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Research Article

Retrosynthesis: An Approach to Explore the Functional Group Interconversions of an Antiviral Drug Pyrrolo[2,1-f][triazin-4-amino] Adenine C-Nucleoside (GS-5734)

Bharathi Mandala[1], Bedabrata Ray[2], Dhanapal Yogananthan[3], Muddukrishnaiah Kotakonda[4], Nipun Abhinav[5,*], Sunnapu Prasad[6,*]

[1]Pharmaceutical Sciences Department, College of Pharmacy, Howard University, Washington DC, USA.
[2]Amity Institute of Pharmacy, Amity University Uttar Pradesh, Noida, Uttar Pradesh, INDIA.
[3]Department of Pharmacology, PSG College of Pharmacy, Coimbatore, Tamil Nadu, INDIA.
[4]Department of Technology, Anna University, Chennai, Tamil Nadu, INDIA.
[5]Institute of Pharmaceutical Sciences, Sanskriti University, Mathura, Uttar Pradesh, INDIA.
[6]Department of Pharmaceutical Chemistry, College of Pharmacy, Sri Ramakrishna Institute of Paramedical Sciences, Coimbatore, Tamil Nadu, INDIA.

ABSTRACT

Planning chemical synthesis is a key feature of many aspects of chemistry, especially drug discovery and development. Retrosynthesis is the process of deconstructing a target molecule into readily available starting materials by the imaginary breaking of bonds or the conversion of one functional group into another. The identification of possible functional group interconversions with stable intermediate compounds is considered to be a successful approach in organic chemistry, which helps in identifying suitable synthetic routes and throws light on the possible synthons. The synthetic plan generated from retrosynthetic analysis will be a roadmap for guiding the synthesis of the target molecule. Herein, we present a multiscale approach for functional group interconversion and bond formation to facilitate an easier sense of the suitable retrosynthetic pathway of pyrrolo (2,1-f)(triazin-4-amino) Adenine C-Nucleoside (GS-5734).

Keywords: COVID-19, Remdesivir, Retrosynthesis, Functional group Interconversion, Synthons.

Correspondence:
Mr. Sunnapu Prasad
Department of Pharmaceutical Chemistry, College of Pharmacy, Sri Ramakrishna Institute of Paramedical Sciences, Coimbatore, Tamil Nadu, INDIA.
Email: prasadpharmachem@gmail.com

Mr. Nipun Abhinav
Institute of Pharmaceutical Sciences, Sanskriti University, Mathura-281401, Uttar Pradesh, INDIA.
Email: nipunabhinav@gmail.com

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INTRODUCTION

Remdesivir, a nucleoside analog antiviral drug, was developed by Gilead Science. This drug was mainly used to treat Ebola virus disease in 2010. It has also shown activity against the Middle East respiratory syndrome-related coronavirus (MERS-coV), the hemorrhagic fever Marburg virus and the severe acute respiratory syndrome coronavirus (SARS-CoV).[1] Recently researchers began extensive studies to evaluate the ability of remdesivir to treat the COVID-19 viral disease. The potential biological activity of remdesivir inspired us to explore the synthetic route of the drug using retrosynthetic analysis.

The task of making complex structures proficiently and in fewer advances than in recently revealed combinations is a progressing challenge in numerous research facilities around the globe.[2] Recent computational tools offer potential new ways to augment retrosynthetic analysis.[3] Among which the disconnection approach is significant for the development of algorithms to promote the identification of chemical bond disconnections.[4-9]

This retrosynthetic investigation was first utilized by Robinson in tropinone synthesis and eventually formalized by Corey *et al*. It is a fundamental technique that organic chemists use to understand the synthetic routes of the target molecule.[10,11] A retrosynthetic disconnection of a chemical structure or Targeted Molecule (TM) leads to two or more fragments, which are recognized as synthons with their corresponding reagents or functional groups. In another way, it is also known as Functional Group Interconversion (FGI).

In this work, we illustrated important reactions that can support a possible synthetic route, along with the substrate scope and functional group interconversions. The article is organized by the functional group interconversions and bond formations to

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facilitate an easier sense of the suitable retrosynthetic pathway of pyrrolo (2,1-f)(triazine-4-amino) Adenine C-Nucleoside (GS-5734) (Figure 1).

Functional group-based strategies

Conversion of functional groups in synthetic organic chemistry is an art that requires careful analysis in order to reduce or avoid side or unwanted reactions. The chemo-, region-, stereospecific- and stereoselective aspects can guide researchers in designing more direct routes to the precise target, consequently decreasing the number of functional group manipulations or alterations. Functional group interconversion is generally used to generate retrons from the target molecule. Antithetical disconnections are thought to divide the target molecule into a negatively and positively charged species made as units in synthesis are called donor synthons (d) and acceptor synthons (a). They are derived from reagents that contain various functional groups.

Formation or cleavage of P-O bond

Phosphate esters are scaffolds that are present in a variety of biologically active molecules and are also widely used in agrochemicals, pharmaceuticals, plasticizers, flame retardants, etc.[12-17] Similarly, phosphate esters are an essential part of various naturally occurring biological molecules, such as proteins, nucleic acids, steroids, carbohydrates and coenzymes and are also used as pro-drugs.[18] Phosphorylation of alcohols leads to the formation of phosphate esters, which have a great diversity of applications. As shown in Figure 2, the intention to install the phosphate ester functional group compound 1 can be achieved by the reaction of an alcohol (compound 2) with halo phosphoramidate (compound 3) in the presence of a polar solvent (step A). The mechanism involves the nucleophilic substitution of alcohol as an alkoxide ion (donor synthons) on a phosphoramidate ion (acceptor synthons) to obtain phosphate esters. The presence of an electron-withdrawing group or a good leaving group favors the attack of alkoxide ions on the electrophilic phosphoramidate ions. The disconnection of phosphate esters (P-O) by acidic hydrolysis provides reagents with practically acceptable donor (alkoxide ion) and acceptor synthons (phosphoramidate ion) information (Table 1). Existing modern and conventional methods support the FGI of Phosphate esters from alcohols via phosphorylation.[19-23]

General Mechanism of Phosphorylation

Formation and cleavage of C-O bonds

The C-O bond is quite common in structural motifs of numerous synthetic molecules and natural products with various important functional groups. In this study, we restricted our focus from alcohol-to-ether and ether-to-alcohol conversion.

Ethers are important functional groups in organic chemistry that contain an oxygen atom bonded to two alkyl or aryl groups. Depending on the nature of the alkyl or aryl groups bonded to the ether side of oxygen, they have different structures. Organic ethers are one of the most important classes of chemicals that have significant applications as herbicides, disinfectants, pharmaceuticals, plasticizers, solvents, drug intermediates and solvents in organic synthesis.[24-29] Generally, ethers are prepared from Brønsted acids and Lewis acid catalysts.[30] Among which a few procedures for the conversion of alcohols into ethers are Mitsunobu-type reactions,[31] hydroalkonylation of alkynes,[32] reductive condensation of esters and ketones,[33] alcoholysis of epoxides[34,35] and oxidative C-H alkoxylation of arenes.[36]

The dehydration of alcohols is the most important organic transformation that is being extensively used for the preparation of ether compounds.[37] The reaction of an alkyl halide with an alkoxy anion under basic conditions (Williamson synthesis) and the acid-promoted dehydrogenate condensation of alcohols gives ether functional group compounds. The dehydration of alcohols using many homogeneous catalysts, such as Lewis acids or Brønsted acids, has been reported for the etherification of alcohol functional groups.[38,39]

The reactions (E, G, I, J, K and L) with the alcohol group undergo dehydration, followed by nucleophilic substitution to give ethers, as depicted in Figure 3. Alcohols are converted to alkoxide ions using an inorganic base, which follows a nucleophilic substitution reaction with primary or secondary alkyl halides (S_N2 displacement mechanism, Williamson ether synthesis) in the presence of an aprotic polar solvent to give ethers. The reaction often competes with the base-catalyzed elimination of the alkylating agent, the nature of the leaving group and the reaction conditions (temperature and solvent), which can have a strong effect on the type of product formation (substitution or elimination). In reaction E, alcohol 13 undergoes intramolecular Williamson ether synthesis to give the cyclic ether compound 12. The disconnection of alcohol (O-H bond) by dehydrogenation condensation gives the donor synthon (alkoxide ion). The generated alkoxide ion attacks the carbon atom attached directly to the halide atom of the alkyl halide by a displacement reaction (halide atom). Here, the carbon atom attached to the halide atom acts as an acceptor synthon in a transition state, with both attacking and leaving groups. The possible synthetic information is presented in Table 2.

The cleavage of carbon-oxygen bonds in ethers can be achieved by nucleophilic substitution, which is a useful synthetic transformation in organic as well as medicinal chemistry.[40-46] The activation energy is significantly higher for bond cleavage in ethers.[47] This may be due to the reluctance of the C-O bond towards the oxidative addition reactions, the lower tendency of the alkoxy group to act as a good leaving group and the nucleophile employed. To promote this ionization, bond cleavage usually requires assistance from a protic or Lewis acid. The reaction may occur either via the S_N1 or S_N2 mechanism, depending on

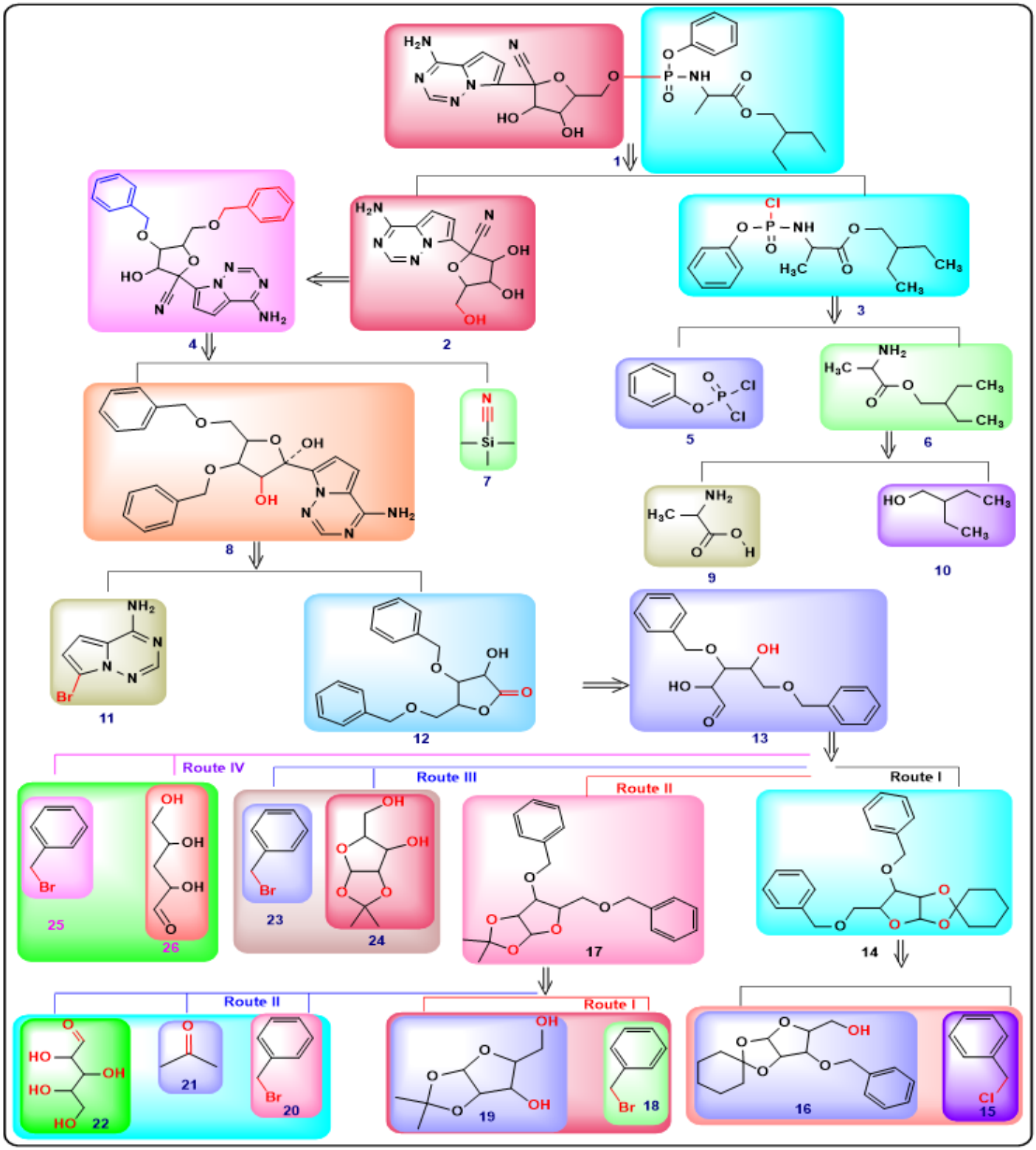
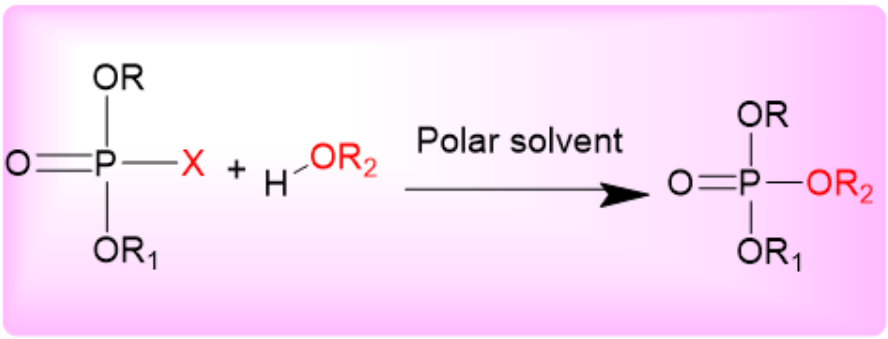


Figure 1: Complete schematic representation of retrosynthetic analysis of Pyrrolo(2,1-f)(triazin-4-amino) Adenine C-Nucleoside (GS-5734).



Retrosynthetic reaction for possible FGI

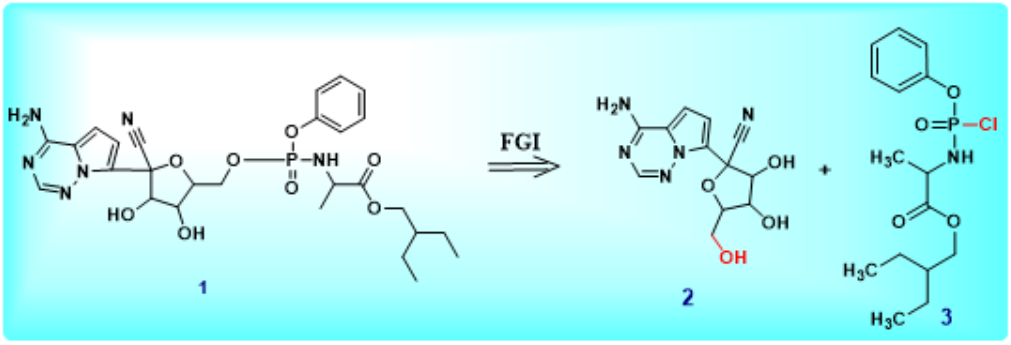
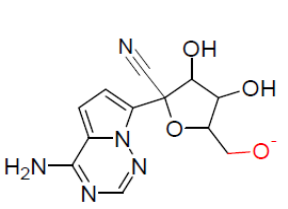
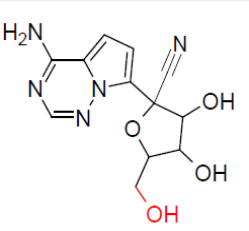
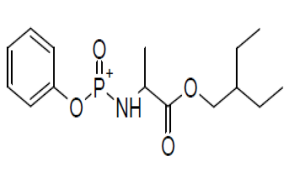
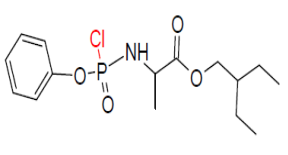
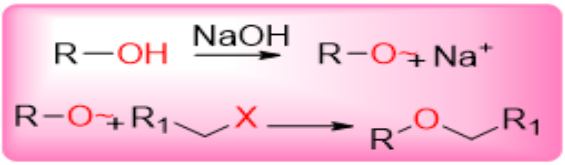


Figure 2: **General mechanism of phosphorylation, Disconnection of compound 1 (Phosphate esters) to compound 2 (alcohol) and compound 3 (Halo phosphoramidate).**

Table 1: **Types of synthons with respect to their available reagents.**

Type of synthons	Structure of synthons	Reagent	Functional group
Donor	Alkoxide ion 		Alcohol
Acceptor	Phosphoramidate 		Halo phosphoramidate

General Mechanism of Ether synthesis



Retrosynthetic reaction for possible FGI

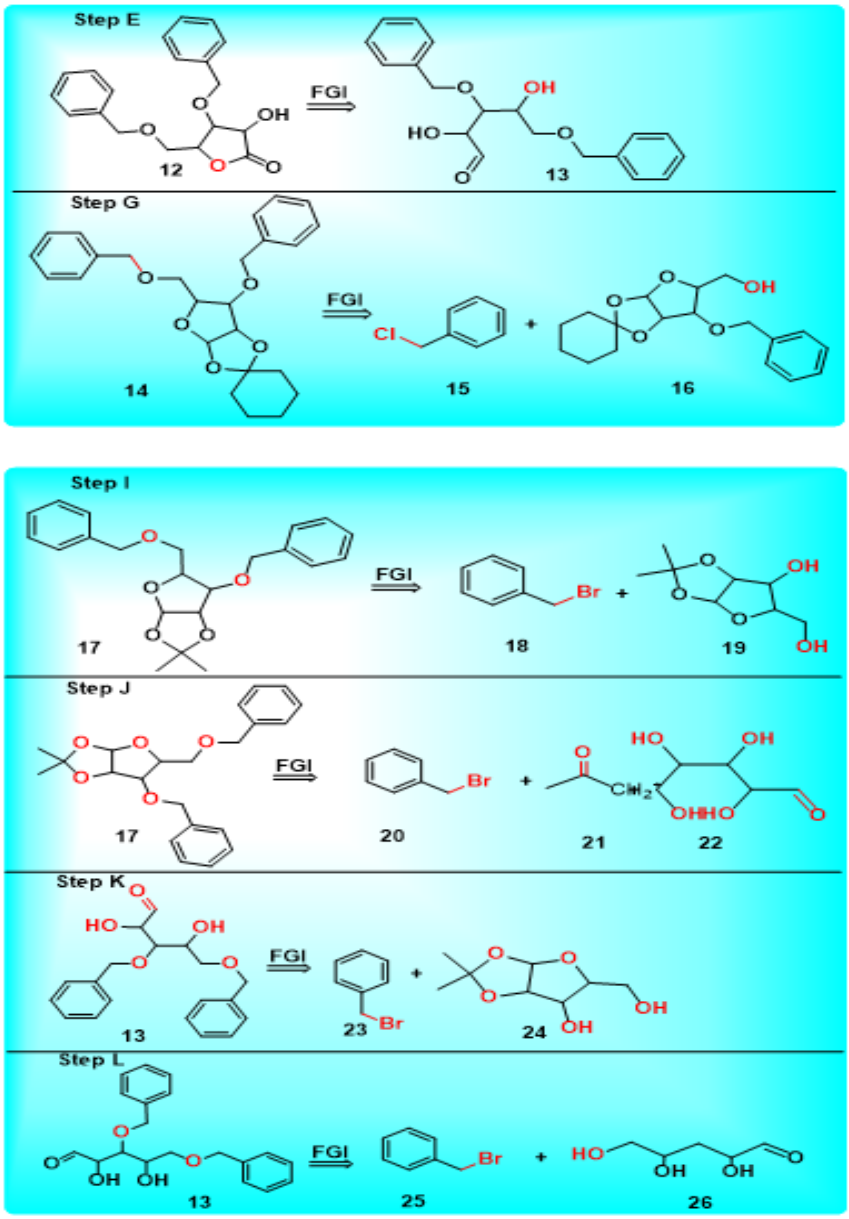
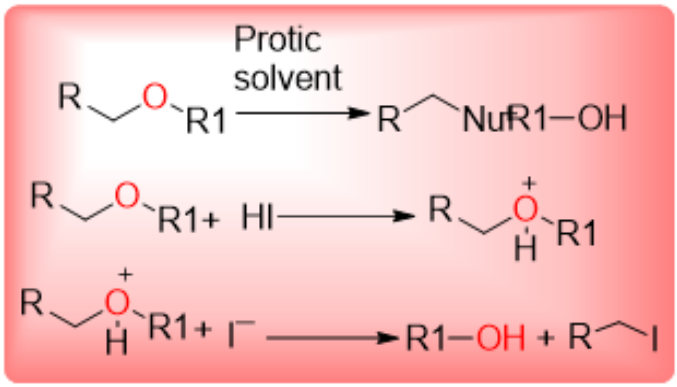


Figure 3: General mechanism of Ether synthesis, Disconnection of compounds 12, 13, 14 and 17 (ether functional group) to compound 13, 15, 16, 18, 19, 20, 21, 22, 23, 24, 25 and 26 (alcohol and alkyl halides).

General Mechanism of Alcohol synthesis



Retrosynthetic reaction for possible FGI

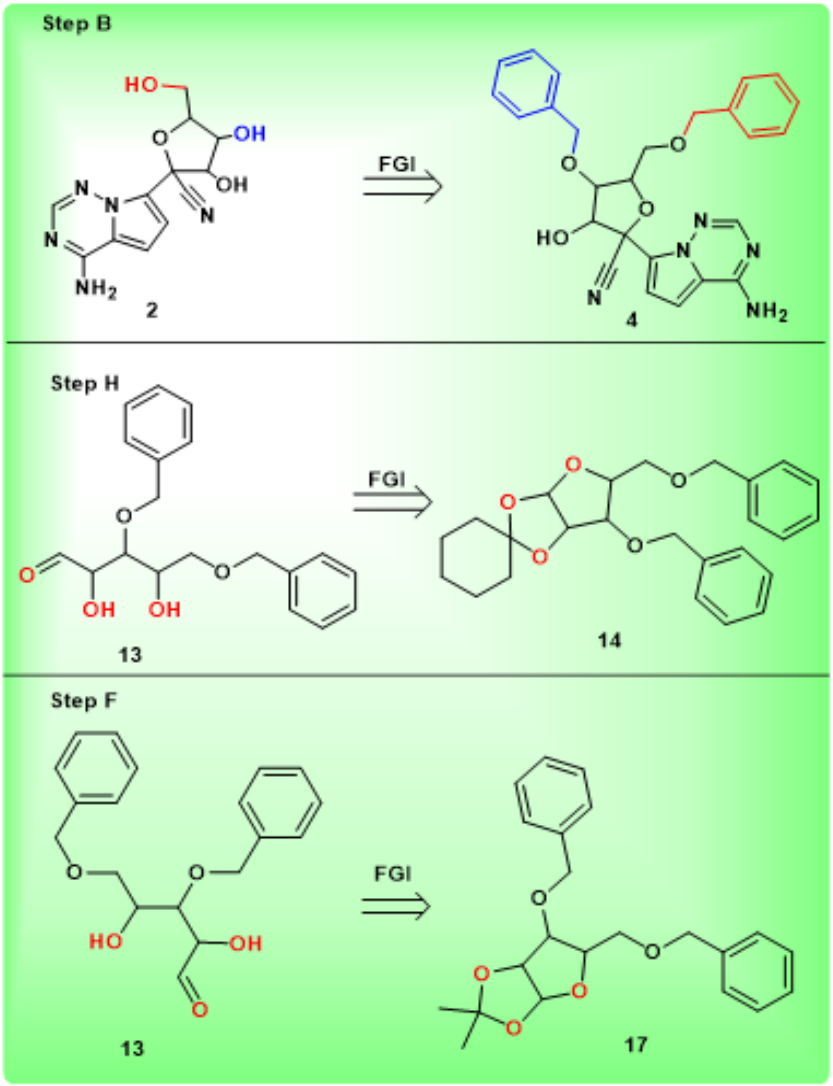
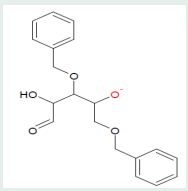
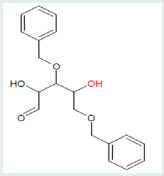
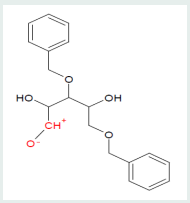
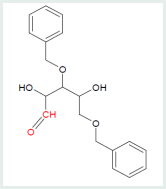
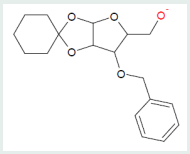
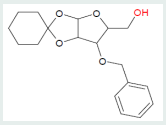
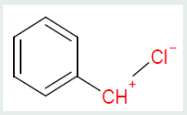
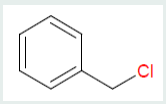
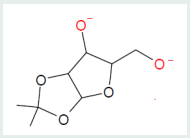
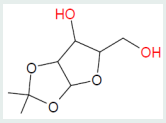
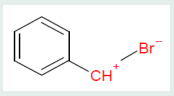
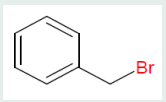
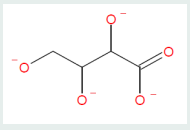
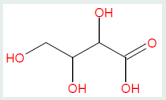
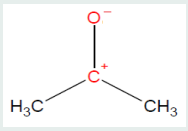
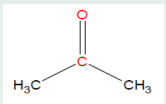
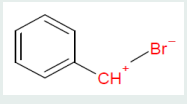
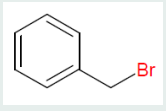
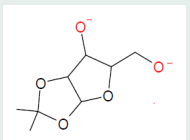
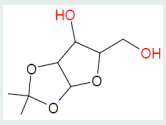
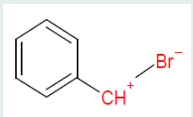
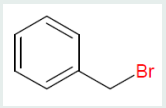
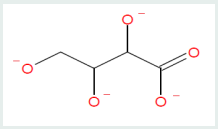
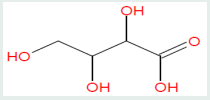
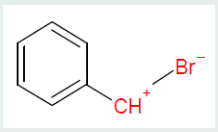
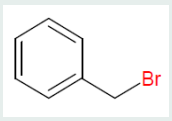


Figure 4: General mechanism of Alcohol synthesis, conversion of compound 2 and 13 alcohol group to compounds 4, 14 and 17 ether group.

Table 2: Types of synthons with respect to the available reagents.

Step	Type of synthons	Structure of synthons	Reagent	Functional group
Step E	Donor	alkoxide ion 		Alcohol
Step E	Acceptor			Aldehyde
Step G	Donor			Alcohol
Step G	Acceptor			Alkyl halide
Step I	Donor			Alcohol
Step I	Acceptor			Alkyl halide
Step J	Donor			Alcohol
Step J	Acceptor			Ketone
Step J	Acceptor			Alkyl halide
Step K	Donor			Alcohol
Step K	Acceptor			Alkyl halide

Step	Type of synthons	Structure of synthons	Reagent	Functional group
Step L	Donor			Alcohol
Step L	Acceptor			Alkyl halide

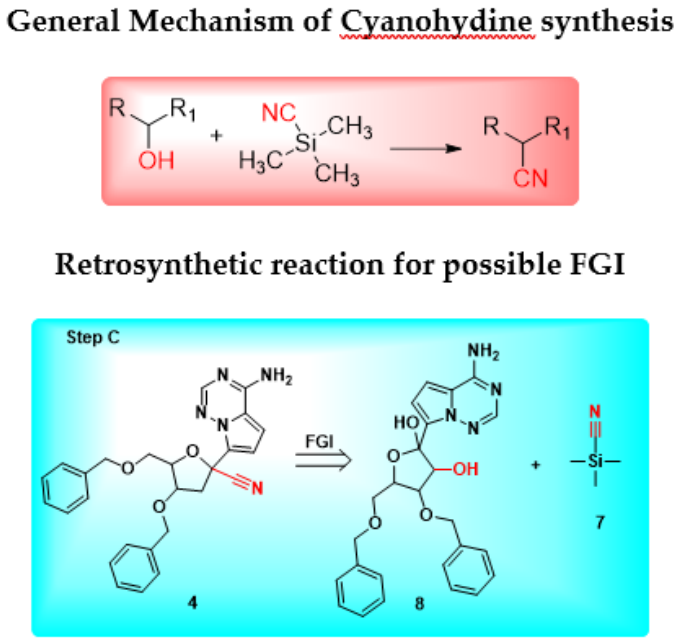


Figure 5: General mechanism of Nitriles synthesis, Disconnection of compound 4(Cyanohydines) to compound 8 (alcohol) and compound 7 (Nitrile).

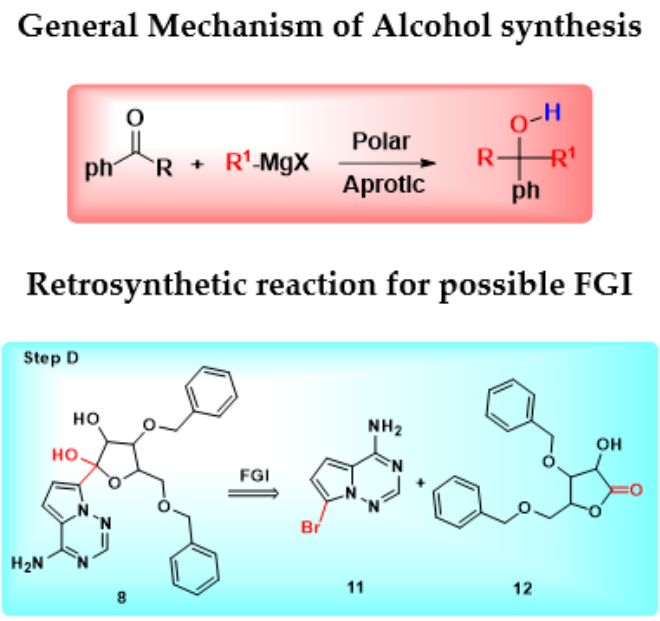


Figure 6: General mechanism of Alcohol synthesis, Disconnection of compound 8 (alcohol) to compound 11 (aryl halide) and compound 12 (ketone).

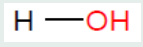
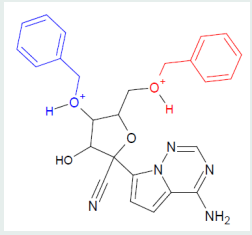
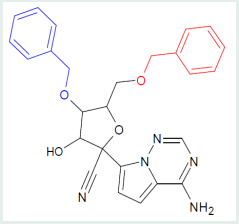
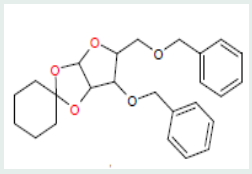
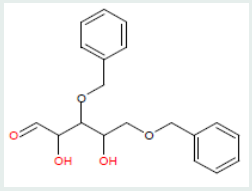
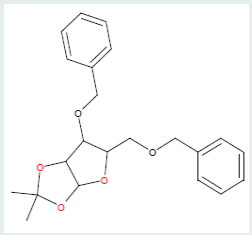
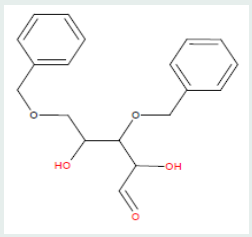
the alkyl group attached to the oxygen atom. Fortunately, recent advances in this area have led to dramatic progress in the use of innovative catalytic techniques that employ the cleavage of aryl alkyl ethers.

In reaction B, the aliphatic ether group undergoes hydrolysis to give alcohol and reactions F and H with cyclic ether undergo hydrogenolysis to give alcohol and carbonyl functional groups. Compound 4 underwent a nucleophilic addition reaction to give compound 2 via the S_N2 mechanism with a transition state in the presence of an acidic solvent, as depicted in Figure 4. Compounds 14 and 17 underwent catalytic hydrogenation to give 13 bearing hydroxyl and carbonyl groups. Possible synthons are listed in Table 3.

Formation of C-C bond by activation of C-O bond

The substitution reactions of alcohols with nucleophiles are generally more difficult than those of the corresponding halides. This was mainly due to the poor ability of the hydroxyl group to act as a good leaving unit. However, substitution is still a fascinating convention in synthetic organic chemistry, mainly due to the greater availability and cost effectiveness of alcohols over other functional groups. Thus, much attention has been paid to the direct substitution of alcohols with various nucleophiles, such as indoles,[48,49] amines,[50] amides,[51] linear thiols,[52] trimethoxybenzene,[52] enolsilane,[53] allylsilanes,[53] 1,3- dicarbonyls[54-58] and silyl ketene acetal.[59] The substitution of a hydroxyl functional group in alcohols with cyanide has attained great interest.[60-69] Nitriles are important precursors for the synthesis of drugs such as naproxen, cicloprofen and indoprofen.[70-72]

Table 3: Types of synthons with respect to the available reagents.

Step	Type of synthons	Structure of synthons	Reagent	Functional group
Step B	Donor			Hydroxy
Step B	Acceptor			Ether
Step F	Intra-molecular conversion		Stereoselective conversion	Ether
Step F	Intra-molecular conversion		Stereoselective conversion	Alcohol
Step H	Intra-molecular conversion		Stereoselective conversion	Ether
Step H	Intra-molecular conversion		Stereoselective conversion	Alcohol

Alcohols can be converted into nitriles by the Mitsunobu reaction[73] in the presence of a condensing agent (dicyclohexyl carbodiimide),[74] Michael reactions,[75] Strecker synthesis.[76] Even homogeneous Lewis acids (indium halides) and $B(C_6F_5)_3$[77,78] were found to be efficient for the transformation of alcohols with trimethylsilyl cyanide into nitriles. To troubleshoot the problems in the previous methods nowadays a heterogeneous along with moisture-tolerant catalyst were using instead of a homogeneous system.[79-92] In reaction C the transformation of alcohol (compound 4) to cyanohydines (compound 8) is achieved by nucleophilic substitution of nitrile group with alcohols (Figure 5). The disconnection of compound 4 gives possible synthons: compound 7 with a nitrile group and compound 8 with an alcohol functional group. Compound 7 acts as a donor synthon and compound 8 acts as an acceptor synthon (Table 4).

Formation of C-C and O-H bond by activation of C-O bond

The carbonyl ketone group undergoes a nucleophilic addition reaction with a Grignard reagent to give alcohol and this is the most versatile method for the synthesis of alcohols.[93-97] Recently, several modifications have been developed to enhance the yield of the product by suppressing side reactions such as changing the solvent,[98-103] addition of an excess amount of organic bases,[104-107]

Table 4: Types of synthons with respect to the available reagents.

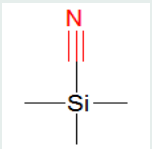
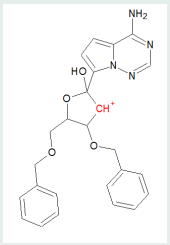
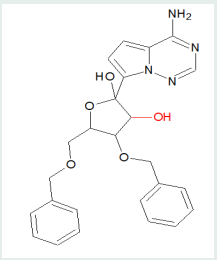
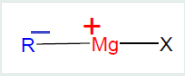
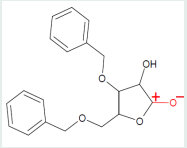
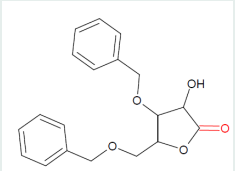
Step	Type of synthons	Structure of synthons	Reagent	Functional group
Step C	Donor			Nitrile
Step C	Acceptor			Alcohol

Table 5: Types of synthons with respect to the available reagents.

Step	Type of synthons	Structure of synthons	Reagent	Functional group
Step D	Donor			Aryl halide
Step D	Acceptor			Ketone

inorganic salts,[108-118] and tetrabutyl ammonium bromide.[119] In reaction D, compound 11 undergoes a nucleophilic addition reaction with a Grignard reagent to give compound 8 in the presence of moderately polar aprotic solvents such as dry ether and tetrahydrofuran (Figure 6). The disconnection of compound 8 gives possible synthons, compound 12 with the ketone group and compound 11 with the aryl halide group. The ketone carbonyl group undergoes ionization and the carbonyl carbon atom gets a positive charge due to the electronegativity of an oxygen atom, which acts as a positive synthon. The aryl halide acts as a donor synthon and attacks the positive carbon atom of the carbonyl carbon atom (Table 5). Simultaneously, the hydride ion or hydrogen atom attacked the carbonyl oxygen atom to facilitate the reaction.

CONCLUSION

In this study, we have proposed a retrosynthetic model for a targeted molecule, Pyrrolo(2,1-f)(triazin-4-amino) Adenine C-Nucleoside (GS-5734), to understand the various transformations of the intermediate scaffolds with possible synthetic routes. The resulting donor and acceptor synthons support the formation of stable intermediate compounds with various functional groups. The disconnection and functional group interconversion were carried out by exploring the inverse route from the target molecule to a pair of reactants in the given synthetic route, where all possible combinations of purchasable reagents spanned the feasible solution space. The identified diverse routes may help stimulate the ideas of organic researchers to narrow down the possibility of the synthetic route for the remdesivir drug. Even inter conversion of the functional group may provide an outlook for adopting alternative green synthetic techniques.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

TM: Targeted Molecule; **FGI:** Functional Group Interconversion.

REFERENCES

1. Siegel, D.; Hui, H. C.; Doerffler E.; Clarke, M. O.; Chun, K.; Zhang, L.; *et al.*, Discovery and Synthesis of a Phosphoramidate Prodrug of a Pyrrolo[2,1-f][triazin-4-amino] Adenine C-Nucleoside (GS-5734) for the Treatment of Ebola and Emerging Viruses. *J Med Chem*. 2017;60:1648-61.
2. De, S. R.; Miranda, L. S. M.; Bornscheuer, U. T. A Retrosynthesis Approach for Biocatalysis in Organic Synthesis. *Chem Eur J*. 2017;23:12040-63.
3. Corey, E. J.; Cheng, X. M. The Logic of Chemical Synthesis; *Wiley*: New York, 1995.
4. Corey, E. J.; Wipke, W. T. Computer-assisted design of complex organic syntheses.*Science*. 1969;166:178-92.
5. Todd, M. H. Computer-aided organic synthesis. *Chem Soc Rev*. 2005;34:247-66.

6. Szymkuć S, Gajewska EP, Klucznik T, Molga K, Dittwald P, Startek M, Bajczyk M, Grzybowski BA. Computer-Assisted Synthetic Planning: The End of the Beginning. *Angew Chem Int Ed Engl*. 2016;55:5904-37.
7. Marth, C. J.; Gallego, G. M.; Lee, J. C.; Lebold, T. P.; Kulyk, S.; Kou, K. G.; Qin, J.; Lilien, R.; Sarpong, R. Network-analysis-guided synthesis of weisaconitine D and liljestrandinine. *Nature*. 2015;528:493-8.
8. Elkin, M.; Newhouse, T. R. Computational chemistry strategies in natural product synthesis. *Chem Soc Rev*. 2018;47:7830-44.
9. Tantillo, D. J. Questions in natural products synthesis research that can (and cannot) be answered using computational chemistry. *Chem Soc Rev*. 2018;47:7845-50.
10. Robinson. R. A synthesis of tropinone. *J Chem Soc Trans*. 1917;111:762-8.
11. Corey, E. J. The Logic of Chemical Synthesis: Multistep Synthesis of Complex Carbogenic Molecules. *Angew Chem Int Ed Engl*. 1991;30:455-65.
12. Thornton, P. J.; Kadri, H.; Miccoli, A.; Mehellou, Y. Nucleoside Phosphate and Phosphonate Prodrug Clinical Candidates. *J Med Chem*. 2016;59:10400-10.
13. Phillips, D. R.; Uramoto, M.; Isono, K.; McCloskey. Structure of the antifungal nucleotide antibiotic phosmidosine. *J A J Org Chem*. 1993;58;854-9.
14. Roush, R. F.; Nolan, E. M.; Löhr, F.; Walsh, C. T. Maturation of an Escherichia coli ribosomal peptide antibiotic by ATP-consuming N-P bond formation in microcin C7. *J Am Chem Soc*. 2008;130:3603-9.
15. Guijarro, J. I.; González-Pastor J. E.; Baleux, F.; San Millán, J. L.; Castilla, M. A.; Rico, M.; Moreno, F.; Delepierre, M. Chemical structure and translation inhibition studies of the antibiotic microcin C7. *J Biol Chem*. 1995;270:23520-32.
16. Dwek, R. A. Glycobiology: Toward Understanding the Function of Sugars. *Chem Rev*. 1996;96:683-720.
17. Berridge, M. J.; Irvine, R. F. Inositol trisphosphate, a novel second messenger in cellular signal transduction. *Nature*. 1984;312:315-21.
18. Corbridge, D. E. C. Phosphorus 2000. Chemistry, Biochemistry & Technology., Elsevier.; Oxford: Amsterdam, 2000; Chapters 10 and 11.
19. Kosolapoff, G. M.; Maier, L. Organic Phosphorus Compounds., Wiley-Interscience: New York, 1972.
20. Hartley, F. R. The Chemistry of Organophosphorus Compounds; Wiley: New York, 1996.
21. Quin, L. D. A Guide to Organophosphorus Chemistry., Wiley: New York, 2000.
22. Gupta, H. K.; Mazumder, A.; Garg, P.; Gutch, P. K.; Dubey, D. K. *N,N*-Dichloro poly(styrene-co-divinyl benzene) sulfonamide polymeric beads: an efficient and recyclable reagent for the synthesis of dialkyl chlorophosphates from dialkylphosphites at room temperature.*Tetrahedron Lett*. 2008;49:6704.
23. Jayaraman, D.; Kandikere, R. P. Cross-Hetero-Dehydrogenative Coupling Reaction of Phosphites: A Catalytic Metal-Free Phosphorylation of Amines and Alcohols. *Org. Lett*. 2013;15:6062-5.
24. Prasad, A.; Nimavat, K. S.; Vyas, K. B. Synthesis and biological studies of N-(3-chlor o-2-aryl-4-oxoazetidin-1-yl)-2-(5- ((naphthalen-1-yloxy)methyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)acetamide. *Der Pharmacia Sinica*. 2011;2:26-32.
25. Nallu, M.; Selvakumar, R.; Krishnapillai, M. A simple method for the preparation of aryl phenacyl ether in micellar medium: Part I. *Indian J Chem Sect B, Org Chem*. 1999;38:1108-10.
26. Moroz, A. A.; Shvartsberg, M. S. The Ullmann Ether Condensation. *Russ. Chem. Rev*. 1974;43:679-89.
27. Kuhn, R.; Low I.; Trishman, H. The constitution of lycotetraose. *Chem Ber*. 1957;90:203-18.
28. Miles W. H.; Connell, K. B. Synthesis of Methyl Diantilis, a Commercially Important Fragrance. *J Chem Educ*. 2006;83:285-6.
29. Pagliaro, M.; Ciriminna, R.; Kimura, H.; Rossi, M.; Della P. C. From glycerol to value-added products. *Angew Chem Int Ed Engl*. 2007;46:4434-40.
30. N. Baggett, in Comprehensive Organic Chemistry, ed. D. Barton, W. D. Ollis and J. F. Stoddart, Pergamon, Oxford, 1st edn, 1979:819.
31. Swamy, K. C.; Kumar, N. N.; Balaraman, E.; Kumar, K.V. Mitsunobu and related reactions: advances and applications. *Chem Rev*. 2009;109:2551-651.
32. Haibach, M. C.; Guan, C.; Wang, D. Y.; Li, B.; Lease, N.; Steffens, A. M.; Krogh-Jespersen, K.; Goldman, A. S. Olefin hydroaryloxylation catalyzed by pincer-iridium complexes. *J Am Chem Soc*. 2013;135:15062-70.
33. Sakai, N.; Moriya, T.; Konakahara, T. An efficient one-pot synthesis of unsymmetrical ethers: a directly reductive deoxygenation of esters using an InBr3/Et3SiH catalytic system. *J Org Chem*. 2007;7215:5920-2.
34. Iranpoor, N.; Zeynizadeh, B. Efficient Dehydration of Aldoximes to Nitriles with TiCl3(OTf). *Synth Commun*. 1999;29:2747-52.
35. Chini, M.; Crotti, P.; Cardelli, C.; Macchia, F. Metal Salt-Promoted Alcoholysis of 1,2-Epoxides. *Synlett*, 1992;8:673-6.
36. Wang, X.; Lu, Y.; Dai, HX.; Yu, J. Q. Pd(II)-catalyzed hydroxyl-directed C-H activation/C-O cyclization: expedient construction of dihydrobenzofurans. *J Am Chem Soc*. 2010;132:12203-5.
37. Mandal, S.; Mandal, S.; Ghosh, S. K.; Sar, P.; Ghosh, A.; Saha, R.; Saha, B. A review on the advancement of ether synthesis from organic solvent to water. *RSC Adv*. 2016;6:69605-14.
38. Kim, S.; Chung, K. N.; Yang, S. Direct synthesis of ethers via zinc chloride-mediated etherification of alcohols in dichloroethane. *J Org Chem*. 1987;17:3917-9.
39. Davies, T. E.; Kondrat S. A.; Nowicka, E.; Graham, J. J.; Apperley, D. C.; Taylor, H. S.; *et al.* Dehydrative Etherification Reactions of Glycerol with Alcohols Catalyzed by Recyclable Nanoporous Aluminosilicates: Telescoped Routes to Glyceryl Ethers. *ACS Sustainable Chem Eng*. 2016;3:835-43.
40. Tehetena, M.; Garg, N. K. Ni- and Fe-Catalyzed Cross-Coupling Reactions of Phenol Derivatives. Org Process Res Dev. 2013;1:29-39.
41. Yamaguchi, J.; Muto, K.; Itami, K. Recent Progress in Nickel-Catalyzed Biaryl Coupling. Eur J Org Chem. 2013;19-30.
42. Correa, A.; Cornella, J.; Martin, R. Nickel-catalyzed decarbonylative C-H coupling reactions: a strategy for preparing bis(heteroaryl) backbones. *Angew Chem Int Ed Engl*. 2013;52:1878-80.
43. Tobisu M.; Chatani, N. Catalytic Transformations Involving the Activation of sp2 Carbon-Oxygen Bonds. *Top Organo met Chem*. 2013;44:35-53.
44. Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A. M.; Garg, N. K.; Percec, V. Nickel-catalyzed cross-couplings involving carbon-oxygen bonds. *Chem Rev*. 2011;111:1346-416.
45. Li, B. J.; Yu, D. G.; Sun, C. L.; Shi, Z. J. Activation of "inert" alkenyl/aryl C-O bond and its application in cross-coupling reactions. *Chemistry*. 2011;17:1728-59.
46. Yu, D. G.; Li, B. J.; Shi, Z. J. Exploration of new C-O electrophiles in cross-coupling reactions. *Acc Chem Res*. 2010;43:1486-95.
47. Pedley, J. B.; Taylor, R. D.; Kirby, S. P. Thermochemical data of organic compounds., 2nd ed.; Chapman and Hall: New York, 1986.
48. Yasuda, M.; Somyo, T.; Baba, A. Direct carbon-carbon bond formation from alcohols and active methylenes, alkoxyketones, or indoles catalyzed by indium trichloride. *Angew Chem Int Ed Engl*. 2006;45:793-6.
49. Bandini, M.; Eichholzer, A. Catalytic functionalization of indoles in a new dimension. *Angew Chem Int Ed Engl*. 2009;48:9608-44.
50. Qin, H.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. Bismuth-catalyzed direct substitution of the hydroxy group in alcohols with sulfonamides, carbamates and carboxamides. *Angew Chem Int Ed Engl*. 2007;46:409-13.
51. Noji, M.; Ohno, T.; Fuji, K.; Futaba, N.; Tajima, H.; Ishii, K. Secondary benzylation using benzyl alcohols catalyzed by lanthanoid, scandium and hafnium triflate. *J Org Chem*. 2003;68:9340-7.
52. Sanz, R.; Martinez, A.; Miguel, D.; Alvarez-Gutierrez, J. M.; Rodriguez, F. Brønsted Acid-Catalyzed Nucleophilic Substitution of Alcohols. *Adv Synth Catal*. 2006;348:1841-5.
53. Cella, J. A. Reductive alkylation/arylation of arylcarbinols and ketones with organosilicon compounds. *J Org Chem*. 1982;47:2125-30.
54. Motokura, K.; Fujita, N.; Mori, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. Brønsted acid mediated heterogeneous addition reaction of 1,3-dicarbonyl compounds to alkenes and alcohols. *Angew Chem Int Ed Engl*. 2006;45:2605-9.
55. Rueping, M.; Nachtsheim, B. J.; Kuenkel, A. Efficient metal-catalyzed direct benzylation and allylic alkylation of 2,4-pentanediones. *Org Lett*. 2007;9:825-8.
56. Kischel, J.; Mertins, K.; Michalik, D.; Zapf, A.; Beller, M. A General and Efficient Iron-Catalyzed Benzylation of 1,3-Dicarbonyl Compounds. *Adv Synth Catal*. 2007;349:865-70.
57. Kothandaraman, P.; Rao, W. D.; Zhang, X. X.; Chan, P. W. H. Direct Synthesis of Nitriles from Alcohols with Trialkylsilyl Cyanide Using Brønsted Acid Montmorillonite Catalysts. *Tetrahedron*. 2009;65:1833-8.
58. Wang, J.; Masui, Y.; Onaka, M. Efficient Nucleophilic Substitution of α-Aryl Alcohols with 1,3-Dicarbonyl Compounds Catalyzed by Tin Ion-Exchanged Montmorillonite. *Synlett*. 2010;16:2493-7.
59. Vicennati, P.; Cozzi, P. G. Facile Access to Optically Active Ferrocenyl Derivatives with Direct Substitution of the Hydroxy Group Catalyzed by Indium Tribromide. *Eur J Org Chem*. 2007;14:2248-53.
60. Brett, D.; Downie, I. M.; Lee, J. B. Sugars with potential antiviral activity. I. Conversion of hydroxy compounds to nitriles. *J Org Chem*. 1967;32:855-6.
61. Schwartz, M. A.; Zoda, M.; Vishnuvajjala, B.; Mami, I. A convenient synthesis of o- and p-hydroxy substituted phenylacetonitriles and phenethylamines. *J Org Chem*. 1976;41:2502-3.
62. Mizuno, A.; Hamada, Y.; Shioiri, T. New Methods and Reagents in Organic Synthesis; 61. A Simple One-Pot Conversion of Primary Alcohols to Nitriles having One C-Atom more. *Synthesis*. 1980;12:1007-9.
63. Davis, R.; Untch, K. G. Direct one-step conversion of alcohols into nitriles. *J Org Chem*. 1981;46:2985-7.
64. Castro.; Bertrand, R. Replacement of Alcoholic Hydroxy Groups by Halogens and Other Nucleophiles via Oxyphosphonium Intermediates. *Org React*. 1983;29:1-162.
65. Camps, F.; Gasol, V.; Guerrero, A. A Simple One-Pot Synthesis of Nitriles from Alcohols. *Synth Commun*. 1988;18:445-52.
66. Kanai, T.; Kanagawa, Y.; Ishii, Y. Hydrogen iodide strategy for one-pot preparation of allylic azides, nitriles and phenyl sulfones from allylic alcohols. J Org Chem. 1990;55:3274-7.
67. Mori, N.; Togo, H. Direct Oxidative Conversion of Primary Alcohols to Nitriles Using Molecular Iodine in Ammonia Water. *Synlett* 2005;12: 1964.
68. Rad, M. N. S.; Khalafi-Nezhad, A.; Behrouz, S.; Faghihi, M. A. A simple one-pot procedure for the direct conversion of alcohols into alkyl nitriles using TsIm. *Tetrahedron Lett*. 2007;48:6779-84.

69. Reddy, K. R.; Maheswari, C. U.; Venkateshwar, M.; Prashanthi, S.; Kantam, M. L. Catalytic oxidative conversion of alcohols, aldehydes and amines into nitriles using KI/I2-TBHP system. *Tetrahedron Lett*. 2009;50:2050-3.
70. Cooper, S. A.; Breen, J. F.; Giuliani, R. L. Replicate studies comparing the relative efficacies of aspirin and indoprofen in oral surgery outpatients. *J Clin Pharmacol*. 1979;19:151-9.
71. Tsuruo, T.; Iida, H.; Tsukagoshi, S.; Sakurai, Y. Overcoming of vincristine resistance in P388 leukemia *in vivo* and *in vitro* through enhanced cytotoxicity of vincristine and vinblastine by verapamil. *Cancer Res*. 1981;41:1967-72.
72. Rahme, E.; Pilote, L.; LeLorier, J. Association between naproxen use and protection against acute myocardial infarction. *Arch Intern Med*. 2002;162(10):1111-5.
73. Swamy, K. C.; Kumar, N. N.; Balaraman, E.; Kumar, K. V. Mitsunobu and related reactions: advances and applications. *Chem Rev*. 2009;109:2551-651.
74. Iranpoor, N.; Firouzabadi, H.; Akhlaghinia, B.; Nowrouzi N. Conversion of alcohols, thiols and trimethysilyl ethers to alkyl cyanides using triphenylphosphine/2,3-dichloro-5,6-dicyanobenzoquinone/n-Bu(4)NCN. *J Org Chem*. 2004;69:2562-4.
75. Kawai, M.; Onaka, M.; Izumi, Y. Clay Montmorillonite: An Efficient, Heterogeneous Catalyst for Michael Reactions of Silyl Ketene Acetals and Silyl Enol Ethers with α,β-Unsaturated Carbonyl Compounds. *Bull Chem Soc Jpn*. 1988;61:2157-64.
76. Wang, J. C.; Masui, Y.; Onaka, M. Synthesis of α-Amino Nitriles from Carbonyl Compounds, Amines and Trimethylsilyl Cyanide: Comparison between Catalyst-Free Conditions and the Presence of Tin Ion-Exchanged Montmorillonite. *Eur J Org Chem*. 2010;9:1763-71.
77. Chen, G.; Wang, Z.; Wu, J.; Ding, K. L. Facile Preparation of α-Aryl Nitriles by Direct Cyanation of Alcohols with TMSCN Under the Catalysis of InX3. *Org Lett*. 2008;10:4573-6.
78. Rajagopal, G.; Kim, S. S. Synthesis of α-aryl nitriles through B(C6F5)3-catalyzed direct cyanation of α-aryl alcohols and thiols. *Tetrahedron*. 2009;65:4351-5.
79. Pinnavaia, T. J. Intercalated clay catalysts. *Science*. 1983;220:365-71.
80. Laszlo, P. Chemical reactions on clays. *Science*. 1987;235:1473-7.
81. Izumi, Y.; Onaka, M. Organic Syntheses Using Aluminosilicates. *Adv Catal*. 1992;38:245-82.
82. Ebitani, K.; Kawabata, T.; Nagashima, K.; Mizugaki, T.; Kaneda, K. Simple and clean synthesis of 9,9-bis[4-(2-hydroxyethoxy)phenyl]fluorene from the aromatic alkylation of phenoxyethanol with fluoren-9-one catalysed by titanium cation-exchanged montmorillonite. *Green Chem*. 2000;2:157-60.
83. Kawabata, T.; Kato, M.; Mizugaki, T.; Ebitani, K.; Kaneda, K. Highly Efficient Deprotection of Acetals by Titanium Cation-exchanged Montmorillonite as a Strong Solid Acid Catalyst. *Chem Lett*. 2003;32:648-9.
84. Kawabata, T.; Kato, M.; Mizugaki, T.; Ebitani, K.; Kaneda, K. Monomeric metal aqua complexes in the interlayer space of montmorillonites as strong Lewis acid catalysts for heterogeneous carbon-carbon bond-forming reactions. *Chemistry*. 2004;11:288-97.
85. Motokura, K.; Nakagiri, N.; Mizugaki, T.; Ebitani, K.; Kaneda, K. Nucleophilic substitution reactions of alcohols with use of montmorillonite catalysts as solid Brønsted acids. *J Org Chem*. 2007;72:6006-15.
86. Motokura, K.; Tada, M.; Iwasawa, Y. Layered materials with coexisting acidic and basic sites for catalytic one-pot reaction sequences. *J Am Chem Soc*. 2009;131:7944-5.
87. Motokura, K.; Matsunaga, S.; Miyaji, A.; Sakamoto, Y.; Baba, T. Heterogeneous allylsilylation of aromatic and aliphatic alkenes catalyzed by proton-exchanged montmorillonite. *Org Lett*. 2010;12:1508-11.
88. Onaka, M.; Hosokawa, Y.; Higuchi, K.; Izumi, Y. Acidity comparison between ion-exchanged clay montmorillonites by using silylation of alcohol. *Tetrahedron Lett*. 1993;34:1171-2.
89. Wang, J. C.; Masui, Y.; Onaka, M. Direct allylation of α-aryl alcohols with allyltrimethylsilane catalyzed by heterogeneous tin ion-exchanged montmorillonite. *Tetrahedron Lett*. 2010;51:3300-3.
90. Izumi, Y.; Onaka, M. Liquid-phase organic reactions catalyzed by inorganic solid acids and bases. *J Mol Catal*. 1992;74:35-42.
91. Higuchi, K.; Onaka, M.; Izumi, Y. Solid Acid and Base-Catalyzed Cyanosilylation of Carbonyl Compounds with Cyanotrimethylsilane. *Bull Chem Soc Jpn*. 1993;66:2016-32.
92. Wang, J. C.; Masui, Y.; Watanabe, K.; Onaka, M. Highly Efficient Cyanosilylation of Sterically Bulky Ketones Catalyzed by Tin Ion-Exchanged Montmorillonite. *Adv Synth Catal*. 2009;351:553-7.
93. Wakefield, B. J. Organomagnesium Methods in Organic Synthesis; Academic Press: San Diego, CA, 1995.
94. Richey, H. G. Grignard Reagents: New Development; Wiley: Chichester, United Kingdom, 2000.
95. Silverman, G. S.; Rakita, P. E. Handbook of Grignard Reagents; Marcel Dekker: New York, 1996.
96. Hatano, M.; Ishihara, K. Recent Progress in the Catalytic Synthesis of Tertiary Alcohols from Ketones with Organometallic Reagents. *Synthesis*. 2008;11:1647-75.
97. Luderer, M. R.; Bailey, W. F.; Luderer, M. R.; Fair, J. D.; Dancer, R. J.; Sommer, M. B. Asymmetric addition of achiral organomagnesium reagents or organolithiums to achiral aldehydes or ketones: a review. *Tetrahedron Asymmetry*, 2009;20:981-98.
98. Gocmen, M.; Soussan, G. Comparaison de la reactivite du bromure d'ethylmagnesium et du diethylmagnesium vis-a-vis des cetones α,β-ethyleniques dans divers solvants. *J Organomet Chem*. 1974;80:303-9.
99. Scala, A. A.; Becker, E. I. Solvent Effects in the Grignard Reaction. Ethylmagnesium Bromide with Benzonitrile. *J Org Chem*. 1965;30:3491-8.
100. Vitt, S. V.; Khristova, E. I.; Bondarev, V. B. Influence of solvents on the reduction of pinacoline with 2-hexylmagnesium halides. *Russ Chem Bull*. 1969;8:1647-9.
101. Tuulmets, A.; Pallin, V.; Tammiku-Taul, J.; Burk, P.; Raie, K. Solvent effects in the Grignard reaction with alkynes. . *J Phys Org Chem*. 2002;15:701-5.
102. Sassian, M.; Tuulmets, A. Solvation Effects in the*Grignard* Reaction with Carbonyl Compounds. *Helv Chim Acta*. 2003;86:82-90.
103. Tuulmets, A.; Panov, D.; Sassian, M. On the mechanism derived from kinetic solvent effects of Grignard reactions with silanes. *Tetrahedron Lett*. 2003;44:3943-5.
104. Canonne, P.; Foscolos, G.; Caron, H.; Lemay, G. Study of the influence of the hydrocarbon diluent in the reaction of primary organomagnesium on congested ketones. *Tetrahedron*. 1982;38:3563-8.
105. Noyori, R.; Suga, S.; Kawai, K.; Okada, S.; Kitamura, M. Enantioselective alkylation of carbonyl compounds. From stoichiometric to catalytic asymmetric induction. *Pure Appl Chem*. 1988;60:1597-606.
106. Sassian, M.; Panov, D.; Tuulmets, A. Grignard reagents in toluene solutions. *Appl Organomet Chem*. 2002;16:525-9.
107. Wang, X. J.; Zhang, L.; Sun, X. F.; Xu, Y. B.; Krishnamurthy, D.; Senanayake, C. H. Addition of Grignard Reagents to Aryl Acid Chlorides: An Efficient Synthesis of Aryl Ketones. *Org Lett*. 2005;7:5593-5.
108. Swain, C. G.; Boyles, H. B.The Mechanism of Addition of Grignard Reagents to Ketones. *J Am Chem Soc*. 1951;73:870-2.
109. McBee, E. T.; Pierce, O. R.; Higgins, J. F. The Reducing Action of Grignard Reagents on Fluorinated Carbonyl Compounds. *J Am Chem Soc*. 1952;74:1736-7.
110. Ashby, E. C.; Noding, S. A. The effects of added salts on the stereoselectivity and rate of organometallic compound addition to ketones. *J Org Chem*. 1979;44:4371-7.
111. Richey, H. G.; DeStephano, J. P. Reactions of dialkylmagnesium-salt mixtures with ketones: increasing the ratio of addition to reduction. . *J Org Chem*. 1990;55:3281-6.
112. Ipaktschi, J.; Eckert, T. LiClO4-Promoted Addition of Alkyl Grignard and Alkynyllithium Reagents to Ketones. Comparison of a 5 M LiClO4/Diethyl Ether Solution with CeCl3. *Chem Ber*. 1995;128:1171-4.
113. Fujii, N.; Nakai, K.; Habashita, H.; Yoshizawa, H.; Ibuka, T.; Garrido, F.; Mann, A.; Chounan, Y.; Yamamoto, Y. SN2' selective alkylation of allylic chlorides and mesylates with RZnX reagents generated from Grignard reagents, zinc chloride, lithium chloride and Cu(II)-salts. *Tetrahedron Lett*. 1993;34:4227-30.
114. Fürstner, A.; Krause, H.; Lehmann, C. W. Unusual structure and reactivity of a homoleptic "super-ate" complex of iron: implications for Grignard additions, cross-coupling reactions and the Kharasch deconjugation. *Angew Chem Int Ed Engl*. 2006;45:440-4.
115. Sada, M.; Matsubara, S. Iron(II) Chloride-mediated Addition of Dialkylmagnesium to Carbonyl Compounds. *Chem. Lett*. 2008;37:800-1.
116. Hitotsuyanagi, Y.; Fujiki, H.; Suganuma, M.; Aimi, N.; Sakai, S.; Endo, Y.; Shudo, K.; Sugimura, T. Isolation and structure elucidation of teleocidin B-1, B-2, B-3 and B-4. *Chem Pharm Bull (Tokyo)*. 1984;32:4233-6.
117. Imamoto, T.; Takiyama, N.; Nakamura, K. Cerium chloride-promoted nucleophilic addition of grignard reagents to ketones an efficient method for the synthesis of tertiary alcohols. *Tetrahedron Lett*. 1985;26:4763-6.
118. Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. Reactions of carbonyl compounds with Grignard reagents in the presence of cerium chloride. *J Am Chem Soc*. 1989;111:4392-8.
119. Chastrette, M.; Amouroux, R. Control of addition: reduction ratio in the Grignard reaction with ketones by a salt effect. *J Chem Soc D Chem Commun*. 1970;8:470-1.