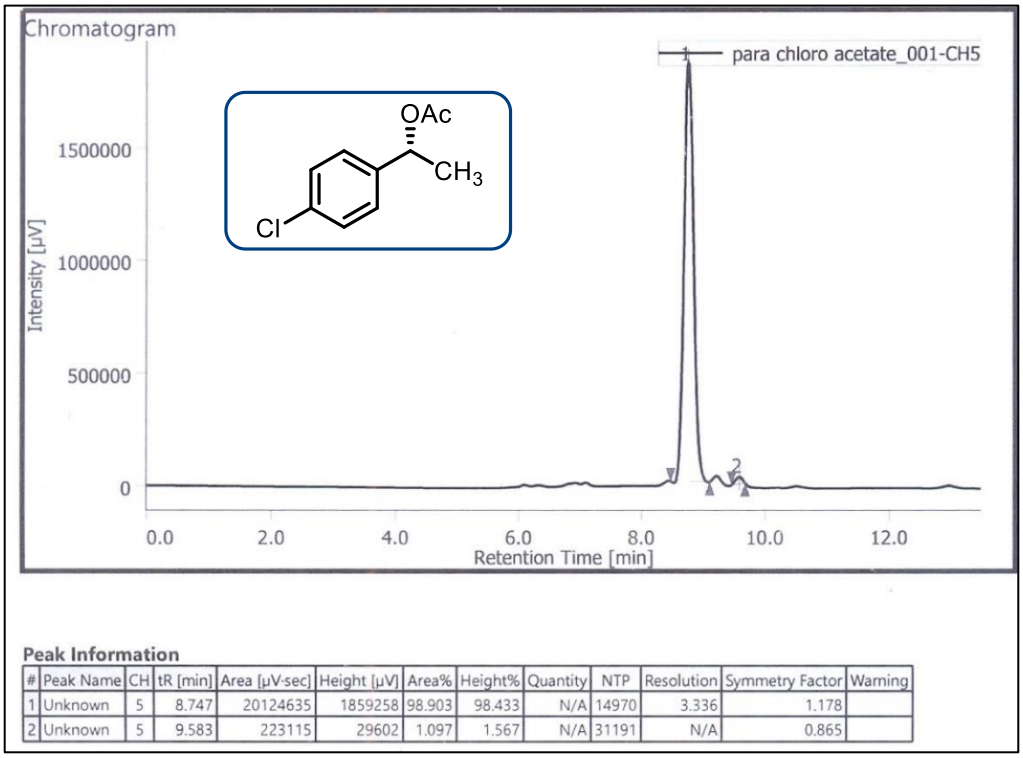


Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	8.343	18488171	1635014	49.324	51.159	N/A	12796	2.837	1.146	
2	Unknown	5	9.210	18995098	1560906	50.676	48.841	N/A	13449	N/A	1.130	

HPLC chromatogram of Racemic 1-(4-chlorophenyl)ethyl acetate **40**

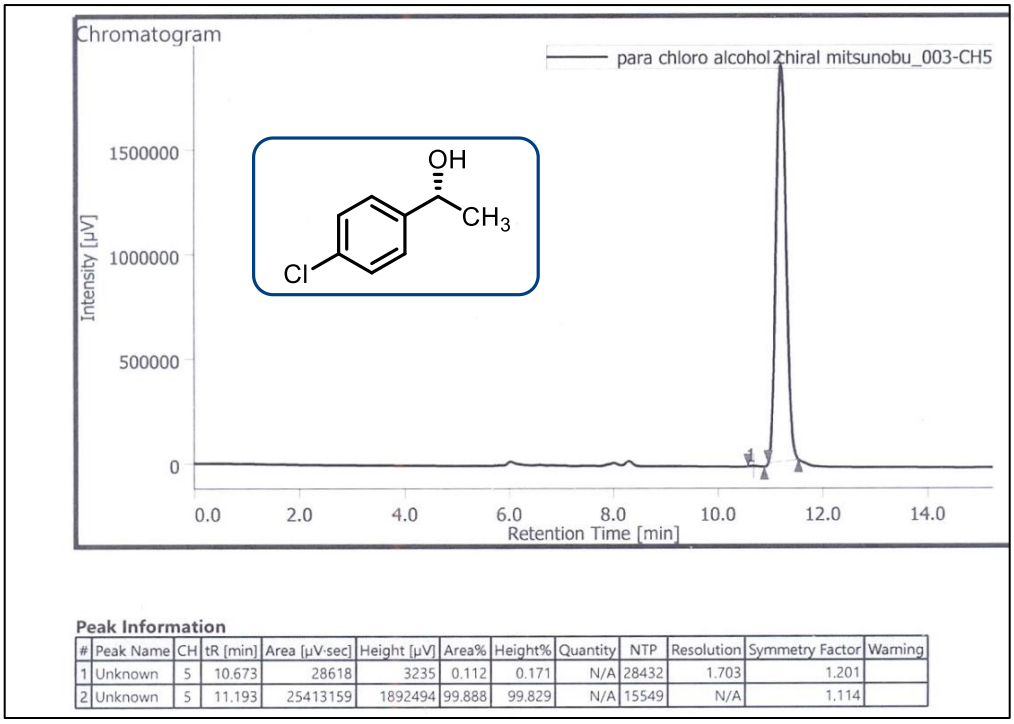
*HPLC Condition for compound 1-(4-chlorophenyl)ethyl acetate Determined by HPLC analysis (chiral column Amylose, IPA 0.5ml/min (10.0%) in hexane; 8.34 min for (R)-**40** and 9.20 min for (S)-**40**)*



Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	8.747	20124635	1859258	98.903	98.433	N/A	14970	3.336	1.178	
2	Unknown	5	9.583	223115	29602	1.097	1.567	N/A	31191	N/A	0.865	

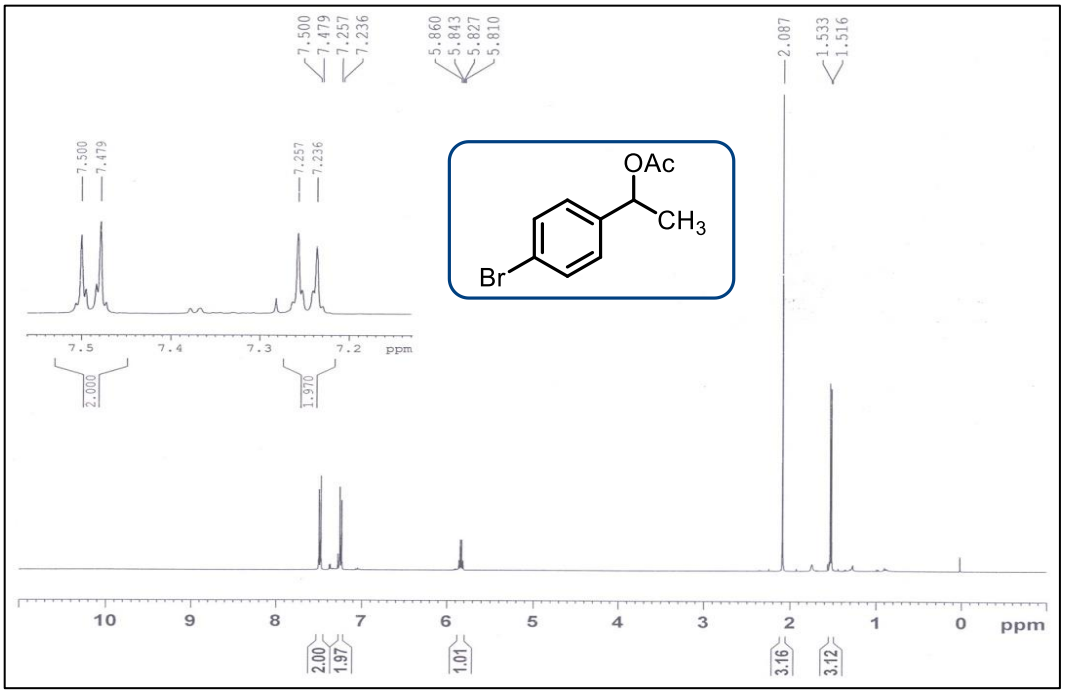
HPLC chromatogram of (*R*) 1-(4-chlorophenyl)ethyl acetate **40**



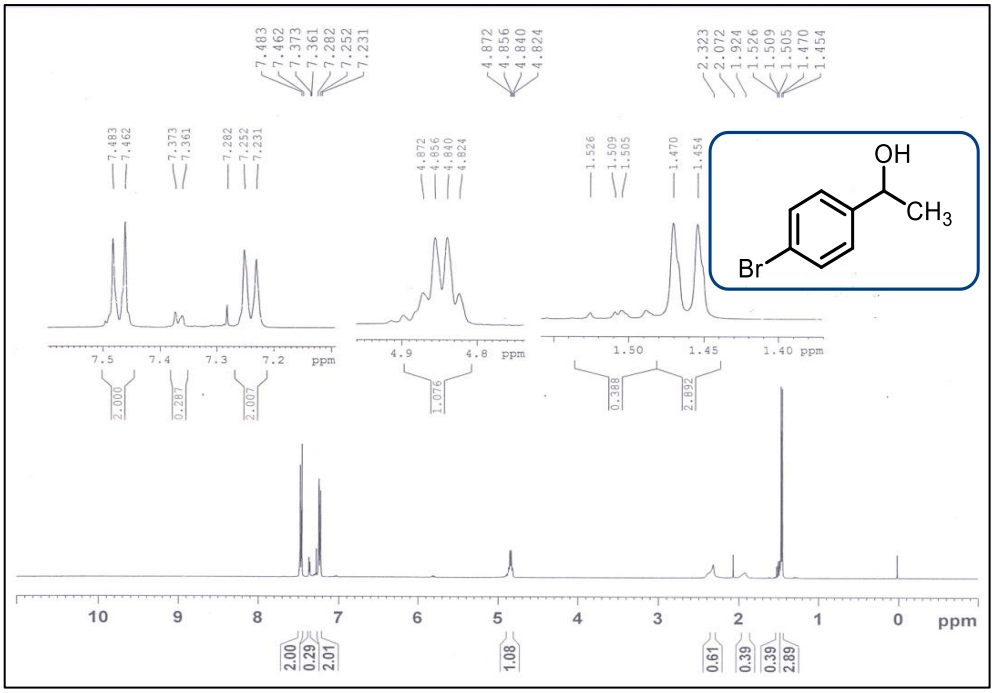
Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	10.673	28618	3235	0.112	0.171	N/A	28432	1.703	1.201	
2	Unknown	5	11.193	25413159	1892494	99.888	99.829	N/A	15549	N/A	1.114	

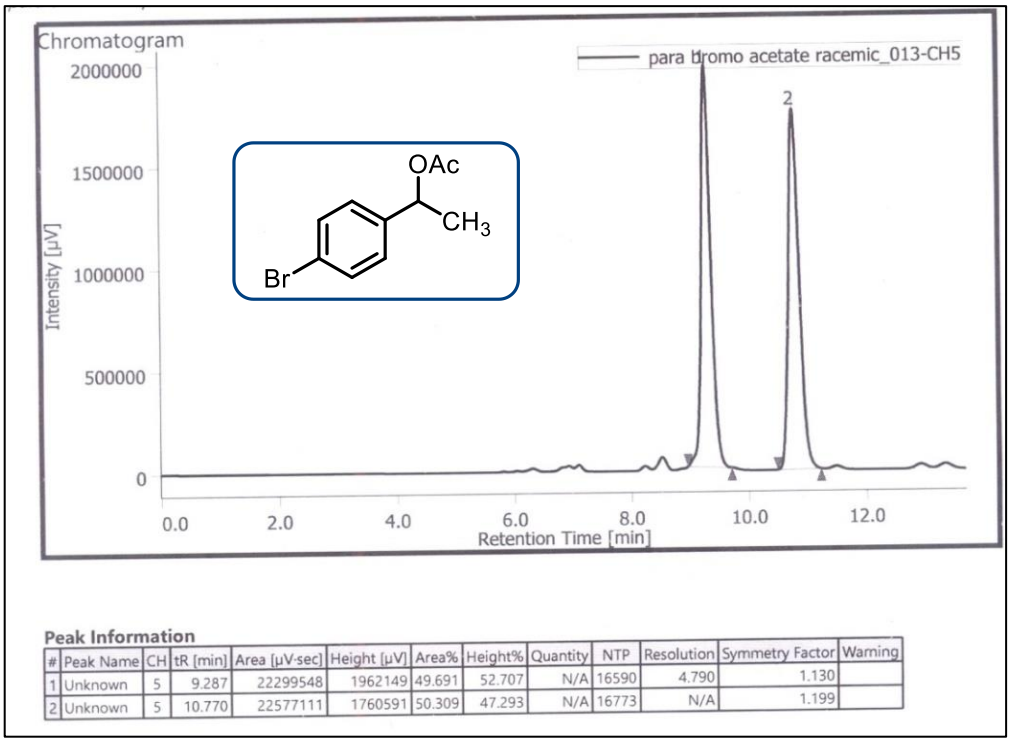
HPLC chromatogram of *(R)* 1-(4-chlorophenyl)ethan-1-ol **39** after Mitsunobu



^{1}H NMR of 1-(4-bromophenyl)ethyl acetate **42**



^{1}H NMR of 1-(4-bromophenyl)ethan 1-ol **41**

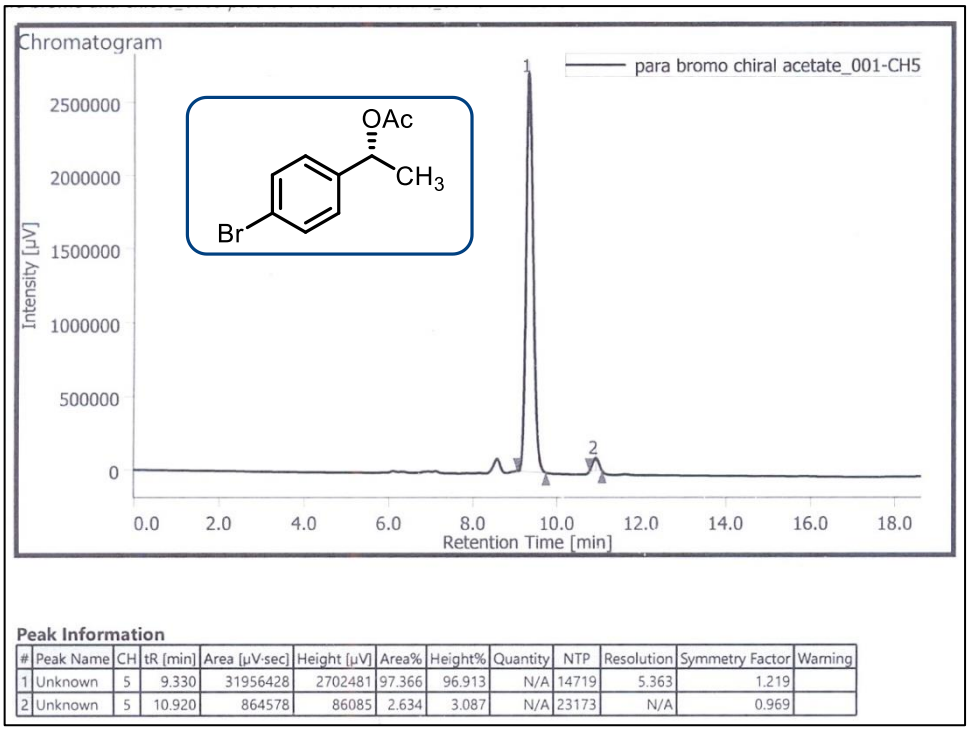


Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	9.287	22299548	1962149	49.691	52.707	N/A	16590	4.790	1.130	
2	Unknown	5	10.770	22577111	1760591	50.309	47.293	N/A	16773	N/A	1.199	

HPLC chromatogram of racemic 1-(4-bromophenyl)ethyl acetate **42**

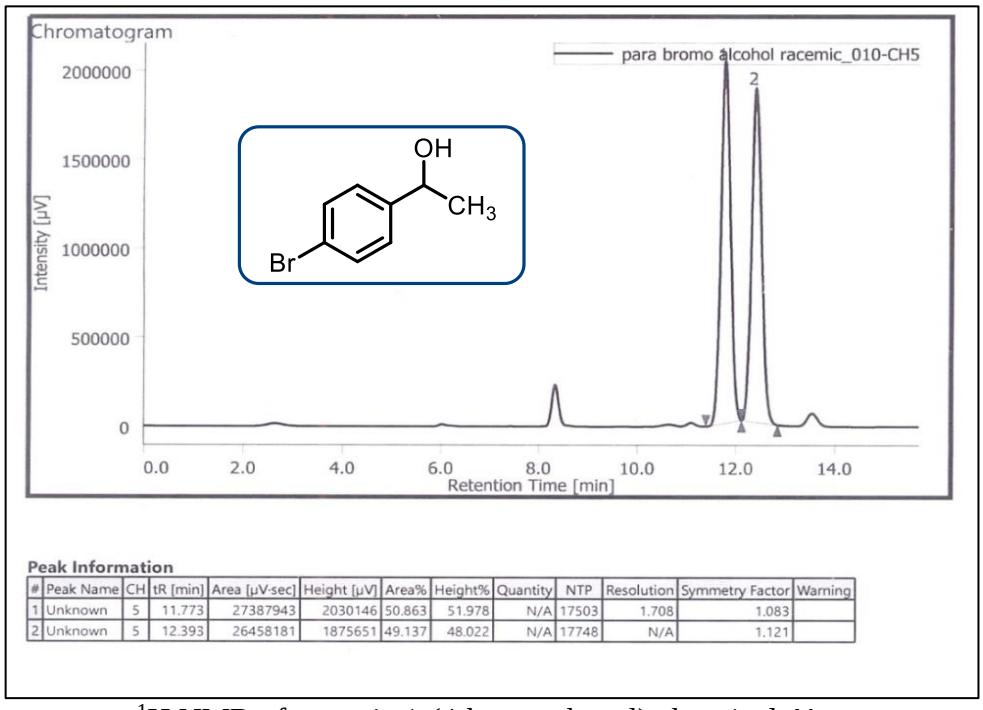
HPLC Condition for compound 1-(4-bromophenyl)ethyl acetate Determined by HPLC analysis (chiral column Amylose, 0.5ml/min IPA (10.0%) in hexane; 9.28 min for (*R*)-**42** and 10.77 min for (*S*)-**42**



Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	9.330	31956428	2702481	97.366	96.913	N/A	14719	5.363	1.219	
2	Unknown	5	10.920	864578	86085	2.634	3.087	N/A	23173	N/A	0.969	

HPLC chromatogram of (*R*) 1-(4-bromophenyl)ethyl acetate **42**

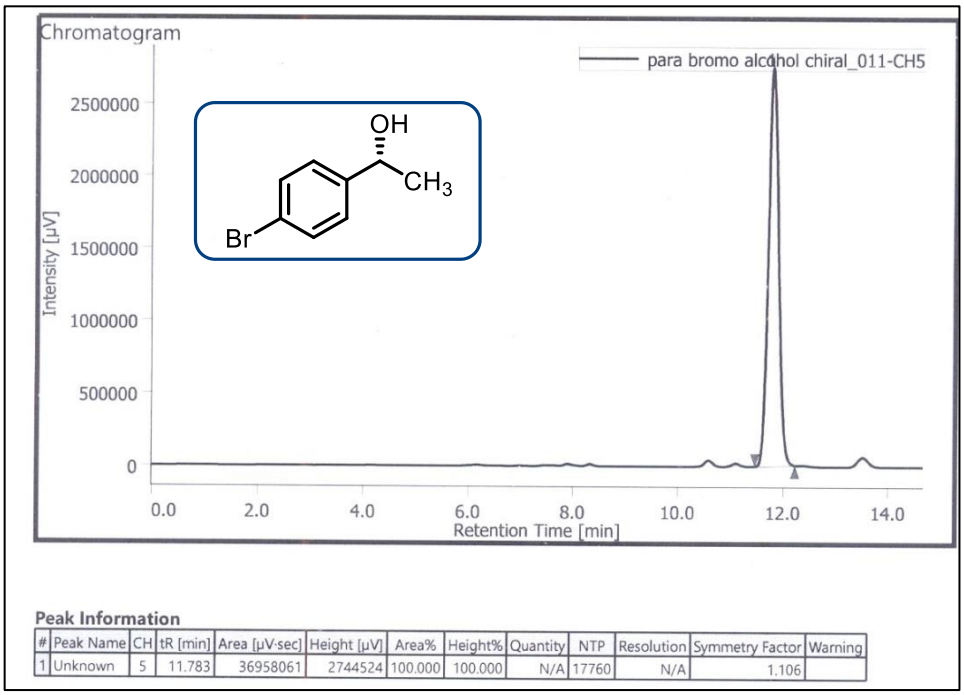


Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	11.773	27387943	2030146	50.863	51.978	N/A	17503	1.708	1.083	
2	Unknown	5	12.393	26458181	1875651	49.137	48.022	N/A	17748	N/A	1.121	

^{1}H NMR of racemic 1-(4-bromophenyl)ethan 1-ol **41**

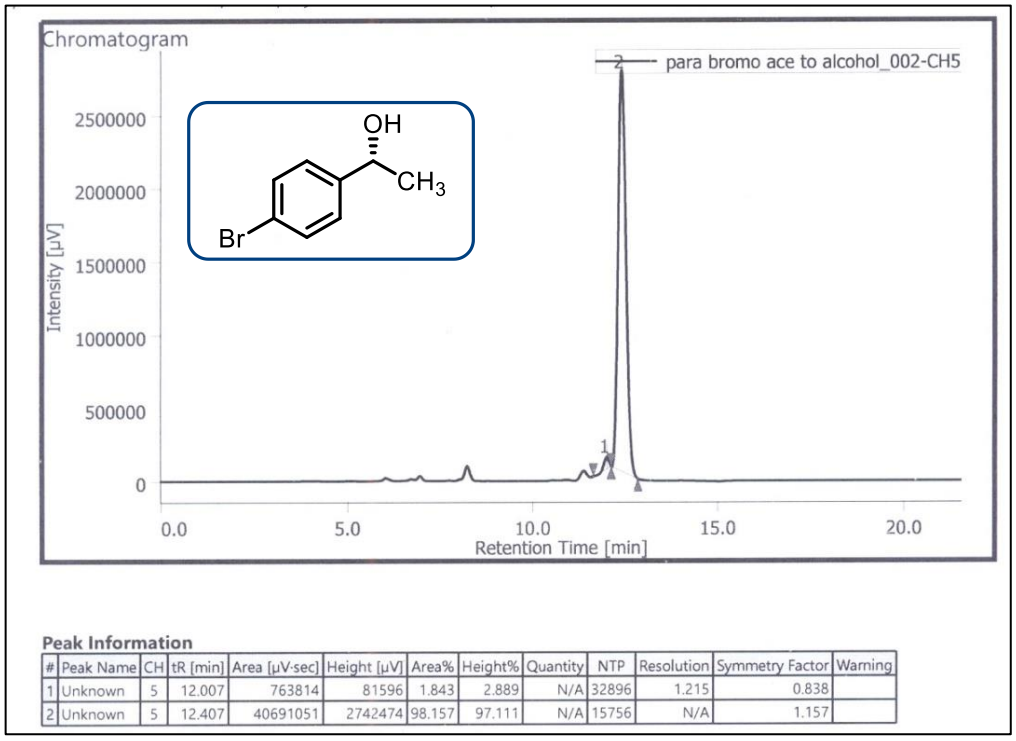
*HPLC Condition for compound 1-(4-bromophenyl)ethan-1-ol Determined by HPLC analysis (chiral column OD-H, 0.5ml/min IPA (10.0%) in hexane; 11.77 min for (R)-**41** and 12.39 min for (S)-**41**)*



Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	11.783	36958061	2744524	100.000	100.000	N/A	17760	N/A	1.106	

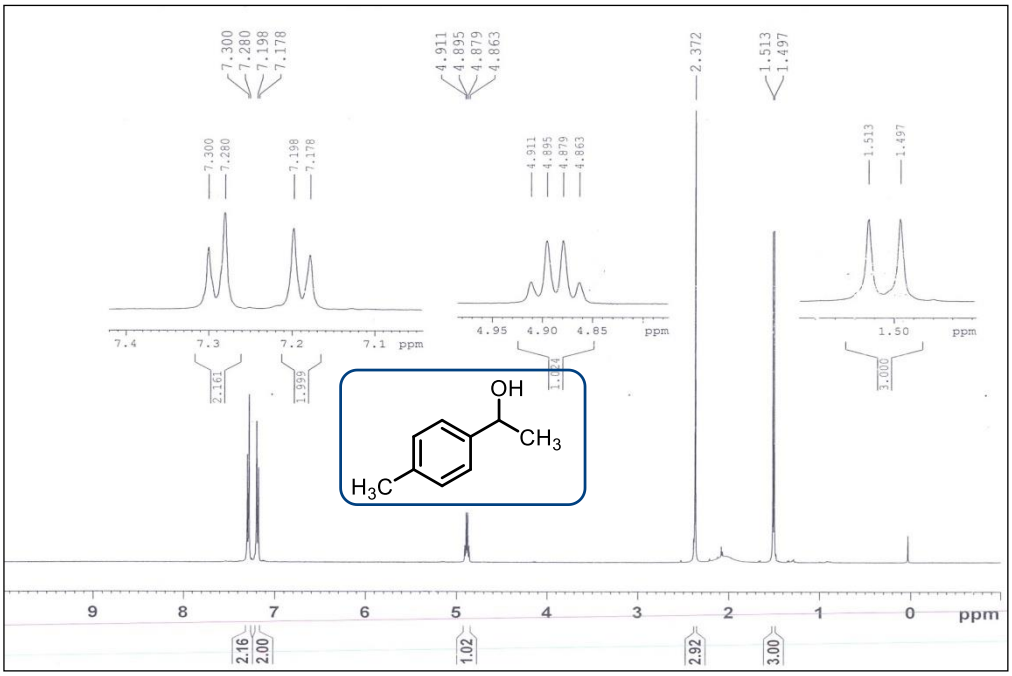
HPLC chromatogram of *(S)* 1-(4-bromophenyl)ethan-1-ol **41**



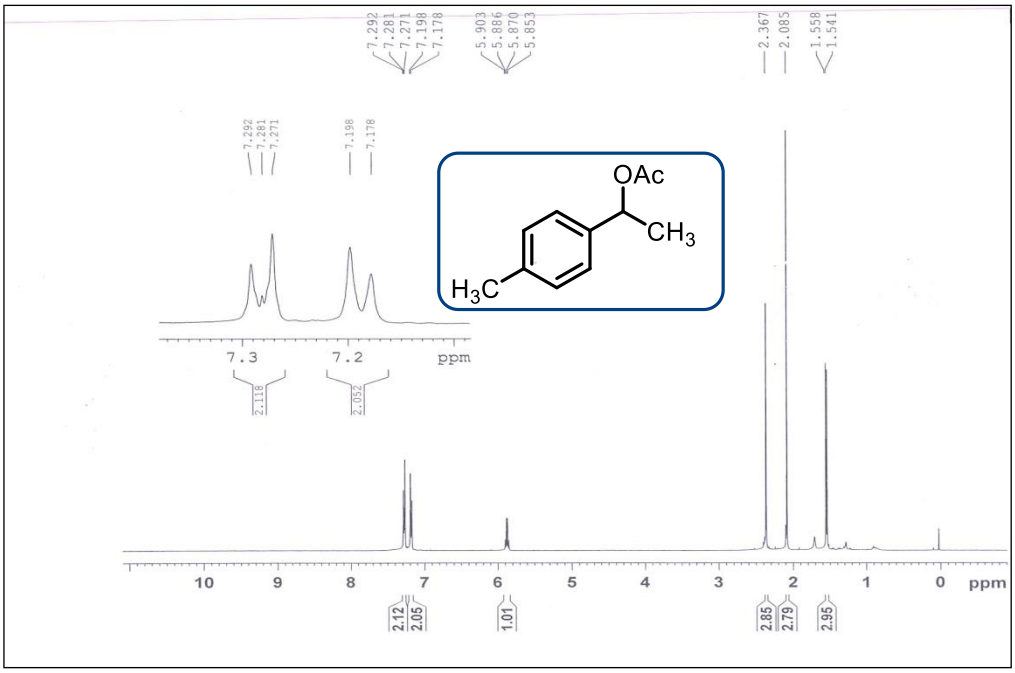
Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	12.007	763814	81596	1.843	2.889	N/A	32896	1.215	0.838	
2	Unknown	5	12.407	40691051	2742474	98.157	97.111	N/A	15756	N/A	1.157	

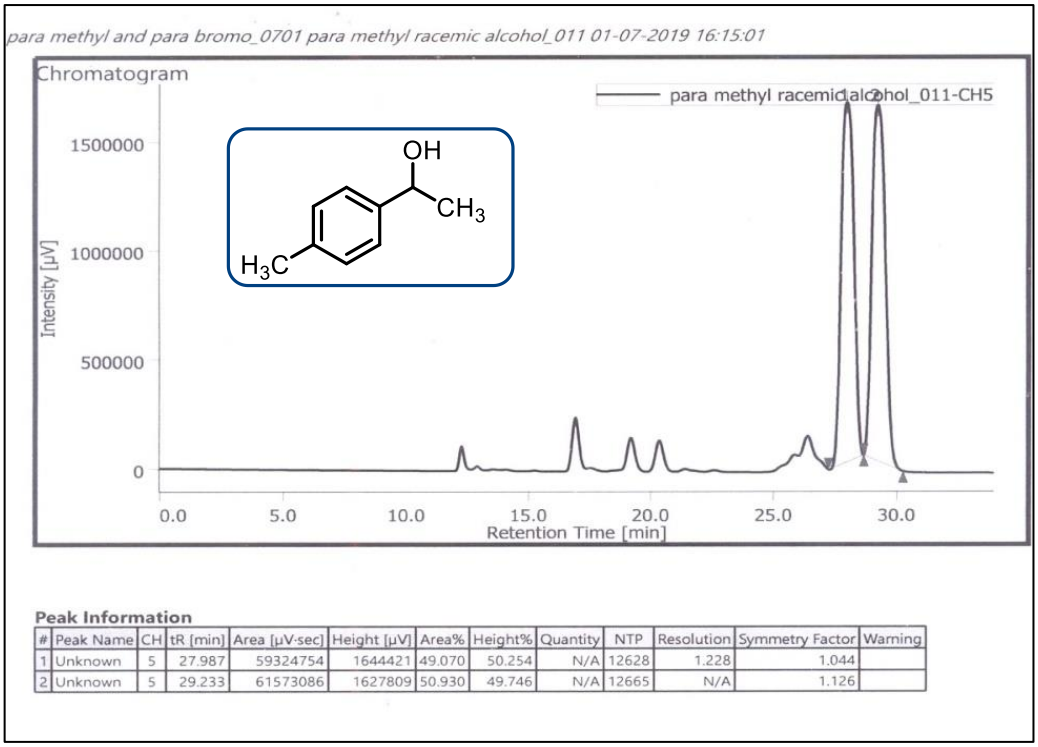
HPLC of *(R)* 1-(4-bromophenyl)ethan-1-ol after Mitsunobu **41**



^{1}H NMR of racemic 1-(p-tolyl)ethan 1-ol **43**



^{1}H NMR of racemic 1-(4-bromophenyl)ethyl acetate **44**

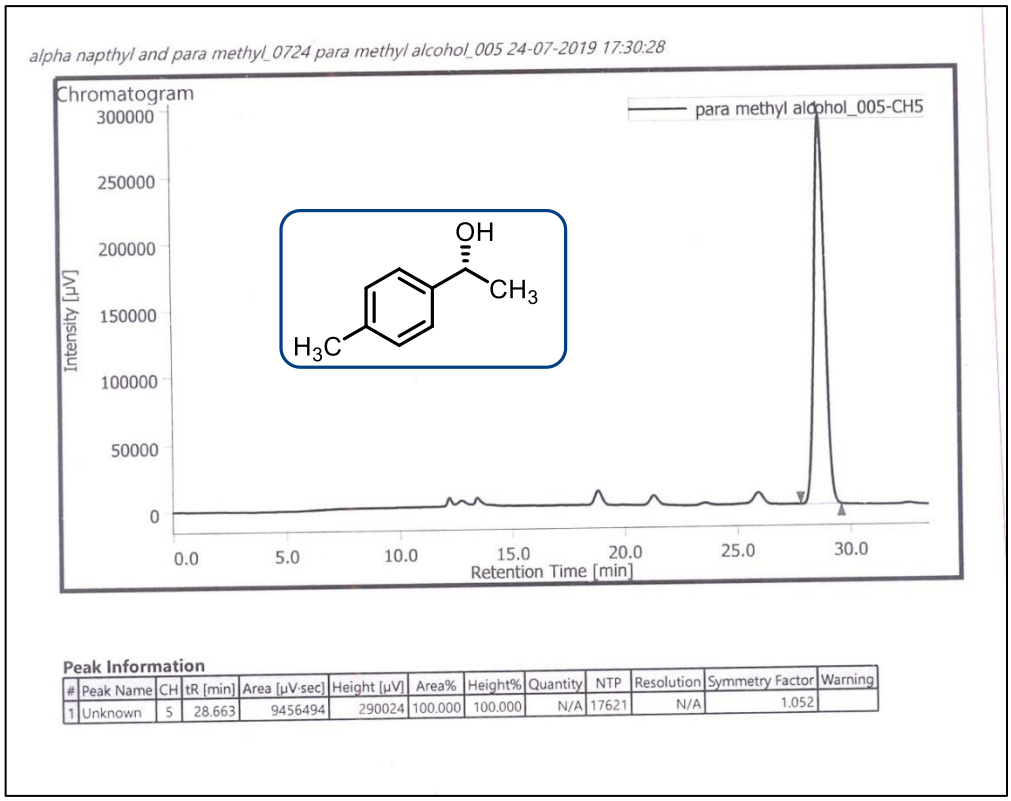


Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	27.987	59324754	1644421	49.070	50.254	N/A	12628	1.228	1.044	
2	Unknown	5	29.233	61573086	1627809	50.930	49.746	N/A	12665	N/A	1.126	

HPLC chromatogram of Racemic 1-(p-tolyl)ethan-1-ol **43**

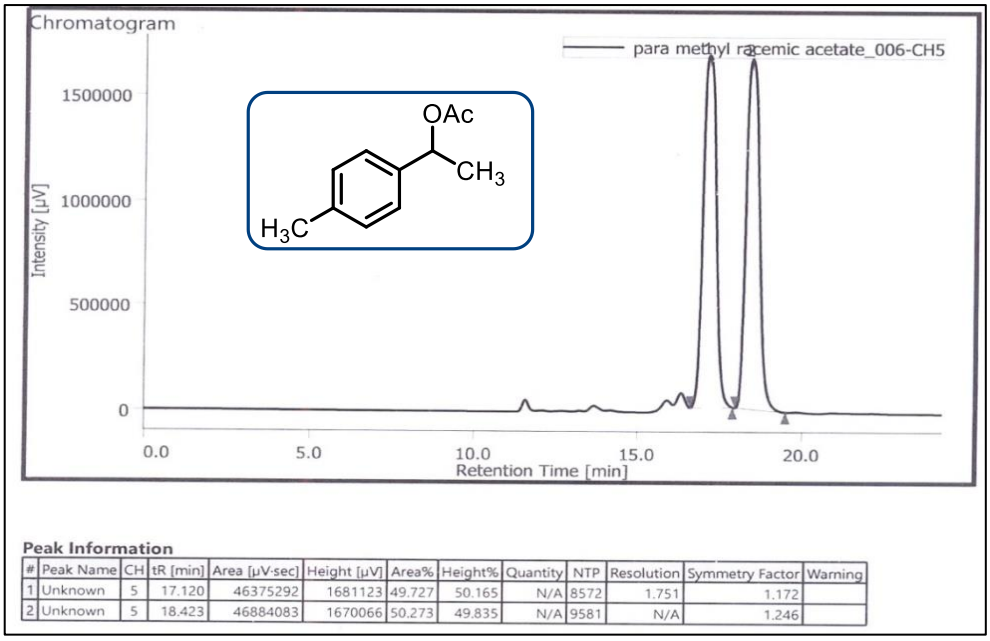
*HPLC Condition for compound 1-(p-tolyl)ethan-1-ol Determined by HPLC analysis (chiral column IE,0.25ml/min IPA (5.0%) in hexane; 27.98 min for (R)-**43** and 29.23 min for (S)-**43**)*



Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	28.663	9456494	290024	100.000	100.000	N/A	17621	N/A	1.052	

HPLC chromatogram of (*S*) 1-(p-tolyl)ethan-1-ol **43**

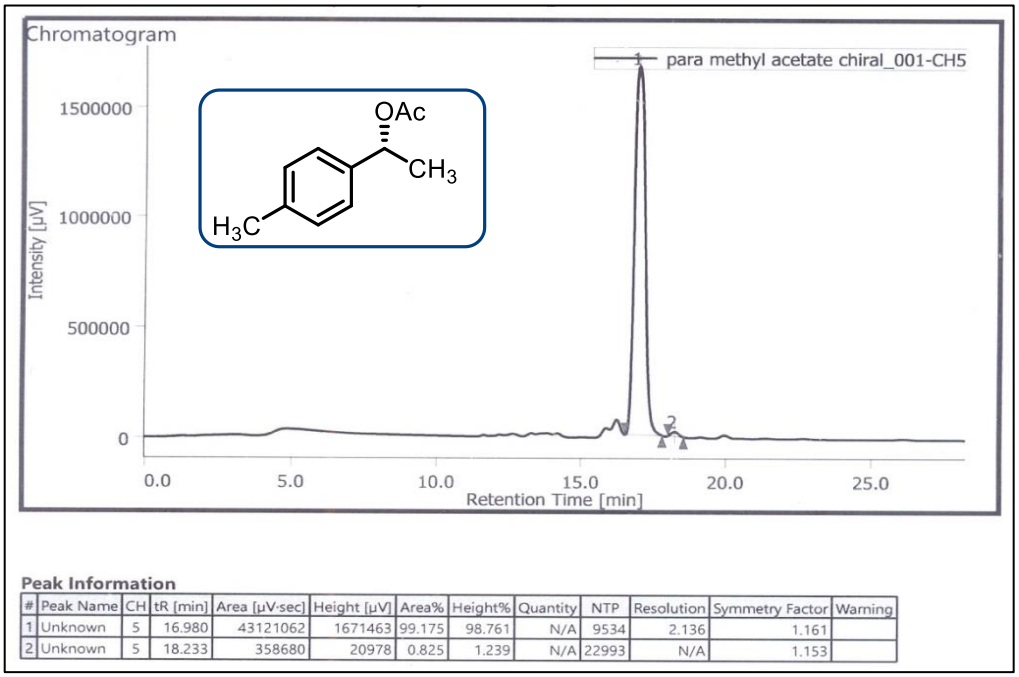


Peak Information

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	17.120	46375292	1681123	49.727	50.165	N/A	8572	1.751	1.172	
2	Unknown	5	18.423	46884083	1670066	50.273	49.835	N/A	9581	N/A	1.246	

HPLC chromatogram of Racemic 1-(p-tolyl)ethyl acetate **44**

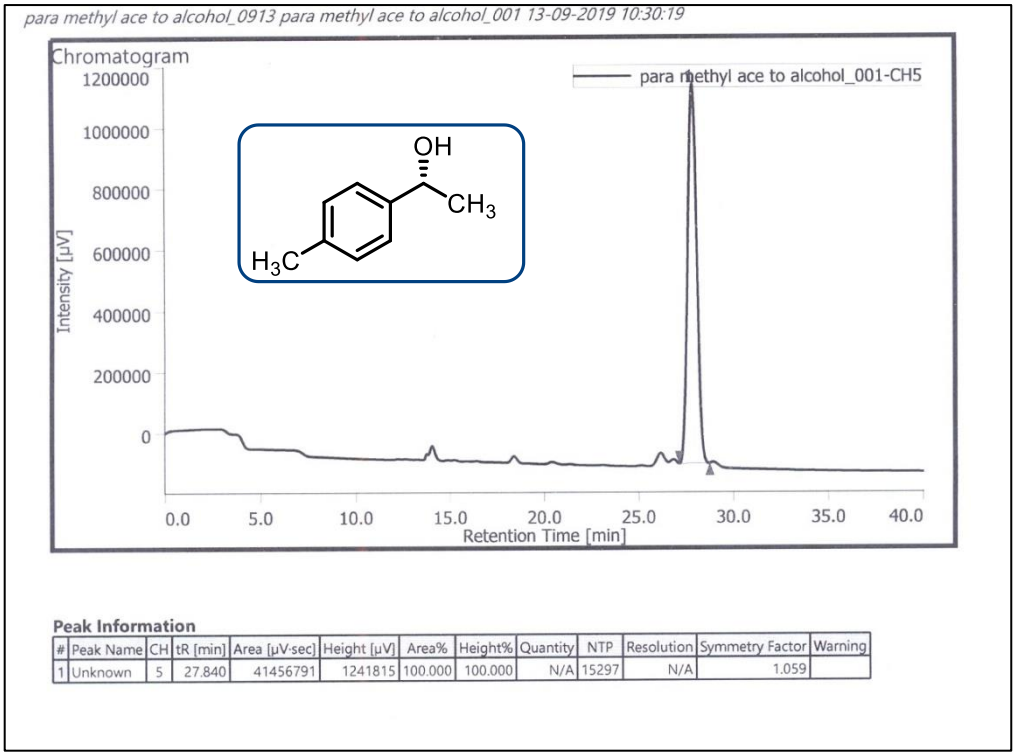
*HPLC Condition for compound 1-(p-tolyl)ethyl acetate Determined by HPLC analysis (chiral column Amylose, 1ml/min IPA (20.0%) in hexane; 4.003 min for (R)-**44** and 4.25 min for (S)-**44**)*



Peak Information

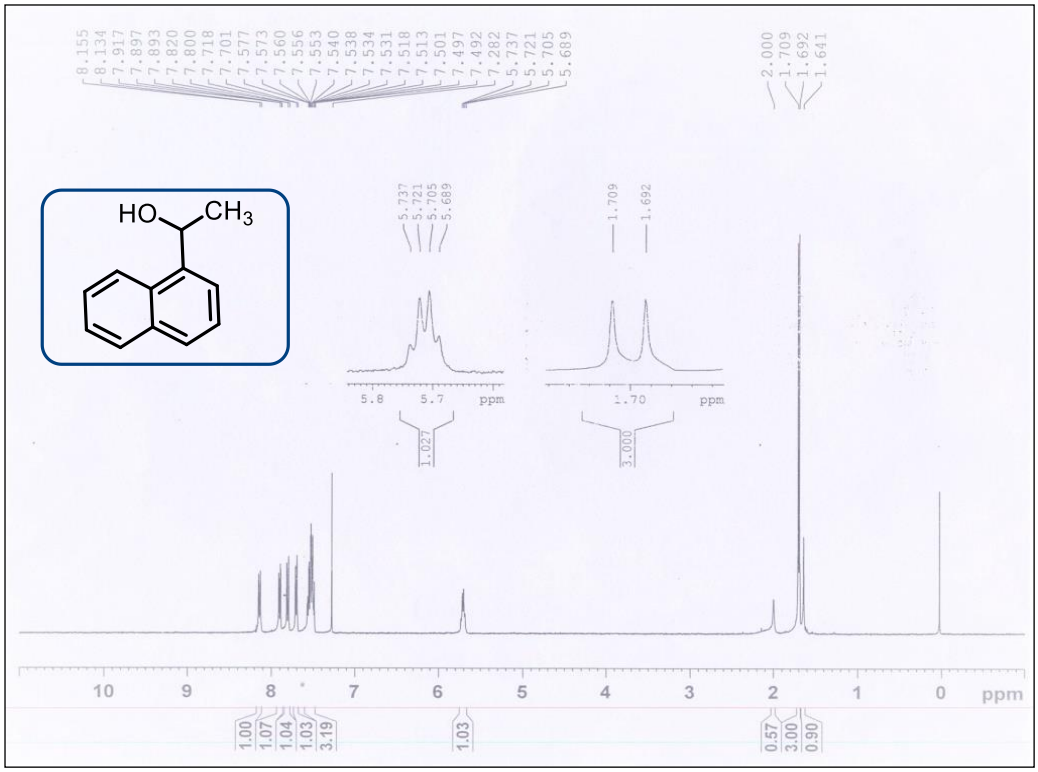
#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	16.980	43121062	1671463	99.175	98.761	N/A	9534	2.136	1.161	
2	Unknown	5	18.233	358680	20978	0.825	1.239	N/A	22993	N/A	1.153	

HPLC chromatogram of (*R*) 1-(p-tolyl)ethyl acetate **44**

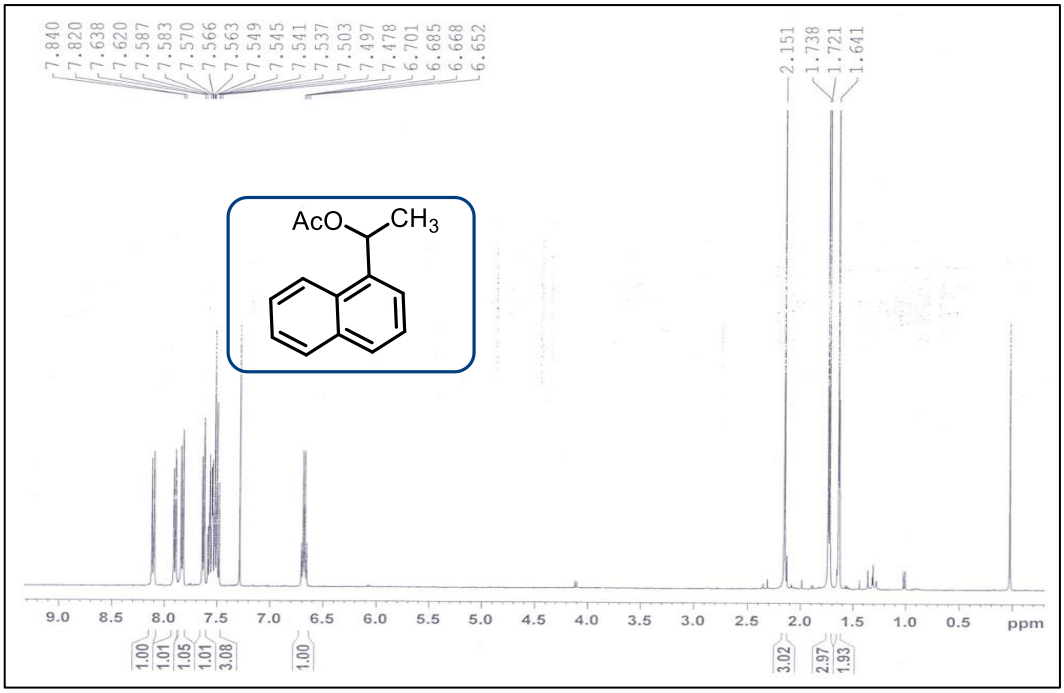


#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	27.840	41456791	1241815	100.000	100.000	N/A	15297	N/A	1.059	

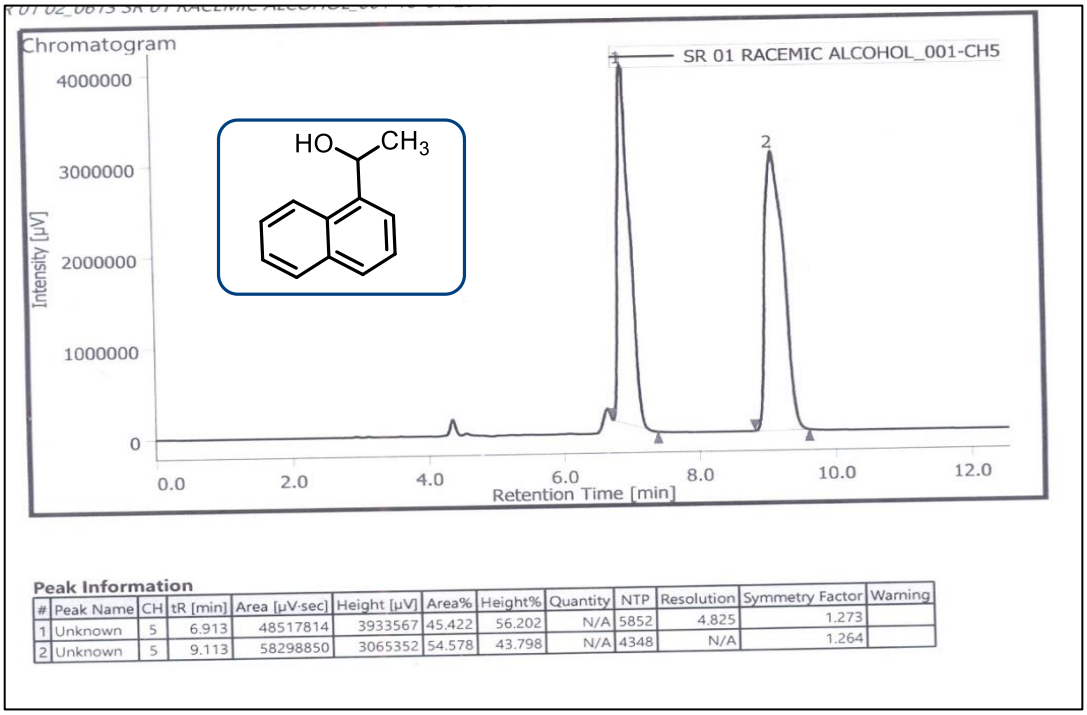
HPLC chromatogram of (*R*) 1-(p-tolyl)ethyl acetate **44** after Mitsunobu



^{1}H NMR of 1-(naphthalen-1-yl)ethan-1-ol **45**



^{1}H NMR of 1-(naphthalen-1-yl)ethyl acetate **46**

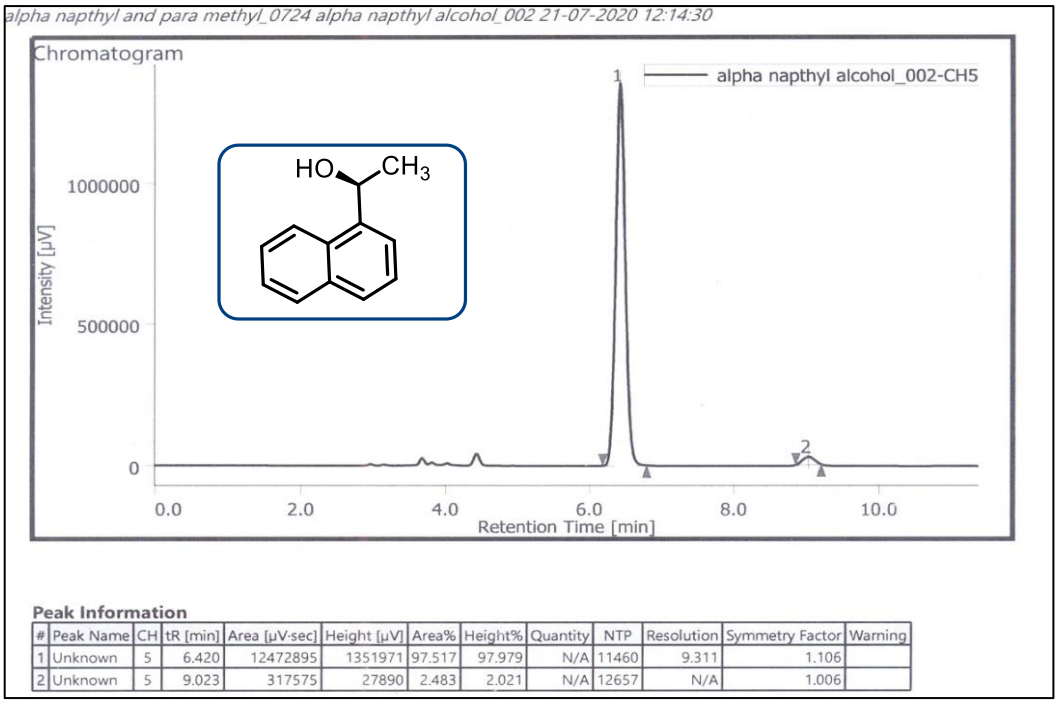


Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	6.913	48517814	3933567	45.422	56.202	N/A	5852	4.825	1.273	
2	Unknown	5	9.113	58298850	3065352	54.578	43.798	N/A	4348	N/A	1.264	

HPLC chromatogram of Racemic 1-(naphthalen-1-yl)ethan-1-ol **45**

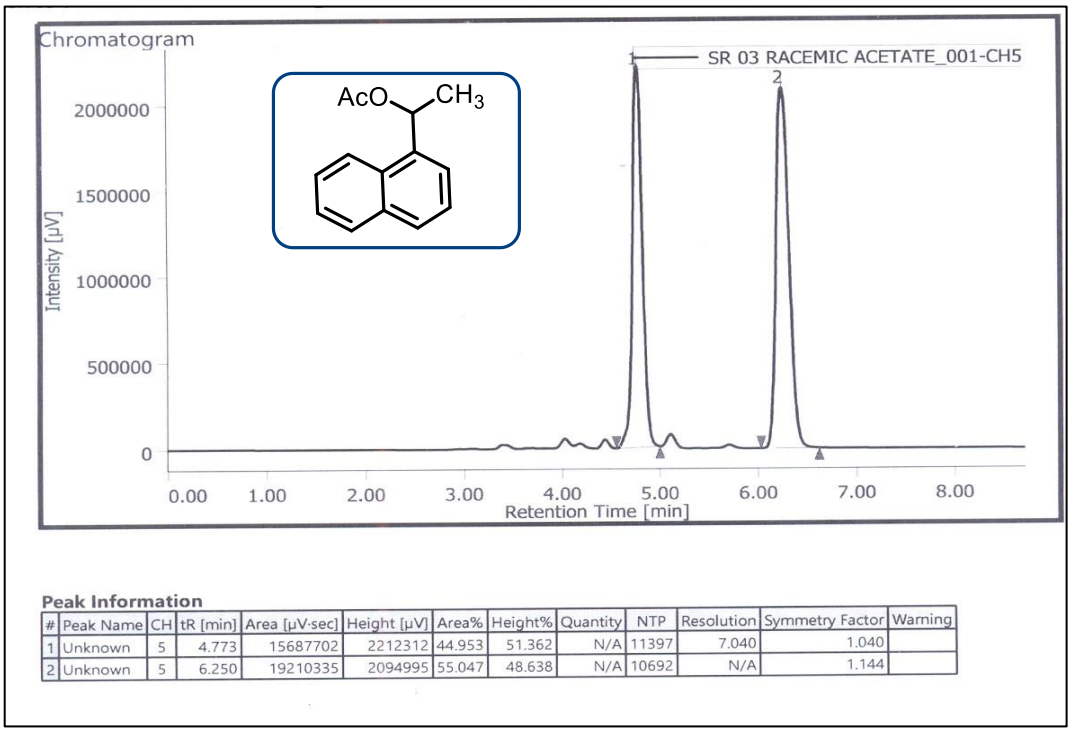
*HPLC Condition for compound 1-(naphthalen-1-yl)ethan-1-ol Determined by HPLC analysis (chiral column OD-H, 1ml/min IPA (20.0%) in hexane; 6.91 min for (R)-**45** and 9.11 min for (S)-**45**)*



Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	6.420	12472895	1351971	97.517	97.979	N/A	11460	9.311	1.106	
2	Unknown	5	9.023	317575	27890	2.483	2.021	N/A	12657	N/A	1.006	

HPLC chromatogram of (S) 1-(naphthalen-1-yl)ethyl-1-ol **46**

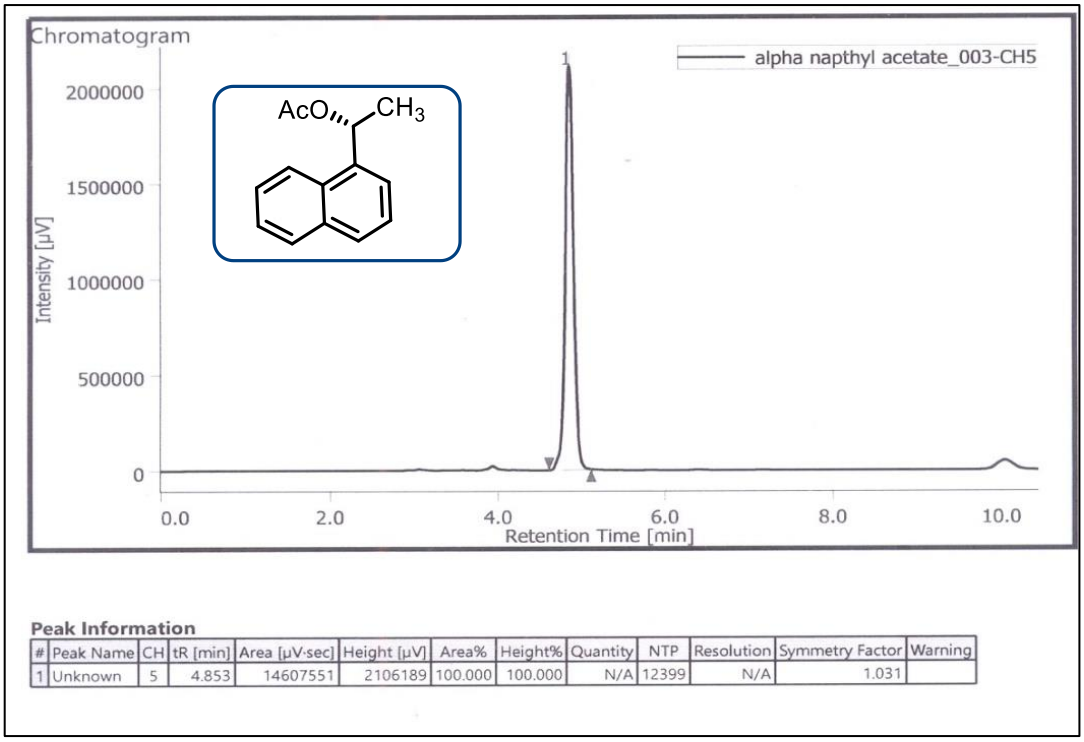


Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	4.773	15687702	2212312	44.953	51.362	N/A	11397	7.040	1.040	
2	Unknown	5	6.250	19210335	2094995	55.047	48.638	N/A	10692	N/A	1.144	

HPLC chromatogram of Racemic 1-(naphthalen-1-yl)ethayl acetate **46**

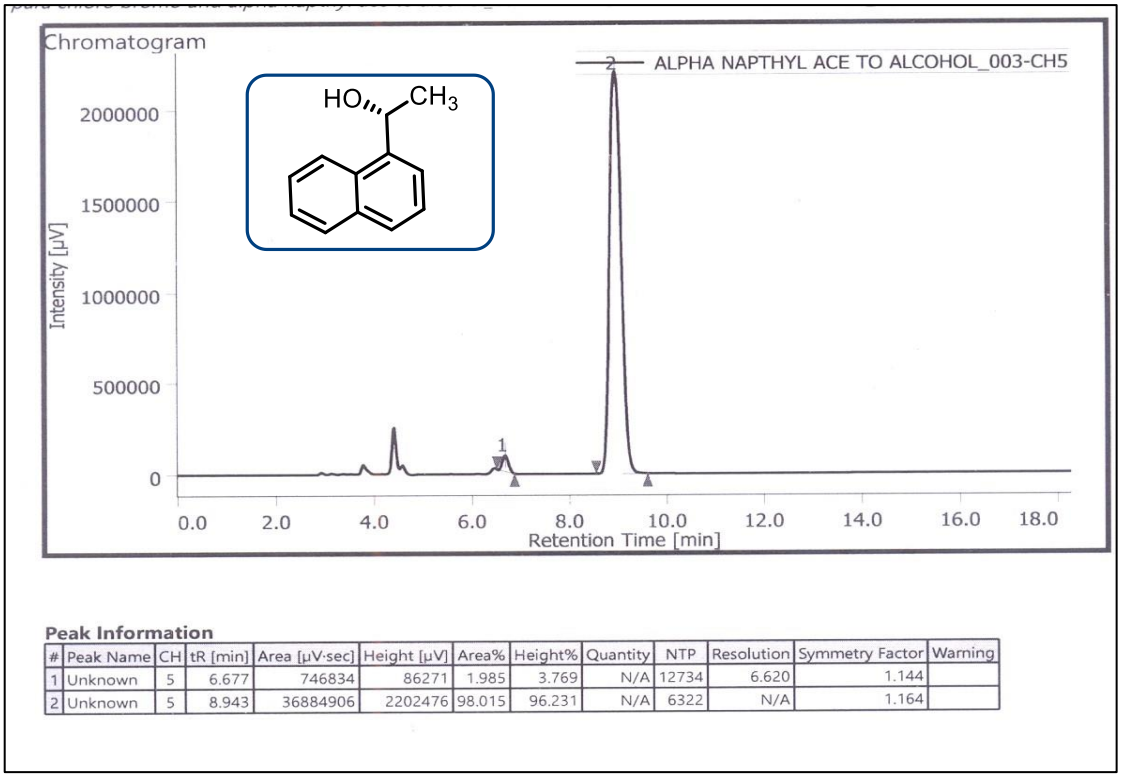
*HPLC Condition for compound 1-(naphthalen-1-yl)ethyl acetate Determined by HPLC analysis (chiral column OD-H,1ml/min IPA (10.0%) in hexane; 4.77 min for (R)-**46** and 6.20 min for (S)-**46**)*



Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	4.853	14607551	2106189	100.000	100.000	N/A	12399	N/A	1.031	

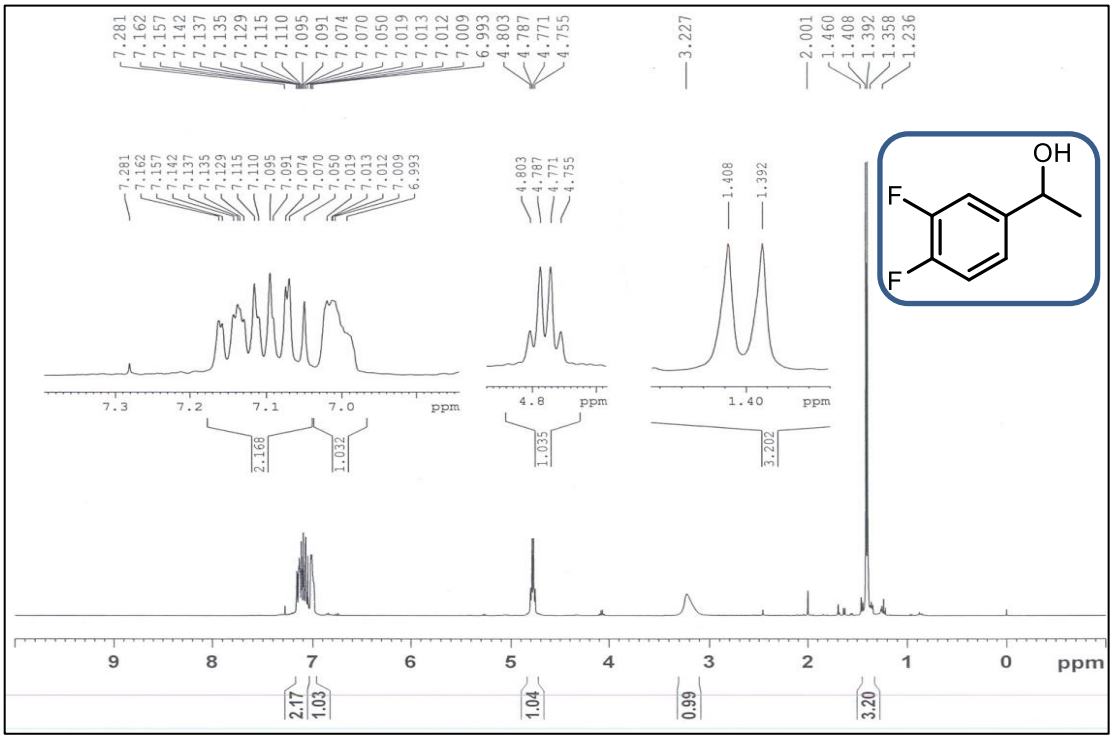
HPLC chromatogram of *(R)* 1-(naphthalen-1-yl)ethyl acetate **46**



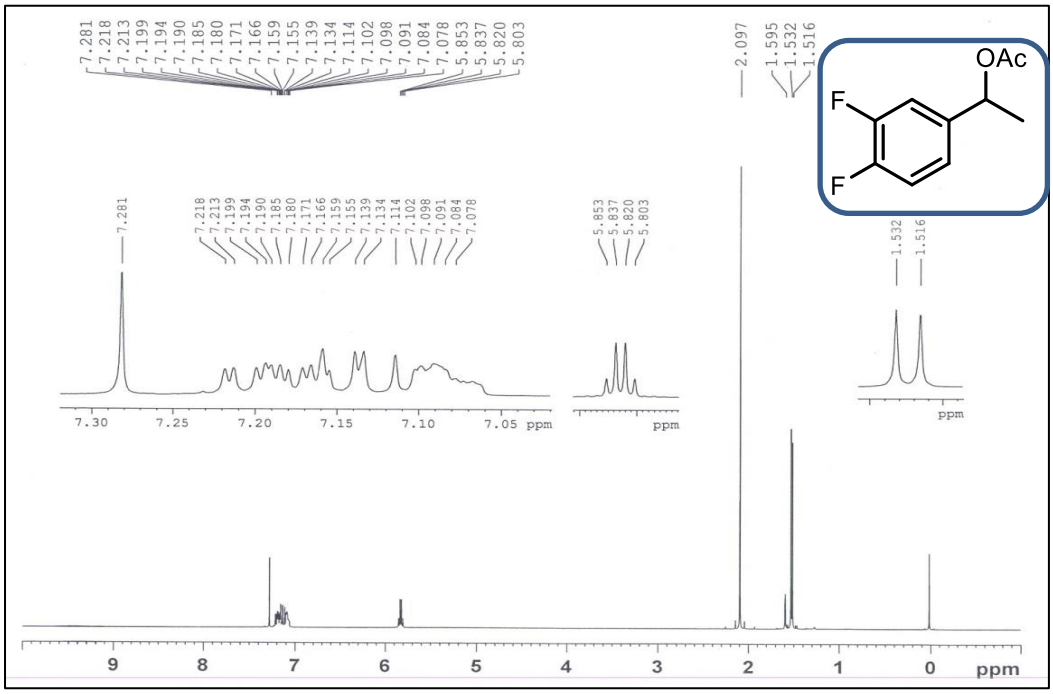
Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	6.677	746834	86271	1.985	3.769	N/A	12734	6.620	1.144	
2	Unknown	5	8.943	36884906	2202476	98.015	96.231	N/A	6322	N/A	1.164	

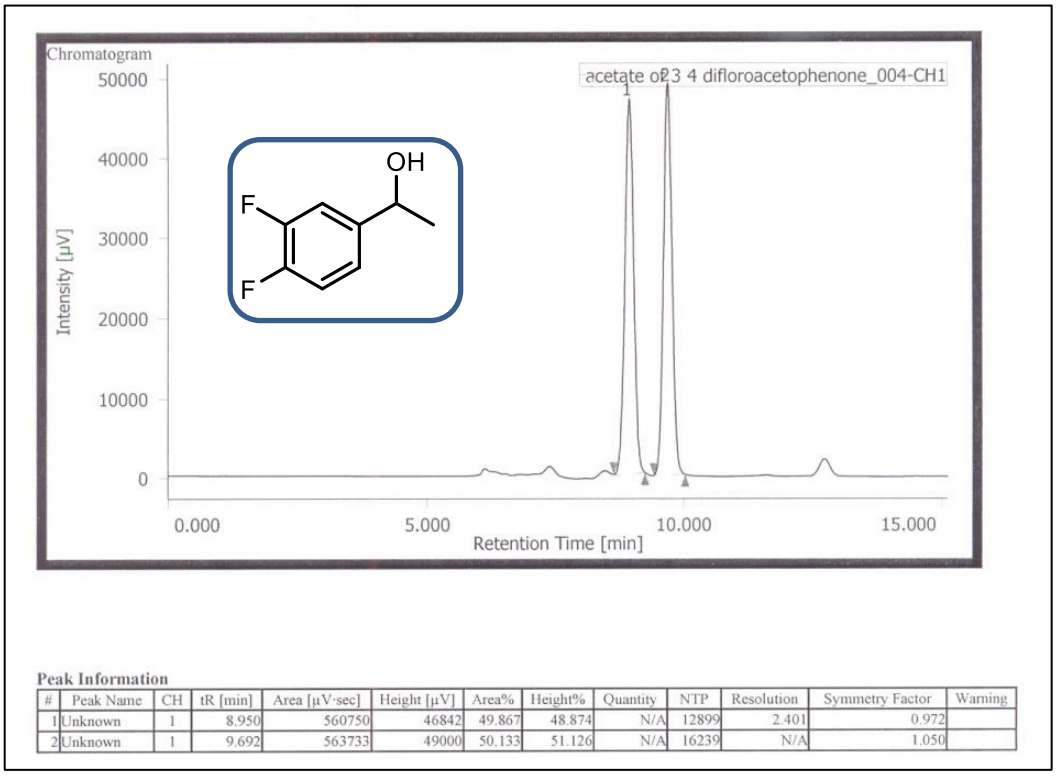
HPLC of *(R)* 1-(naphthalen-1-yl)ethan-1-ol after mitsunobu **46**



^{1}H NMR of 1-(3,4-difluorophenyl)ethan-1-ol **47**



^{1}H NMR of 1-(3,4-difluorophenyl)ethyl acetate **48**

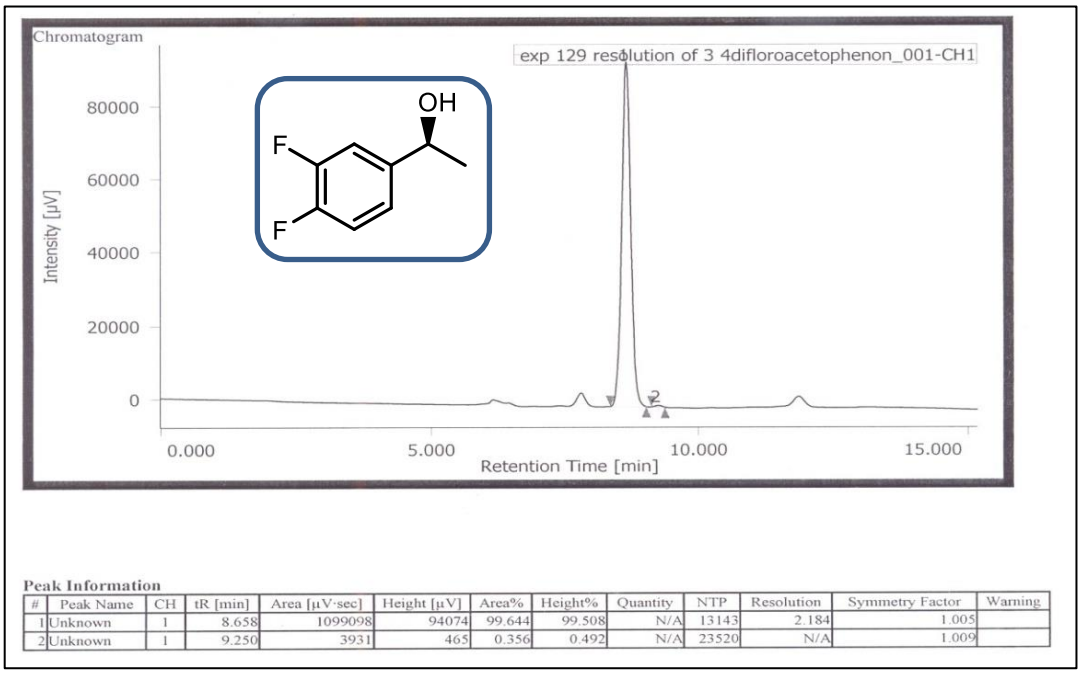


Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	1	8.950	560750	46842	49.867	48.874	N/A	12899	2.401	0.972	
2	Unknown	1	9.692	563733	49000	50.133	51.126	N/A	16239	N/A	1.050	

HPLC chromatogram of Racemic 1-(3,4-difluorophenyl)ethan-1-ol **47**

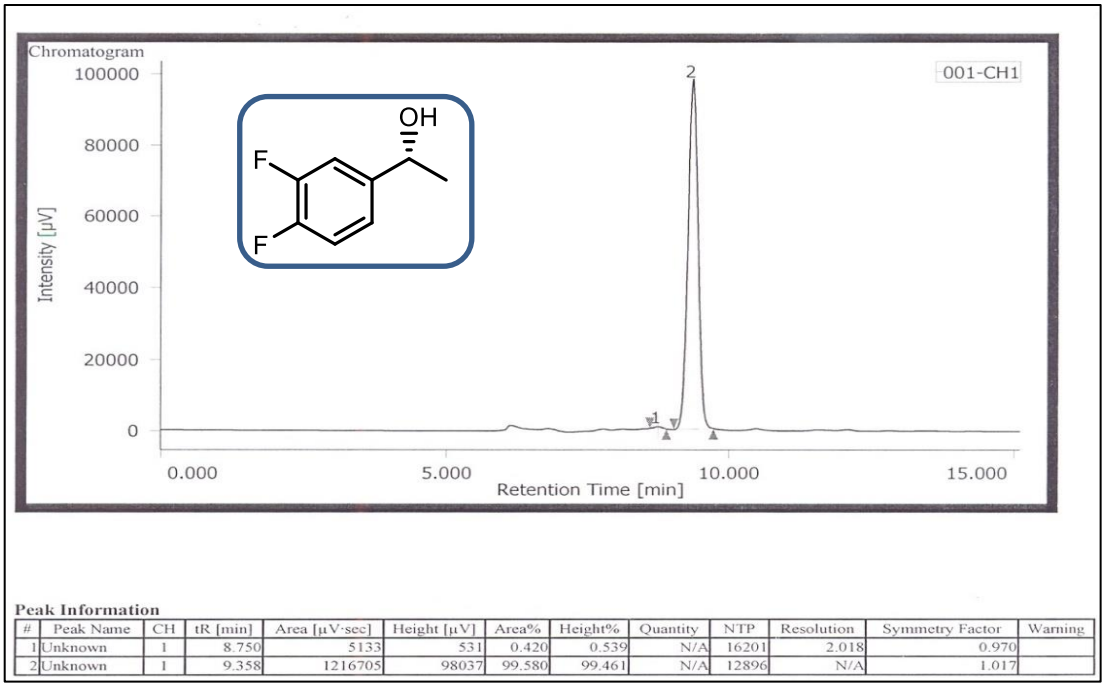
*HPLC Condition for compound 1-(3,4-difluorophenyl)ethan-1-ol Determined by HPLC analysis (chiral column Amylose, 0.25ml/min IPA (7.0%) in hexane; 8.9 min for (R)-**47** and 9.6 min for (S)-**47**)*



Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	1	8.658	1099098	94074	99.644	99.508	N/A	13143	2.184	1.005	
2	Unknown	1	9.250	3931	465	0.356	0.492	N/A	23520	N/A	1.009	

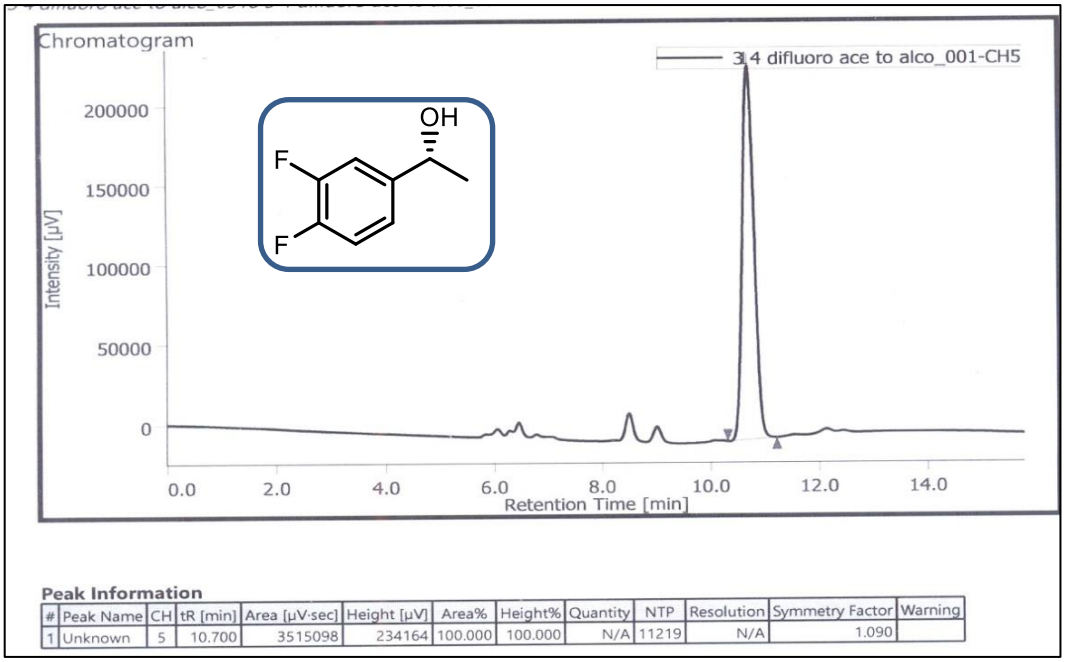
HPLC chromatogram of *(S)* 1-(3,4-difluorophenyl)ethan-1-ol **47**



Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	1	8.750	5133	531	0.420	0.539	N/A	16201	2.018	0.970	
2	Unknown	1	9.358	1216705	98037	99.580	99.461	N/A	12896	N/A	1.017	

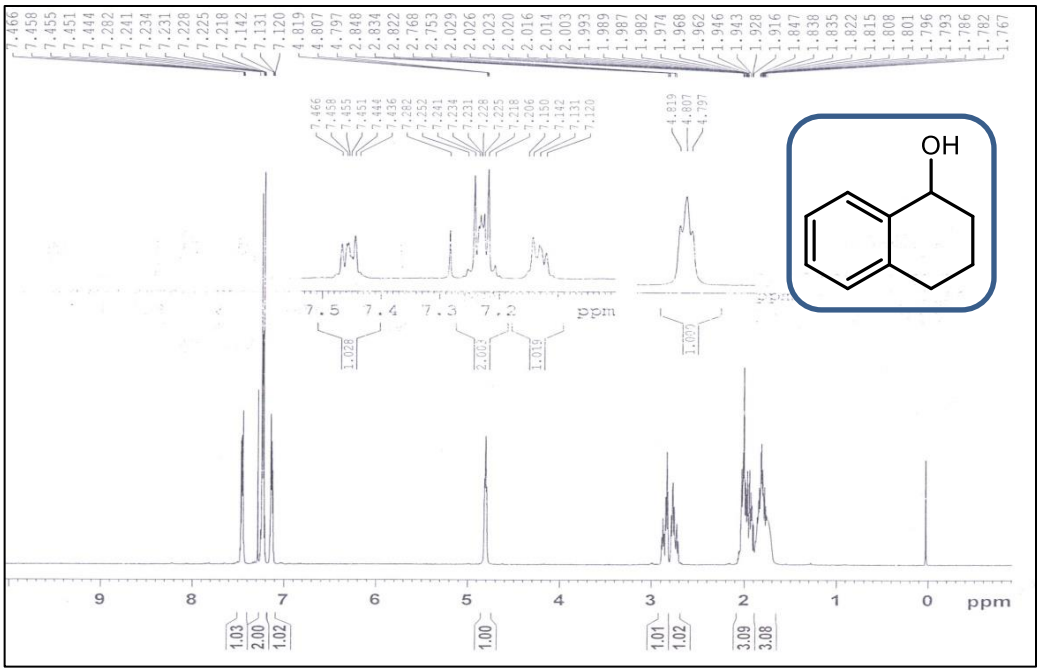
HPLC chromatogram of *(R)* 1-(3,4-difluorophenyl)ethan-1-ol **47**



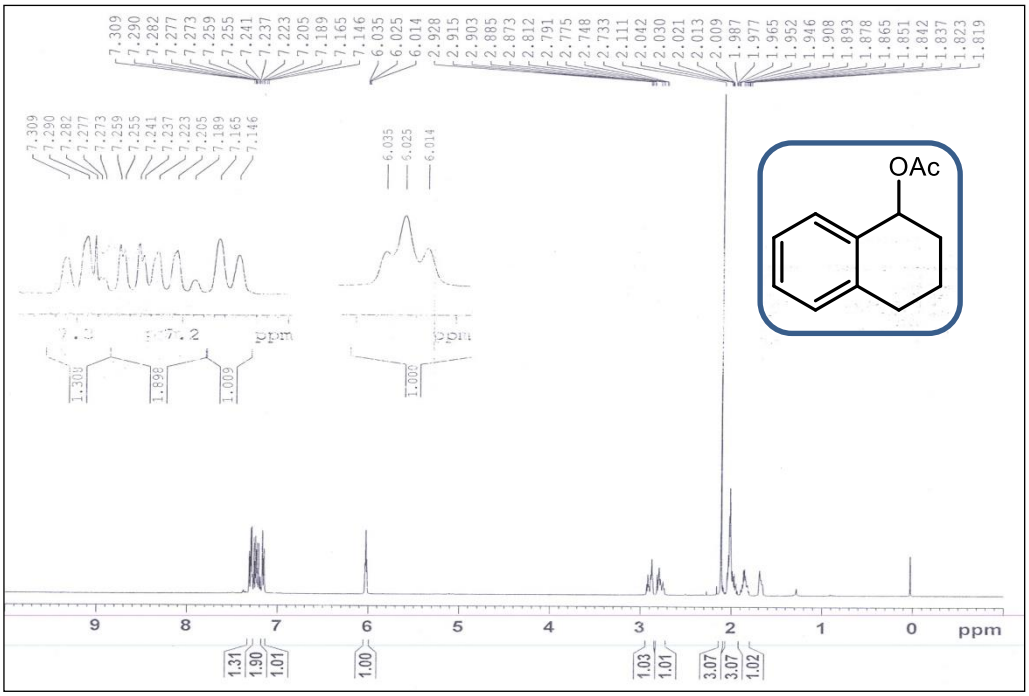
Peak Information

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	10.700	3515098	234164	100.000	100.000	N/A	11219	N/A	1.090	

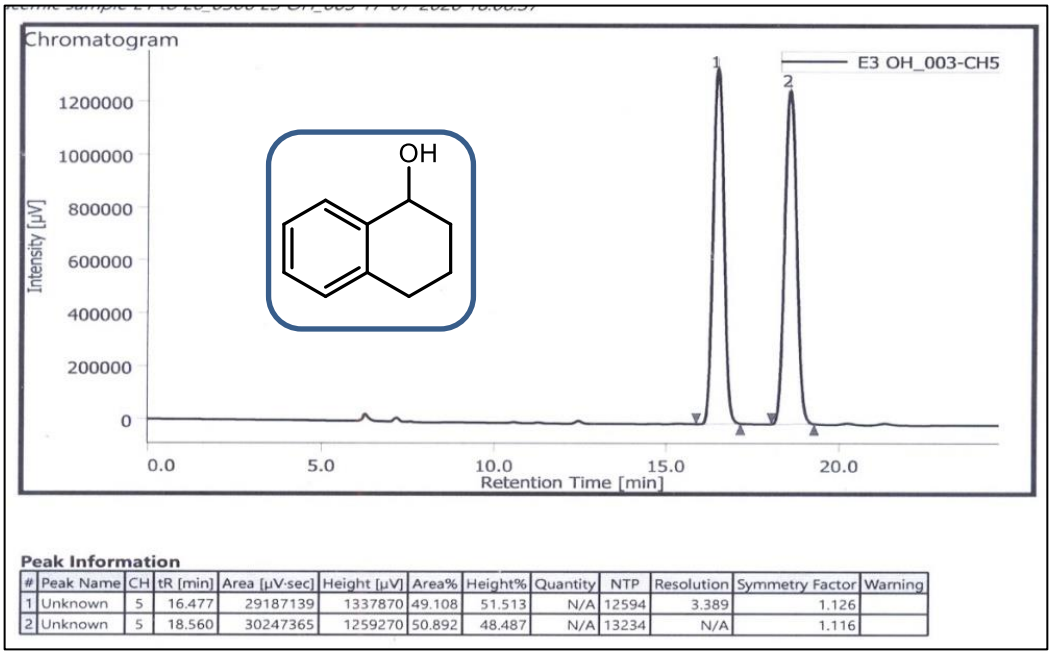
HPLC chromatogram of *(R)* 1-(3,4-difluorophenyl)ethan-1-ol after mitsunobu **47**



^{1}H NMR of 1,2,3,4-tetrahydronaphthalen-1-ol **49**



^{1}H NMR of 1,2,3,4-tetrahydronaphthalen-1-yl acetate **50**

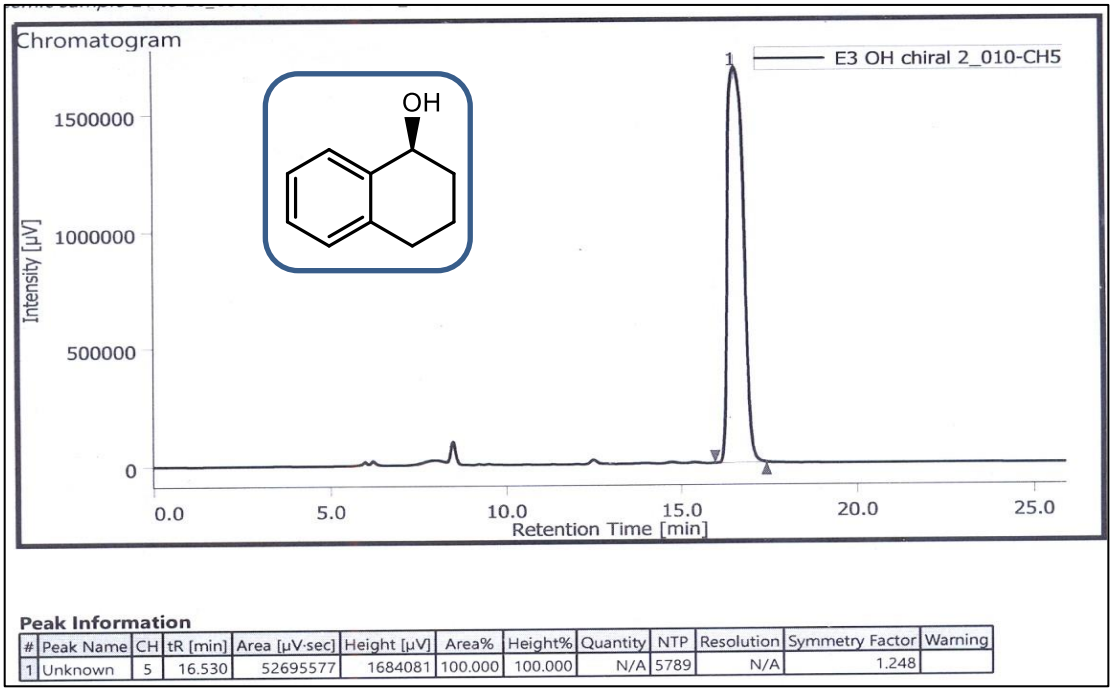


Peak Information

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	16.477	29187139	1337870	49.108	51.513	N/A	12594	3.389	1.126	
2	Unknown	5	18.560	30247365	1259270	50.892	48.487	N/A	13234	N/A	1.116	

HPLC chromatogram of Racemic 1,2,3,4-tetrahydronaphthalen-1-ol **49**

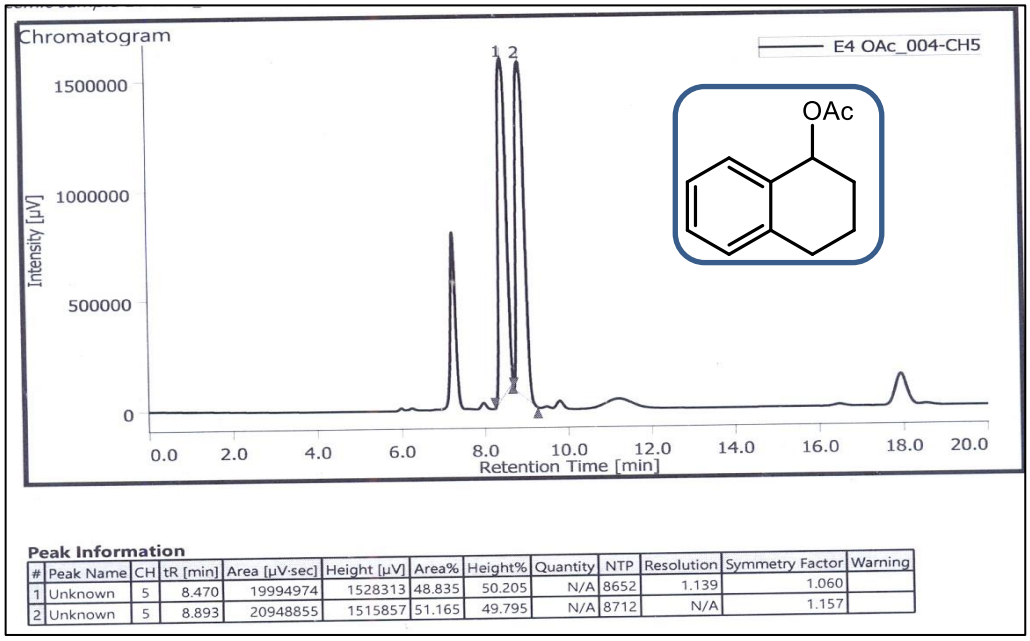
*HPLC Condition for compound 1,2,3,4-tetrahydronaphthalen-1-ol Determined by HPLC analysis (chiral column OD-H,0.5ml/mil IPA (5.0%) in hexane; 16.47 min for (R)-**49** and 18.56 min for (S)-**49**)*



Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	16.530	52695577	1684081	100.000	100.000	N/A	5789	N/A	1.248	

HPLC chromatogram of *(S)* 1,2,3,4-tetrahydronaphthalen-1-ol **49**

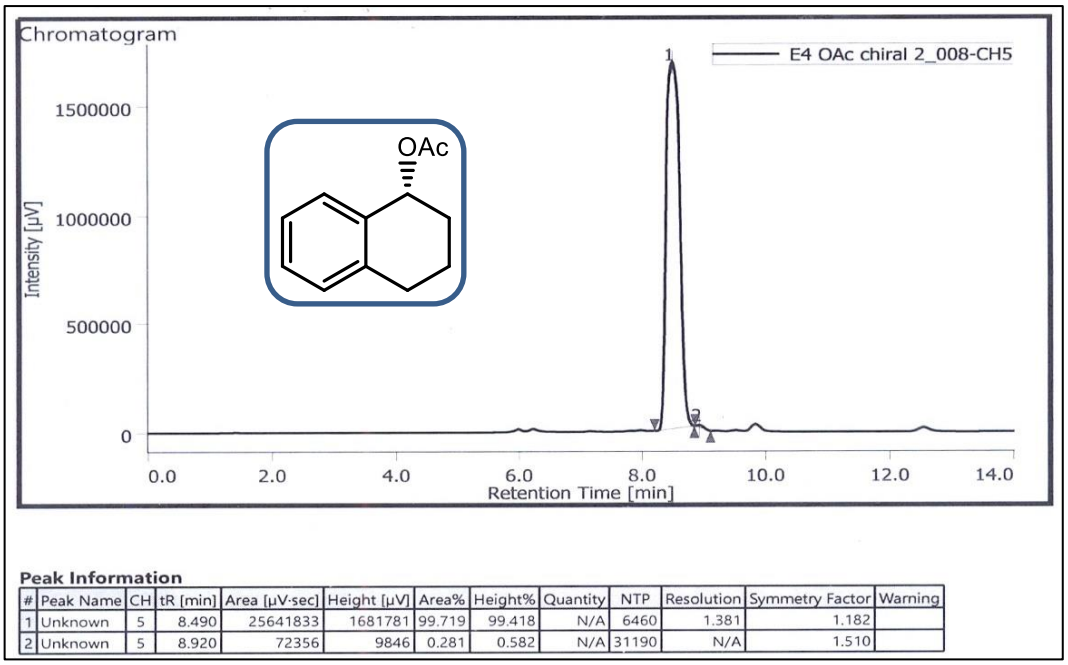


Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	8.470	19994974	1528313	48.835	50.205	N/A	8652	1.139	1.060	
2	Unknown	5	8.893	20948855	1515857	51.165	49.795	N/A	8712	N/A	1.157	

HPLC chromatogram of Racemic 1,2,3,4-tetrahydronaphthalen-1-yl acetate **50**

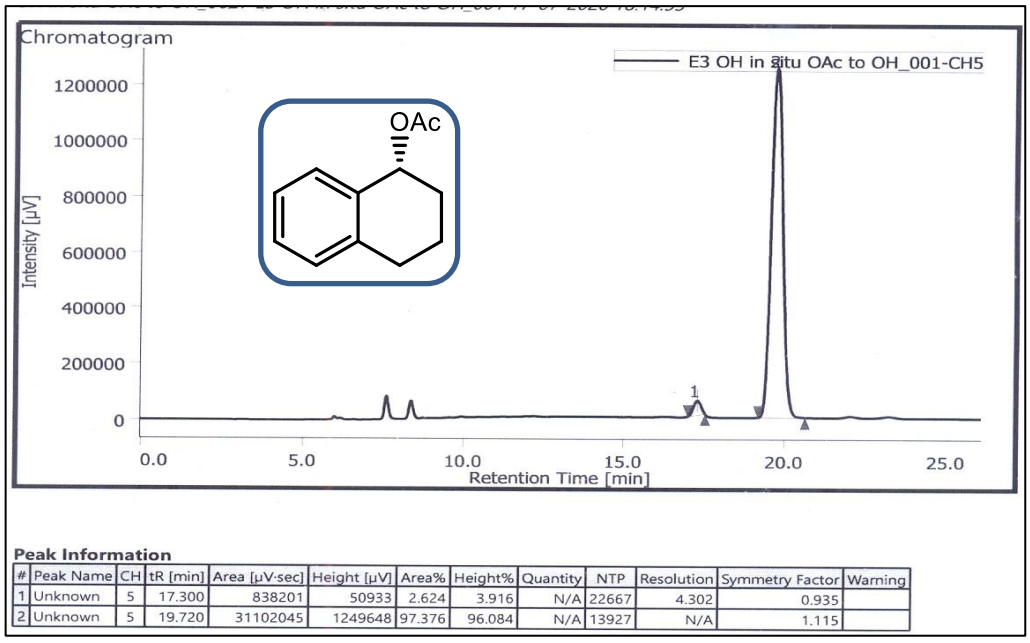
HPLC Condition for compound 1,2,3,4-tetrahydronaphthalen-1-yl acetate [b] *Determined by HPLC analysis (chiral column Amylose 0.5ml/min, IPA (5.0%) in hexane; 8.47 min for (R)-**50** and 8.89 min for (S)-**50**)*



Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	8.490	25641833	1681781	99.719	99.418	N/A	6460	1.381	1.182	
2	Unknown	5	8.920	72356	9846	0.281	0.582	N/A	31190	N/A	1.510	

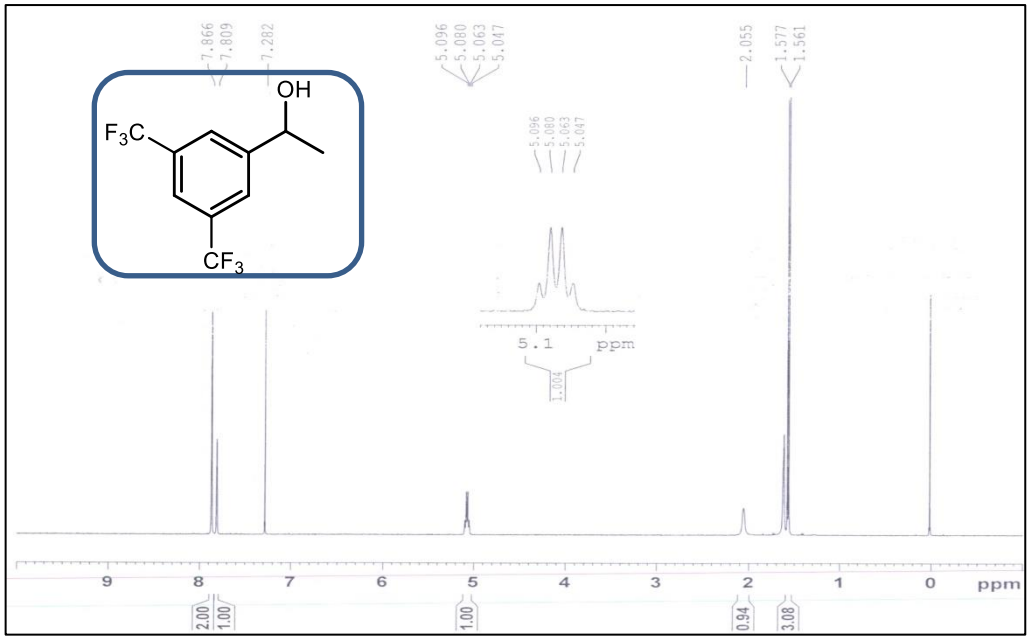
HPLC chromatogram of *(R)* 1,2,3,4-tetrahydronaphthalen-1-yl acetate **50**



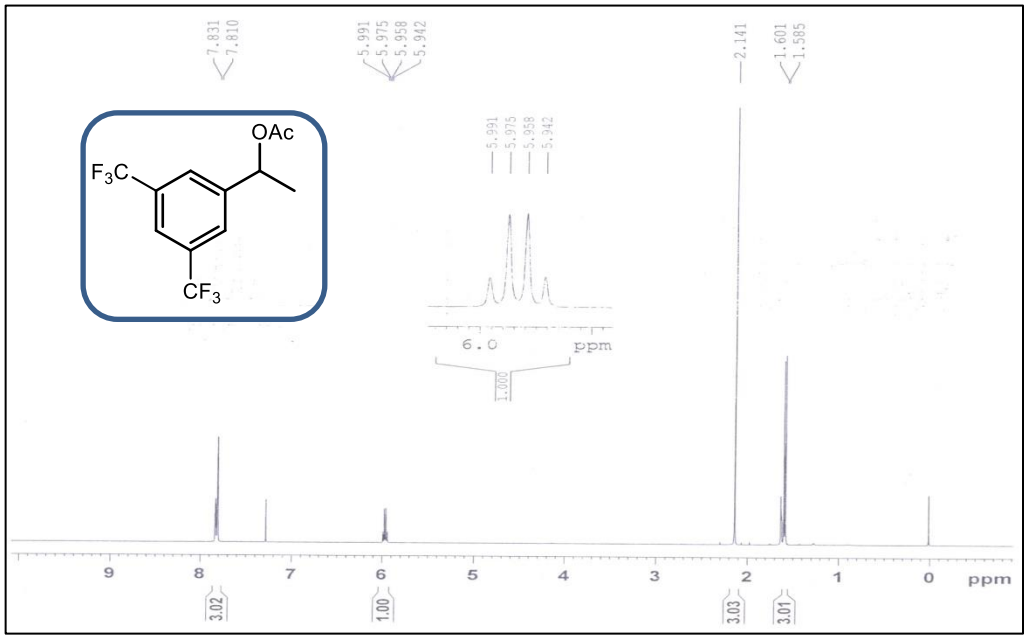
Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	17.300	838201	50933	2.624	3.916	N/A	22667	4.302	0.935	
2	Unknown	5	19.720	31102045	1249648	97.376	96.084	N/A	13927	N/A	1.115	

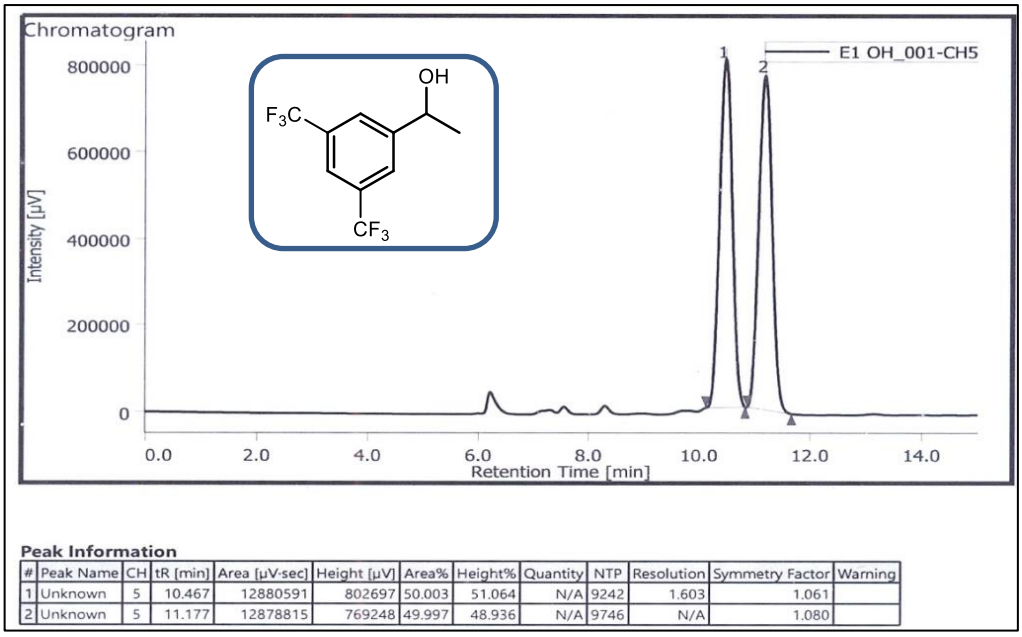
HPLC chromatogram of *(R)* 1,2,3,4-tetrahydronaphthalen-1-ol **49** after mitsunobu



^{1}H NMR of 1-(3,5-bis(trifluoromethyl)phenyl)ethan-1-ol **51**



^{1}H NMR of 1-(3,5-bis(trifluoromethyl)phenyl)ethyl acetate **52**

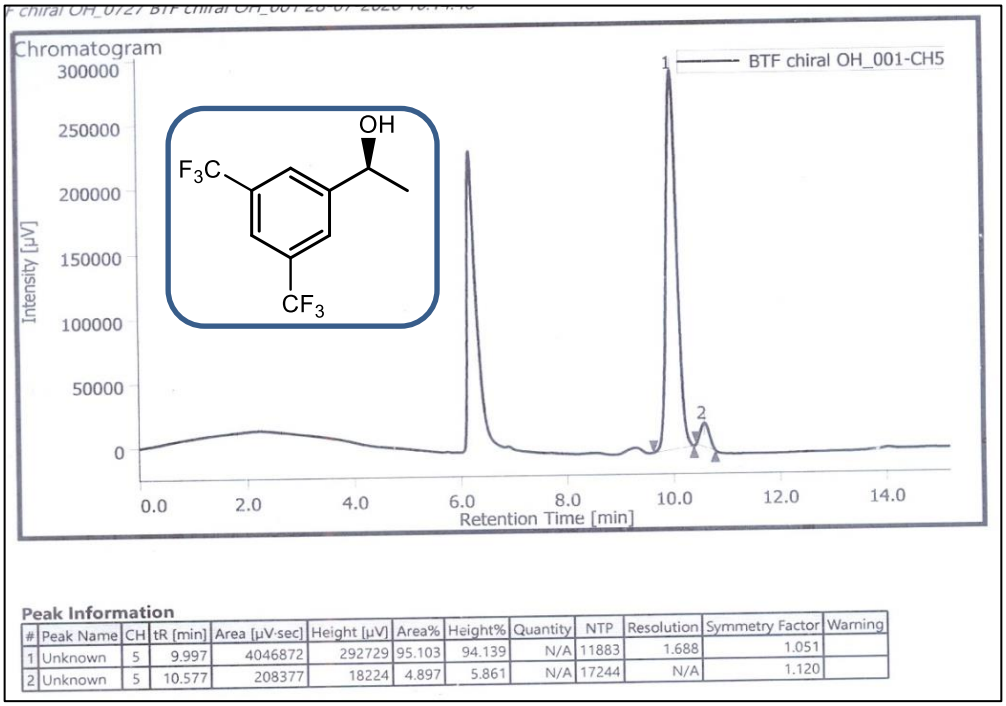


Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	10.467	12880591	802697	50.003	51.064	N/A	9242	1.603	1.061	
2	Unknown	5	11.177	12878815	769248	49.997	48.936	N/A	9746	N/A	1.080	

HPLC chromatogram of Racemic 1-(3,5-bis(trifluoromethyl)phenyl)ethan-1-ol **51**

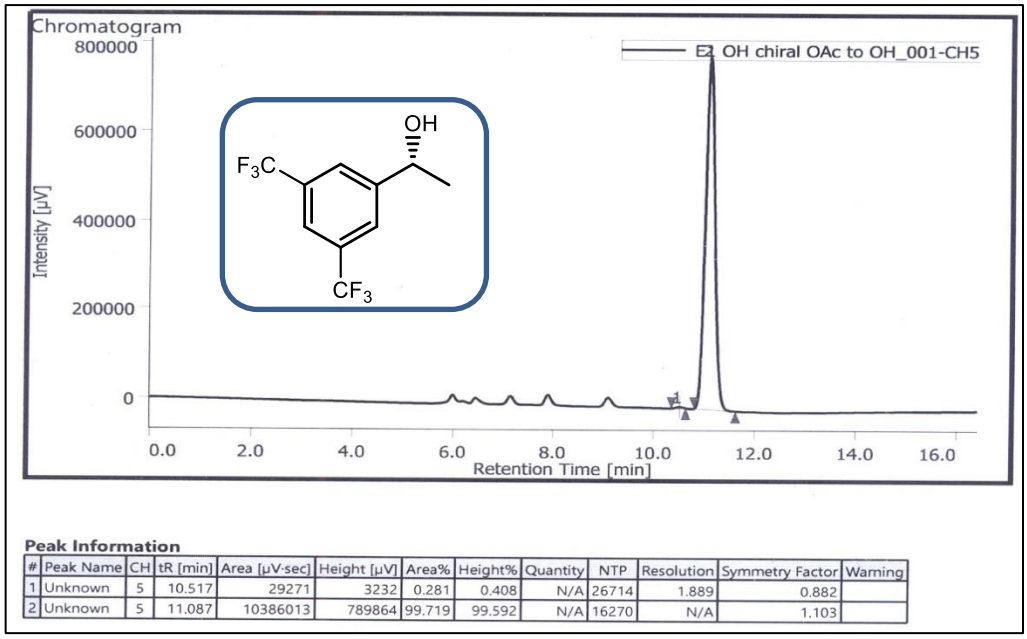
HPLC Condition for compound 1-(3,5-bis(trifluoromethyl)phenyl)ethan-1-ol
*[b]Determined by HPLC analysis (chiral column OD-H 0.5ml/min, IPA (5.0%) in hexane; 10.46 min for (R)-**51** and 11.17 min for (S)-**51**)*



Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	9.997	4046872	292729	95.103	94.139	N/A	11883	1.688	1.051	
2	Unknown	5	10.577	208377	18224	4.897	5.861	N/A	17244	N/A	1.120	

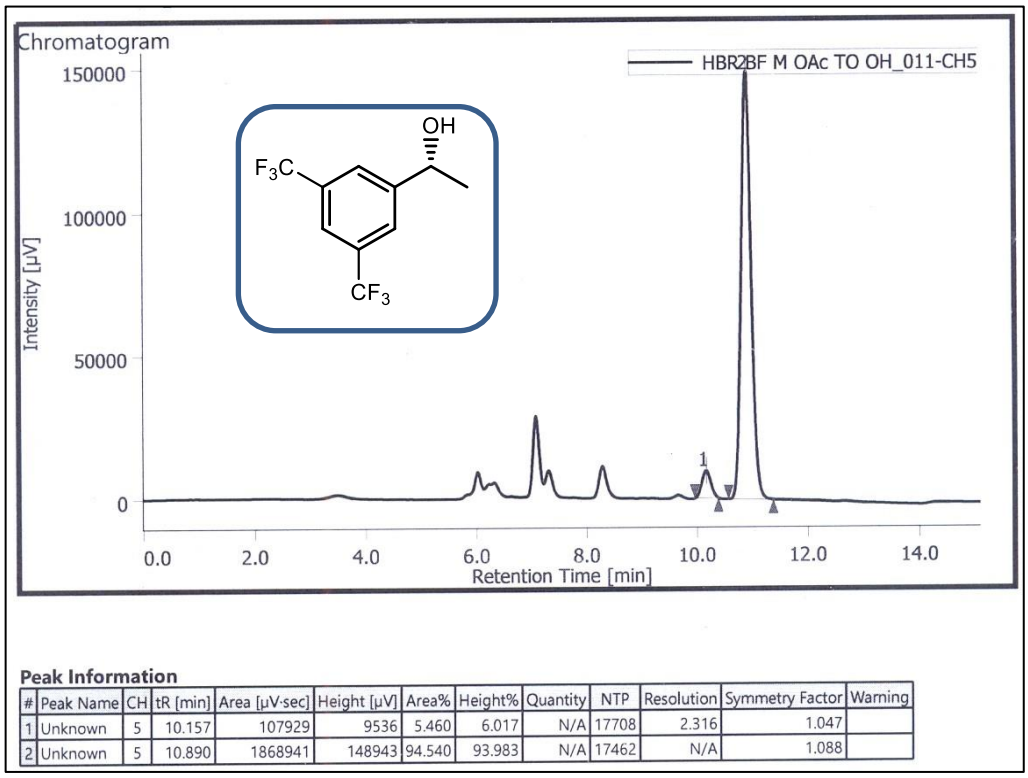
HPLC chromatogram of (S) 1-(3,5-bis(trifluoromethyl)phenyl)ethan-1-ol **51**



Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	10.517	29271	3232	0.281	0.408	N/A	26714	1.889	0.882	
2	Unknown	5	11.087	10386013	789864	99.719	99.592	N/A	16270	N/A	1.103	

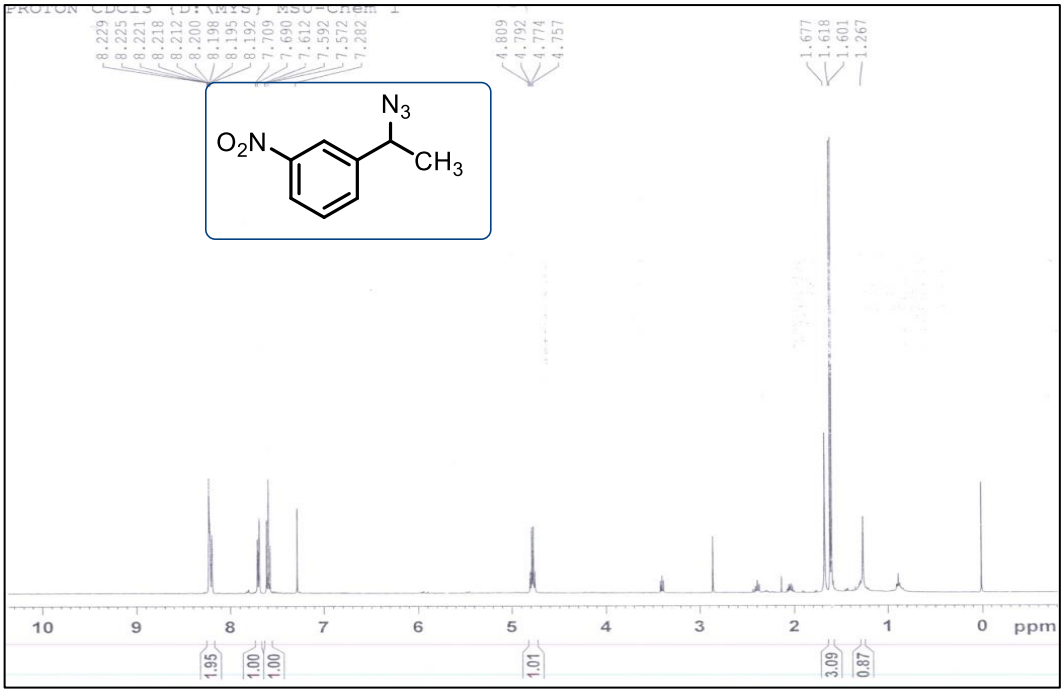
HPLC chromatogram of (R) 1-(3,5-bis(trifluoromethyl)phenyl)ethan-1-ol **51**



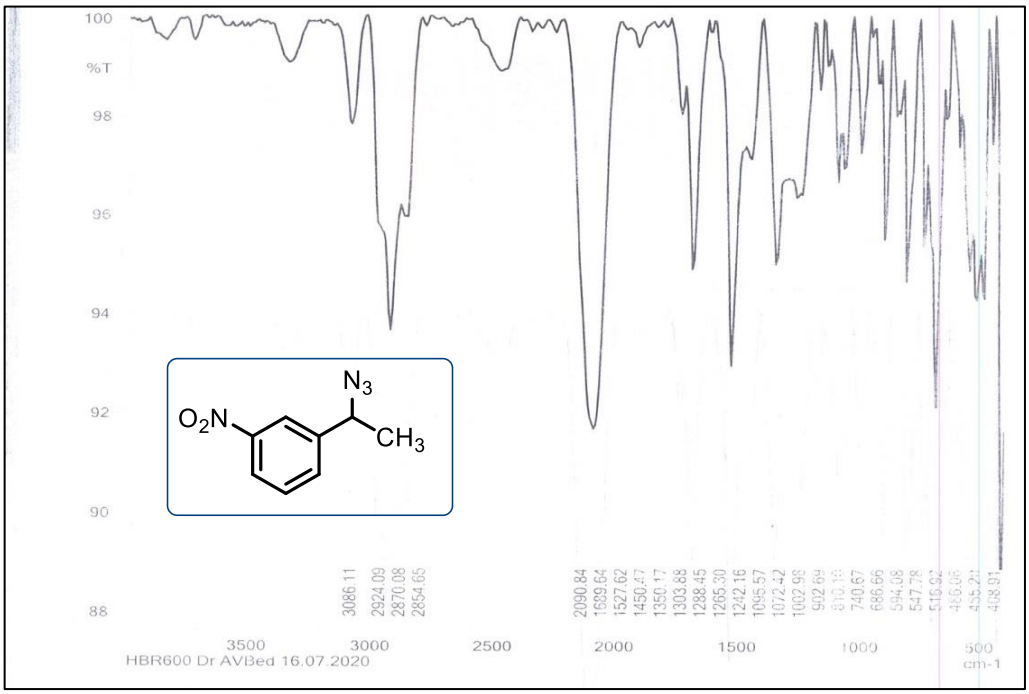
Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	10.157	107929	9536	5.460	6.017	N/A	17708	2.316	1.047	
2	Unknown	5	10.890	1868941	148943	94.540	93.983	N/A	17462	N/A	1.088	

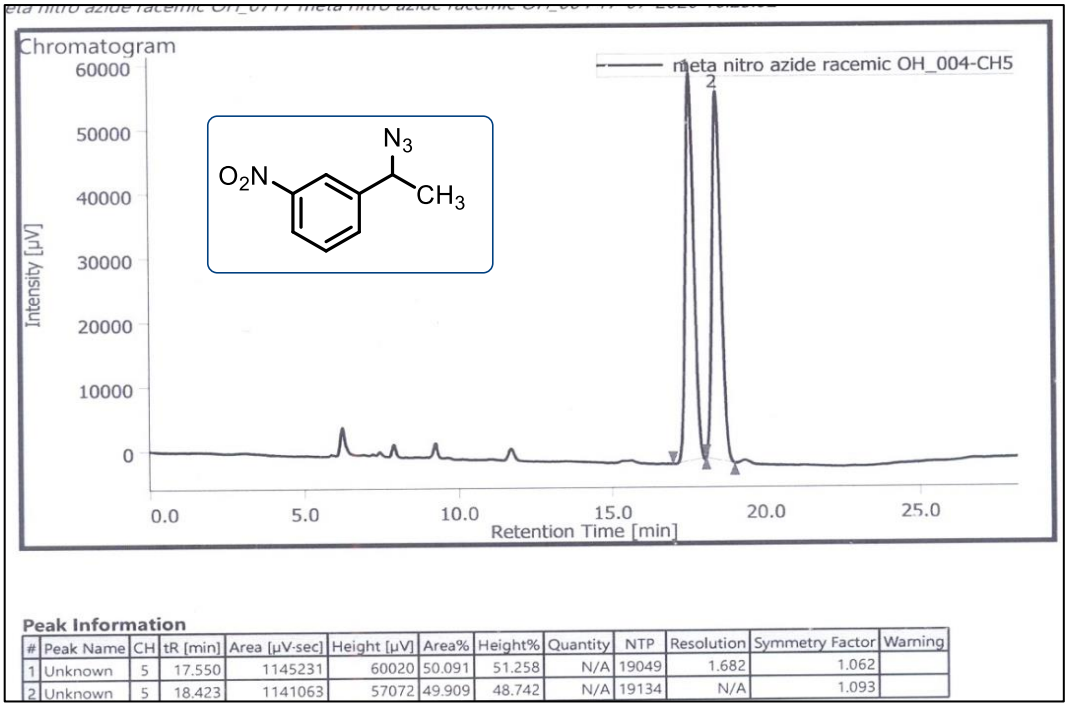
HPLC chromatogram of *(R)* 1-(3,5-bis(trifluoromethyl)phenyl)ethan-1-ol **51** after mitsunobu



^{1}H NMR 1-(1-azidoethyl)-3-nitrobenzene **53**



IR 1-(1-azidoethyl)-3-nitrobenzene **53**

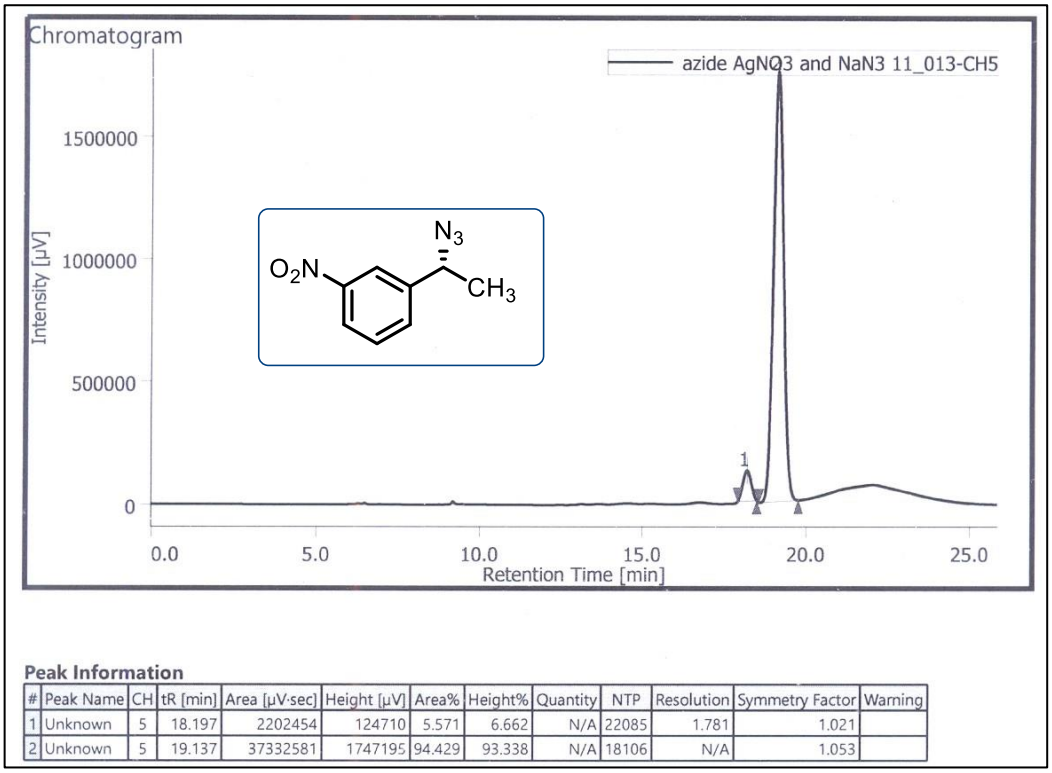


Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	17.550	1145231	60020	50.091	51.258	N/A	19049	1.682	1.062	
2	Unknown	5	18.423	1141063	57072	49.909	48.742	N/A	19134	N/A	1.093	

HPLC chromatogram of racemic 1-(1-azidoethyl)-3-nitrobenzene **53**

*HPLC Condition for compound 1-(1-azidoethyl)-3-nitrobenzene [b]Determined by HPLC analysis (chiral column OD-H 0.5ml/min, IPA (5.0%) in hexane; 10.46 min for (R)-**53** and 11.17 min for (S)-**53**)*

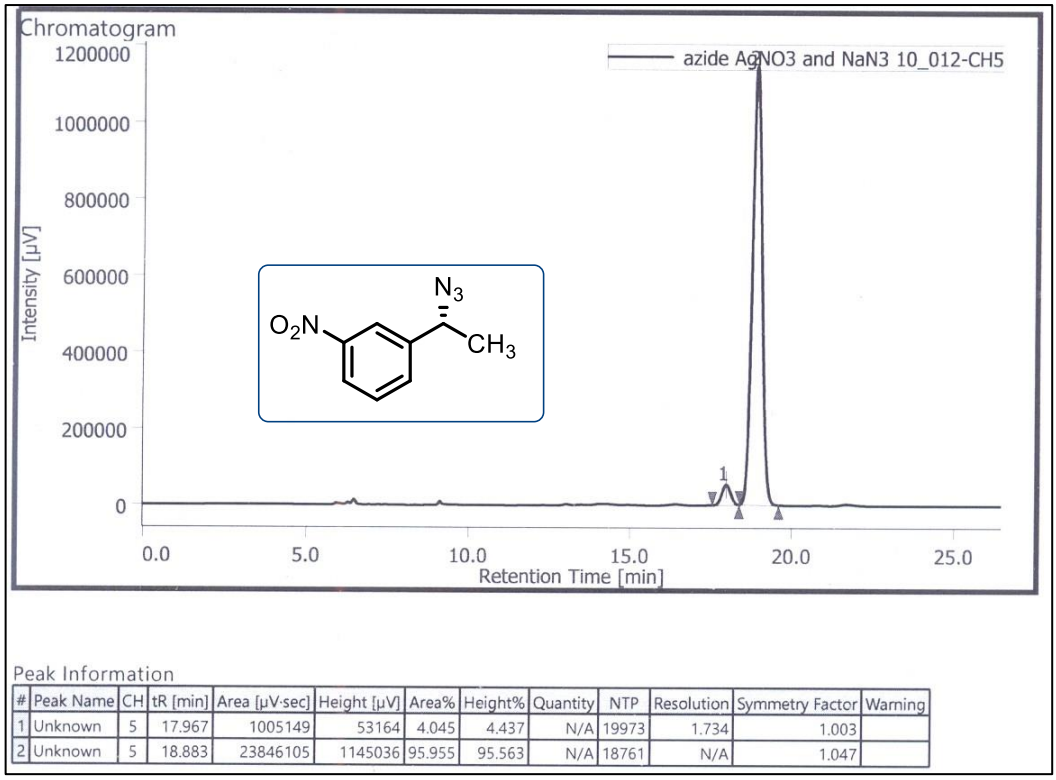


Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	18.197	2202454	124710	5.571	6.662	N/A	22085	1.781	1.021	
2	Unknown	5	19.137	37332581	1747195	94.429	93.338	N/A	18106	N/A	1.053	

HPLC chromatogram of chiral *(R)* 1-(1-azidoethyl)-3-nitrobenzene **53**

(NaN_3/AgNO3:2.0/0.0)

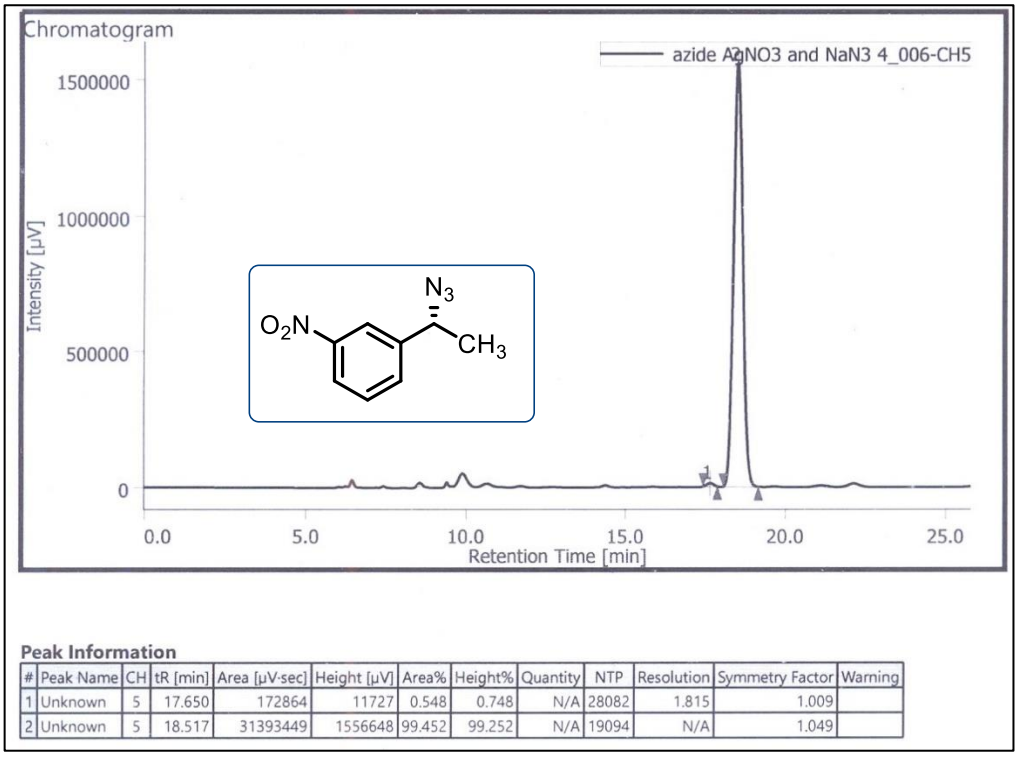


Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	17.967	1005149	53164	4.045	4.437	N/A	19973	1.734	1.003	
2	Unknown	5	18.883	23846105	1145036	95.955	95.563	N/A	18761	N/A	1.047	

HPLC chromatogram of *(R)* 1-(1-azidoethyl)-3-nitrobenzene **53**

(NaN_3/AgNO3:1.75/0.25)

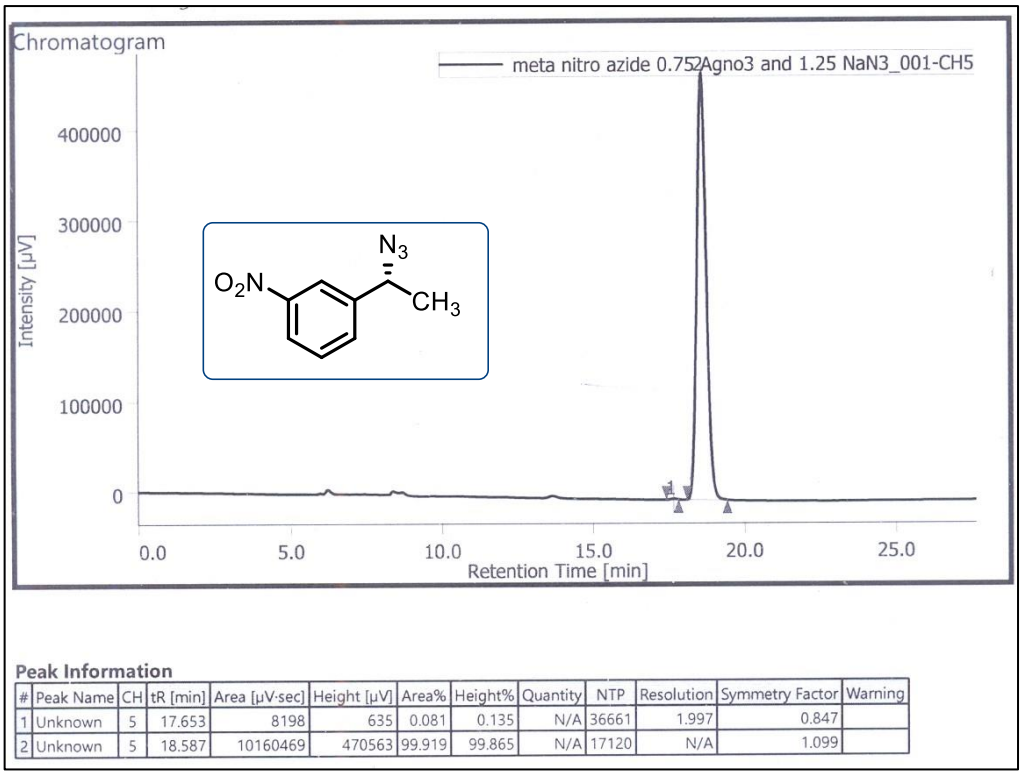


Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	17.650	172864	11727	0.548	0.748	N/A	28082	1.815	1.009	
2	Unknown	5	18.517	31393449	1556648	99.452	99.252	N/A	19094	N/A	1.049	

HPLC chromatogram *(R)* 1-(1-azidoethyl)-3-nitrobenzene **53**

(NaN_3/AgNO3:1.50/0.50)

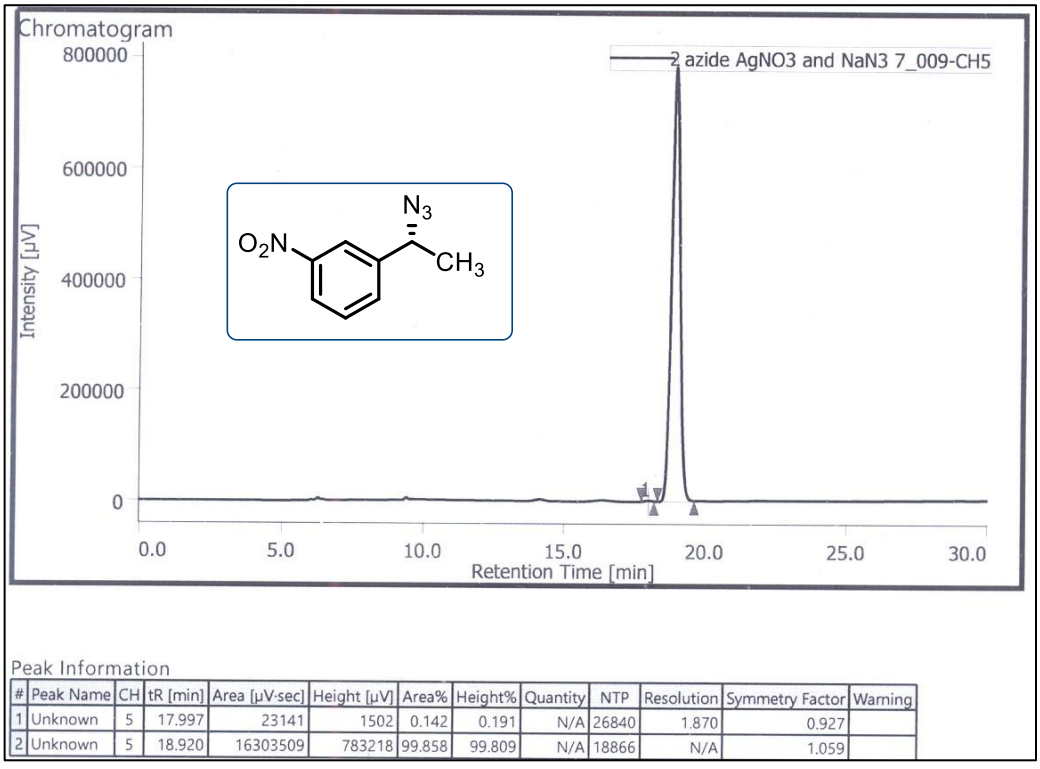


Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	17.653	8198	635	0.081	0.135	N/A	36661	1.997	0.847	
2	Unknown	5	18.587	10160469	470563	99.919	99.865	N/A	17120	N/A	1.099	

HPLC chromatogram of *(R)* 1-(1-azidoethyl)-3-nitrobenzene **53**

(NaN_3/$AgNO_3$:1.25/0.75)

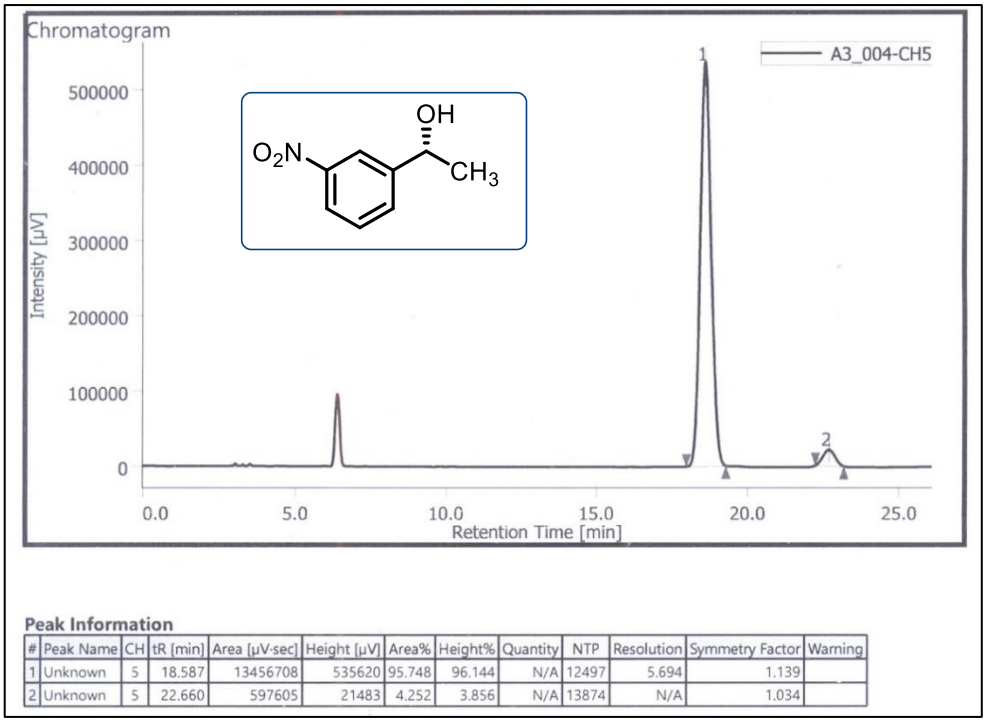


Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	17.997	23141	1502	0.142	0.191	N/A	26840	1.870	0.927	
2	Unknown	5	18.920	16303509	783218	99.858	99.809	N/A	18866	N/A	1.059	

HPLC chromatogram of *(R)* 1-(1-azidoethyl)-3-nitrobenzene **53**

(NaN3/AgNO3:2.0/0.75)

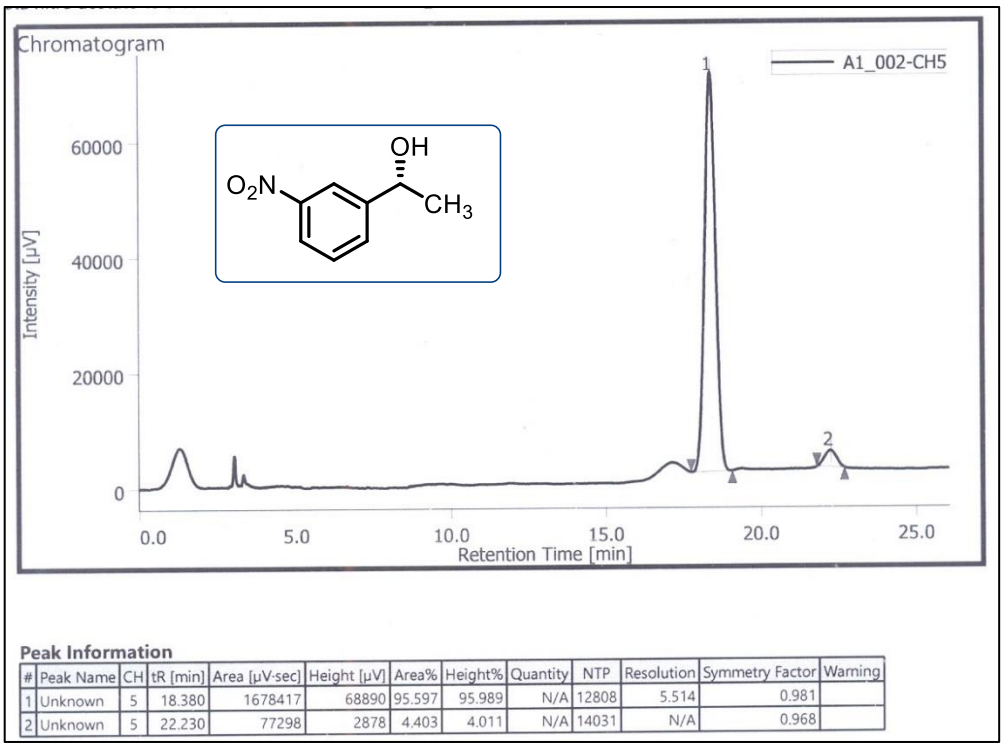


Peak Information

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	18.587	13456708	535620	95.748	96.144	N/A	12497	5.694	1.139	
2	Unknown	5	22.660	597605	21483	4.252	3.856	N/A	13874	N/A	1.034	

HPLC chromatogram of *(R)* 1-(3-nitrophenyl)ethan-1-ol **37** (NaN_3/$AgNO_3$:2.0/0.0)

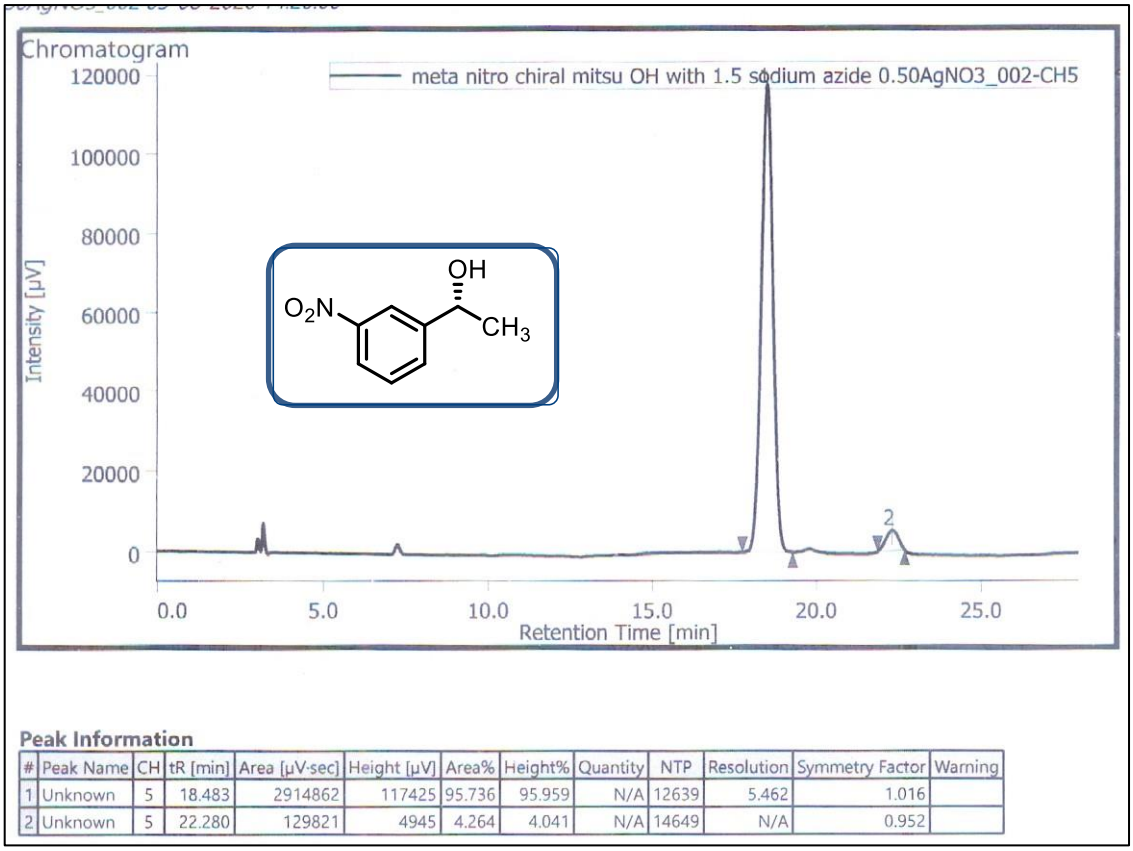
HPLC Condition for compound 1-(3-nitrophenyl)ethan-1-ol [b] *Determined by HPLC analysis (chiral column Amylose, 1ml/min IPA (5.0%) in hexane; 18.42 min for (R)-**37** and 22.37 min for (S)-**37**)*



Peak Information

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	18.380	1678417	68890	95.597	95.989	N/A	12808	5.514	0.981	
2	Unknown	5	22.230	77298	2878	4.403	4.011	N/A	14031	N/A	0.968	

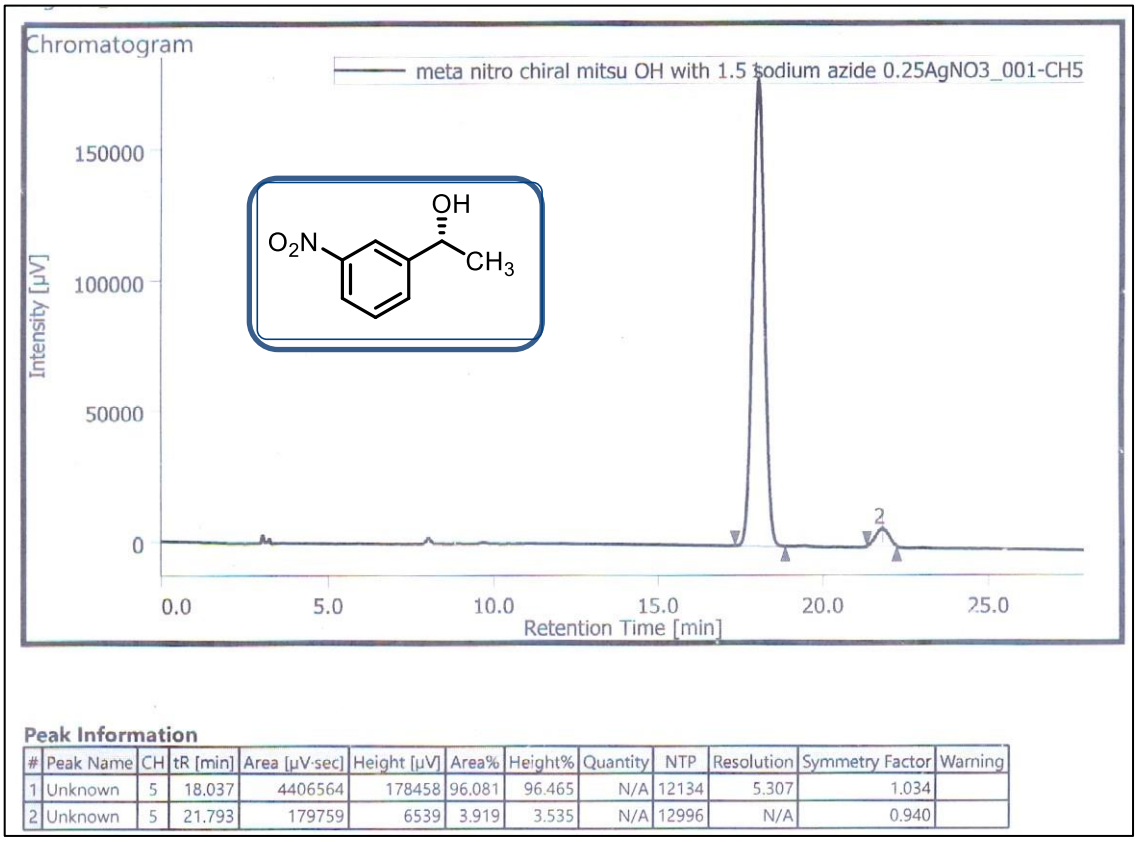
HPLC chromatogram of *(R)* 1-(3-nitrophenyl)ethan-1-ol **37** (NaN_3/$AgNO_3$:1.75/0.25)



Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	18.483	2914862	117425	95.736	95.959	N/A	12639	5.462	1.016	
2	Unknown	5	22.280	129821	4945	4.264	4.041	N/A	14649	N/A	0.952	

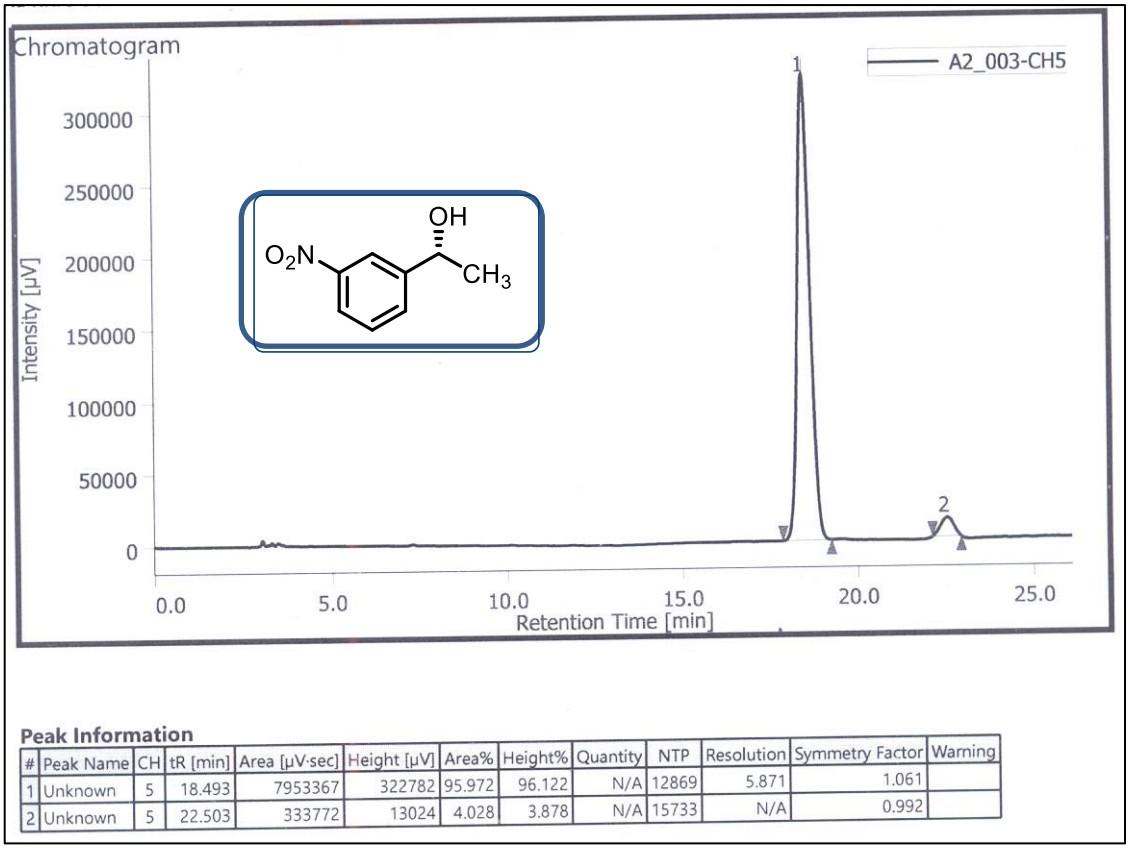
HPLC chromatogram of *(R)* 1-(3-nitrophenyl)ethan-1-ol **37** (NaN_3/$AgNO_3$:1.50/0.50)



Peak Information

#	Peak Name	CH	tR [min]	Area [µV·sec]	Height [µV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	18.037	4406564	178458	96.081	96.465	N/A	12134	5.307	1.034	
2	Unknown	5	21.793	179759	6539	3.919	3.535	N/A	12996	N/A	0.940	

HPLC chromatogram of *(R)* 1-(3-nitrophenyl)ethan-1-ol **37** (NaN_3/$AgNO_3$:1.25/0.75)



Peak Information

#	Peak Name	CH	tR [min]	Area [μV·sec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	5	18.493	7953367	322782	95.972	96.122	N/A	12869	5.871	1.061	
2	Unknown	5	22.503	333772	13024	4.028	3.878	N/A	15733	N/A	0.992	

HPLC chromatogram of *(R)* 1-(3-nitrophenyl)ethan-1-ol **53** ($NaN_3/AgNO_3$:2.0/0.75)

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