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ISSN: 2090-4568
Journal of Advanced Chemical Engineering

Review Article

Recent Advancement in Alkylative Cyclization Reactions: Application in Synthesis of Natural Products

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ABSTRACT

Alkylative factionalized alkynes and radical alkenes to alkylative cyclic product, Alkynals and alkyl from cyclic compounds, alkylative cyclisation for heterocycles, and aromatic alkylative cyclisation by using alkylative condition such as photoredox , catalyst, condensation, cyclic intermediate have become one of the most important and useful methodologies for construction of C-C, C-N, C-O ,C-S etc. bonds for their synthesis applications. In order to demonstrate the growth in this area, this review highlights last twenty years of success in the fields cyclisation of aromatic compounds , alkylative cyclisation of natural product by using aromatic compounds and functionalized alkynes cyclic intermediate approaches for involving reaction carbocation , carboanion and radical mechanisms. We believe that summarizing these methods would be very useful for the chemists who are interested in the synthesis of natural products for carbon – based materials for industrial applications.

Keywords: Alkylative; Radical Alkenes; Racemic; De-sulfurization

INTRODUCTION

Alkylative cyclization with C-N bond formation (N-alkylation) is one of the most important methods in organic synthesis for the contraction of aza-cycles. Many well known reactions (e.g., aza-Diels-Alder, aza-Michael, aza- Mannich, aza-Henry reactions, etc.). This reaction is typically divided into classical and modern variants, depending on the reagents and substrates employed. The alkylative cyclization reaction proceeds through a sequence of intramolecular cyclization *via* radical, carbocation or anion intermediate. This reaction has done in presence of catalyst like as Ni, Cu, Pd, Fe etc. Alkylative is the transfer of an alkyl group from one molecule to another. The alkyl group may be transferred as an alkyl carbocation, a free radical, a carbo anion or a carbene. Although alkylative can be take place at high temperatures without catalyst The only processes of commercial importance's today operate at low to moderate temperatures using either sulfuric or hydrofluoric acid catalysts. The reactions occurring in the alkylative process are complex and produce an alkylate product that has a wide boiling range.

RECENT ADVANCEMENT IN ALKYLATIVE CYCLIZATION REACTIONS

Recent Advancement in Alkylative Cyclization Reactions: Application in Synthesis of Natural Product and Natural Products like Compounds. Physostigmine is an alkaloid isolated from the seeds of *Physostigma Venenosum* (Calabal beans) and has been shown to be a clinically useful anticholinergic drug. Analogues of 3 have shown a promise in the treatment of Alzheimer's disease. Thus, Calabar alkaloids are very interesting biochemical tools and several syntheses of 3 Kawahara Michiaki and his group in 2000 reported that using Corey-Kim reagent reacted with tryptamine or tryptophan carbamates to give 3a-(methylthiomethyl)hexahydropyrrolo (2,3-b) indole skeletons. Formal total synthesis of racemic and chiral physostigmine was accomplished in excellent overall yields, in short steps. Alkylative cyclization of 1,3-dimethylindole(1) reaction with (Z)-aziridine (A) in presence of TMS-Cl (1eq) and low temperature (-30°C) produced pyrroloindole. Pyrroloindole further can be easily reduced to desoxyeseroline. Many step of formal reaction totally synthesis of physostigmine (1). Utilizing in this process developed by few natural product such as Esermethole (4), Desoxyeseroline (5) (Scheme 1).

The scarcity of flustramines and pseudophyrnamines from natural sources, coupled with diverse biological activities such as muscle relaxant properties, and antimicrobial and cytotoxic effects, has led to continued interest in total synthesis of these alkaloids *via* either biomimetic or non-biomimetic approaches. Regioselective C_3 alkylation of indoles promoted by Lewis acid under mild conditions has become the potential methodology for construction of hexahydropyrrolo (2,3-b)-indoline natural product debromoflustramine by alkylative cyclization In 2003, He described the synthesis of debromoflustramine by from tryptamine, which was converted to the known ethyl carbamate. The carbamate group was chosen to modulate the reactivity of the side chain nitrogen such that it does not undergo direct alkylation in

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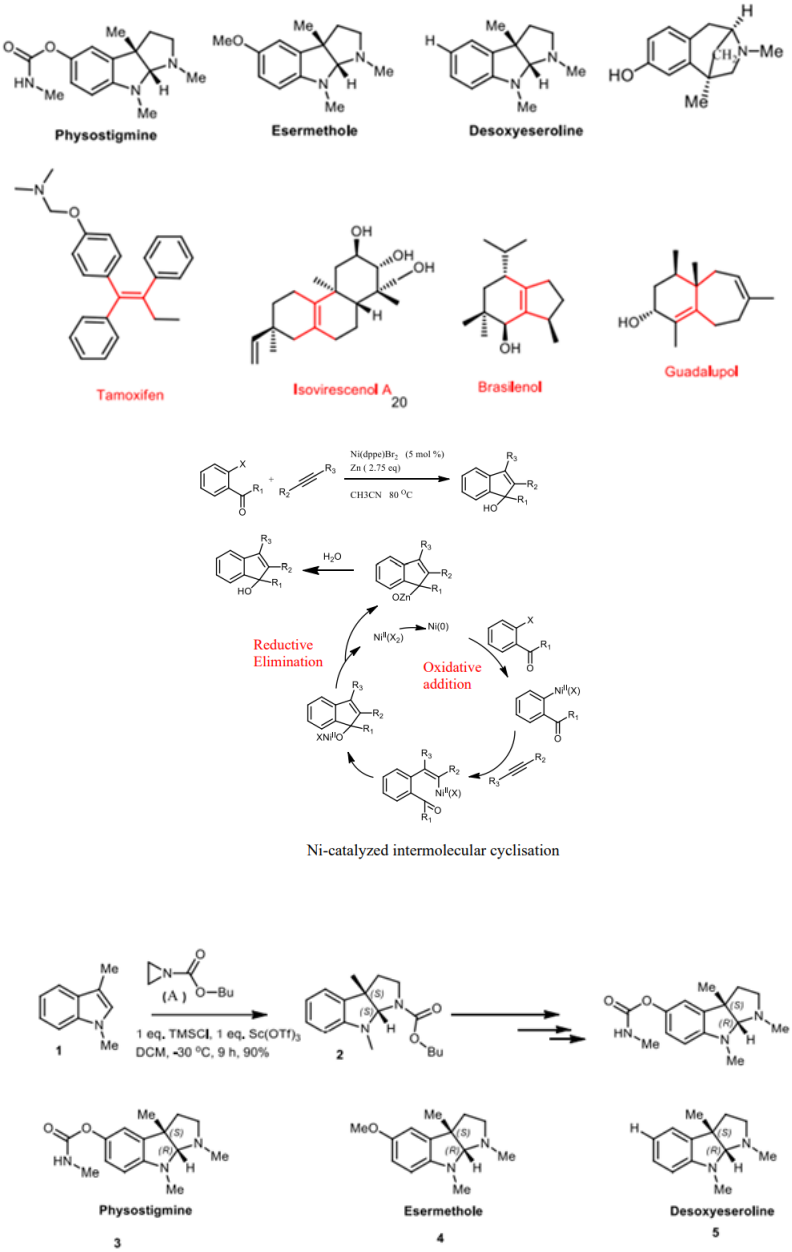
Received: 07-Jul-2022, Manuscript No. ACE-21-01-PreQc-22; **Editor assigned:** 11-Jul-2022, PreQC No ACE-21-01-PreQc-22 (PQ); **Reviewed:** 01-Aug-2022, QC No ACE-21-01-PreQc-22; **Revised:** 08-Aug-2022, Manuscript No. ACE-21-01-PreQc-22 (R); **Published:** 15-Aug-2022, DOI: 10.35248/2090-4568.22.12.245.

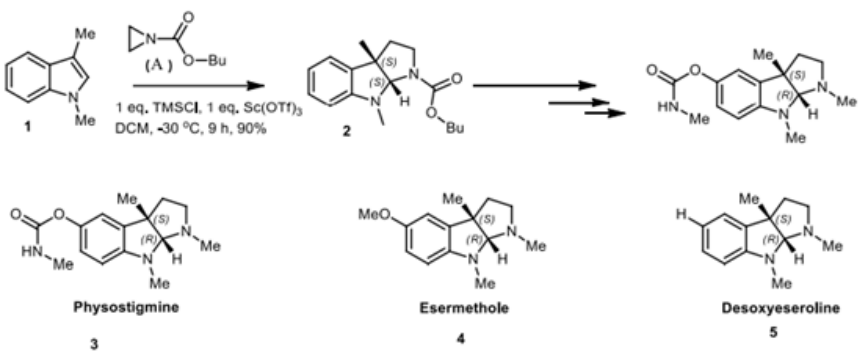
Citation: Das A, Khatravath M (2022) Recent Advancement in Alkylative Cyclization Reactions: Application in Synthesis of Natural Products. Adv Chem Eng. 12:245.

the next step but is sufficiently nucleophilic for the intramolecular iminium ion capture. In addition to this function, the carbamate serves as a latent methyl group upon reduction. Pleasingly, subjection to our zinc triflatemediated prenylation conditions gave 42% of the desired hexahydropyrrolo (2,3-b) indoline 06, accompanied by a small amount (10%) of the dialkylated product 11. But when the reaction was carried out at stoichiometric amounts of reagents only alkylated product is formed, which serves as a precursor for pseudophyrnaminol and debromoflustramine E after reduction (Scheme 2).

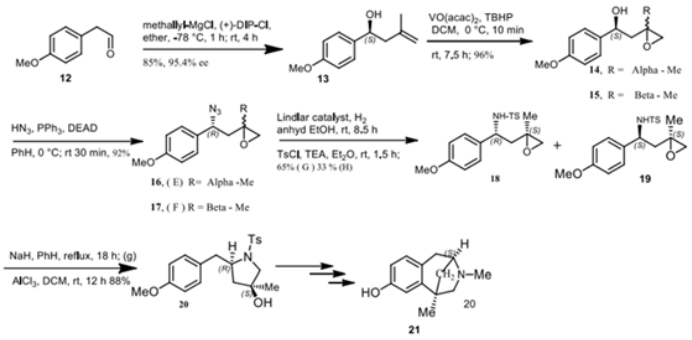
(-) Aphanorphine (21) is tricyclic 3-benzazepine alkaloid isolated by Shimizu and Clardy from the freshwater blue-green alga for the Aphanizomenon flos-aquae (2). It has raised a virtual explosion of synthetic interest due to its unique structure resembling benzomorphane analgesics such as pentazocine (16) The potential pharmacological activity should award aphanorphine and its analogues with great value as lead compounds in new drug development by using of friedel-Crafts alkylative cyclization with the concomitant stereospecific introduction of the benzylic quaternary carbon center. The current work constitutes an efficient enantioselective formal synthesis of 3-benzazepine marine alkaloid (-) aphanorphine. A highly symmetric 1,4-disubstituted benzene (12) react with the enantiopure diisopinocamphenyl(methyl) borane reagent in ether condition to give in 85% yield (R)-homoallylic alcohol (13) as a colorless oil. Stereoseletive epoxidation with TBHP in the presence of 2 mol% of $VO(acac)_2$ in dichloro methane at room temperature produced epoxy alcohol (14) and (15) (96%, 2:1). Continuously treated with HN_3PPh_3 and in benzene to form (16) and (17) in high yields (92%) which are azides. Finally (+) 89-methylaphanorphine (18) was delivered by reductive de-sulfurization with RED-Al in refluxing xylene (96%) followed by N-methylation with formaldehyde and $NaBH_3CN$ in MeOH at room temperature (98%). This process has been made through many steps finally to get as a tricyclic 3-benzazepine alkaloid (-) aphanorphine (21) in 86% yield (Scheme 3).



Scheme 1: Synthesis of debromoflustramine natural product.



Scheme 2: Synthesis of debromoflustramine natural product by alkylative cyclization.



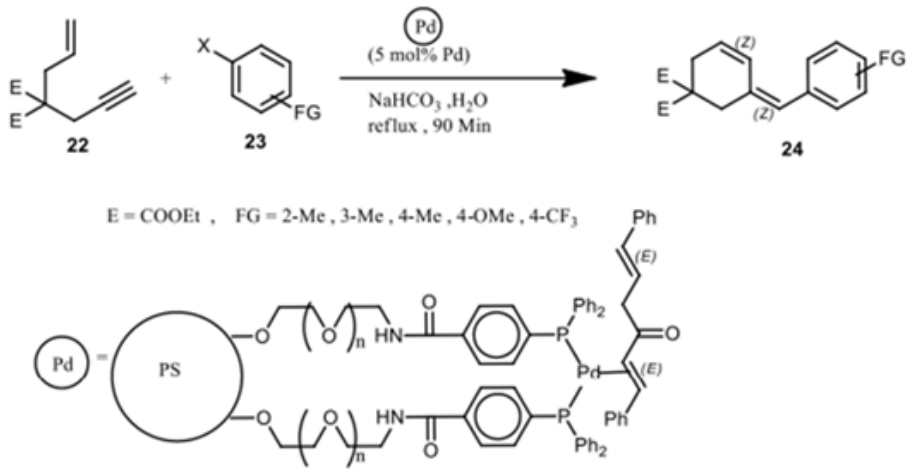
Scheme 3: Synthesis of (-) aphanorphine natural product by alkylative cyclization.

He reported that, an alkylative cyclization of a 1,6-enyene with aryl halides was performed with an amphiphilic polystyrene-poly(ethyl-ene glycol) (PS-PEG)resin –supported phosphine palladium complex in a refluxing aqueous $NaHCO_3$ solution under heterogeneous condition to give benzylidene cyclohexenes in good to high yields 63%-84%. The reaction proceeded *via* formation of a vinyl palladium intermediate and subsequent intermolecular heck reaction (Scheme 4).

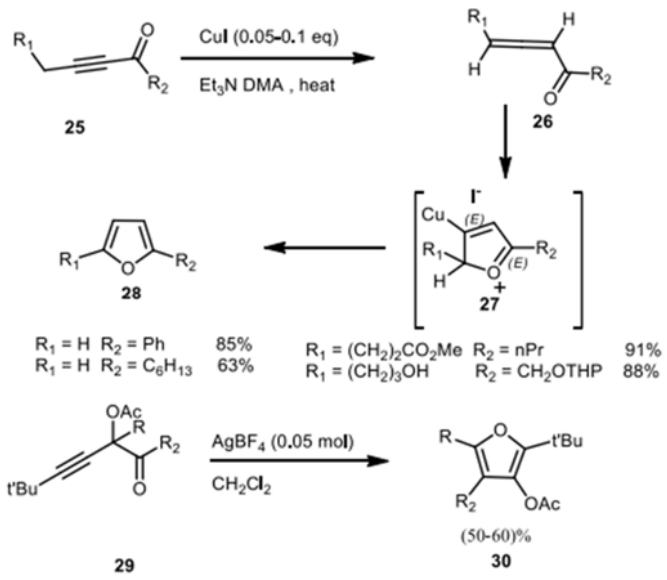
They reported by this process that in the Substituted furans from acetylenic and allenic compounds. Favourable views, including good functional group tolerance, predictable regioselectivity, and the skill to synthesize highly substituted furans, and the use of more easily common acetylene compounds, add to the practical attraction of these heterocyclization processes. Substituted furans have related the cyclocondensation of dicarbonyl compounds or equivalents, or the substitution of an existing furan ring. There are some limitations, including ease of access to allenyl substrates that contain sensitive functional groups and the inability to prepare 3,4- substituted furans by the direct cycloisomerization of allenes (4). Common alkynones (25) through cycloisomerization to furans 3 in the presence of a copper catalyst and an amine base proceed through the intermediate of allenyl isomers 27, which were previously known to undergo cyclization in the presence of a number of transition metals including Cu(I). Again tetra substituted furans are also available through a complementary Ag(I) catalyzed cycloisomerization of 2-acetoxybut-3-yn-1-ones .The modified approach made use of a formal 1,3-acyloxy shift to provide a tetra substituted allene that through the cycloisomerization sequence with attached 1,2-migration of the acyloxy group at ambient temperature (Scheme 5).

Clavepictines A and B and Pictamine are three quinolizidine alkaloids that were isolated from the tunicate ClaVelina picta in by the Cardellina and Faulkner groups. Tri-substituted piper dine moiety *via* condensation of an alpha-keto sulfone with an L-alanine-derived bromide and F following alkylative cyclization and form of its quinolizidine skeleton *via* diastereoselective intramolecular conjugate addition. And his group announcement by using the required piper dine ring make from Bocprotected γ-amino bromide 32, which prepare from N-Boc-L-alanine *via* Arndt-Eistertsynthesis [5]. After cleavage of the Boc group in 32 with $AlCl_3$, the released amine immediately condense with a-keto sulfone 33 under solvent free conditions to provide an enamine sulfone, which then treat with triethylamine and sodium iodide at 120°C to produce the alkylative cyclization product 34 in 75% overall yield,32 For further conversion to protect the enamine with a Boc group, which prove a challenging task owing to its poor reactivity and satirically hindered environment by treatment of 34 with n-BuLi and anion with di-tert-butyl dicarbonate. Next, Raney-Ni catalyzed hydrogenolysis of 35 carried out at 60°C to afford alcohol, which reduce with $NaBH_3CN$ in the presence of TFA to yield 2,6-trans-substituted piperidine .After Swern oxidation of olefination of the resultant aldehyde *via* a Wittig reaction (Scheme 6).

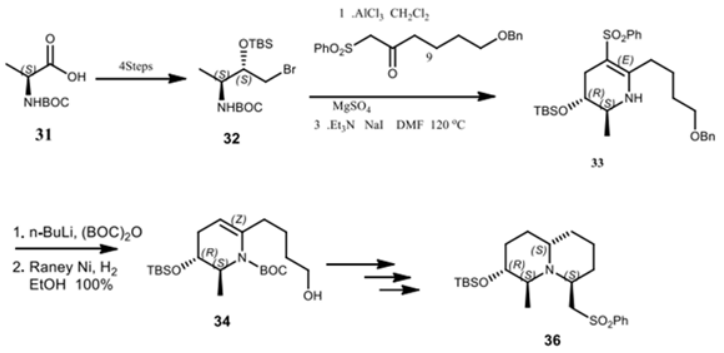
Alkynals such as (39) and alkynones undergo a series of trans-selective, alkylative, arylative, and alkenylative cyclization reactions with organoboronic reagent in the presence of $Pd(PPh_3)_4$ and solvent like as alcohol or toluene . Internal alkynes require to more sigma donating tricyclohexylphosphine ligand to give mixtures of trans addition products with internal and external alkene functionalities, the ratios depending on the both steric and electronic requirements. The functional group compatibility, availability, stability and non-toxicity of the organo-boronic reagents. It is reported by the alkyative cyclization reaction of terminal alkyne aldehyde 37 heated at 65°C in the presence of an excess of phenylboronic acid and a catalytic amount of $Pd(PPh_3)_4$, 1a undergoes phenylative cyclization to afford a single cyclized product (Scheme 7) [6].



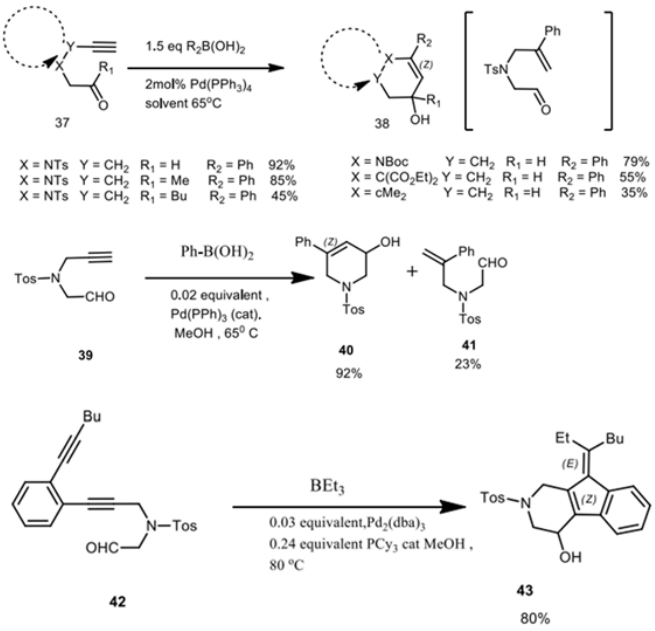
Scheme 4: Synthesis of heterogeneous aquaticatalytic akylative cyclization of 1,6- enyenes.



Scheme 5: Synthesis of 3,4-substituted furans akylative cyclization.



Scheme 6: Synthesis of clavepictines A and B and pictamine.



Scheme 7: Synthesis of alkylative cyclization of alkynals and alkynones.

A palladium (0)-tricyclohexylphosphine catalyzed cash selective alkylative and arylative cyclization of alkyne-contain with organo-boron reagents to provide five and six membered rings with exo tri or tetra substituted alkyne. Organ boron reagents are generally non-toxic, commercially available, stable, and compatible with various functional groups, and often employed for a wide variety of Pd0-catalyzed carbon–carbon bond formations such as cross-coupling reactions, arylations of unsaturated carbon–carbon bonds.

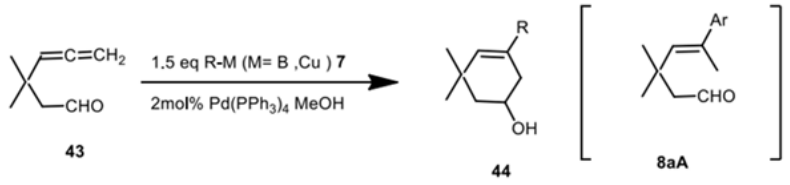
The alkylative cyclization of carbon-carbon bonds in the reaction (2E)-1-phenyl-2-octen-7-yn-1-one (4a) with a slight excess of phenyl-boronic acid and its anhydride mixture proceeds in the presence of 5 mol% of PdCp(g3– C_5H_5) and 15 mol % of PCy_3, and provides cis-addition product 5Af in good yield (Scheme 8).

Synthetic method for 3-substituted 3-cyclohexenols and -cyclopentenol from allene carbonyl compounds. Microwave irradiations eject to increase not only the reaction rate but also the product yield and formation of hydroarylation by products viewed in the same catalytic system. In addition to sp^2- and sp^3-carbonucleophiles, sp-carbon and boron nucleophiles also participate in this process allenyl aldehydes(43) react with arylboronic acid in presence of MW palladium(0) catalyzed and alcoholic condition give 3-substituted-3- cycloalken-1-ol product (7). Reactions finish in clean, dry glassware under argon atmosphere using high quality solvents. Anhydrous dichloromethane and methanol were obtained by distillation from phosphorus (V) oxide and magnesium respectively yields refer to chromatographically homogeneous material. Allenyl aldehyde 4a under the best reaction conditions for that of alkynes 8 (1.5 equiv of 7, 2 mol % of $Pd(PPh_3)_4$ MeOH, 65°C). As compared with the alkynal cyclization, the reaction rate is faster and gives 3-cyclohexenol 44 in lower yield along with a considerable amount of hydroarylated product 8aA (Scheme 9).

Intermolecular variant of highly diastereoselective Co-catalyzed alkylative aldol cyclizations of alpha beta unsaturated amides with ketones using trialkylaluminum (R_3Al) reagents gives substituted piperidinones. This process to beta Hydroxylactams containing three stereo enters with high diastereoselective . During studies of cobalt-catalyzed reductive aldol cyclizations, it was found that certain substrates containing a beta-un-substituted R, Alpha - beta-unsaturated amide as the conjugate acceptor furnished small quantities of alkylative aldol products when triethylaluminum was used in place of diethyl zinc as the stoichiometric reluctant (Scheme 10).

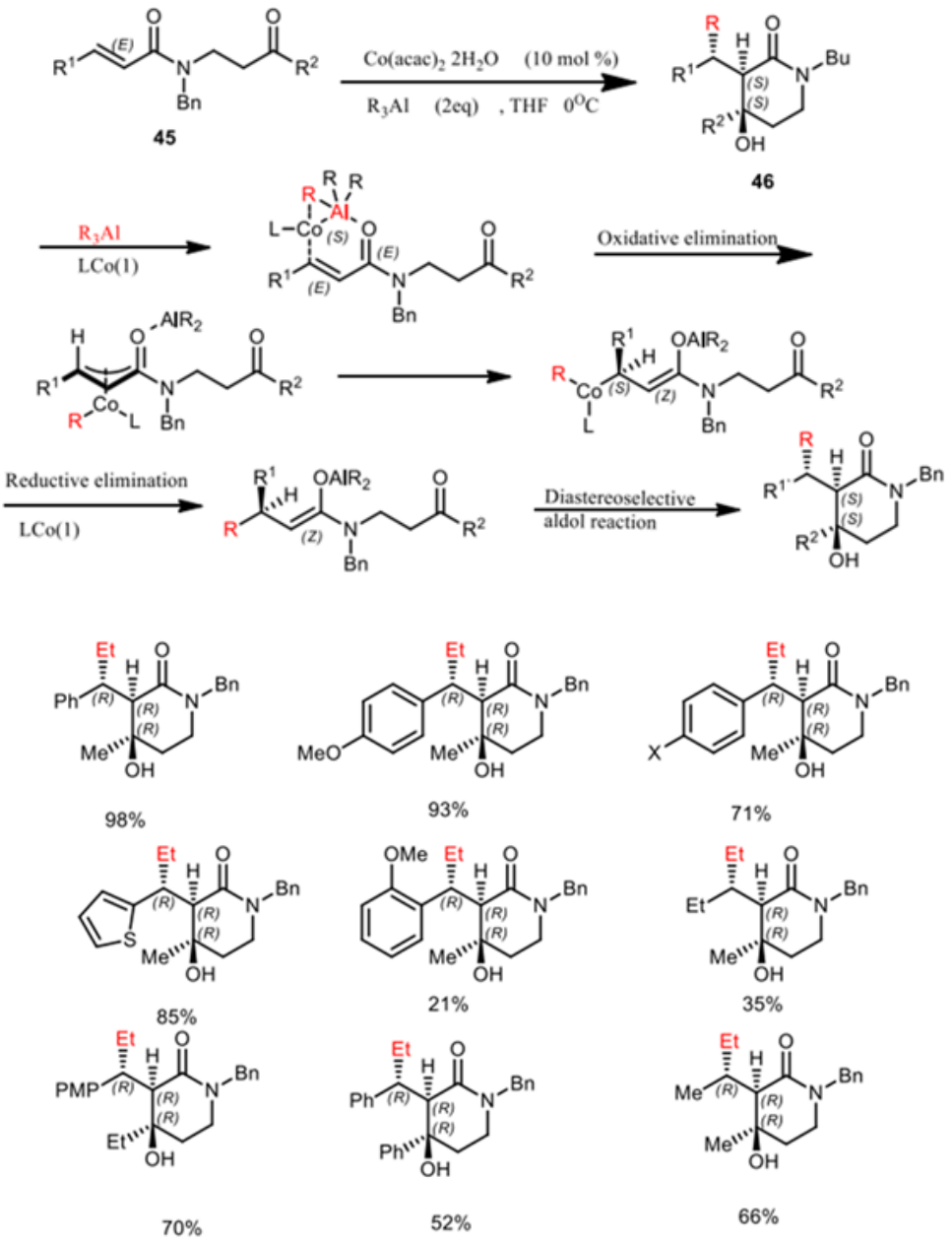
The 2-aminothiazole ring system is a useful structural element in medicinal as well as agricultural chemistry.

Alkynals such as (39) and alkynones undergo a series of trans in that reaction of Propargylbromide 1 was first reacted with thiouracyl 2 leading to derivative 3 as the only product and in high yield. The reaction of propargyl bromide 1 with the S-DABO compound 4 led to a mixture of two isomers 5a-b which was isolated in a 2:1 ratio. An efficient copper-catalyzed amino trifluoro-methylation of alkenes has been gained using amides as nucleophiles under mild conditions. These reactions provide CF_3-containing lactams in good yields. It offers a useful method to access a variety of CF_3-containing lactams, which are valuable building blocks in organic synthesis and drug development. Inquiry of the reaction mechanism is currently operative. Towards the synthesis of CF_3-containing lactams. In contrast to the successful oxytrifluoromethylation of unsaturated carboxylic acids, it remains challenging to employ amides as nucleophiles in trifluoromethylation-organized olefin functionalization copper-catalyzed reactions of 2-vinylbenzamides containing different protecting groups using Togni's (0.3 mmol, 1 equiv), Togni's reagent (0.6 mmol, 2 equiv), Cu (acac) 2 (0.06 mmol, 20 mol%), Scheme 7: Synthesis of Alkylative cyclization of Alkynals and Alkynones. MeoH (3 ml), 80°C, 2-5 h isolation yields (Scheme 11).

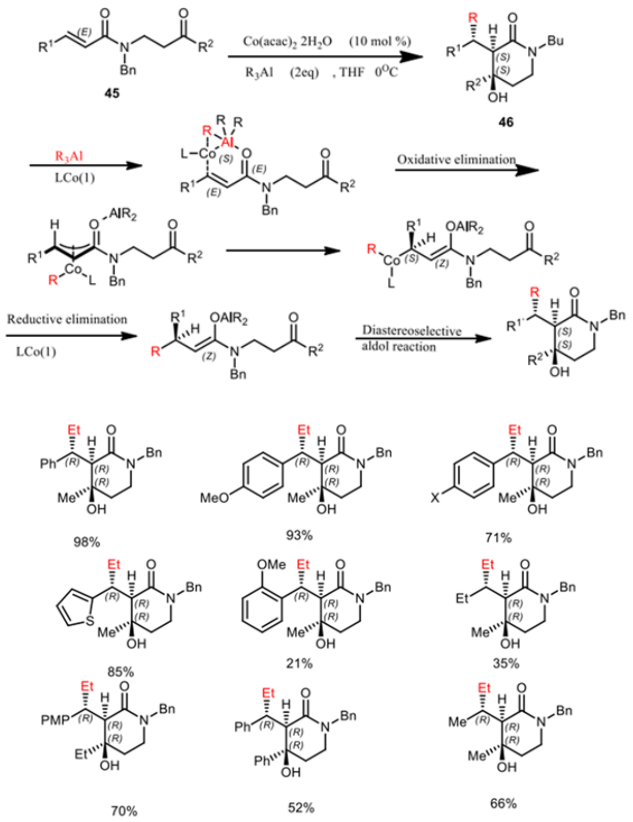


entry	7	44	yield (%)
1	p-Me_2N-C_6H_4-$B(OH)_2$ 7A	44aA	90
2	C_6H_5-$B(OH)_2$ 7B	44aB	84
3	p-Cl-C_6H_4-$B(OH)_2$ 7C	44aC	85
4	p-OHC-C_6H_4-$B(OH)_2$ 7D	44aD	80
5	o-OHC-C_6H_4-$B(OH)_2$ 7E	44aE	82
6	p-F_3C-C_6H_4-$B(OH)_2$ 7F	44aF	78
7	p-NC-C_6H_4-$B(OH)_2$ 7G	44aG	88
8	m-NO_2-C_6H_4-$B(OH)_2$ 7H	44aH	65
9	2-furan-$B(OH)_2$ 7I	44aI	94
10	3-furan-$B(OH)_2$ 7J	44aJ	93
11	e PhCCH-cat. CuI 7K	44aK	78

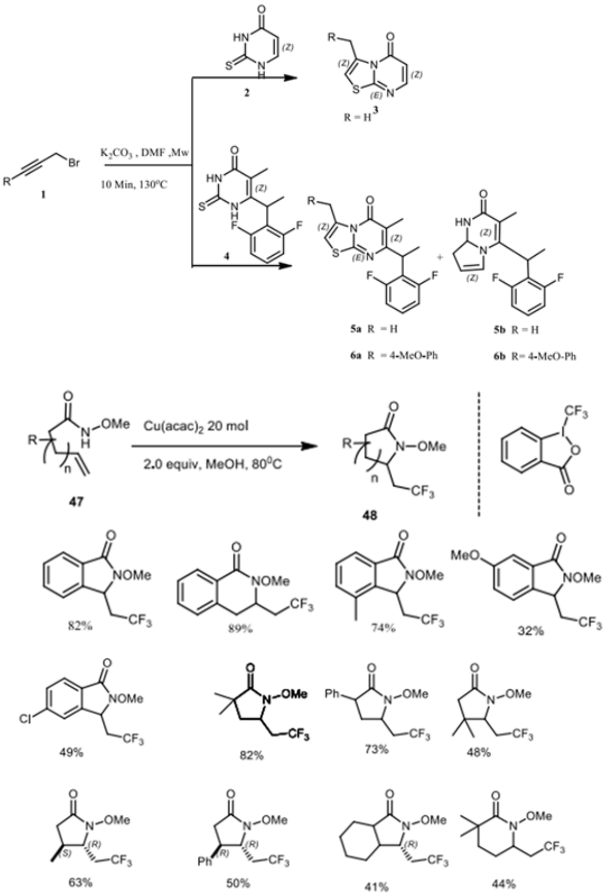
Scheme 8: Synthesis of microwave-assisted palladium (0) catalyzed alkylative cyclization of allenyl aldehydes.



Scheme 9: Synthesis of microwave-assisted palladium (0) catalyzed.



Scheme 10: Synthesis of beta- hydroxylactams and co- catalysed alkylative aldol cyclization.



Scheme 11: Synthesis of CF_3--containing lactams.

An unusual Wittig rearrangement/alkylative cyclization reaction of methyl O-propargyl glycol ate derivatives. The reactions produce potentially useful 3-hydroxy-furan-2-one products in moderate yield and appear to proceed *via* radical alkylation of an intermediate allenes (8). These reactions proceed with excellent diastereoselectivity, and use of the readily available chiral auxiliary 2-phenylcyclohexanol provides access to enantiomerically enriched products with up to 94% ee after helpful cleavage. that ester (49) is treated with Bu_2BOTf and iPr_2NEt and formed at rt for 15 min, and then an aldehyde is added to the resulting mixture then get the sequential rearrangement/aldol reaction and instead is transformed to the substituted 3-hydroxy-2-furanone (50) (Scheme 12).

Carbocyclic and heterocyclic ring systems bearing asymmetric substitution patterns are widely distributed among medicinal agents and bioactive natural products. In 2013 that this method has been proposed transformation was first evaluated in the context of the amine-tethered phenyl aldehyde substrate 8 treated with base and Fe(III) trisphenanthroline in the prece of an imidazolidinone catalyst led to the stereoseletive formation of piperidine 9 with high levels of trans diastereoselectivity and enantiocontrol.

The organ boron reagents are generally non-toxic, at which it contains ring systems are abundant in naturally occurring biologically important compounds as well as drug candidates. In this approach, 2-subsituted O-allyl ethanolamine 11 has been synthesized from NBoc-protected amino alcohol by simple O-alkylation, Boc- deprotection, and Pd-catalyzed N-arylation reactions. For substrate 11 when treated with an external aryl bromide and $Pd(OAc)_2$ catalyst in the presence of NaOtBu base and P(2-furyl)3 ligand under the optimized condition in toluene solvent, cis-3,5- disubstituted morph line derivatives are obtained in good yield and as a single stereoisomer.

3(2H)-Furanone is a substance structural unit of many natural products, 3(2H)-furanone derivatives develop antitumor, ant allergic, antiulcer, anti-proliferative, selective COX-2 inhibitory, and selective MAO-B inhibitory activities. Inagaki, et al. informed that use of substrate 3-ethoxycarbonyl-2-oxopropyldiphenylsulfonium tetrafluroborate (51) in examination forms intramolecular cyclization. As sulfonium salt (51) treat with t-BuOK in THF at room temperature, the desired 3(2H) furanone (52) is obtained in 88% yield. In presence of alkyl halide and same condition give (53) 4-Alkylated 3(2H)Furanones as a product (Scheme13).

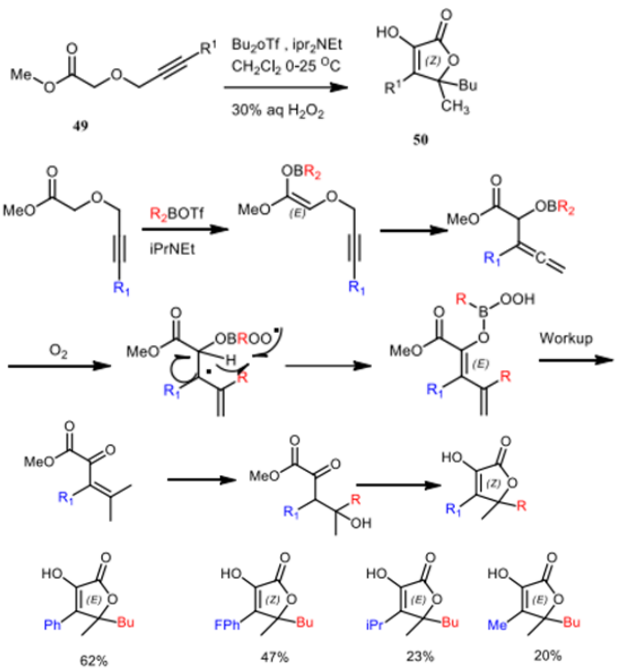
A nickel-catalyzed addition/cyclization of alkyne-nitriles with organoboronic acids, owning the form of highly functionalized 1-naphthylamines in moderate to high yields. On the basis of mechanistic studies, the author proposed a catalytic cycle triggered by Ni(I) species, which is produced by the disproportionation reaction of Ni(0) and Ni(II). By transmetalation of Ni(I) species with arylboronic acid leading to an aryl nickel(I) complex, followed by migratory insertion of carbon-carbon triple bond into Ar-Ni(I) species affords an alkenylnickel(I) intermediate. An intramolecular nucleophilic addition of the alkenylnickel (I) to the cyano group, followed by protonation and tautomerization, will prepared 1-naphthylamines and regenerate the active Ni(I) catalyst. Reaction of o-(cyano) phenyl propargyl ether (54) and arylboronic acid as a model reaction for the optimization of the reaction conditions. Initially, in the presence of $Ni(cod)_2$ and various phosphine ligands such as PPh_3 in 1,4-dioxane at 90°C. However, only make of the desired cyclization product was observed (Scheme 14).

Isoquinoline-1,3-diones are important structural motifs of pharmaceuticals and natural products. Thus, developing convenient methods for the synthesis of such molecules has attracted a great deal of attentions for medicinal and organic chemists. Oxidative decarbonylative carbocyclization of N-alkyl-Nmethacryloylbenzamide (56) with aliphatic aldehydes (57) as the alkyl radical source to generate alkyl-substituted isoquinoline-1,3-dione derivatives (58) in moderate to good yields. This reaction gives better yields with TBHP in toluene at 130°C for 20 h. This reaction is also working with other oxidants such as DTBP, TBPB in various solvents; however the yields obtained were low. Methyl, methoxyl, tert-butyl, trifluoromethyl, methylamino and acetyl were all well tolerated, and the presence of halogen provided potential handles for further functionalization. The reaction is also well tolerable for various aliphatic aldehydes (Scheme 15).

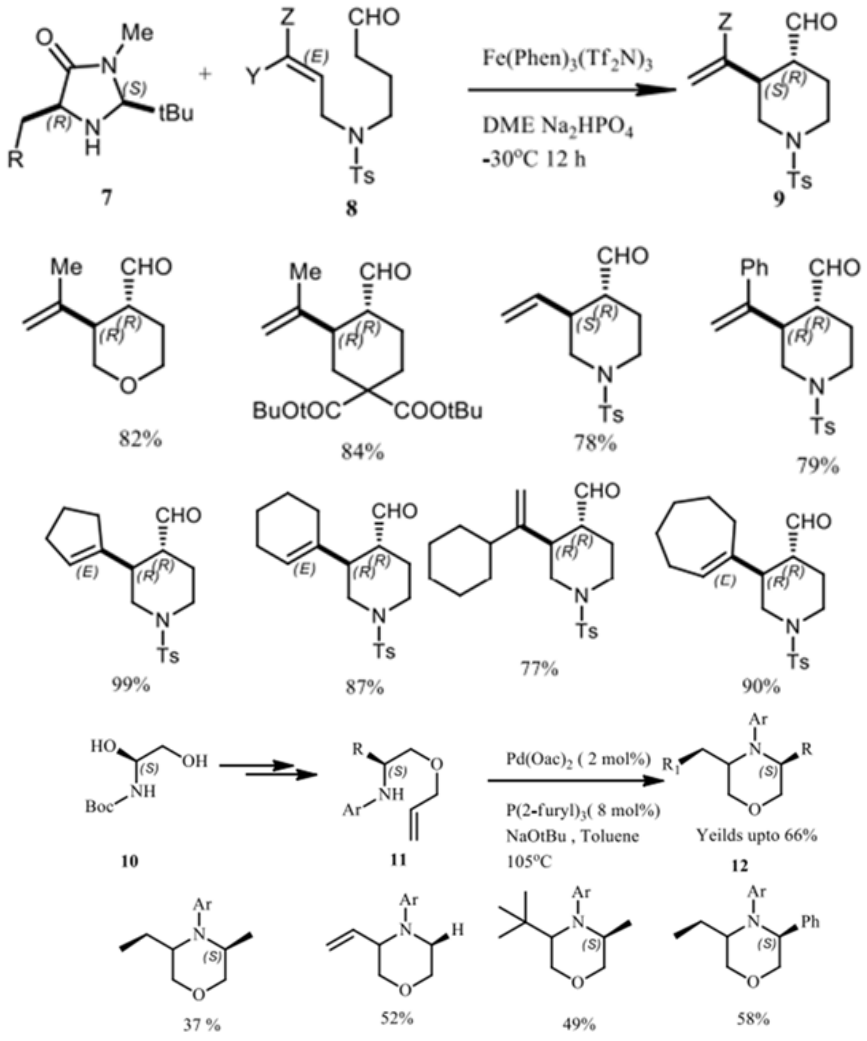
A synthesis of furans that complements the metal-catalyzed intermolecular cyclization approaches. The advantages include easy access to fully substituted furans, mild reaction conditions, and the opportunity to organize both alkyl and aryl substituents on the furan ring. A major distinction of this intermolecular approach from the known intramolecular allene cyclizations is the use of the allene moiety as a two-carbon unit in the construction of five membered ring systems. Debanjan Bakshi and Anand Singh made a report by allenoate (59) reaction with α-iodo-arylketone (60) is consumed using K_2CO_3 as the base. It is discovered that addition of tetrabutylammonium bromide (TBAB) resulted in a higher yield (61) using different solvent (Scheme 16).

O-Quinone met hides (o-QMs) have been well-studied and applied in a variety of transformations during the last few decennary. They are also the key intermediates in a number of biomimetic natural product syntheses, in (4+2) hetero-Diels–Alder reactions. Several way have been developed towards in situ generation of these highly reactive intermediates, and their application in catalytic asymmetric transformations. The first catalytic asymmetric intramolecular (4+2) cycloadditions. Informed that this method allows fast access to a variety of highly functionalized furanochromane and pyranochromane derivatives. Diastereoand enantioselective synthesis *via* kinetic resolution is possible when using racemic chiral dienyl alcohols. The high diastereo- and enantioselectivity observed in this reaction is a result of the activation of orthoquinone met hide intermediate in the confined chiral pocket of IDP catalyst. Alkyl salicyladehyde (62) reaction with alylic alcohol (63) in presence of IDP 5(mol%) in cyclohexane condition to get orthoquinone (64) (Scheme 17).

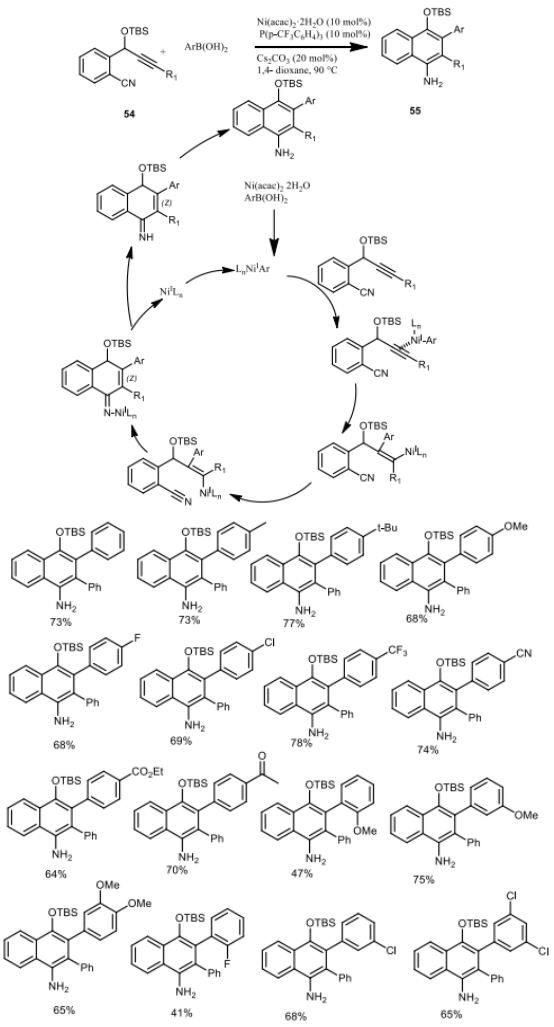
The alkylative semipinacol rearrangement of a kind of TMS safe α-styrenyl substituted cyclic alcohols with unactivated bromoalkanes that unite photoredox and Au (I)/Au (III) catalysis has been achieved. This redox neutral rearrangement is marked by a dimeric Au (I) photocatalyst that plays two roles; photo-redox activation of bromoalkanes and Au(III)-mediated semipinacol rearrangement coupled with $C(sp^3)$-$C(sp^3)$ reductive elimination; a reaction mode ever obtained. This process displayed an Au(III)- treat coupling of the starting materials rather than a polar radical crossover triggered semipinacol rearrangement pathway. That the photo redox reaction of α-styrenyl substituted cyclic alcohol (65) with cyclohexyl bromide and ethyl bromoacetate provided the semipinacol rearrangement products in 27%-67% yields. Used without silyl protection since degradation occurred in presence of the TMS group. When the unprotected version was used, the desired products 66fa and 66fc were obtained in a diastereomeric a ratio of 2:1 in 57% and 53% yields (Scheme 18).



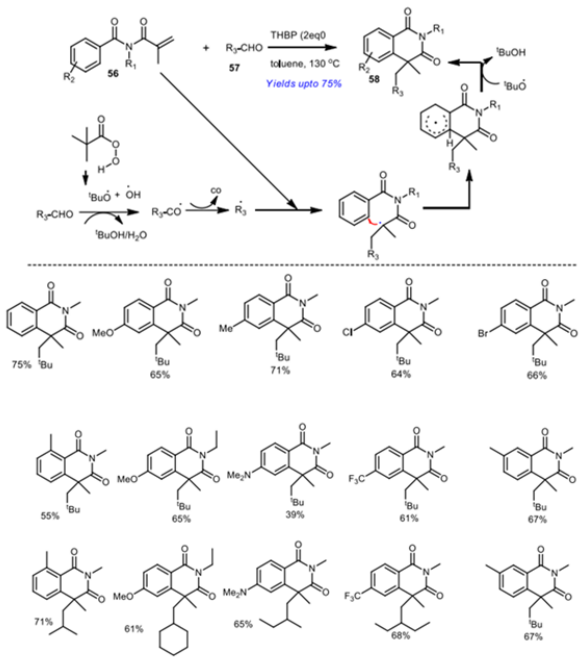
Scheme 12: Synthesis of substituted 3-hydroxy-2-furanone derivatives *via* unusal enolate alkylative cyclization.



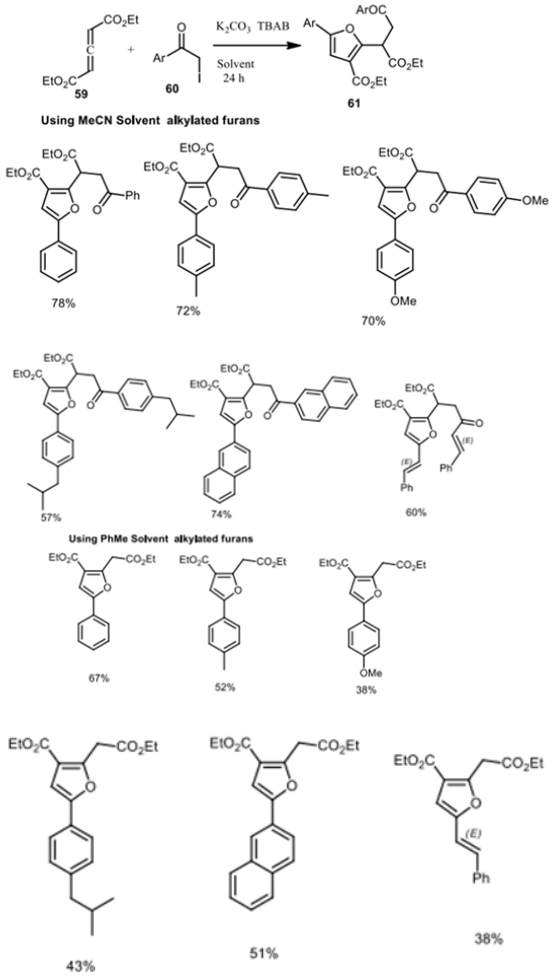
Scheme 13: Synthesis of substituted 3(2H)-furanones using alkylative intramolecular cyclization of sulfonium salts.



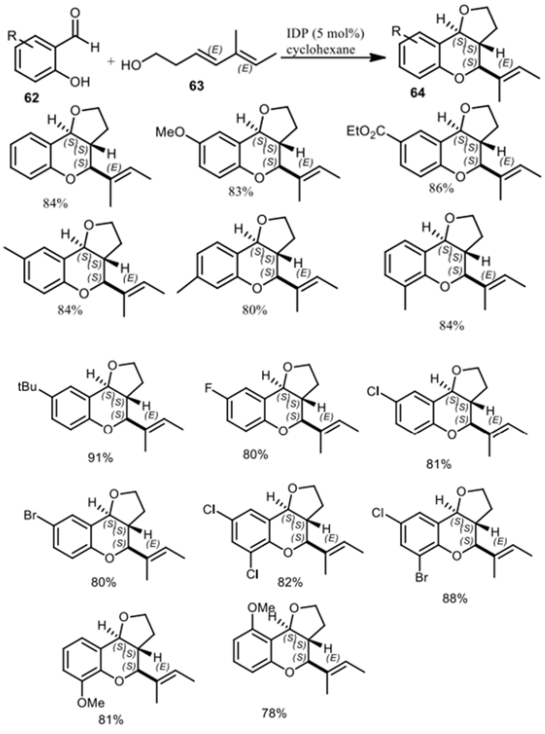
Scheme 14: A nickel-catalyzed addition/cyclization of alkyne-nitriles with organoboronic acids.



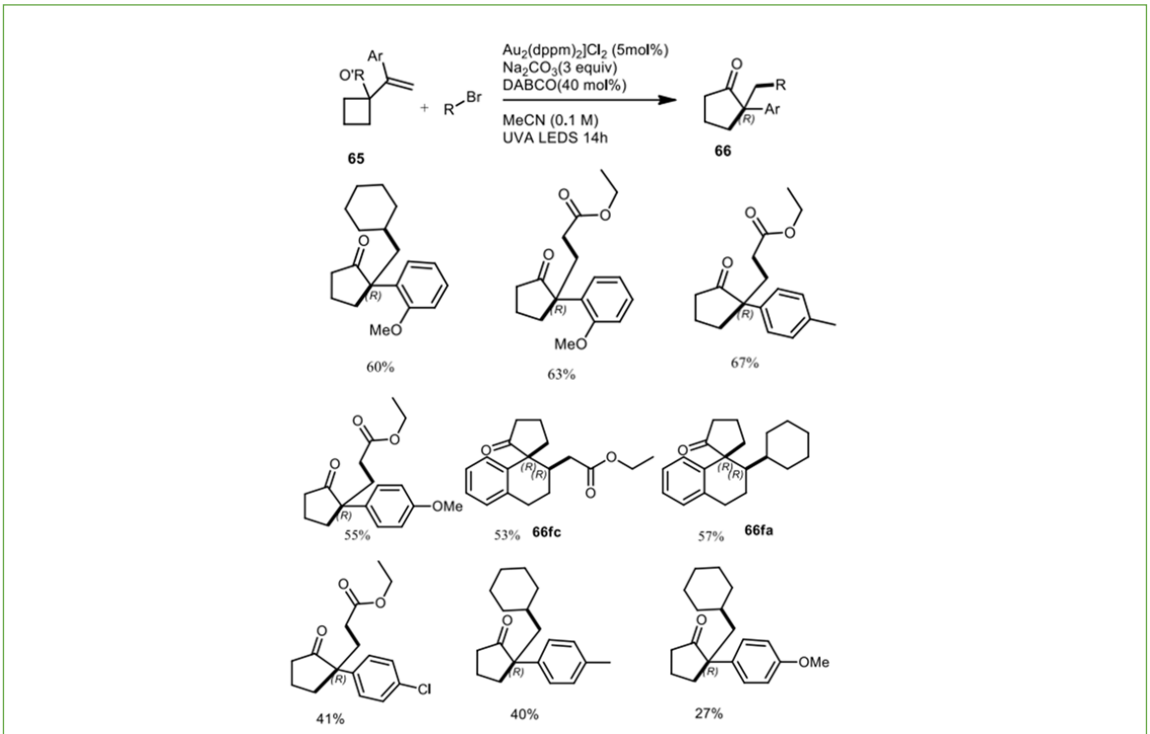
Scheme 15: Isoquinoline-1,3-diones are important structural motifs of pharmaceuticals and natural products.



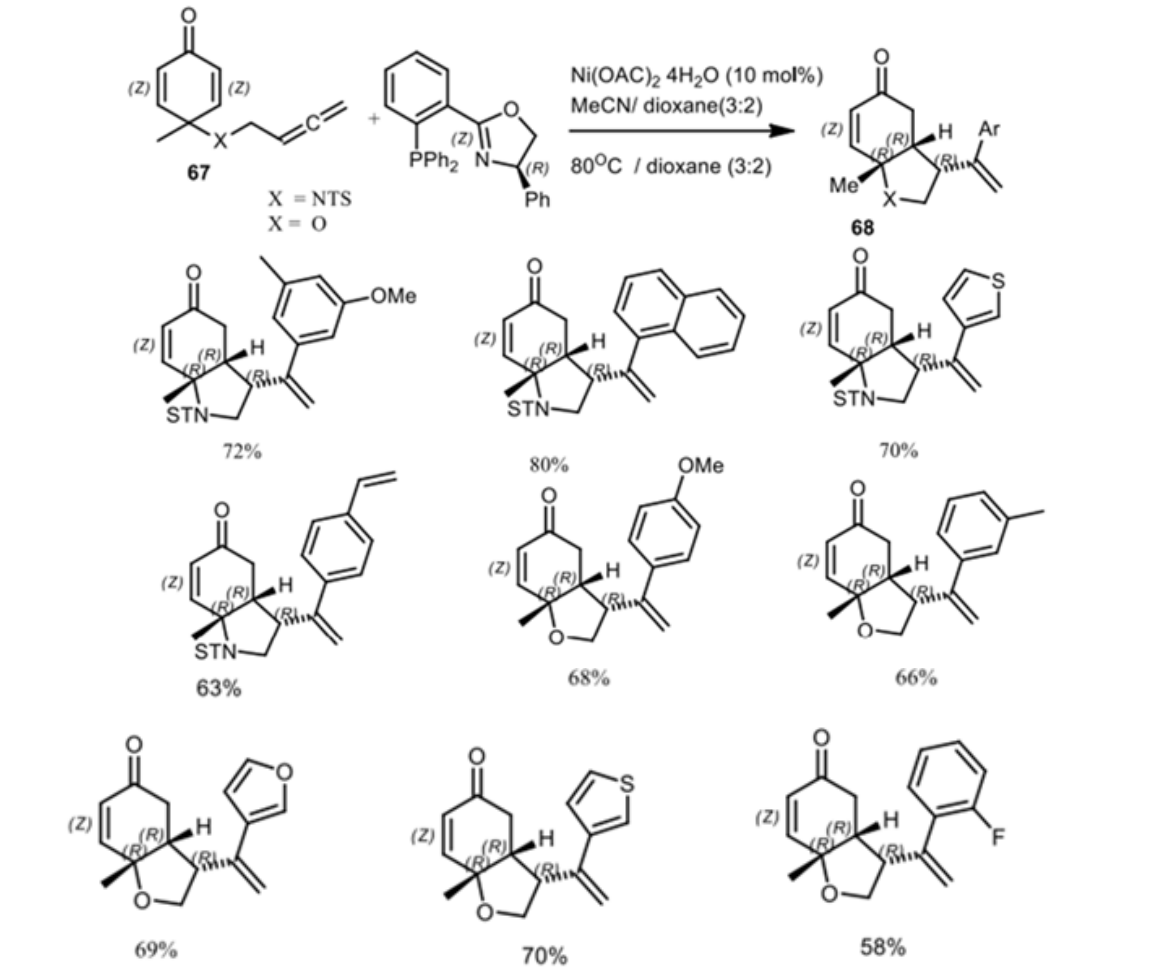
Scheme 16: Synthesis of furans that complements the metal-catalyzed intermolecular cyclization.



Scheme 17: First catalytic asymmetric intramolecular [4+2] cycloadditions of o-QMs.



Scheme 18: Alkylative semipinacol rearrangement of a kind of TMS safe α-styrenyl substituted cyclic alcohols.



Scheme 19: The enantioselective nickel-catalyzed desymmetrization of allenyl cyclohexa-2,5-dienones by reaction.

The enantioselective nickel-catalyzed desymmetrization of allenyl cyclohexa-2,5-dienones by reaction with arylboronic acids is drawn. Nickel-catalyzed arylation of the allene gives ally nickel species, which undergo cyclization by 1,4-allylation to yield hexahydroindol-5-ones and hexahydrobenzofuran-5-ones with three contiguous stereo enters in high diastereo- and enantioselectivities. Catalytic enantioselective 1,4-additions of organometallic reagents to electron-imperfect alkenes are important reactions for the formation of new carbon–carbon bonds. The catalytic enantioselective 1,4-addition of alylic nucleophiles remains considerably underdeveloped. Allenylcyclohexa2,5dienone(66) With $PhB(OH)_2$ (2.0 equiv).and $Ni(OAc)_24H_2O$(10mol%) in MeCN / dioxane (3:2) at 80°C for 18 h satisfied to observe that 6,5-bicycle(67) was obtained in 35% ^1H NMR yield (Scheme 19).

The external challenges joined with a strong basicity of organometallic reagents on the one hand, and a lower reactivity of stabilized carbon nucleophiles, such as Enolate, toward non-conjugate cyclopropenes on the other hand, has limited the application of this chemistry. Within this goal, the addition of strongly nucleophilic organometallic reagents to cyclopropenes has been known Base-helped dehydrohalogenation/5-exo-trig nucleophilic cyclization of stabilized benzyl anions to cyclopropenes was found out. This reaction represents the first example of the non-catalytic addition of carbon nucleophiles to unactivated cyclopropenes. The got results are valuable as a proof of concept and are being applied in design of the diastereoselective cyclization of carbon-based nucleophiles to obtain six- and seven-membered ring systems. N- benzyl amides reaction with 18-crown-6 in presence of base and THF solvent get cyclopropenes (Scheme 20).

This particular review article, established the fact that thiophene derivatives could be a rich source of potential entities in search of new generation of biologically active compounds and be worthwhile to explore the possibility in this area by fusing differently substituted moieties which may result in better pharmacological activities. Thus the quest to explore many more modifications on thiophene moiety needs to be continued. In 2018 Rashmi Shah and Prabhakar Kumar Verma central chemical journal (2018) 12:137 described that Synthesis of thienopyrimidines and triazolothienopyrimidines derivatives using 2-Amino-6-methyl-4,5,6,7-tetrahydro-benzo-[b]thiophene-3-carbonitrile react with $HCONH_2$ as a product 7-Methyl-5,6,7,8-tetrahydro[1] benzothieno[2,3-d]pyrimidin-4-amine (Scheme 21).

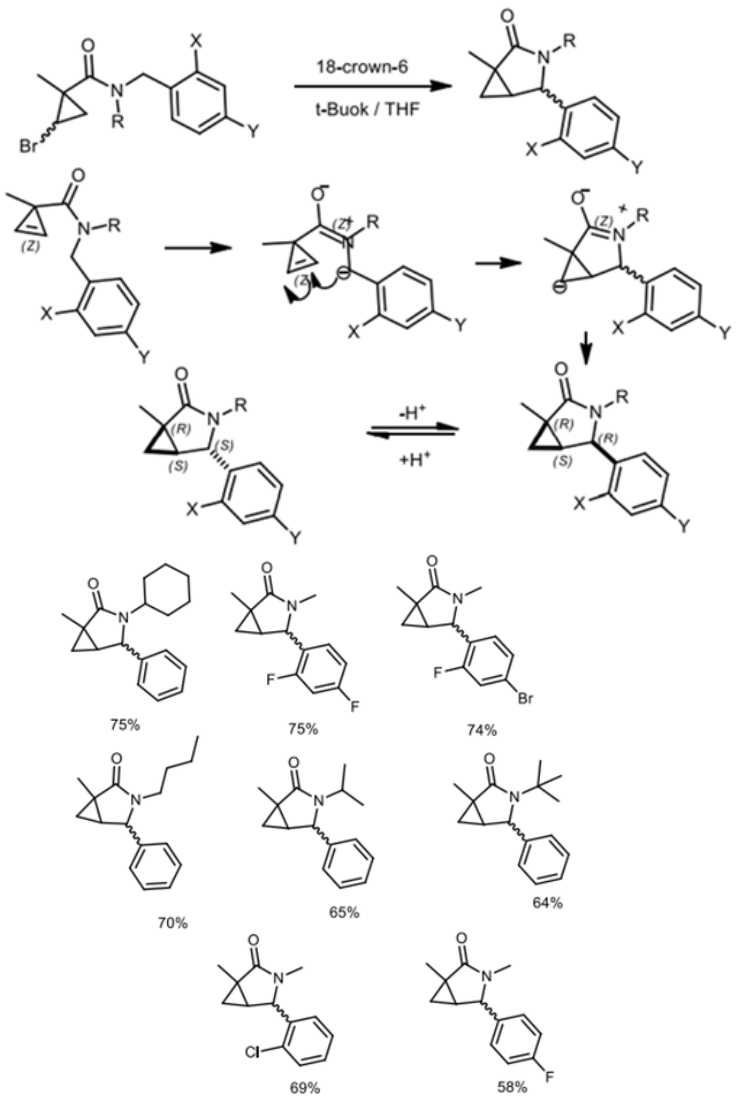
The importance of the amide linkage and the selectivity of the6-endo-trig over 5-exo-trig cyclization pathway were well understood to apply light on further design and application of these radical cyclization reactions .Xiangtan University, Hunan, 411105, PR China reported that N-methyl N-phenylcinnamamide (69, 0.2 mmol, 1 equiv), $Fe(acac)_3$ (0.04 mmol, 20 mol%) and isoalkylraldehyde (0.8 mmol, 4 equiv) in chlorobenzene (1.0 ml) at ambient temperature, then DTBP (0.6 mmol, 3.0 equiv) added with vigorous stirring under argon atmosphere. The reaction mixture is formed at 110°C (oil bath temperature) for 12 h. The resulting mixture is cooled to room temperature, transferred to silica gel column directly and purified by column chromatography with a mixture of EtOAc in petroleum ether as eluent to give the pure product (70). Again the presence of electron withdrawing group same condition gets high yields. Fe-catalyzed dicarbonyl active cascade reaction of N-aryl cinnamamides with aliphatic aldehydes to provide C_3 alkylated 3,4-dihydroquinolin-2(1H)-ones With DTBP playing a double role of a radical initiator and a terminal oxidant, readily available aliphatic aldehydes were decarbonylated into 1°, 2° and 3° alkyl radicals for the cascade construction of $C(sp^3)$–$C(sp^3)$ and $C(sp^3)$–$C(sp^2)$ bonds (Scheme 22).

1,3-dicarbonyl compounds as efficient nucleophiles, further transformations of o-NQMs with αmethylene ketones are tested. Both acyclic and cyclic 1,3-dicarbonyl compounds could serve as two carbon components to afford the benzo[f]chromenes 4b in 51-62% yields *via* 1,4-conjugated addition/condensation cascade. The generation of the o-NQMs was supported by its self-dimerization in the absence of nucleophiles at lower temperature, which indicates that nucleophiles somehow poisoned the catalyst and higher temperatures were required to assist the circulation for the 1,4-addition process (Scheme 23).

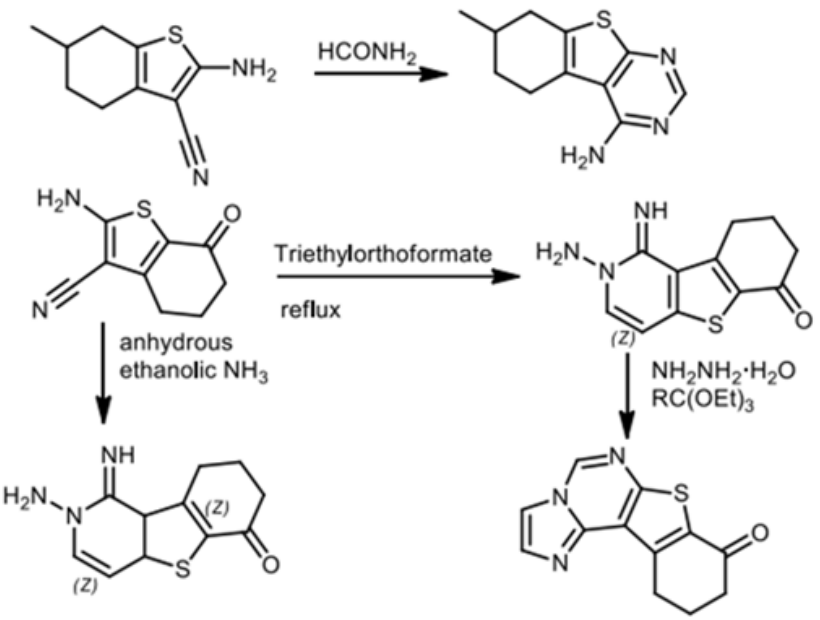
Ni-catalyzed hydroborylative cyclization reaction that gives one C-C and one C-B bond in a single operation, and have proposed a reasonable reaction mechanism. The reaction provides homoallylic- or alkenylboronates, the regioselectivity depending on the substitution of the alkyne. The formation of carbo- and heterocyclic in a single step, smooth conditions, with an inexpensive catalytic system and full atom economy. Experimental and computational results suggest that the reaction involves a Ni(0)-Ni(II) catalytic cycle, initial oxidative cyclometalation on the enzyme coordinated to Ni(xantphos). A following possible metathesis reaction, followed by reductive elimination explains the formation of the final boronates. They reported that Catalysis Science and Technology Royal society, the reaction between 1,6- enzyme(71) and HBpin in the presence of $Ni(cod)_2$ and several ligands. The use of xantphos afforded the corresponding alkylboronate as the major reaction product, although in low yield (25% yields). After extensive the best reaction conditions comprise the use of $Ni(acac)_2$ (5 mol%) and xantphos (5 mol%) in toluene at room temperature. However, when we extended the reaction to a wide variety of different substrates containing an aryl ring on the alkyne, much better yields were obtained (74%) (Scheme 24).

Tri- and tetra-substituted alkenes are widely present in many biologically and pharmacologically active molecules, including tamoxifen, isovirescenol A, brasilenol and Guadalupe. In 2020 Wenfeng Liu and Wangqing Kong announcement that Ni-catalyzed intermolecular reductive carbonic elation of ohalophenyl ketones with alkynes using Zn power as reducing agent, providing an efficient route to functionalized indenol derivatives. Oxidative addition of aryl halides to nickel(0) species, followed by migratory insertion of alkynes into the Ni-Ar bond affords alkenyl nickel intermediate. Intramolecular nucleophilic addition of alkenylnickel to the carbonyl, followed by transmetalation with zinc halide, delivers the indenol product upon hydrolysis (Scheme 25).

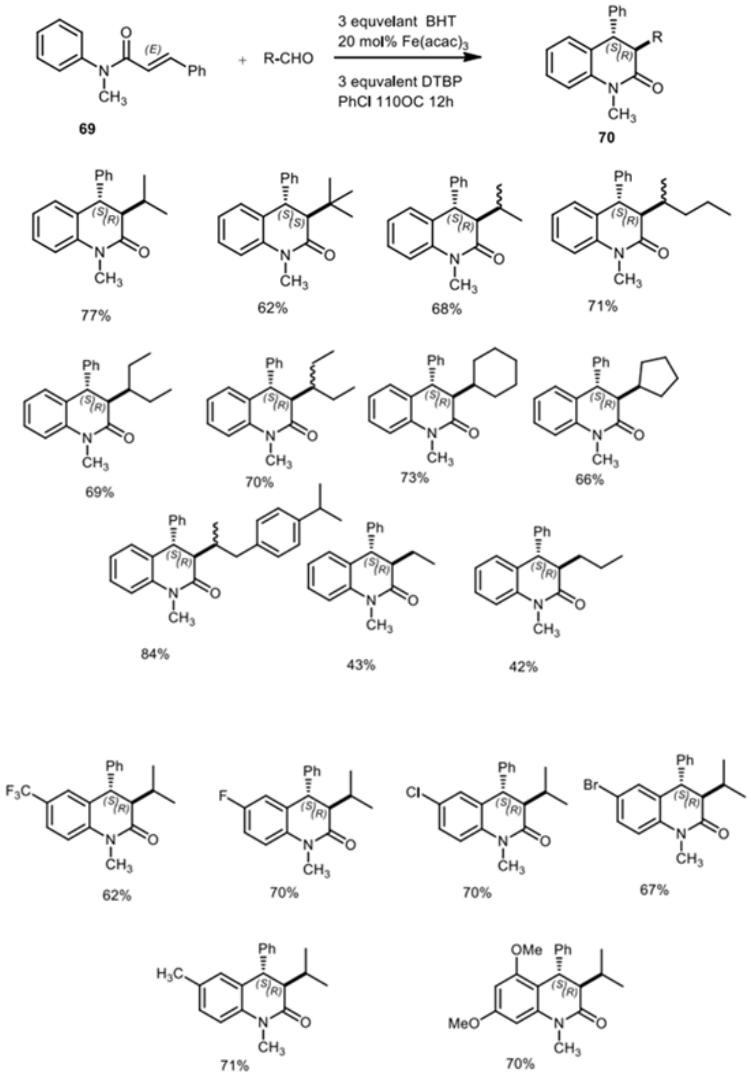
γ,δ unsaturated aryl or alkyl oxime esters oxime ester (73) as the model substrate and B_2pin_2 as a nucleophile to optimize the reaction conditions evaluate a series of reaction parameters, identified that the reaction can afford the desired α(borylmethyl)pyrrolidine 3a in 89% isolate yield by using CuCl (10 mol%) and XantPhos (10 mol%) as the catalytic system, MeOLi (2.5 equiv.) as the base in THF at 50°C for 20 h. A copper-catalyze intermolecular boronation and intramolecular amination of γ,δ -unsaturated aromatic oxime esters with B_2pin_2. A range of α -(borylmethyl) pyrrolidine derivatives were obtained in moderate to excellent yields under mild conditions. The protocol provides an efficient method for the synthesis of useful boron modified pyrrolidinium compounds and mean while guides a new direction for constructing the functionalize indoles (Scheme 26).



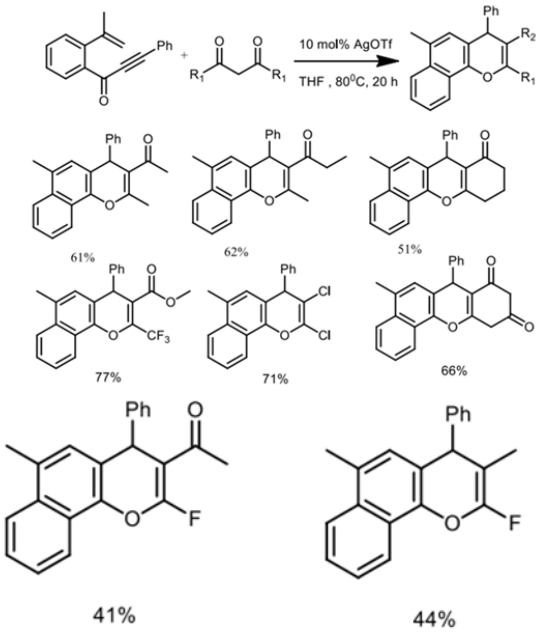
Scheme 20: Dehydrohalogenation /5-exo-trig nucleophilic cyclization of stabilized benzylic anions to cyclopropenes.



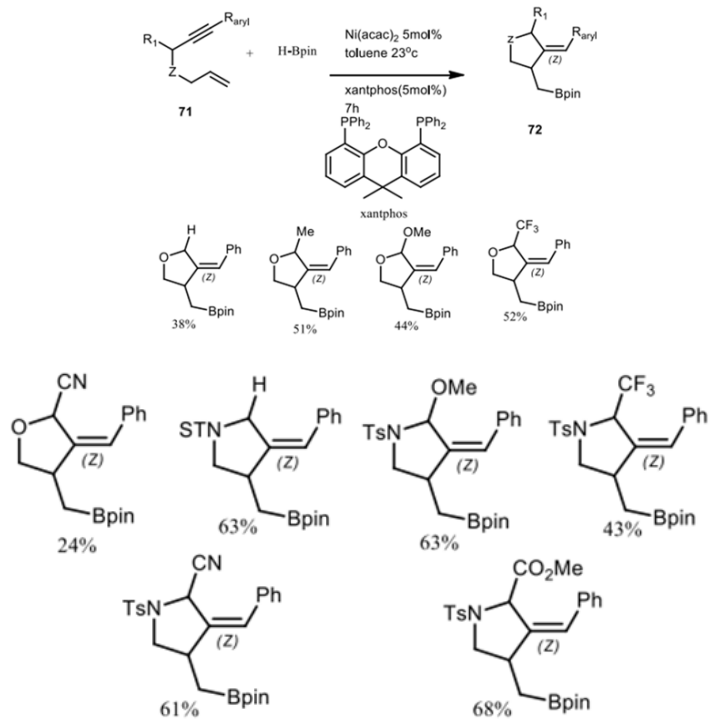
Scheme 21: Synthesis of thienopyrimidines and triazolothienopyrimidines.



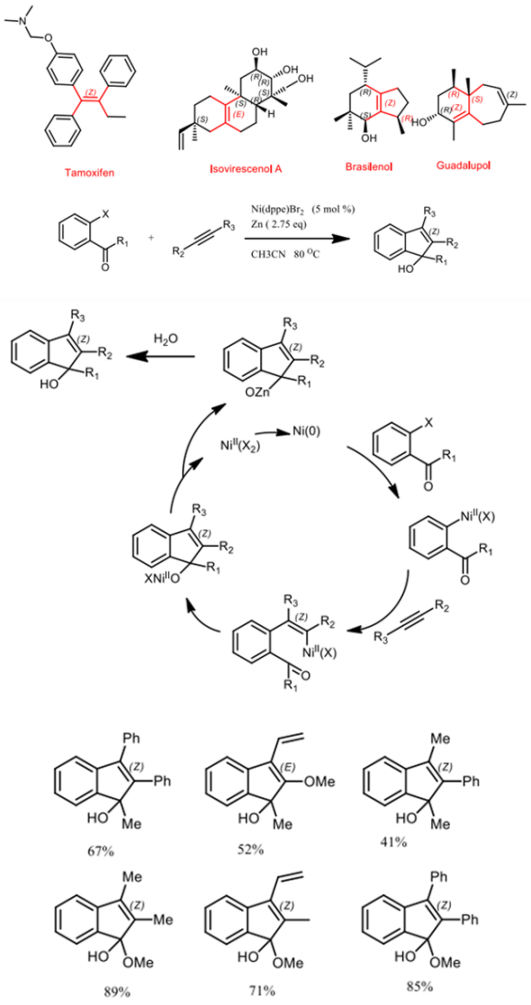
Scheme 22: The amide linkage and the selectivity of the6-endo-trig over 5-exo-trig cyclization.



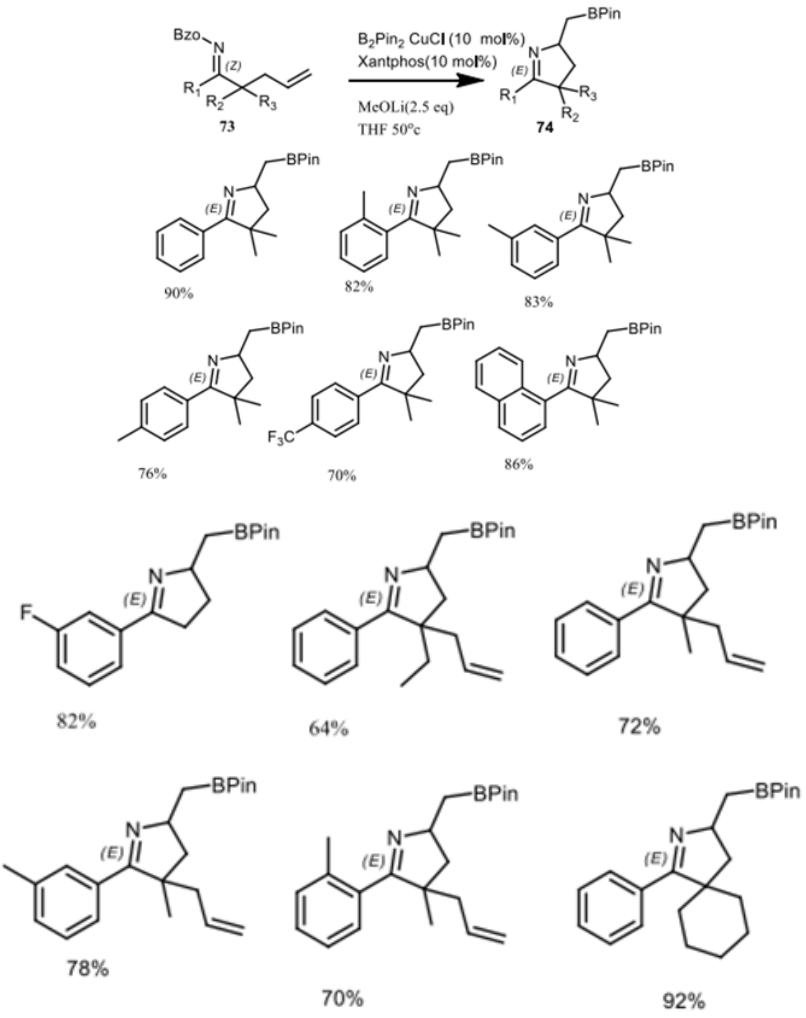
Scheme 23: o-NQMs with α-methylene ketones.



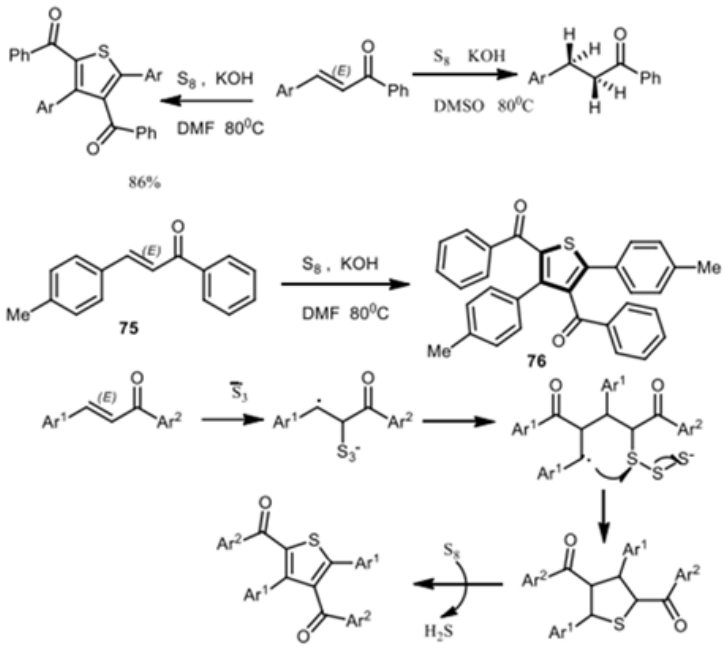
Scheme 24: Ni-catalyzed hydroborylative cyclization reaction that gives one C-C and one C-B bond in a single operation.



Scheme 25: Ni-catalyzed intermolecular reductive carbonic elation of ohalophenyl ketones with alkynes.

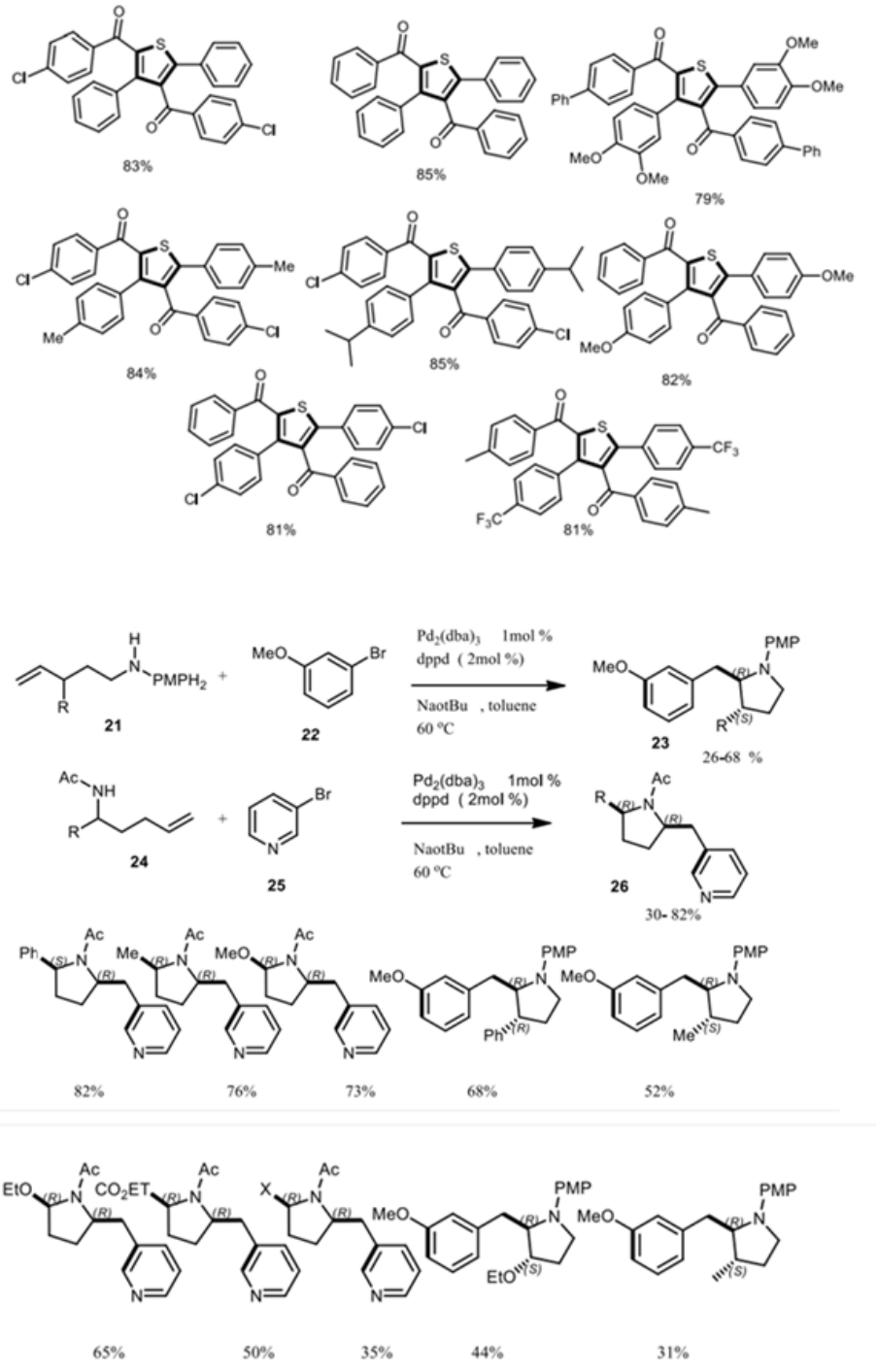


Scheme 26: γ,δ unsaturated aryl or alkyl oxime esters oxime ester.



Scheme 27: Cascade cyclization versus chemo selective reduction: a solvent controlled product divergence.

A novel and suitable controllable fall cyclization as well as partial reduction of enones for divergent construction of two types of valuable compounds including polysubstituted thiophenes and saturated ketones from identical starting materials under exceptionally mild reaction conditions. A simple and skilled strategy for assembly of polysubstituted thiophenes as well as chemo selective reduction of α, β-unsaturated ketones *via* reactions of enones with elemental sulfur and by simple switching the reaction solvent is described. Mechanistic studies revealed that both reactions proceeded *via* radical paths and two hydrogen atoms came from H_2O in the reduction course and the reaction of chalcone 1a with elemental sulphur as the model reaction. When substrate 1a was reacted with elemental sulphur (2.0 eq.) in the presence of KOH (1.0 eq.) in DMSO for 5 h, selective reduction of chalcone ensued to afford 2a and 3a as product but when it presence of K_2CO_3 and presence of DMF reduce the double bound (Scheme 27).



Scheme 28: Solvent controlled product divergence.

The use of a carbo amination reaction for the first time for the stereo selective synthesis of substituted pyrrolidine derivatives *via* Pd-catalyzed intermolecular N-alkylation followed by intramolecular cyclization reaction sequences. The reaction proceeds *via* a innersphere mechanism with the formation of the Pd(Ar)(NRR0) complex. In this reaction, a g- (N-arylamino) alkene is treated with an aryl or heteroaryl bromide in the presence of NaOtBu as the base and Pd catalyst; the corresponding 2,3- or 2,5-disubstituted pyrrolidine derivatives are obtained in good yields and excellent diastereoselectivity.

Application

a) Alkylative cyclisation reaction is chemical synthesis of many heterocyclic compounds by using biologically activity compounds and pharmaceuticals.

b) This reaction has been involved in synthesis of natural products.

c) It is very important in synthetic of the addition of carbon radicals to N- arylcinnamides and subsequent ipso-cyclization synthesis of azaspiro-compounds.

d) Synthesis of heterocyclic compound by using alkylative cyclisation.

CONCLUSION

Alkylative cyclisation reaction using in Chemically and catalytic cyclisation of alkenes, alkynes, heterocyclic compounds, catalytic cross coupling and aryl cyclisation have become instrument for the construction of C-N, C-C, C-O etc. bond in organic chemistry as the aromatic compounds are becoming industrially significant for library generation in drug discovery, pharmacy chemistry, application in medicinal chemistry and natural product synthesis. The synthetic approaches to form natural products and aromatic like compounds by using alkylative cyclisation processes under mild reagents, base and high temperature reactions condition were summarized in this review .

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