PROPERTIES OF CHIRAL 1,2,4-TRIAZOLES

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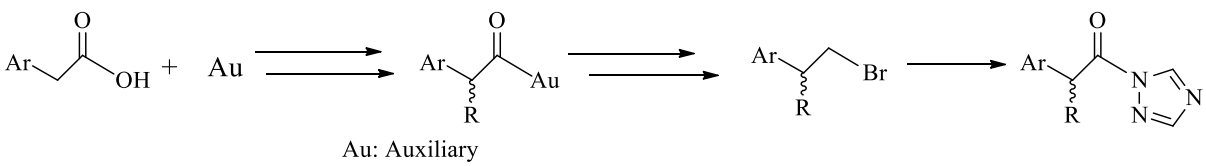
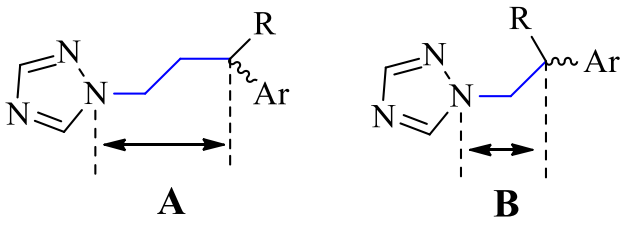
Chirality is generally a very popular feature that works in many fields. It is an important factor in the chemicals used in agriculture, especially in the field of pharmacy and in many areas of our lives. The reason for this is that the system in which life exists is very closely related to chirality. Many biologically active substances, whether synthetic or natural, have chiral structures. In addition, the triazole derivative has a wide range of studies in many compounds. In this section, a study is presented about what features these two very special structures have when they come together.

The triazole compounds belonging to the group of demethylase inhibitor (DMI) fungicides represent a large and important well-known fungicide species used in agriculture to control a wide variety of fungi in fruits and vegetables. Penicillium digitatum is one of the most common pathogens causing green mold rot in Citrus species and can be found in many parts of the world. In the study, both the in vitro antifungal activities of the chiral *β*-arylalkyl-1*H*-1,2,4-triazole derivative against Penicillium digitatum and the binding activity of P. digitatum (PdCYP51) to the CYP51 protein were studied. Molecular models were studied and also docking studies with chiral triazole were performed. As a result of the study, the in vitro inhibitory activities of the R- and S-enantiomers have been seen in good agreement with the suitable binding activities in cultured cells (Cao et al., 2011)

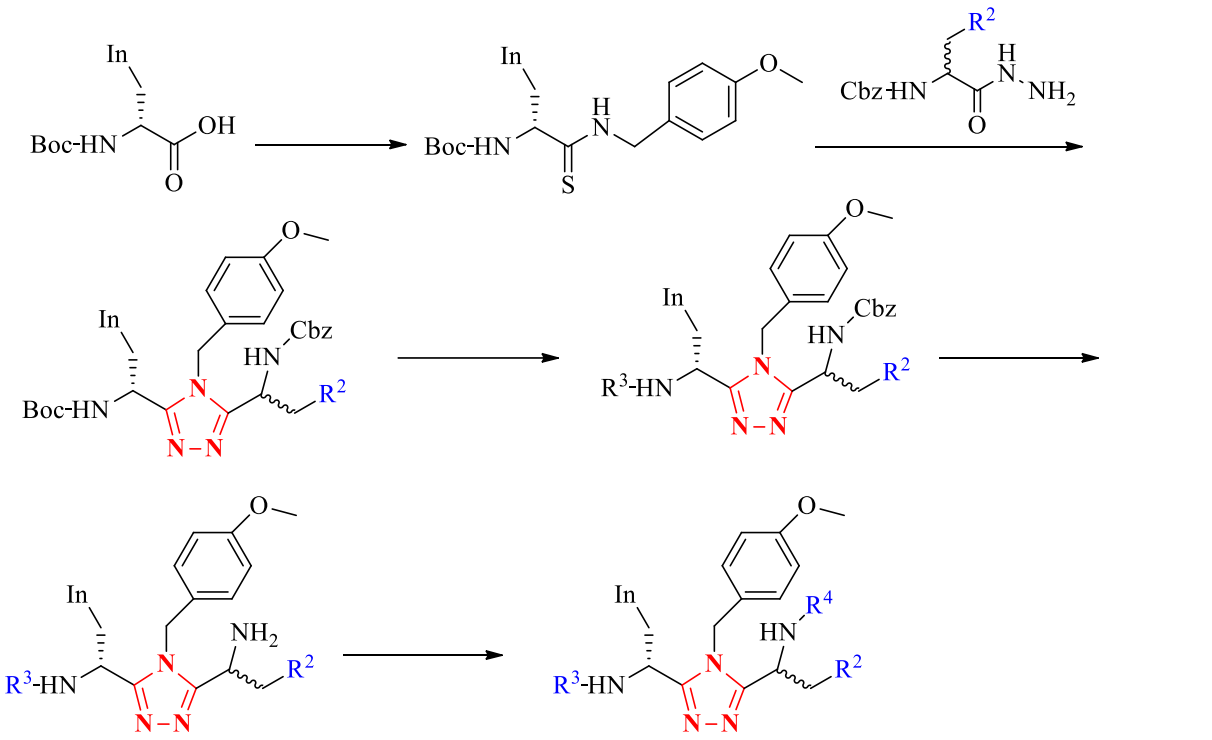


Au: Auxiliary

As a result of the study, it is estimated that the chiral β-arylalkyl-1*H*-1,2,4-triazole derivative B series shows better activity than the chiral *r*-aryl-1*H*-1,2,4-triazole derivative A. These two series of chiral triazole derivatives are similar in chemical structure and differ only in the length of the alkyl chain between the aryl group and the triazole moiety (Cao et al., 2011).

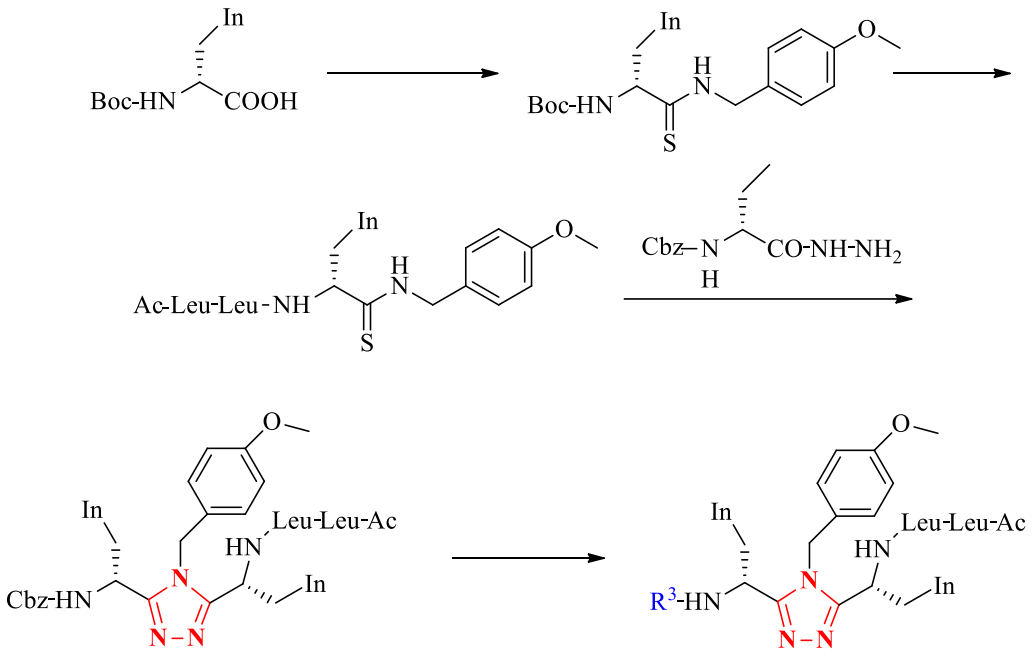


In a cyclic AMP response element CRE-luciferase reporter gene assay, triazole-bearing compounds obtained during the study were examined for their affinity to GHS-R1a, their capacity to induce intracellular calcium mobilization, and confirmation of their agonist/antagonist character. It has been shown by compounds with an indole group as R2 that compounds with the R configuration of the new chiral center have ligands with a higher affinity than those with the S configuration of this carbon. In two functional assays, each of these agents exhibited receptor antagonistic effects. The R configuration for the new chiral center contained the best compounds in the series, providing good affinities and strong biological activity (Maingot et al., 2016).



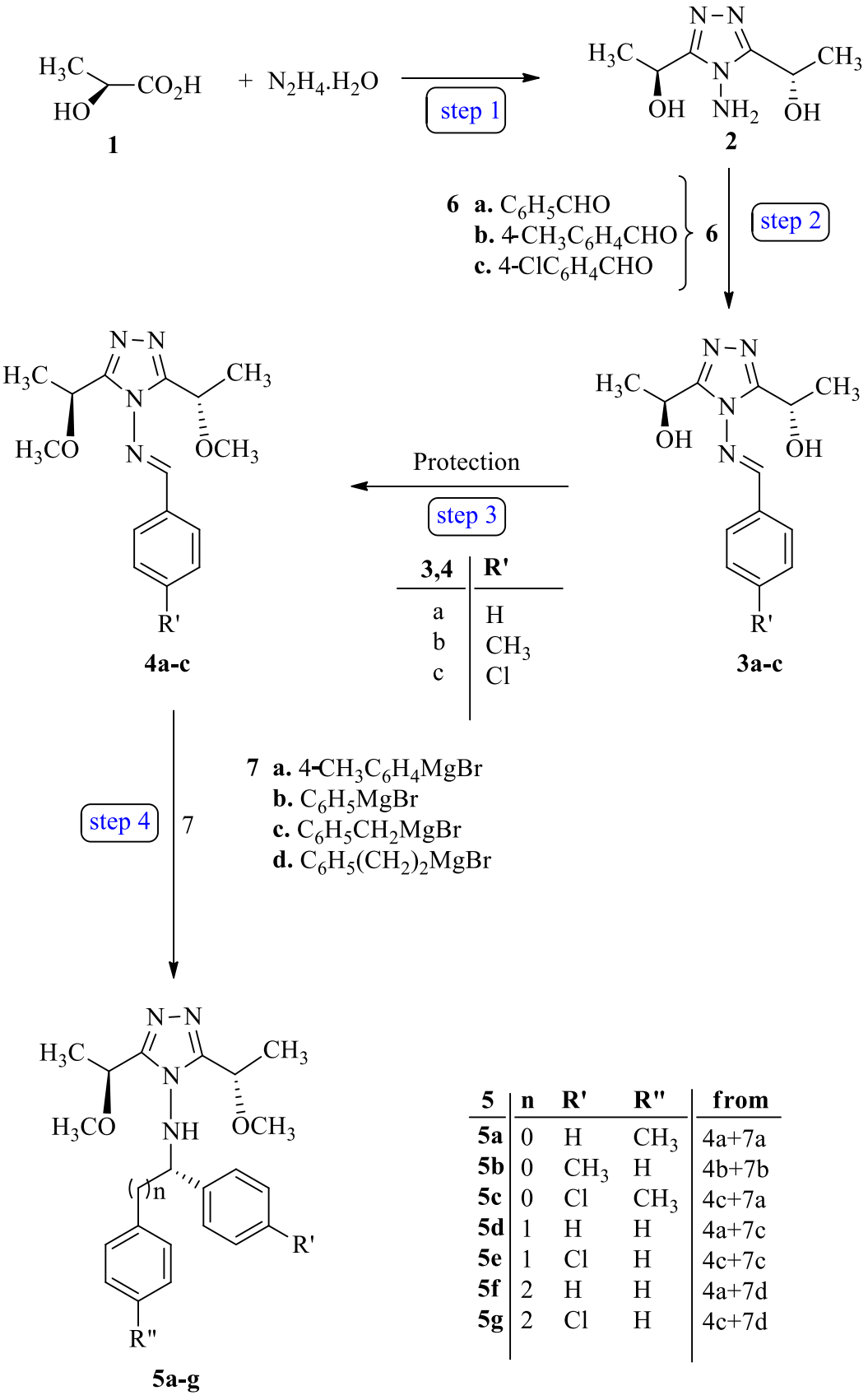
R²= Phenyl, indol
R³= Aib (pyridin-2-yl)carboxyl, 4,6-difluoro(pyridin-2-yl)carboxyl, 3,4-dihydro-2H-pyran-6-carboxyl, 2-hydroxylacetyl, (s)morpholine-2-carboxyl
R⁴=CHO, CH_3CO

In the continuation of this study, the corresponding tripeptide containing a thioamide bond with the 1,2,4-triazole structure was obtained and six different acylating groups were included in its N-terminal part. Then, the reactions were carried out with appropriate structures to reach the target compounds. As a result of the study, the following evaluations can be made; The possibility has been observed that the incorporation of a second chiral center at position 3 of the 1,2,4-triazole scaffold may result in potent ligands offering good to high affinities for the receptor. The presence of an amino function in the chiral center led to the extension of the C-terminal portion of the molecule and the incorporation of the Leu-Leu dipeptide sequence, which is included in the identified potent inverse agonists. In short, it has been seen that the trisubstituted 1,2,4-triazole scaffold carrying a second chiral center may be an alternative for generating more diverse molecules and obtaining high affinity ligands (Maingot et al., 2016).



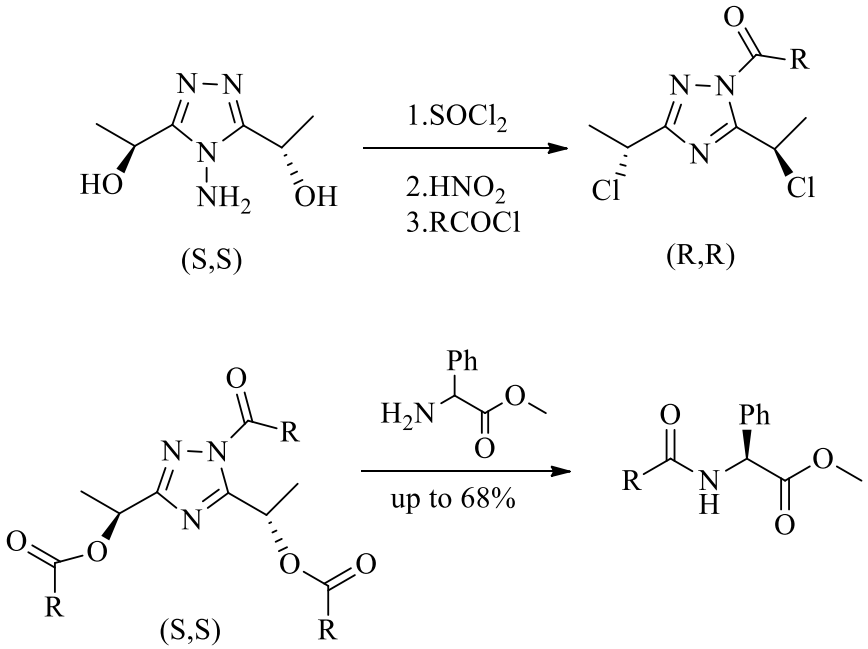
R^3= Aib (pyridin-2-yl)carboxyl, 2-hydroxylacetyl, (s)morpholine-2-carboxyl, 2-Hydroxyl-2-methylpropionyl, Isonipecotyl, Lys.

Here, the use of this new C2-symmetric triazole as a chiral aid for the nucleophilic1,2-addition reaction of Grignard reagents to the CN double bond of hydrazone 4 is reported. Protection of the free hydroxyl groups is successfully accomplished by reacting the hydrazones 3 with sodium hydride and methyl tosylate using DMF as solvent, to generate the corresponding protected chiral hydrazones 4 in excellent yields 88-98% (Katrizky et al., 1996).

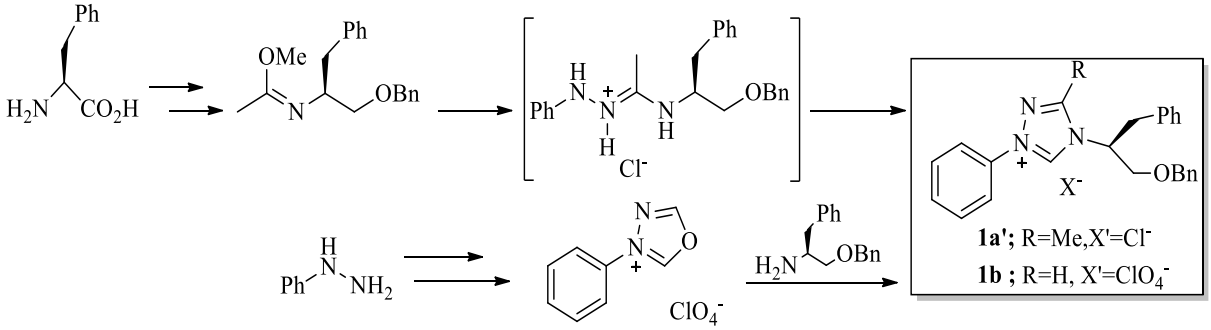


5	n	R'	R''	from
5a	0	H	CH_3	4a+7a
5b	0	CH_3	H	4b+7b
5c	0	Cl	CH_3	4c+7a
5d	1	H	H	4a+7c
5e	1	Cl	H	4c+7c
5f	2	H	H	4a+7d
5g	2	Cl	H	4c+7d

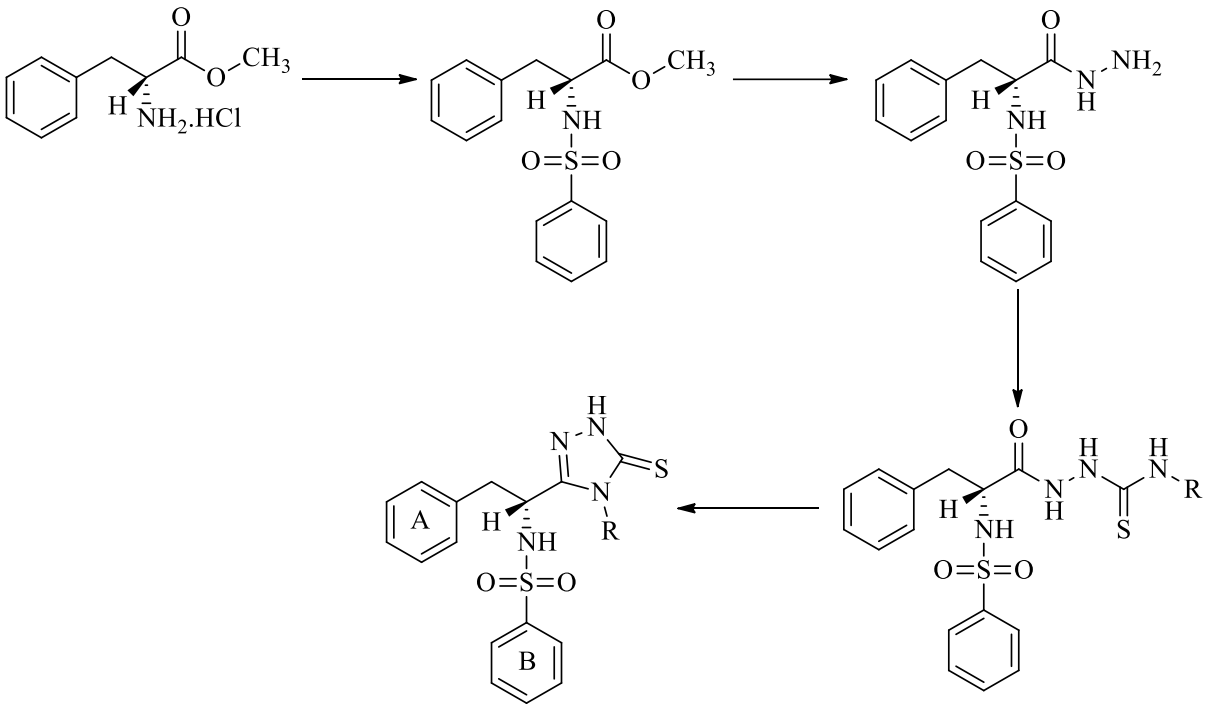
Chiral 1,2,4-triazoles are encouraging reagents for chiral acylation; In the study given below, a good yield of enantiomeric excess is achieved for triazole compounds.This study also revealed stereospecific control of the amino group upon substitution of a beta hydroxy group with thionyl chloride (Katritzky et al., 2010).



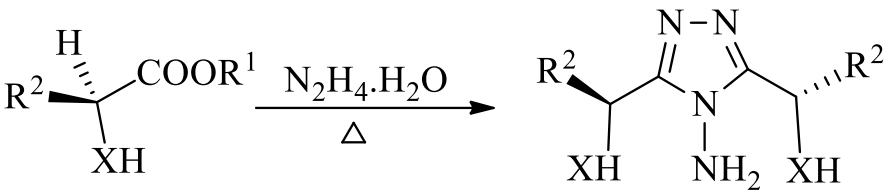
Chiral 1,2,4-triazolium NHC salt precursors Ia' and Ib are presented in another study to demonstrate the benefits of chiral 1,2,4-triazole derived compounds and their potential as catalysts in stereoselective reactions (Strand et al., 2012).



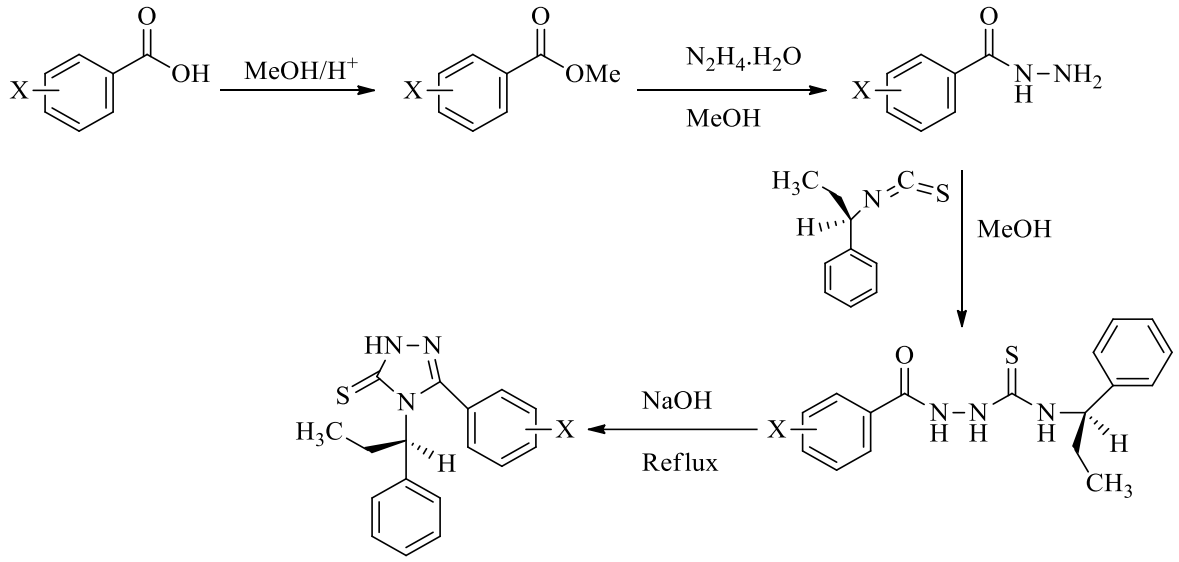
The combination of chiral N-sulfonylated α-amino acid group with a 1,2,4-triazole-3-thione core was designed in studies on the development of new effective and broad-spectrum homochiral compounds that can be used for the treatment of viral infection (Başaran et al., 2016).



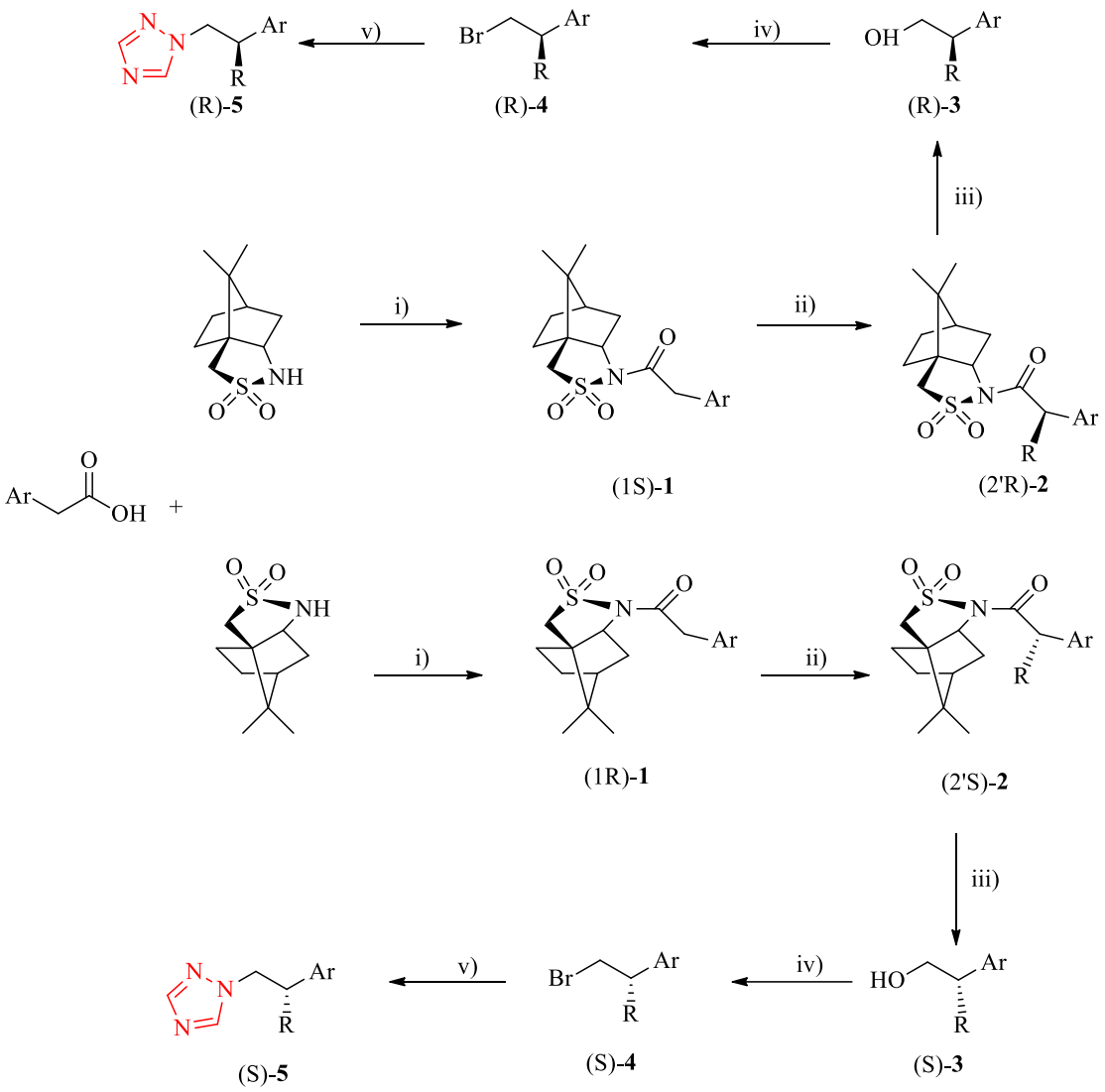
A few novel chiral synthons established on the 4-amino-1,2,4-triazole moiety have been arranged by the condensation reaction of optically active α-hydroxy- and α-aminoacids with hydrazine (Martínez-Díaz et al., 1994)



When a chiral drug interacts with a chiral receptor site; the two enantiomers of the drug interact differently and might caus to varied impacts. In this regard, studies have been conducted to examine the synthesis of some chiral 5-aryl-4-(1-phenyl)propyl-1,2,4-triazol-3-thiones in terms of their urease inhibition and antimicrobial activity properties (Serwar et al., 2009).

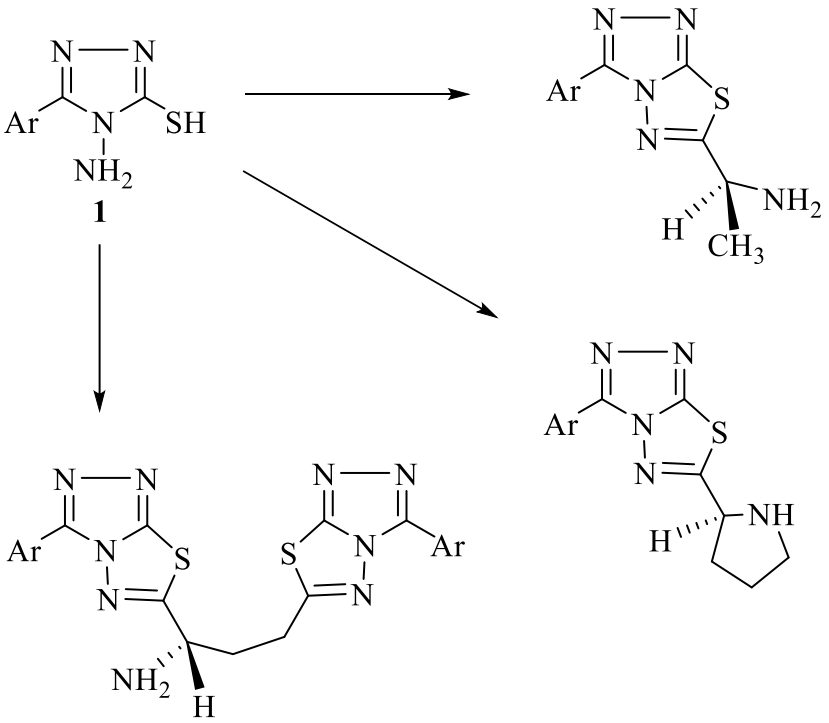


A number of chiral triazole derivatives have been synthesized as potential antifungal agents. In these studies, the compounds were obtained with very high yields. As a result of the studies, most of the synthesized compounds showed significantly higher fungicidal activities than the commercial agent triadimefon against Fusarium oxysporium, Dothiorella gregaria, Botrytis cinereapers, Colletotrichum gossypii, Rhizoctonia solani and Gibberella zeae species. Again in these studies, some enantiomers were found to show significant differences in activity (Lu et al., 2011).

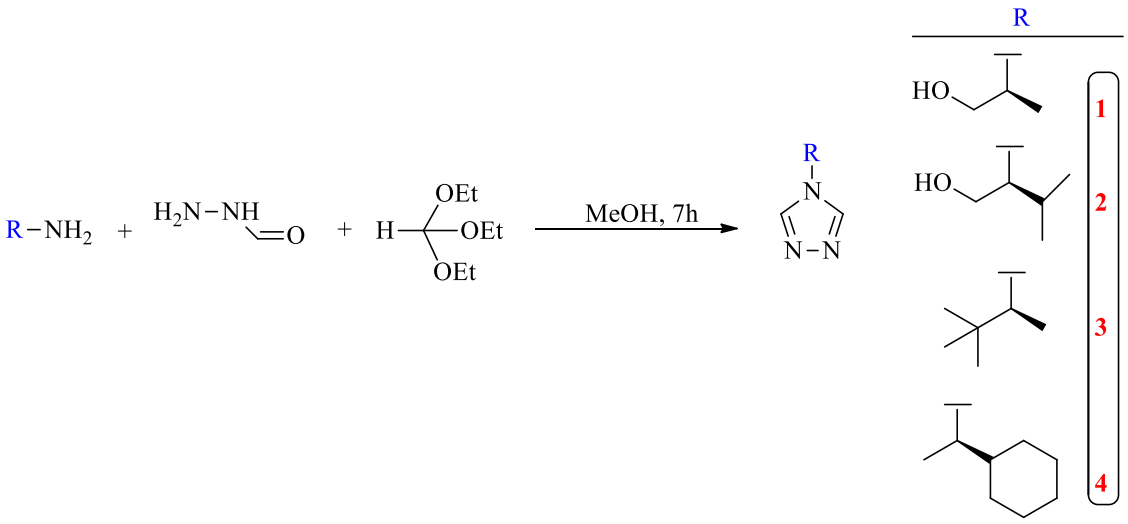


i) 1. Et_3N; 2. Me_3CCOCl, toluene, 80-110°. ii) 1.BuLi, THF, -78°; 2. hexamethylphosphori triamide (HMPA)/RX (MeI, PrI, BuI, $PhCH_2Br$, $CH_2=CHCH_2Br$). iii) $NaBH_4$, aq, THF. iv) HBr. v) 1H-1,2,4-Triazole, K_2CO_3, MeCN, reflux, 5-7h.

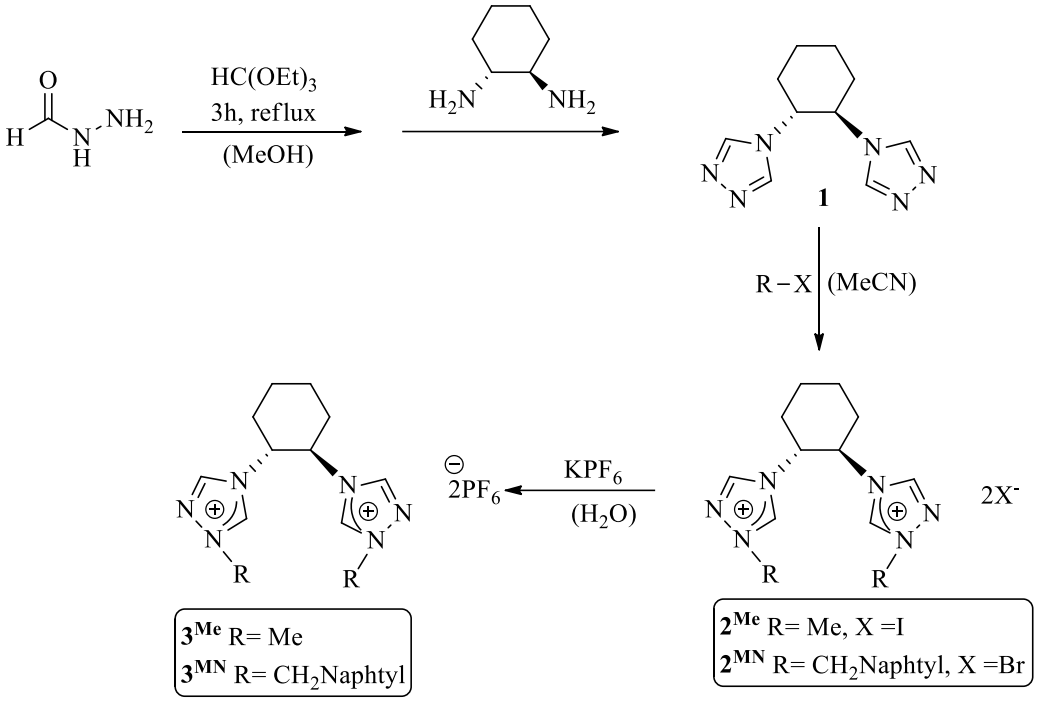
The effect of stereospecificity is a well-known fact in the biological activity of enzyme inhibitors and drug efficacy in compounds that bind to receptors. In recent years, nitrogen-containing heterocyclic compounds have received great attention due to their biological activities. Likewise, S-Triazoles and 1,3,4-thiadiazoles are also widely used. They are known to exhibit a wide spectrum of biological activity. In this study, some new compounds were synthesized to examine the relationship between stereochemistry and the performance of antibiotics. Antibacterial studies of the compounds have been done and it has been seen that it gives positive results when compared to penicillin as standard (Shi et al., 2001).



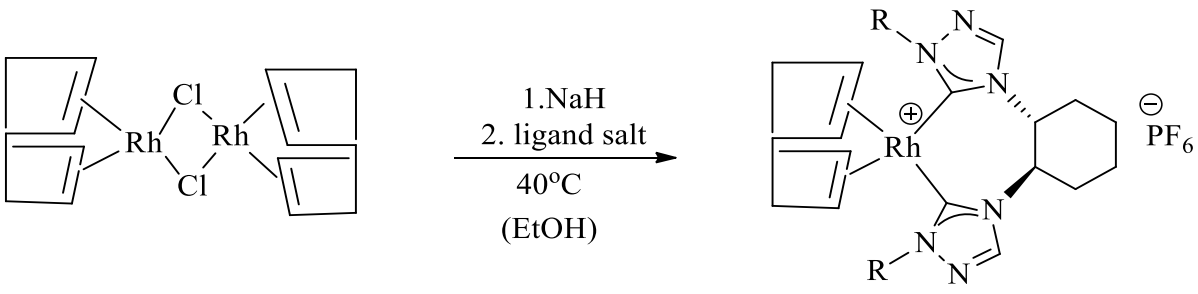
1,2,4-Triazoles also appear as drugs and ligands that are actively used to form coordination structures. Elaboration of pharmaceutically important homochiral molecules, studies for medical applications, and synthesis of stereoselective catalysis, chiral ligands is a crucial step for the construction of advanced materials. Therefore, in this study, its characteristic chiro-optical properties were investigated and its suitability for the elaboration of chiral exchangeable nanoparticles and composites and for the magnetic stereoselective detection of alcohols was investigated (Gural'skiy et al., 2017).



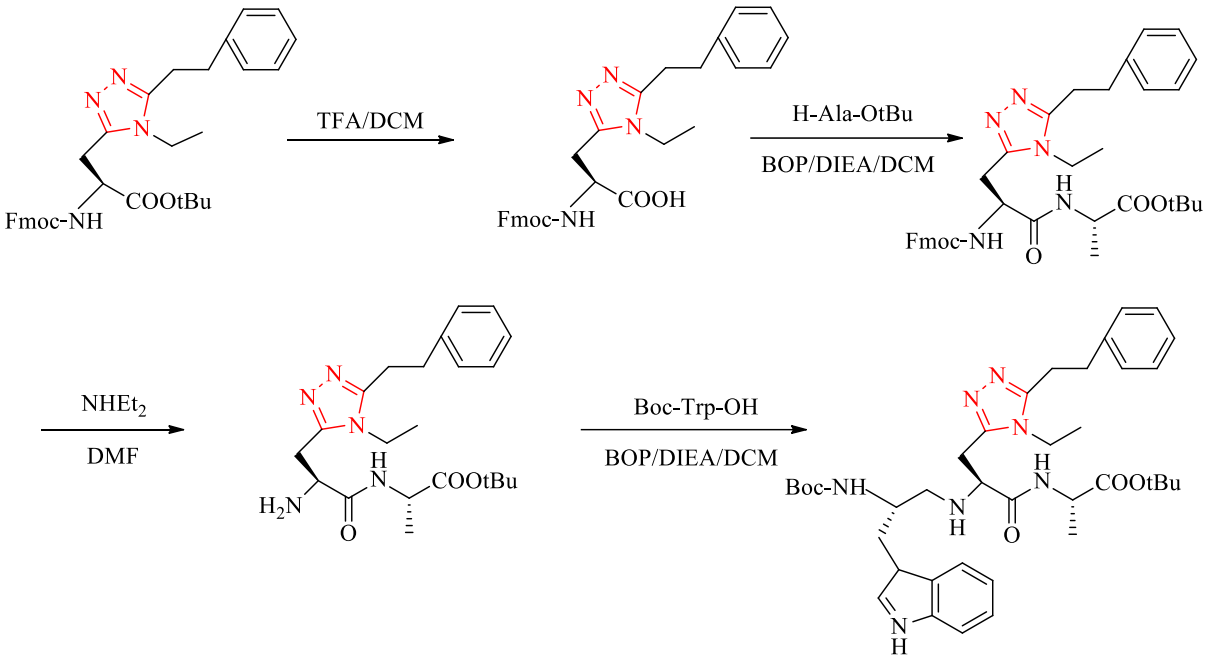
In this part, a study was carried out to obtain chiral bistriazolium salts starting from chiral R,R-(-)-1,2-diaminocyclohexane. They have been successfully applied as enantioselective catalysts for the hydrogenation of prochiral olefins in good yields.



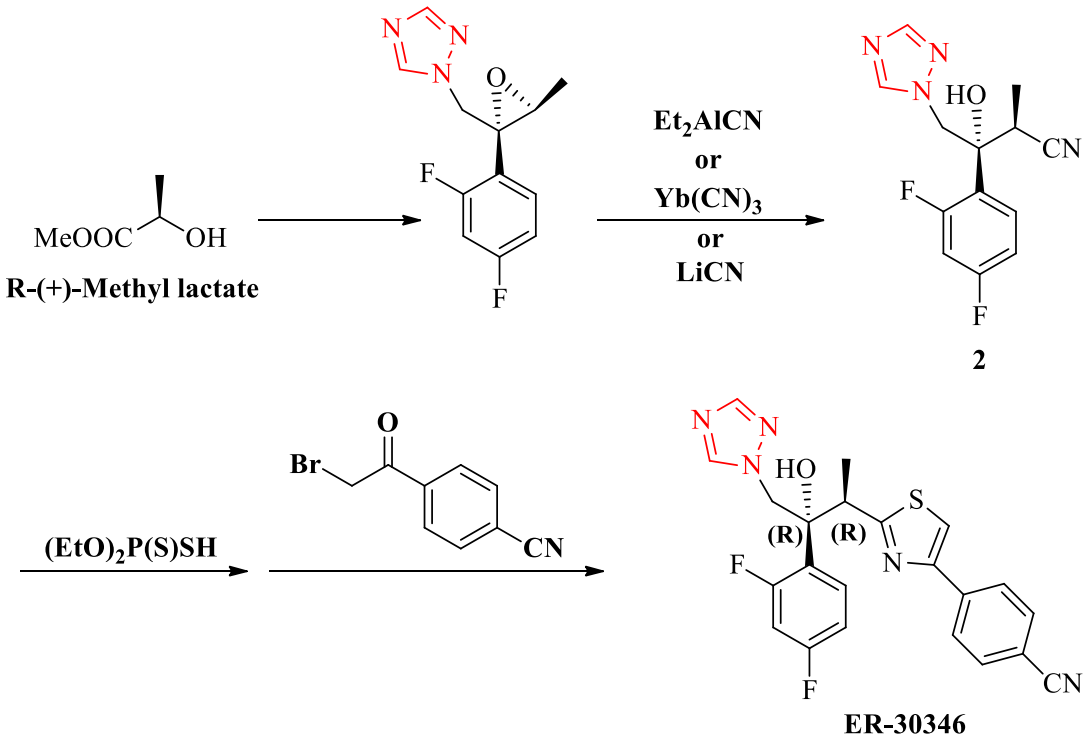
In the continuation of this synthesis, two new chiral biscarbene rhodium(I) complexes were obtained. The properties of the new chiral ligands and their suitability for various catalytic applications are being investigated (Riederer et al., 2011).



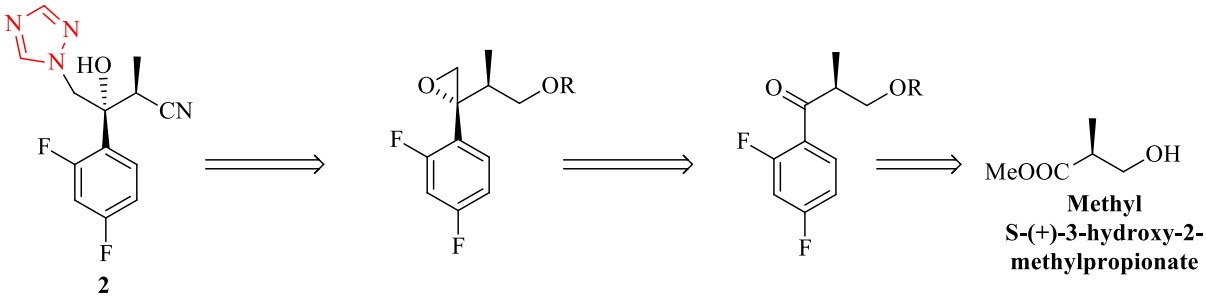
It was obtained by using N- and C-protected aspartic or glutamic acids in the synthesis of unnatural α-amino acids containing 3,4,5-trisubstituted 1,2,4-triazole heterocycles in their side chains. Through this study, it was found that it is possible to produce amino acids containing 1,2,4 triazole rings. It seems possible to synthesize many more new compounds with a wide variety in this structure.(Blayo et al., 2011).



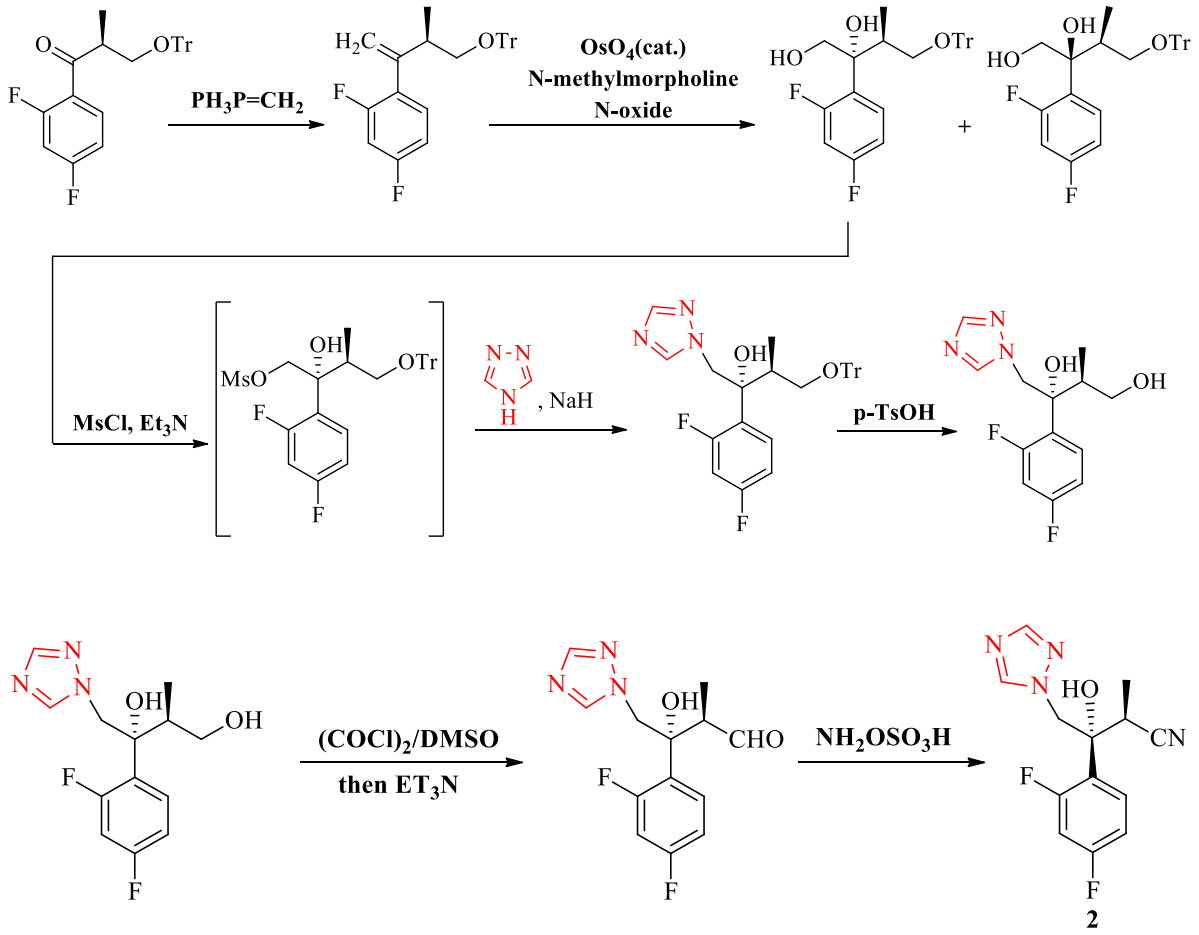
As another example of a study involving triazole groups, we can give the following; We can give a new synthetic route for compound 2, an intermediate for obtaining ER-30346, a triazole antifungal agent, from a commercially available chiral compound, methyl S-(+)-3-hydroxy-2-methylpropionate (Kaku et al., 1998).



As mentioned in the previous paragraph, we chose commercially available methyl S-(+)-3-hydroxy-2-methylpropionate as the chiral starting material. A retrosynthetic analysis is shown below.



As a result of studies, a new synthetic route has been found starting from the commercially available compound to compound 2, which is a key intermediate for the new antifungal triazole ER-30346.



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