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Review

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The recent applications of zinc and its compounds in coupling reactions

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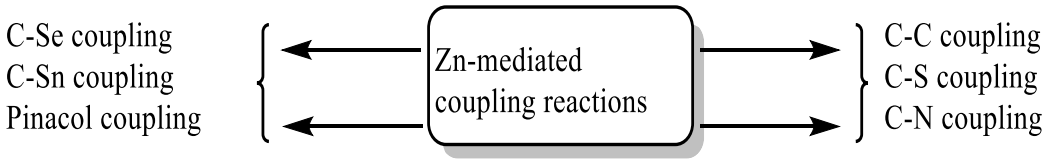
Abstract

The coupling reactions are powerful tools for the fabrication of C-C bonds in natural products. Several synthetic methods were used for this purpose. Metal-based coupling reactions, such as metal-catalysed or metal-mediated coupling reactions, were developed for C-C bond formation. Metallic zinc is an essential element in biological systems. In addition, it is a harmless, low-cost, easily available, and environmentally friendly metal. In this review, we focus on the Zn-mediated coupling reactions in which zinc only promotes the reaction instead of serving as a catalyst. These reactions are extensively applied in the construction of C-C bonds in natural products.



Keywords: Alkyl halides, coupling, sulphones, synthesis, zinc-mediated

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1. Introduction

The C-C coupling reactions are widely used in the field of pharmaceuticals and are powerful tools to synthesise natural products. Many synthetic methodologies were devised to construct carbon-carbon bonds, including reactions like Peterson olefination,[1] Wittig reactions,[2] Horner-Emmons-Wadsworth reaction,[3] Julia olefination,[4] etc. The metal-catalysed coupling reactions such as Negishi,[5,6] Suzuki,[7] Heck,[8] Sonogarshira,[9] Stille,[10] Kumada,[11,12] Hiyama,[13] Cadiot-Chodkiewicz,[14] Buchwald-Hartwig,[15] Fukuyama[16] coupling etc. also led to the C-C bond formation. When coupling reactions are mediated by metals to improve the yields of the products, they are referred to as metal-mediated coupling reactions. Herein, we focus on the Zn-mediated coupling reactions.

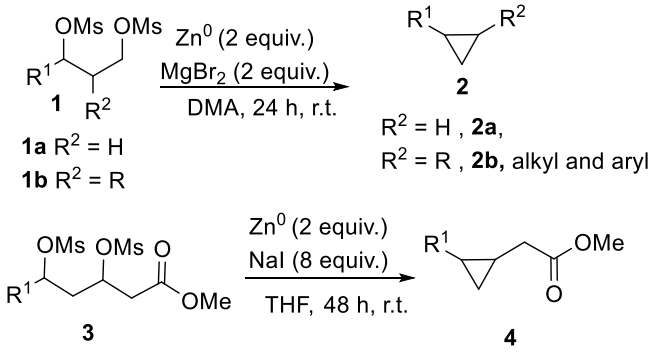
The metallic zinc shows a variety of special features, such as being inexpensive, environment-friendly, harmless, easily available and, furthermore, an essential element in human body.[17] Infection susceptibility, growth retardation and retardation in sexual maturation were the symptoms of the zinc deficiency.[18] Chemically, zinc acts as a reducing agent and it has a tendency to form stable compounds with sulphur as well as nitrogen donors. In 1848, diethylzinc was initially developed; since then it has been used in a number of synthetic transformations.

The zinc-mediated coupling reactions are one of the well-known reactions that can be used for the formation of C-C, C-Se, C-S bonds. Due to this, these reactions play an important role in synthetic organic chemistry. The zinc mediated coupling reactions are simple reactions that required mild reaction conditions, a short reaction time and also provided the resultant products in high yields.[19] Usually, zinc-mediated coupling occurs at room temperature.

This review focuses on the current achievements in the zinc-mediated coupling reactions and covers literature till the year 2023. The topic is classified based on the nature of the bond formed.

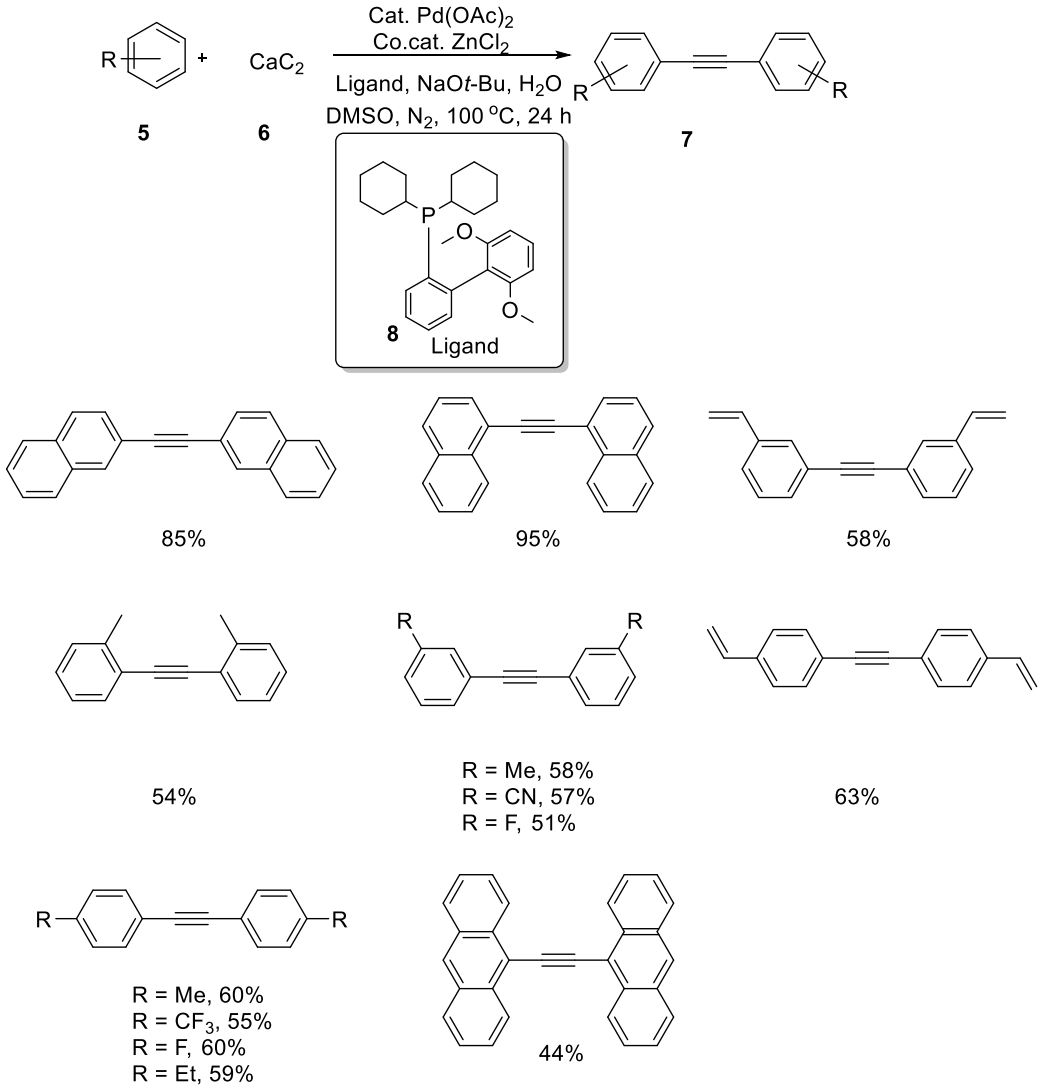
2. C-C Coupling Reactions

For the late-stage modification of statin agents and natural products, the aryl or alkyl cyclopropane was synthesised via Zn-mediated CEC (cross electrophile coupling) reaction as reported by Jarvo *et al*.[20] Monosubstituted 1,3-mesylates **1a**, 1,2-disubstituted 1,3-mesylates **1b**, and polyketide frames were used in the coupling reaction for the generation of cyclopropanes (Scheme 1). **1a** underwent the reaction in the presence of 2 equiv. of Zn(0) and 2 equiv. of $MgBr_2$ in DMA for 24 h at room temperature to yield monosubstituted cyclopropane **2a**. The 1,2-disubstituted alkyl or aryl cyclopropane **2b** was obtained from **1b** under the same reaction conditions. Furthermore, the authors also demonstrated the synthesis of the resultant product **4** by using this strategy. This synthetic methodology became more appealing due to the mild reaction conditions that tolerated functional groups such as amides, esters, alkenes, and heterocycles. A scale-up synthesis of compound **2** could be achieved using the developed protocol, as 400 mg of **1**, 3-dimesylate gave 87% of the expected product.



Scheme 1. Synthesis of substituted cyclopropanes via Zn-mediated coupling reaction.

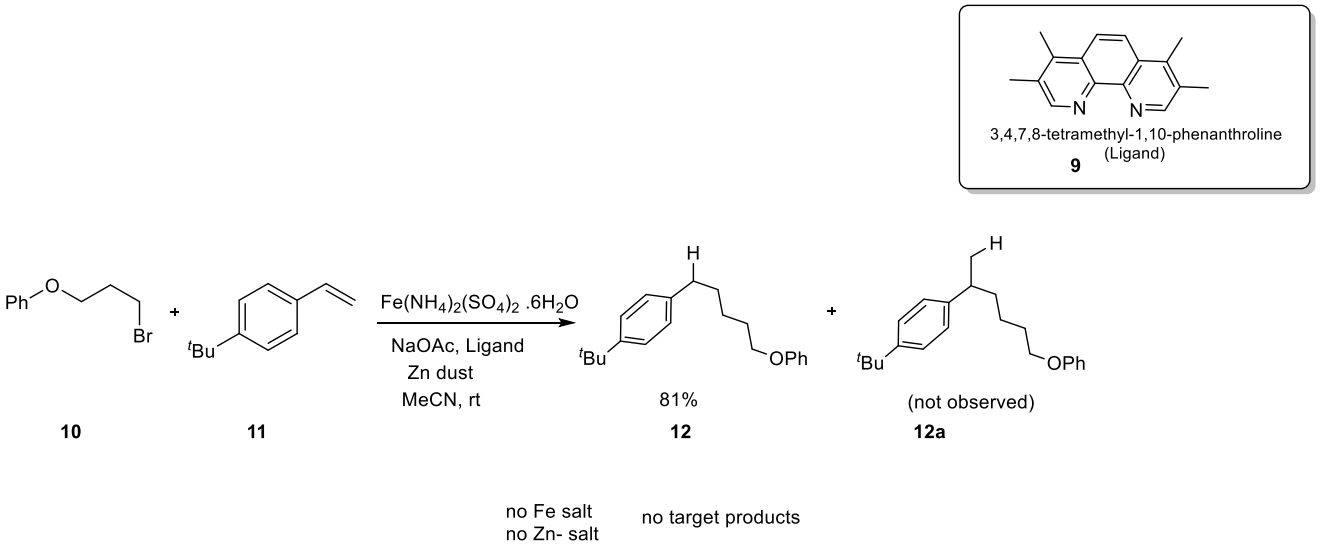
The $ZnCl_2$-promoted palladium-catalysed coupling reaction was carried out between aryl chlorides and calcium carbide for the synthesis of diarylethynes.[21] A variety of diarylethynes **7** were synthesized using a zinc chloride-mediated coupling reaction of CaC_2 **6** with aryl chlorides **5** in dimethyl sulfoxide solvent for 24 h in the presence of $Pd(OAc)_2$ catalyst, dicyclohexyl(2',6'-dimethoxy-[1,1'-biphenyl]-2-yl)phosphane ligand **8** and NaO^t-Bu base at 100 ^oC under N_2 atmosphere. The substrate scope studies revealed that the electron-releasing substituents (methyl, naphthyl, ethyl etc.) on aryl chlorides provided the expected product in good to excellent yields. The aryl chlorides bearing electron-withdrawing groups like F^-, CN^-, CF_3 etc. also tolerated the coupling reaction, providing the desired product in moderate to good yield. Naphthalene derivatives gave excellent yields of the coupled product while sterically crowded substrate, 9-chloro anthracene gave only 44% yield. Reasonable yields were obtained with vinyl group substituted chloro benzene derivatives (Scheme 2).



Scheme 2. The synthesis of diarylethynes via Pd-catalyzed zinc chloride-mediated coupling reaction.

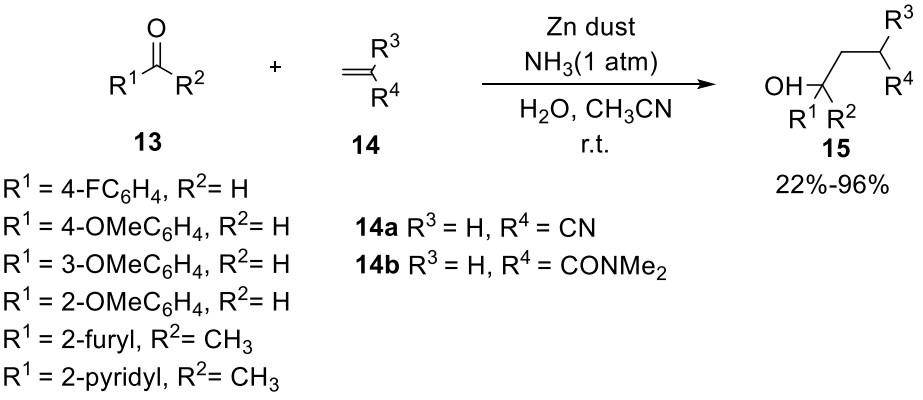
4-*t*-Butylstyrene **11** underwent iron and Zn-promoted reductive coupling reaction with (3-bromopropoxy) benzene **10** in micellar aqueous medium.[22] Li *et al.* carried out a theoretical study utilizing the density functional theory (DFT) calculations for identifying a catalytic mechanism and the source of regioselectivity of these transformations (Scheme 3). According to the study, the reaction barriers are enhanced when zinc or iron are used alone, but their combination lowers the barriers. Additionally, the preferred regioselectivity of C-C coupling with carbon of 4-*tert*-butyl styrene at the β-position rather than its α-carbon is due to a lower distortion energy.

The ϒ-hydroxy esters, ϒ-hydroxy nitriles, ϒ-hydroxy ketones, ϒ-hydroxy sulfones, and ϒ-lactones are the ϒ-hydroxybutyric acid derivatives (GHBA) that are ϒ-aminobutyric acid's metabolites (GABA). These compounds are utilized to cure cataplexy disease. The synthesis of such compounds (ϒ-hydroxybutyric acid derivatives) **15** was accomplished by a Zn-promoted ene-carbonyl reductive coupling of carbonyl compounds **13** with alkenes **14** in the presence of a Zn/NH_3 reagent.[23] The substrate scope studies conducted using a wide range of activated alkenes and aldehydes or ketones afforded the expected products in 22-96% yield (Scheme 4).

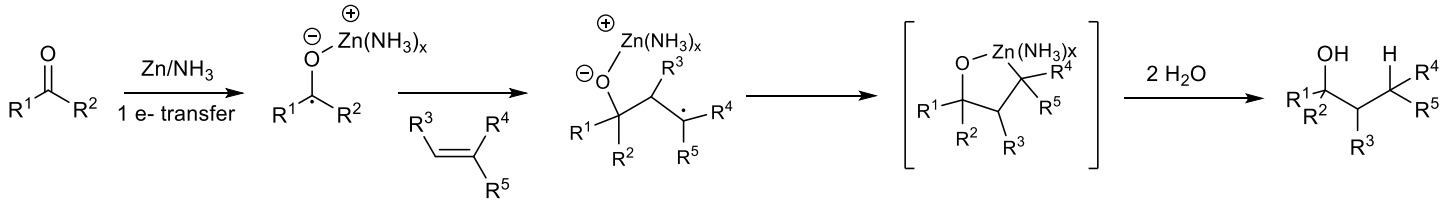


Scheme 3. Fe-catalyzed Zn-promoted reductive coupling reaction of (3-bromopropoxy)benzene with 4-*tert*-butyl styrene.

The studies extended to heterocyclic ketones and aldehydes gave the corresponding desired products in reasonable yields. The acrylonitrile under reducing conditions with 4-benzoylpyridine afforded 70% yield of the unexpected amide product. In the mechanism, a zinc ketyl radical is formed when the zinc-ammonia catalytic system transfers one electron to the carbonyl group. Then, a five membered zincacycle is produced by adding this radical to an olefin substrate and continuing the reduction process. Finally, the reductive coupling product is obtained by protonation (Scheme 5).

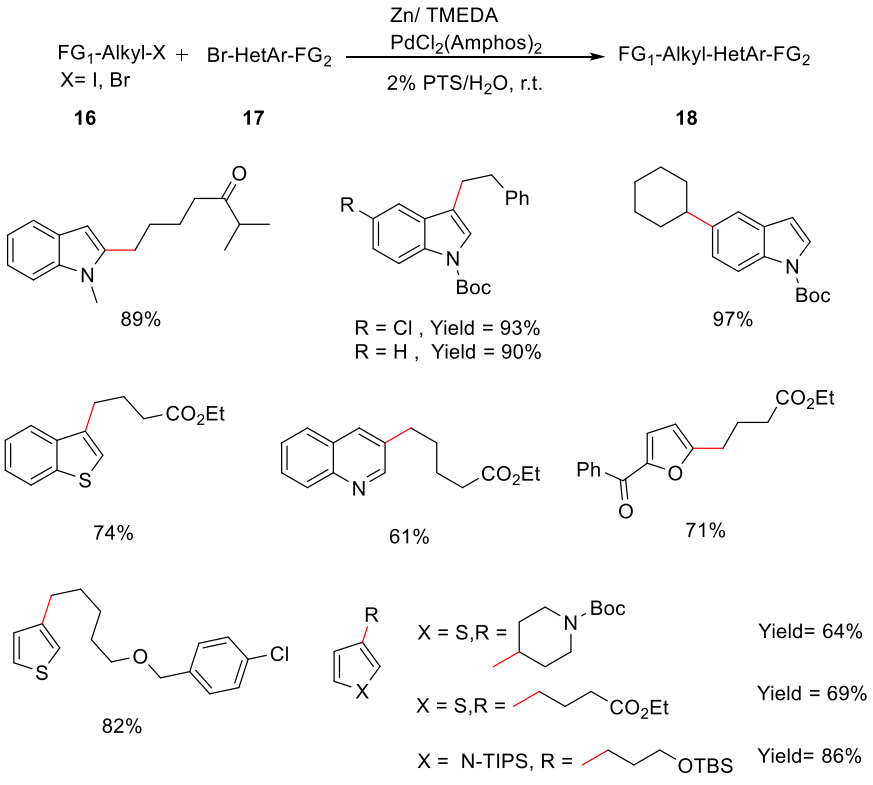


Scheme 4. The synthesis of ϒ-hydroxybutyric acid derivatives via Zn/NH_3-promoted ene-carbonyl reductive coupling reaction.



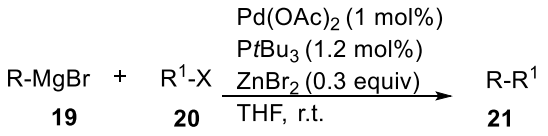
Scheme 5. The proposed mechanism of the reaction. *Reproduced with permission from [23].*

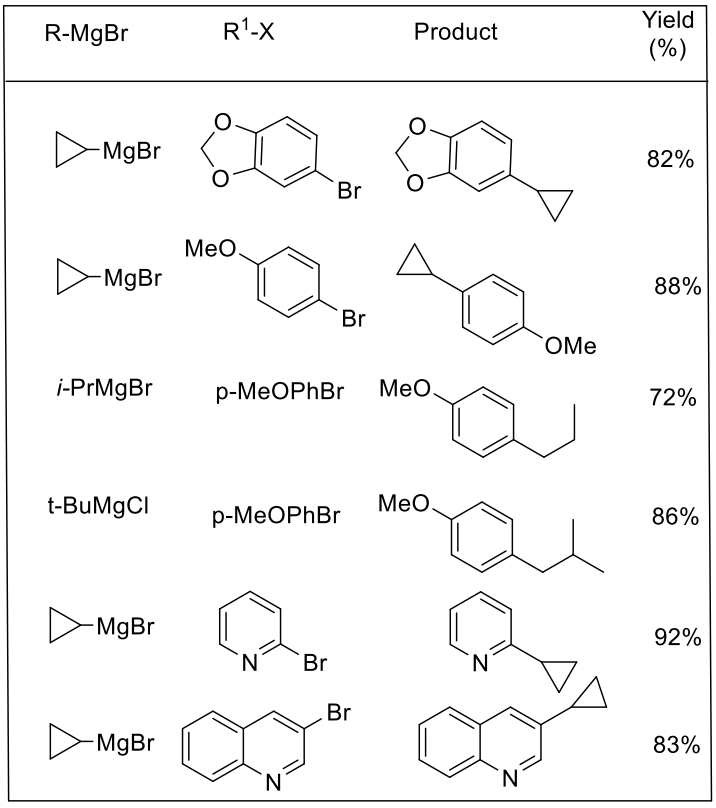
Lipshutz and co-workers demonstrated the zinc-mediated palladium-catalysed coupling reaction between heteroaromatic bromides and alkyl halides at room temperature (Scheme 6).[24] The metallic Zn was selectively inserted into the sp^3 C-X bond during the oxidative addition of Pd to the sp^2 carbon bond. The use of polyoxyethanyl α-tocopheryl sebacate (PTS) as the surfactant increased the rate of the coupling reaction. The substrate scope study of the cross-coupling reaction using various alkyl halides and heteroaromatic bromides showed that the aromatic ring bearing alkyl halides and aliphatic ketones, esters, ethers, boc, benzyl and TBS-protected hydroxyl groups were well tolerated during the reaction. Heterocyclic compounds such as pyrrole, indole, thiophene, benzo[*b*]thiophene, quinolone derivatives, furan etc. were coupled smoothly with functionalized 1° and 2° alkyl halides. Furthermore, the lipophilicity of the nucleophile enhanced the formation of the expected product under the developed condition.



Scheme 6. The substrate scope study of Zn-mediated palladium-catalysed coupling of heteroaromatic bromides with alkyl halides.

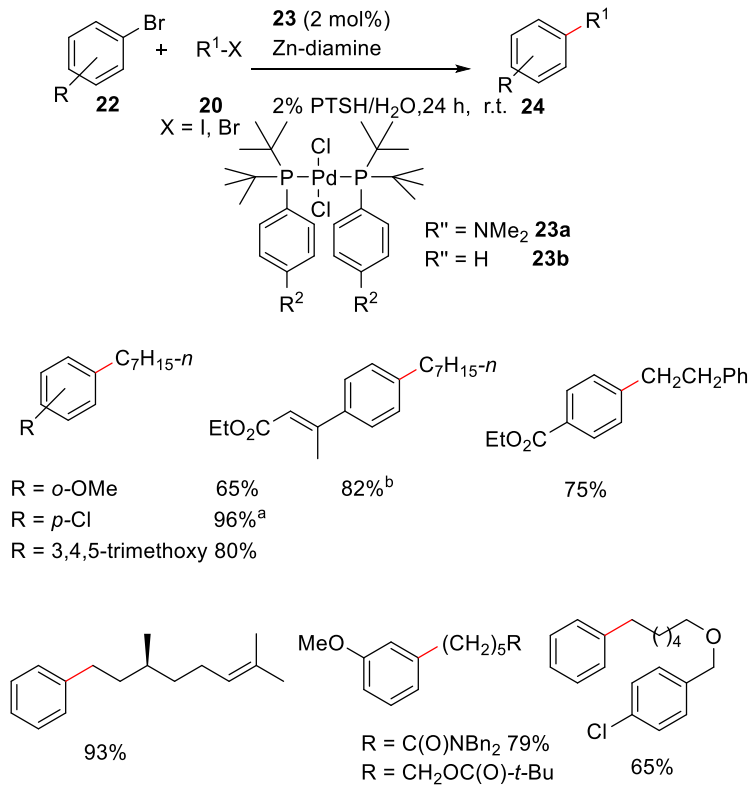
A variety of Grignard reagents **19** were reacted with alkyl bromide/triflates **20** via palladium-catalyzed coupling reactions to produce substituted arenes **21** in high yields by using substoichiometric amounts of $ZnBr_2$ additive.[25] The reaction carried out in presence of electron rich organo halides delivered the desired products in excellent yields (Scheme 7). The heteroaryl compounds such as quinolinyl and pyridyl bromides underwent the coupling reaction providing high yield of the desired products. The organo triflates underwent the cross-coupling giving the corresponding coupled products in acceptable yields while 4-chlorobenzonitrile and 4-iodobenzonitrile gave the expected products only in poor yields. The *tert*-butyl and isopropyl Grignard reagents remained unreactive under the strategy. When compounds containing lactone and ester substituents were subjected to this protocol, the coupling occurred affording moderate yield of the desired products.





Scheme 7. The Zn-mediated Pd-catalysed coupling reaction of aryl bromides with alkyl magnesium bromide.

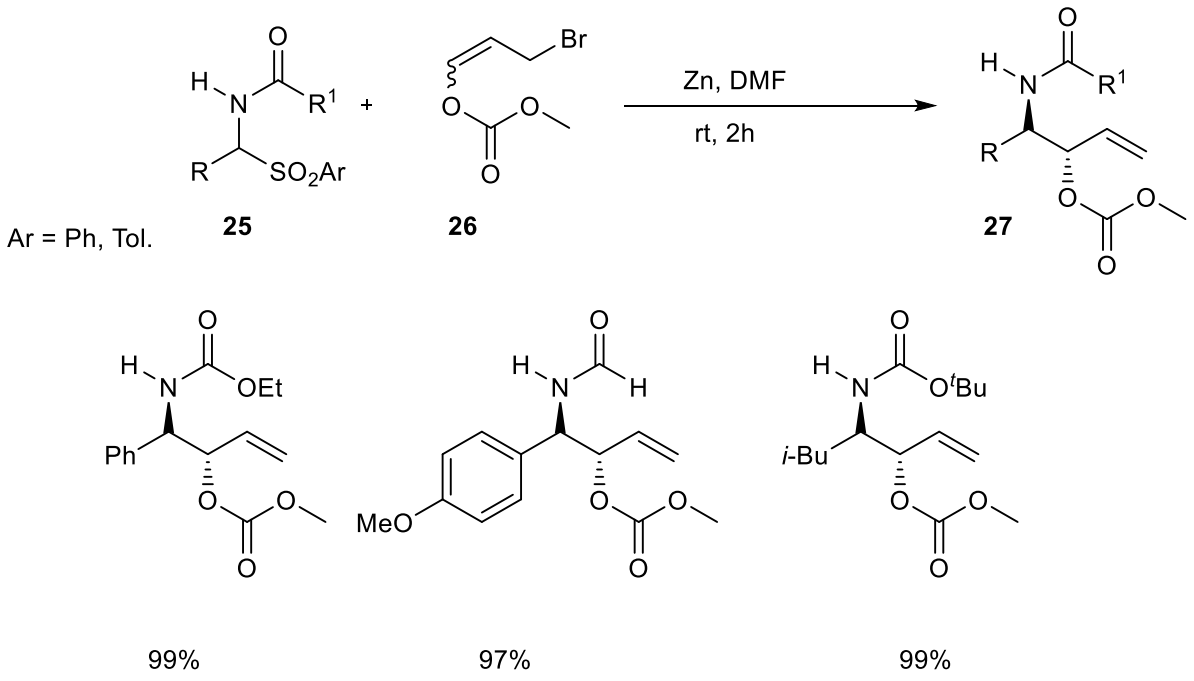
Lipshutz *et al.* developed a solvent-free novel synthetic methodology using palladium-catalysed Zn-promoted coupling reaction of aryl bromides with alkyl halides.[26] The reaction of aryl bromides **22** with alkyl halides **20** in the presence of Pd-catalyst **23** and Zn-dust in 2% PTS/H_2O afforded the required products in good to excellent yields (Scheme 8). The variously functionalized 1° alkyl and simple alkyl iodides underwent the reaction and gave good yields of the products. Moreover, this novel approach provided C(sp^2)-C(sp^3) bonds without using the stoichiometric amount of the organometallic coupling partner.



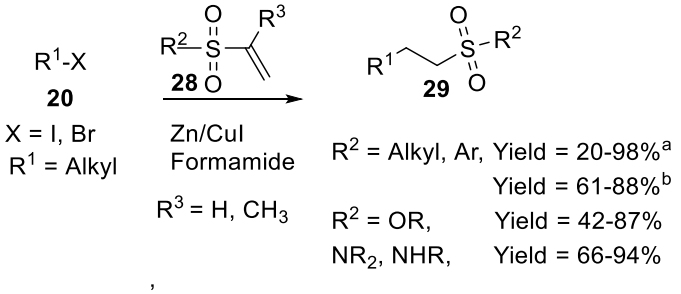
Scheme 8. Substrate scope studies of novel Pd-catalysed zinc promoted coupling reaction. Reaction times = [a]12 h, [b]48 h.

Trombini *et al.* developed an efficient method for the synthesis of protected anti-4-amino-1-alken-3-ols **27** using 3-bromo-propenyl methyl carbonate **26** and α-amidoalkyl arylsulfones **25** through Zn-mediated α-hydroxyallylation reaction.[27] The strategy was carried out in the presence of Zn in DMF at room temperature for 2 h and afforded the desired products in 78-99% yields with good diasteroselectivity (Scheme 9). The research team also demonstrated the synthetic value of this approach by the deprotection of protected anti-4-amino-1-alken-3-ols to amino alcohol. Additionally, this protected amino alcohol underwent base hydrolysis and cyclization that afforded *Cis*-4-substituted-5-vinyl-oxazolidinones.

In a recent study by Zhao *et al*., vinyl sulfonyl derivatives such as vinyl sulphonamides, vinyl sulfones, and vinyl sulfonates were coupled with alkyl halides in a new Zn/CuI-promoted coupling procedure (Scheme 10).[28] Here, alkyl halides **20** were reacted with several sulfonyl derivatives **28** in the presence of Zn/CuI in formamide to afford the corresponding products **29**. The reaction proceeded well with 1°, 2° and 3° alkyl iodides and bromides, but not with alkyl chlorides, vinyl and aromatic halides.

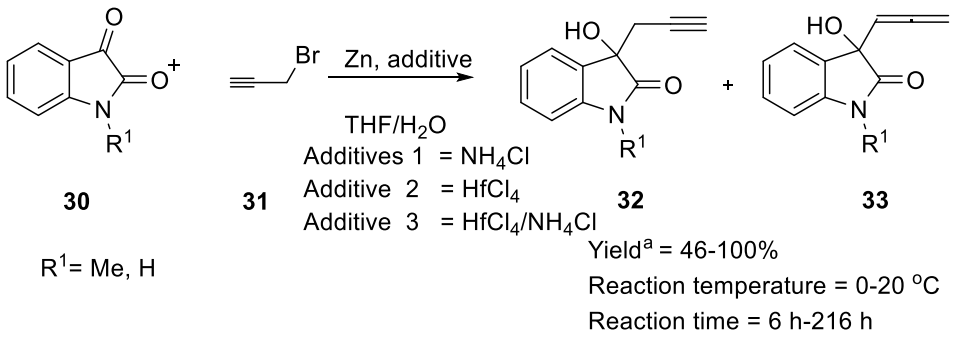


Scheme 9. Synthesis of protected anti-4-amino-1-alken-3-ols via Zn-promoted coupling reaction of 3-bromo-propenyl methyl carbonate with α-amidoalkyl arylsulfones.



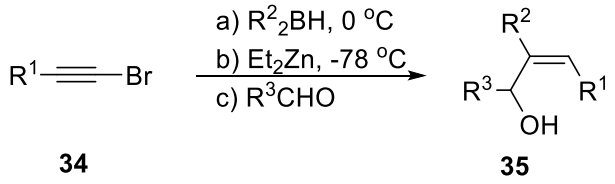
Scheme 10. Zn/CuI-promoted coupling reaction between alkyl halides and vinyl sulfones.[a] Sulfonyl derivative coupled with alkyl iodide; [b]Sulfonyl derivatives coupled with alkyl bromide.

The reaction of 2,3-indolinediones (isatins) **30** with 3-bromoprop-1-yne **31** in the presence of zinc and additives such as NH_4Cl, $HfCl_4$ and $HfCl_4/NH_4Cl$ in THF/H_2O afforded the acetylenic and allenic products **32** and **33** in 46-100% yield.[29] Here, isatin **30** was reacted with a variety of unsaturated halides under Barbier-type conditions in the presence of metallic zinc and additives, resulting in bromoallylation, carbonyl-allylation, propargylation, or 1,3-butadien-2-ylation reactions of isatins in an aqueous medium (Scheme 11)**.** The developed protocol successfully delivered the potentially bioactive moiety, 3-substituted 3-hydroxyoxindole.



Scheme 11. Reactions of isatins (2,3-indolinediones) with organozinc reagents.

Chen and co-workers disclosed the synthesis of *(Z)*-trisubstituted allylic alcohols **35** through a zinc-promoted coupling reaction. Initially, 1-bromoalkynes **34** underwent hydroboration giving 1-bromo vinyl boranes, which on treatment with diethyl zinc resulted in *(Z)*-trisubstituted vinyl zinc.[30] The reaction of the synthesized vinyl zinc reagent with aldehydes delivered the desired allylic alcohols. The substrate scope study using several aldehydes, 1-bromo-1-alkynes or its protected alcohols gave the corresponding allylic alcohols **35** in good yields (Scheme 12). This approach is used for introducing *(Z)*-trisubstituted allylic alcohol, a fragment in (+)-discodermolide and (+)-migrastatin.



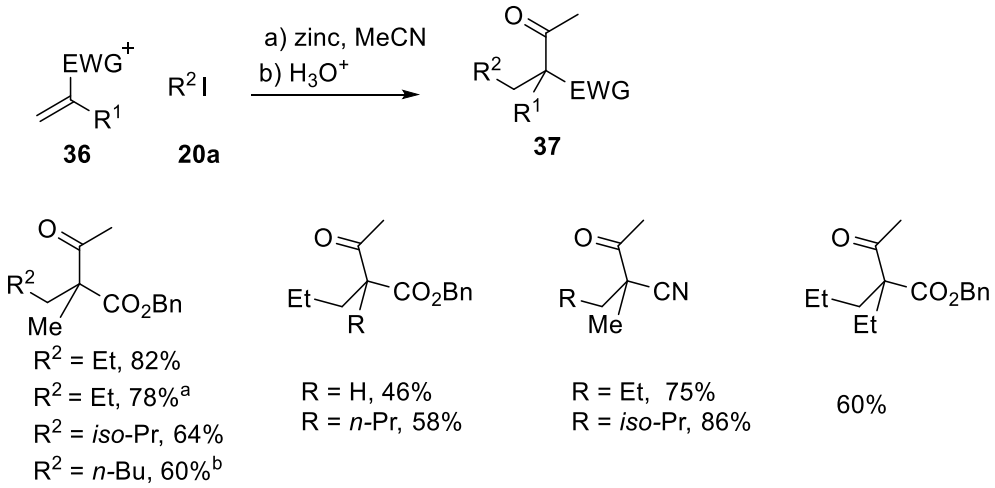
R^1	R^2	R^3CHO	Yield (%)
n-Bu	Et	Me_2CHCH_2CHO	61
CH_2OBn	Et	*p*-ClC_6H_4CHO	65
n-Bu	Cy	*p*-MeC_6H_4CHO	60
$CH_2OTBDPS$	Et	*p*-ClC_6H_4CHO	84
n-Bu	Cy	*o*-$MeOC_6H_4CHO$	63
$CH_2OTBDPS$	Et	Me_2CHCH_2CHO	71

Scheme 12. The (*Z*)-Trisubstituted allylic alcohols were synthesised via a Zn-promoted reaction.

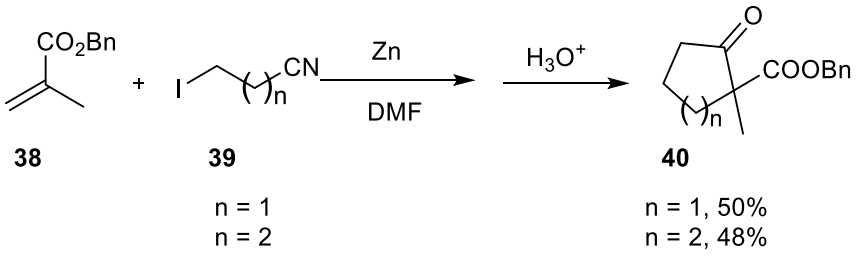
Nishiguchi *et al*. reported a room-temperature Zn-mediated three-component reaction of alkyl iodides **20a**, α,β-unsaturated esters **36**, or nitriles with acylating agents such as acid anhydrides or nitriles.[31] The three-component reaction began with the sequence selective and regioselective C-alkylation at β-position followed by C-acylation at the α-position of α, β-unsaturated esters or nitriles yielding α,α-dialkylketonitriles or α,α-dialkylketoesters **37** in moderate to good yields (Scheme 13). The substrate scope studies carried out using benzyl methacrylate and various alkyl iodides afforded the desired product in good yields.

Cyclopentanone and cyclohexanone were synthesised via this method, when 4-iodopropionitrile and 3-iodopropionitrile were reacted respectively with benzyl methacrylate **38** using Zn in DMF.

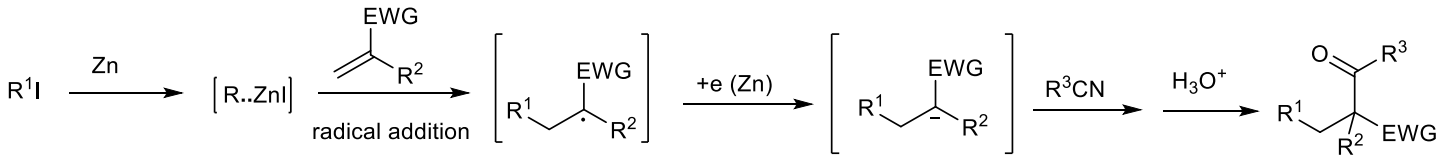
The detailed mechanistic studies of the reaction are yet to be unraveled. However, the plausible mechanism involves the generation of radical species via single electron transfer (SET) of metallic zinc to alkyl iodide. This alkyl radical intermediate undergoes addition reaction with α,β-unsaturated compound affording β-alkylated compound bearing new radical species. The carbanion was formed from this new radical species through SET. Finally, the carbanion undergoes electrophilic attack with nitriles followed by hydrolysis to afford α,α-dialkylketoesters (Scheme 14).



Synthesis of cyclohexanone and cyclopentanone via zinc mediated coupling reaction



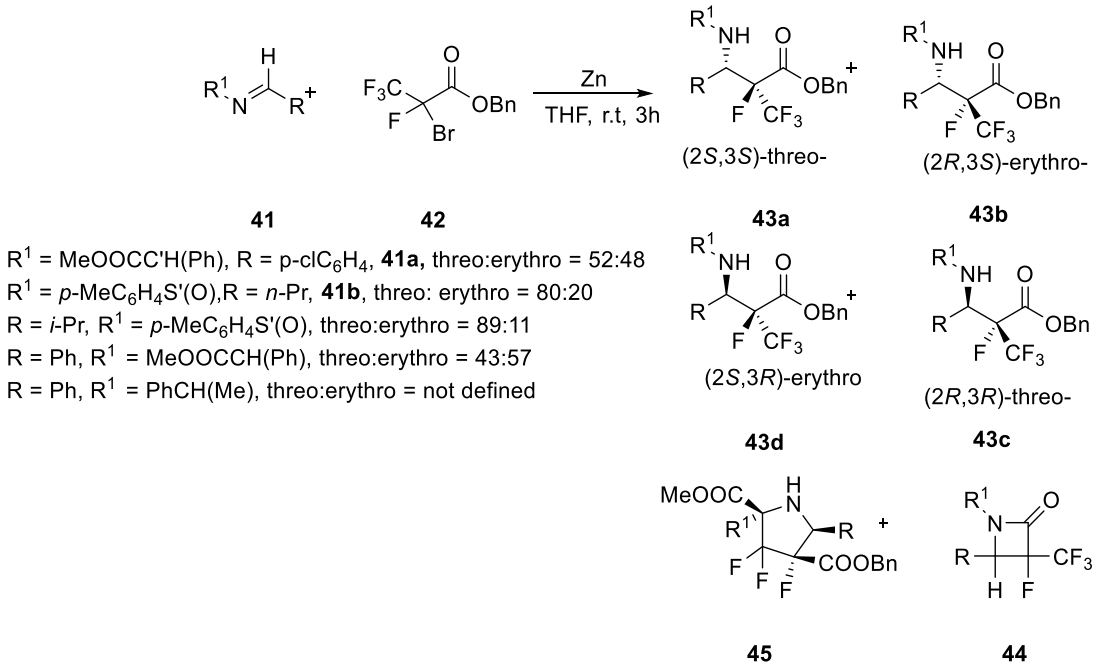
Scheme 13. The one-pot Zn-mediated three-component synthesis of *α, α*-dialkylketoesters or *α,α*-dialkylketonitriles. [a] Reaction carried out using 0.3 equiv. trimethylsilyl chloride, [b] The reaction time is 20 h.



Scheme 14. The proposed mechanism of the reaction. *Reproduced with permission from [31].*

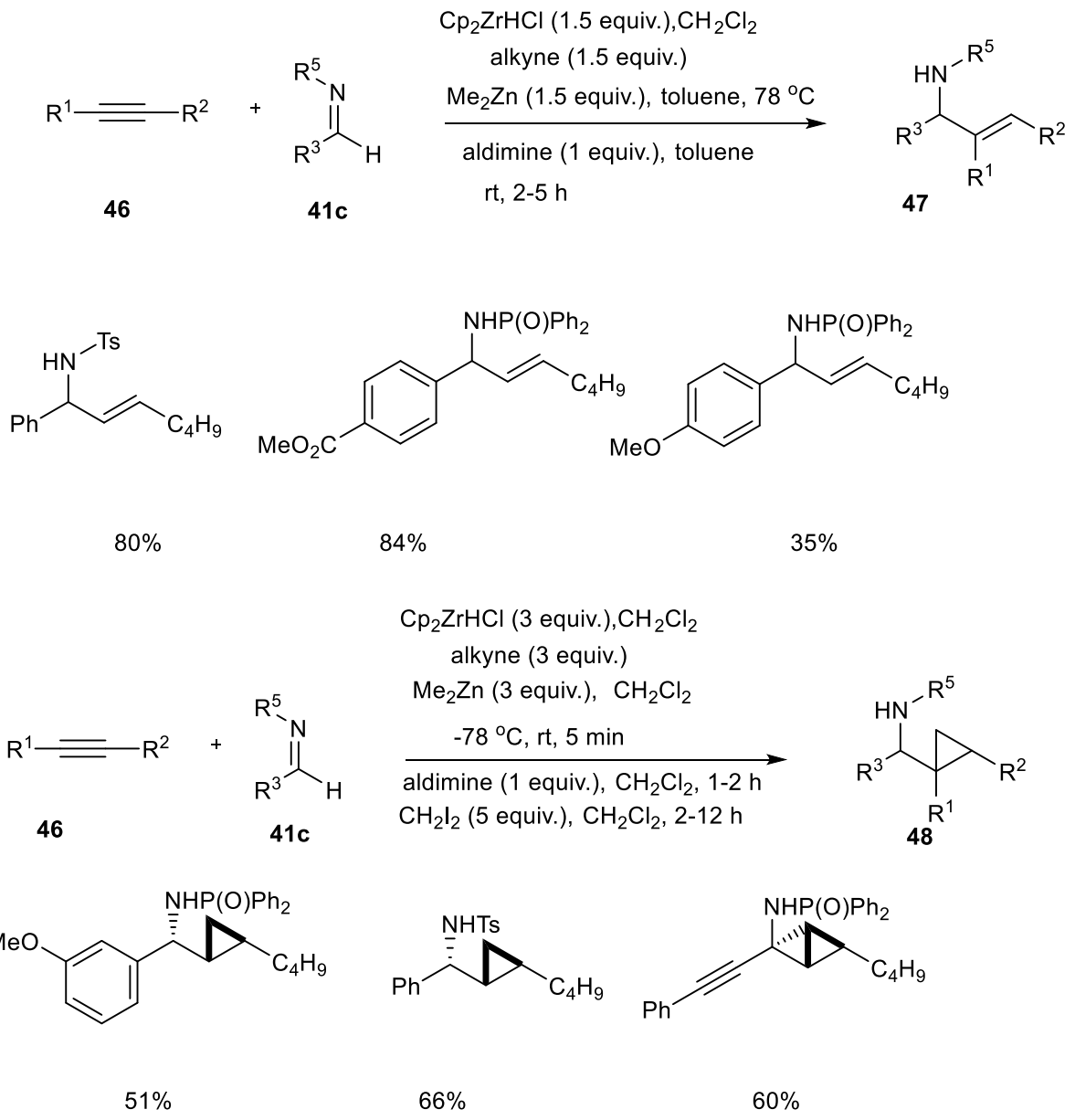
(*S*)-Sulfinimines **41b** were coupled with α-bromo ester **42** in the presence of zinc to give (2*S*,3*R*)-*erythro*- and (2*R*, 3*R*)-*threo* isomers of *α*-fluoro-*α*-(tri-fluoromethyl)-*β*-amino esters **43a**and **43b**(> 90% *de*)(**Scheme 15**).[32] The zinc-mediated coupling reaction was carried out between (*S*)-imines **41a** and α-bromo ester (benzyl

2-bromo-2,3,3,3-tetra-fluoropropanoate) **42**, giving the corresponding (2*S*,3*R*)-*erythro* and (2*R*,3*R*)-*threo*-isomers of **43d**and **43c** (>82% *de*). The coupling reaction with **41b**, obtained from aliphatic aldehyde like 2-methyl propanal and *n*-butanal afforded the desired product with good diastereoselectivity. But, the imine from the sterically hindered aldehyde (2, 2-dimethylpropanal) did not give the reaction.



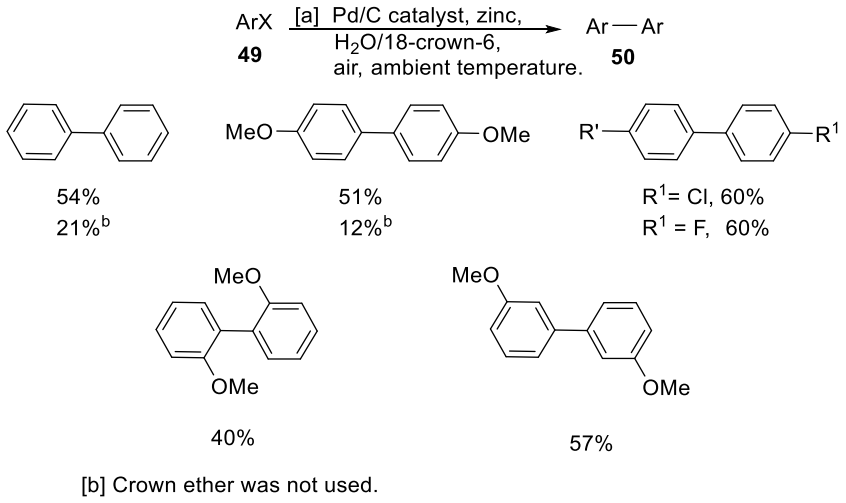
Scheme 15. The synthesis of isomers of *α*-fluoro-*α*-(tri-fluoromethyl)-*β*-amino esters using zinc-promoted coupling reaction.

A novel strategy for the synthesis of C-cyclopropylalkylamine and allylic amine via Zn-mediated coupling reaction was reported by Stephenson and coworkers.[33] The protocol involves the reaction of alkyne with aldimine to generate allylic amine under the standard conditions of 1.5 equiv. Cp_2ZrHCl in CH_2Cl_2, 1.5 equiv. Me_2Zn in toluene at room temperature for 2-5 h (Scheme 16). When aldimine and alkyne underwent the same reaction conditions in the presence of CH_2I_2 and CH_2Cl_2, afforded the cyclopropylalkylamine in good yield and high diasteroselectivity. Electron-rich and electron-deficient groups substituted aldimine well reacted with alkyne to furnish the desired products.



Scheme 16. Synthesis of C-cyclopropylalkylamine and allylic amines via Zn-mediated coupling reaction.

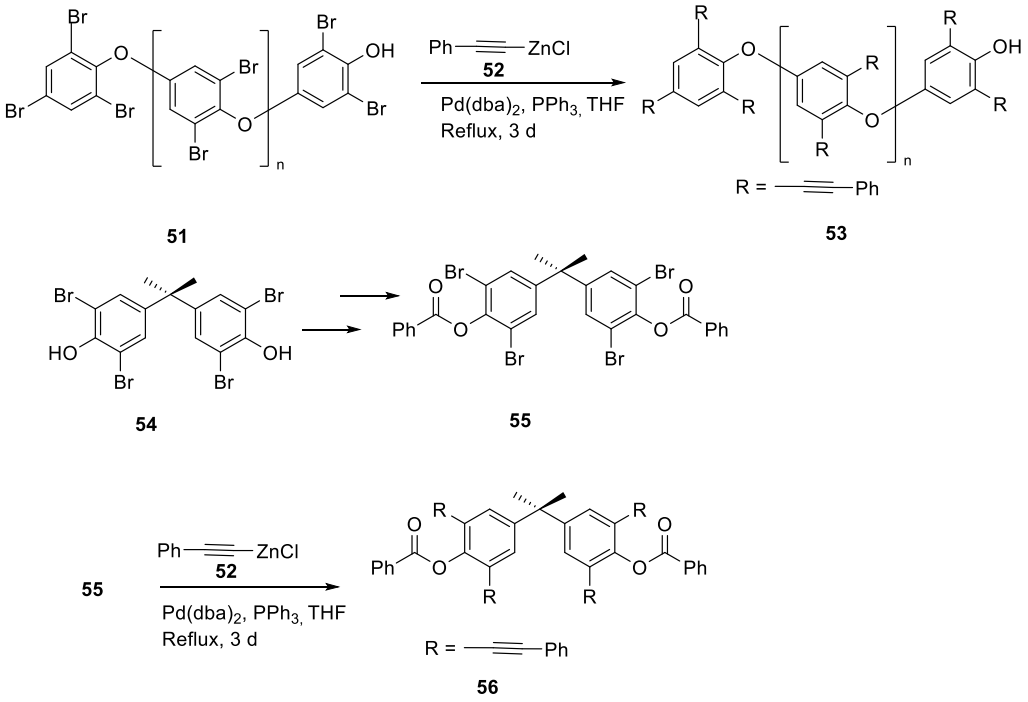
The aryl halides **49** underwent Zn-promoted reductive coupling in the presence of a Pd/C catalyst and 18-crown ether and gave the desired Ullmann-type coupled products in good yield.[34] The authors have studied this Ullmann-type reductive coupling reaction using several aryl bromides and iodides promoted by Zn in H_2O in the presence of crown ether and palladium catalyst (Scheme 17). The studies revealed that the yield of the desired products was decreased due to the enhanced steric hindrance and lack of crown ether. The aryl chlorides and fluorides remained unreactive under the developed conditions.



[b] Crown ether was not used.

Scheme 17. Synthesis of diaryl compounds through Pd-catalysed zinc mediated reductive coupling reaction.

Tour *et al*. synthesised a variety of non-halogenated alkyne derivatives with material characteristics (**53** and **56**) through the Pd- and Zn-mediated coupling reaction of phenylacetylene **52** with multi-bromine substituted aromatic ring.[35] The methodology was also applied for the synthesis of carbonates, oligomers, diphenyl ethers, and polymers (Scheme 18).

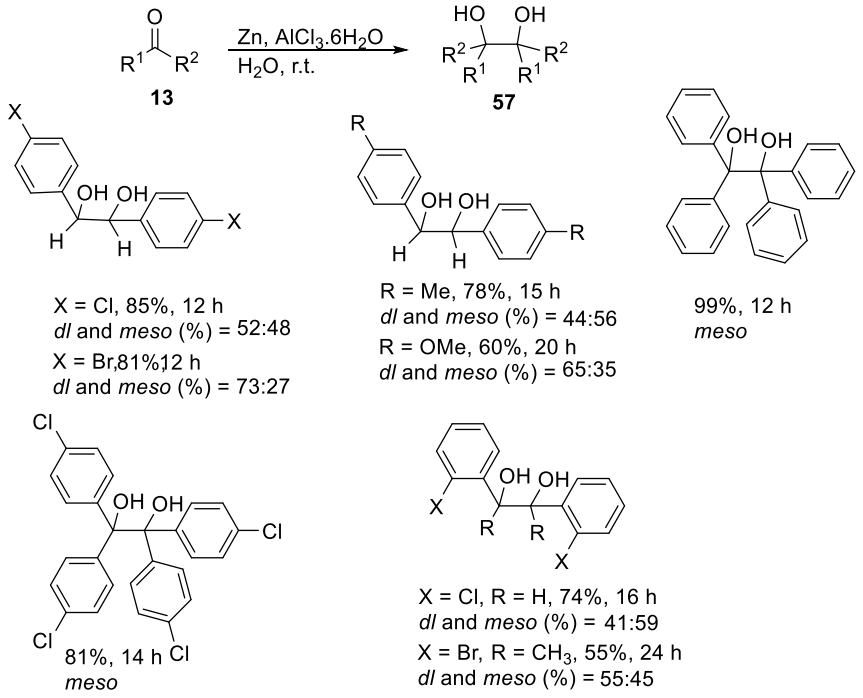


Scheme 18. The preparation of phenylethynylated compounds via Pd/Zn-mediated coupling reaction.

2.1 Pinacol Coupling

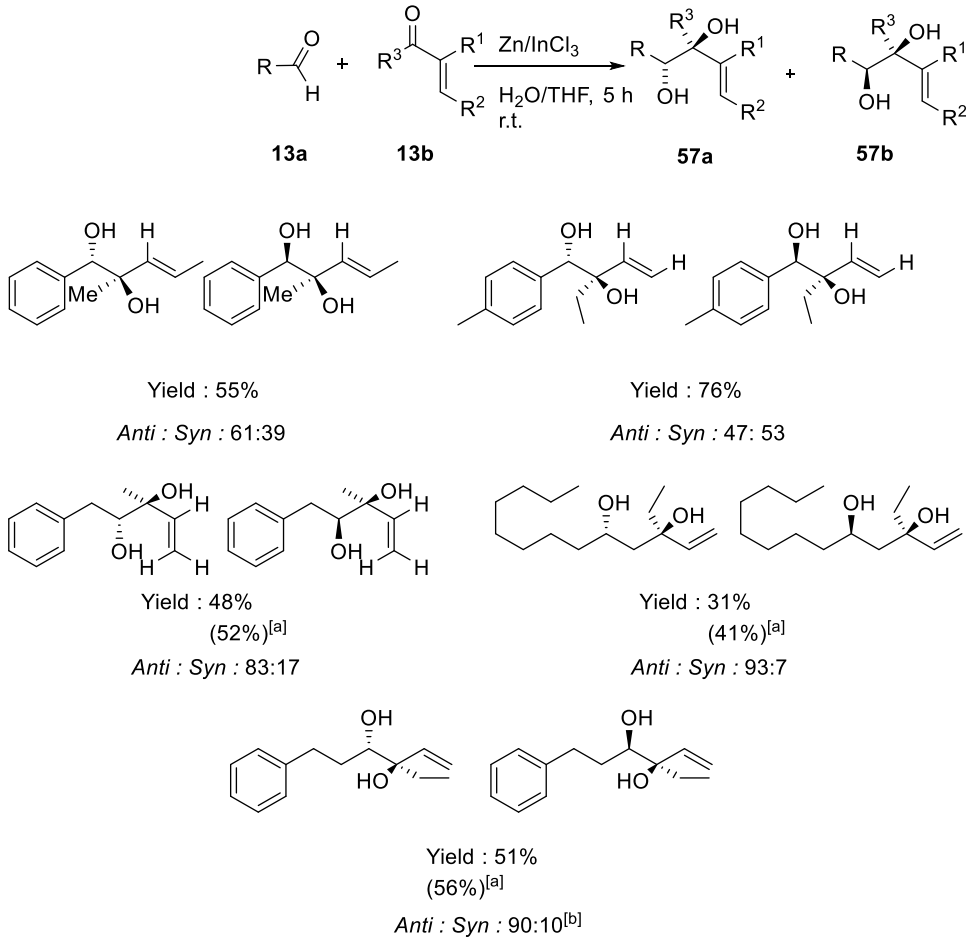
The carbonyl compounds such as aromatic aldehydes and ketones **13** underwent pinacol coupling reaction in the presence of Zn and $AlCl_3.6H_2O$ in H_2O at ambient temperature (Scheme 19).[36] The developed protocol provided the desired vicinal diols **57** in good yields with enhanced diastereoselectivity. The aromatic aldehydes

or ketones bearing electron-deficient groups reacted more rapidly compared to those with electron-releasing groups. Also, *para*- and *meta*- substituted aryl ketones and aldehydes reacted well compared to the *ortho*-derivative, while the aryl ketone derivatives gave only the *meso* products. Aliphatic ketones and aldehydes were unreactive under this reaction conditions. The key advantages of this synthetic technique were the devised protocol's environmental friendliness, water-mediated catalytic system, mild reaction temperatures, side product-free reaction, and affordability. The actual mechanistic pathway was not proposed. However, the authors presumed that a complex was formed by reacting a carbonyl compound with $AlCl_3.6H_2O$ and then the zinc metal acts as an electron carrier (electron transfer agent) that afforded a ketyl radical. Pinacol was formed when this radical underwent dimerization.

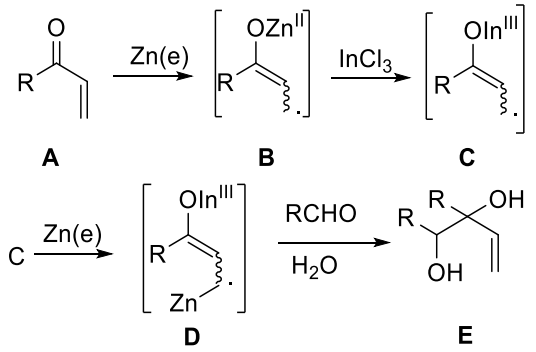


Scheme 19. The Zn-mediated pinacol coupling reaction.

The synthesis of 1,2-diols was devised by Lohn *et al. via* a Zn/$InCl_3$-mediated pinacol coupling reaction as the key step.[37] The pinacol cross-coupling reaction of α,β-unsaturated ketone **13b** and aldehyde **13a** with Zn/$InCl_3$ in H_2O/THF as the solvent produced racemates of 1,2-diols **57a** and **57b** in 41-85% yields with good diastereoselectivity (up to 93:7) (Scheme 20). Notably, the reaction carried out in the presence of $InBr_3$ increased the yield to some extent for the coupling of aliphatic aldehydes with α,β-unsaturated ketones. When the reaction temperature was increased from room temperature to 75 ^oC, the *anti:syn* ratio was reduced from 90:10 to 65:35. A possible mechanism was proposed by the group and it involves the formation of a radical enolate anion **B** by single electron transfer (SET) from Zn to α,β-unsaturated ketone **A**. Then, indium chloride readily traps the oxygen–metal bond in the radical enolate anion, which leads to the formation of γ-In(III)- substituted allylic radicals **C**. The reduction of these radicals using Zn provides the resultant allylic zinc species **D**. Then, the coupling of aldehyde with γ-In (III)-substituted allylic zinc species affords 1,2-diolate, which on quenching with water produces the required product **E** (Scheme 21).



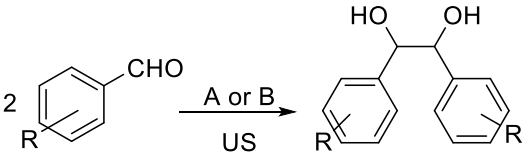
Scheme 20. The synthesis of 1,2-diols via Zn/$InCl_3$-mediated coupling reaction. [a] Using $InBr_3$ rather than $InCl_3$. [b] When the temperature is 75 °C, the anti : syn ratio is 65 : 35.



Scheme 21. The plausible mechanism of the Zn/$InCl_3$-mediated cross-coupling reaction. *Reproduced with permission from [37].*

The aryl aldehyde underwent a Zn-mediated pinacol homo coupling reaction in aqueous H_3PO_4 or NH_2SO_3H for the synthesis of 1,2-diols (pinacols) in 14-88% yield using ultrasound irradiation (Scheme 22).[38] 3-Chloro-, 3-bromo- and 2-chloro benzaldehydes gave the corresponding products in 74%, 70% and 63%, respectively, when the reaction was carried out in the presence of Zn powder in aqueous NH_2SO_3H (A system). The same substrates gave the corresponding pinacols in 88%, 85% and 79%, respectively, in the presence of

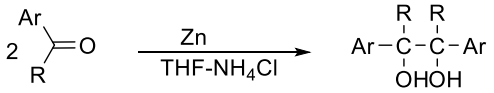
the B system (Zn-powder/H_3PO_4). However, in both systems, enhanced reactivities were shown when the liquid aryl aldehydes bearing electron-deficient substituents were used. Furthermore, solid aryl aldehydes with electron-deficient substituents and aryl aldehydes with electron-releasing groups exhibited lower reactivity. The steric hindrance present around the carbonyl group can lead to the inhibition of the coupling reaction.



13c **57c**

R = 3-ClC_6H_4-	74%[a], 88%[b]
R = 2-ClC_6H_4-	70%[a], 85%[b]
R = Ar-	21%[a], 45%[b]
R = 4-ClC_6H_4-	42%[a], 34%[b]
R = 2, 4-$Cl_2C_6H_3$-	54%[a], 43%[b]
R = 4-$CH_3C_6H_4$-	23%[a], 49%[b]
R = 3, 4-$(OCH_2O)C_6H_3$-	14%[a], 28%[b]
R = 3-BrC_6H_4-	63%[a], 79%[b]

Scheme 22. The Zn-mediated pinacol coupling reaction under ultrasound irradiation. [a] A: zinc powder/NH_2SO_3H. [b] B: zinc powder/H_3PO_4.



13d **57d**

R	Ar	Yield (%)	DL:Meso
CH_3	C_6H_5	32	51:49
H	C_6H_5	65	55:45
H	*p*- $CF_3C_6H_4$	82	74:26
H	*m*-BrC_6H_4	70	52:48
H	*p*-FC_6H_4	73	55:45
H	*o*-BrC_6H_4	68	50:50
H	*p*-ClC_6H_4	77	58:42
H	*p*-BrC_6H_4	76	50:50

Scheme 23. The synthesis of pinacols by using Zn-promoted reductive coupling reaction.

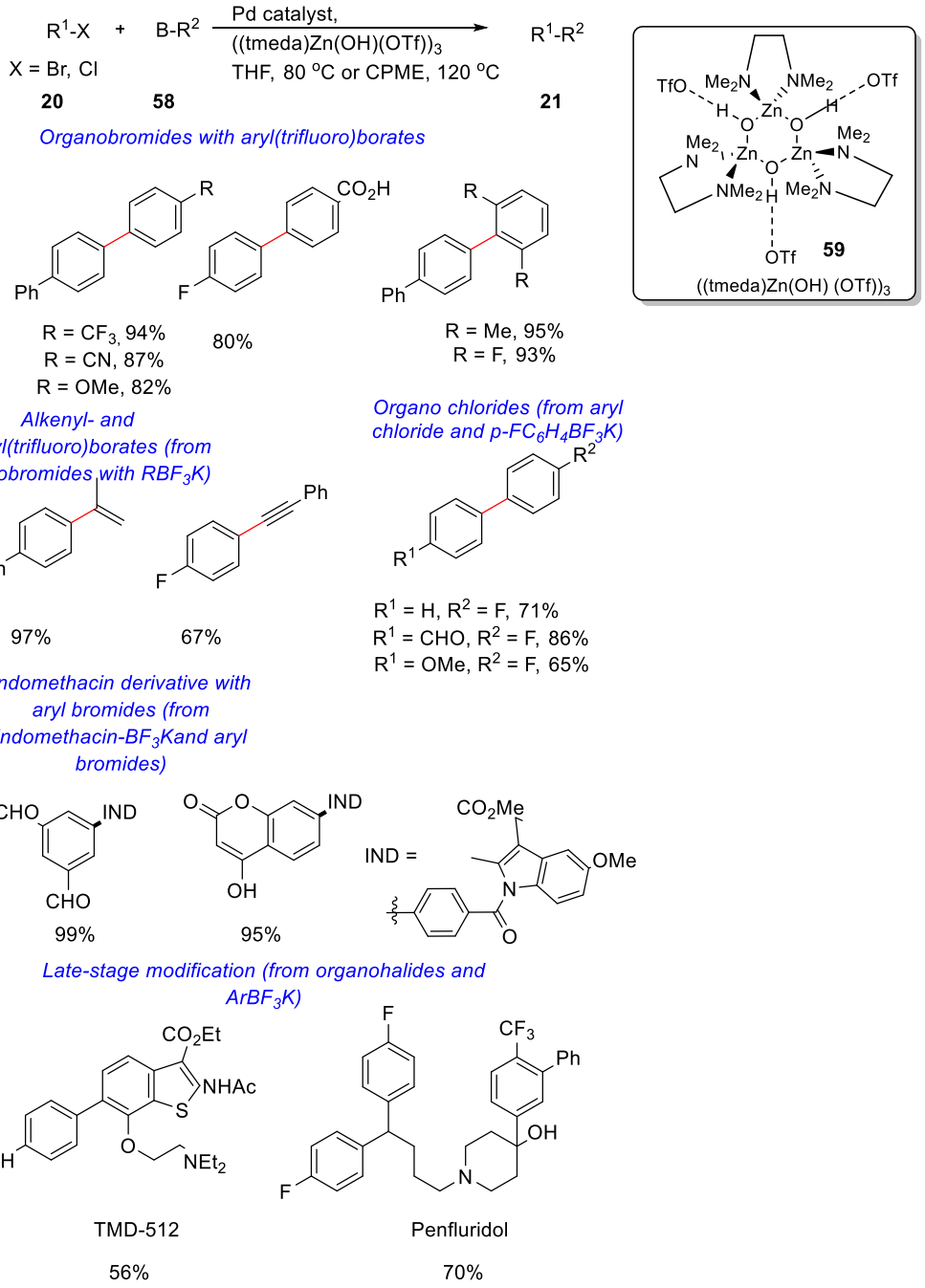
At room temperature, the aromatic carbonyl compounds **13d** underwent Zn-promoted reductive coupling, giving the corresponding pinacols **57d** in moderate to good yields.[39] This pinacol coupling was carried out in the presence of Zn-powder in saturated aqueous ammonium chloride-tetrahydrofuran solution (NH_4Cl (aq.)-THF) (Scheme 23). The moderate to good yield of 1,2-diols was obtained when aromatic aldehyde

underwent the Zn-mediated reductive coupling reaction by using Zn-powder in an aqueous solution of NH_4Cl-THF at room temperature. Lower yields were obtained when aromatic ketones underwent the Zn-promoted reductive coupling reaction. The *meso*: *DL* ratio of pinacols (1,2-diols) was approximately 1:1 except in the case of 4-(trifluoromethyl) benzaldehyde.

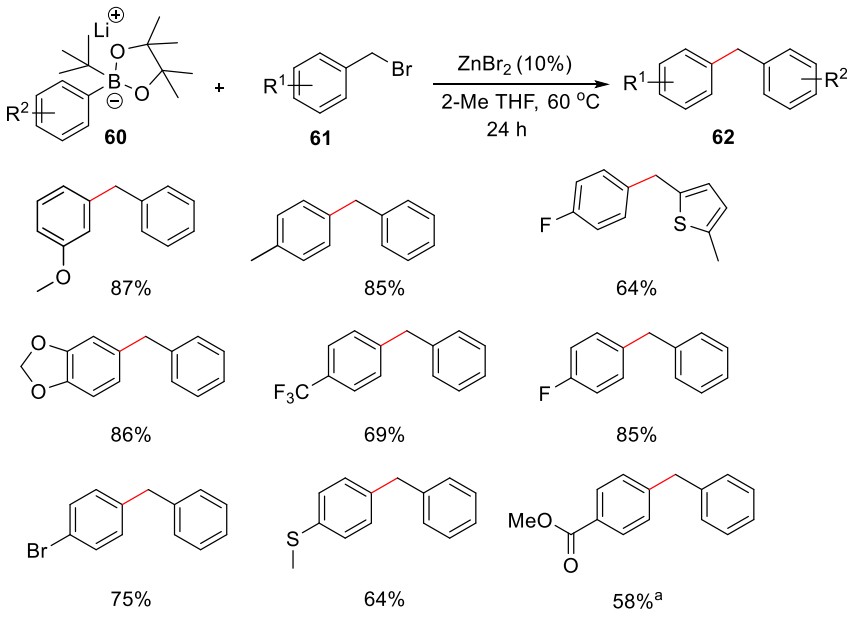
2.2 Suzuki Coupling

The C-C bond was constructed through the Lewis acid-promoted Suzuki–Miyaura coupling reaction by Hosoya *et al*.[40] Herein, organoborons **58** were reacted with organohalides **20** in the presence of a Pd catalyst and a Zinc trimer, chemically ((tmeda)Zn(OH) $(OTf))_3$ **59** in THF at 80 °C or in cyclopentyl methyl ether (CPME) at 120 °C (Scheme 24). In this synthetic strategy, controlled delivery of a transmetallation-active catalytic intermediate provided a base-free Suzuki-Miyaura cross-coupling reaction. The active Pd-based intermediate was formed by the debromination of the Pd centre using a zinc complex. The substrate scope of this reaction was studied using organoborates, mainly potassium aryl(trifluoro)borates and various organohalides such as aryl bromides, aryl chlorides, etc. The biaryls were obtained in high yields when a wide range of aryl(trifluoro)borates bearing numerous substituents were used in the SMC reaction. The use of base-sensitive groups such as acidic functionalities, specifically carboxylic and phenolic moieties containing substrates, was enabled under Zn-mediated conditions. Heteroaryl and perfluorophenyl substrates, as well as alkynyl and alkenyl-borates, provided the corresponding desired products in 25-99%. For aryl chlorides, the authors reoptimized and modified the Pd-catalytic system with a biaryl(dialkyl). The Suzuki-Miyaura coupling reaction was carried out between aryl bromides bearing coumarin, amino, and diformyl groups, with indomethacin methyl ester affording the desired arylated products. This synthetic strategy is used for the modification or synthesis of bioactive compounds and commercial medicines.

Ingleson *et al.* devised the ligand-free Suzuki-Miyaura coupling of aryl borates with benzyl bromides utilizing Zn catalysts in 2017.[41] The reaction of aryl borates **60** with benzyl bromides **61** in 2-methyl tetrahydrofuran at 60 °C in the presence of 10 mol% $ZnBr_2$, produced the desired products **62** in good yields (Scheme 25). The reaction was tolerated by CF_3, halides, thioether, heteroaryl, ether, alkyl, acetals, and ester groups. The aldehyde and ketone groups were not suitable for this reaction. Notably, methyl allyl bromide and bromodiphenyl methane were viable substrates for the reaction. The other bromo compounds, like cycloheptylbromide and octylbromide, were incompatible in this reaction. The mechanistic pathway indicates that this protocol is mediated by triaryl zincate, formed during the reaction, serves as a nucleophile.

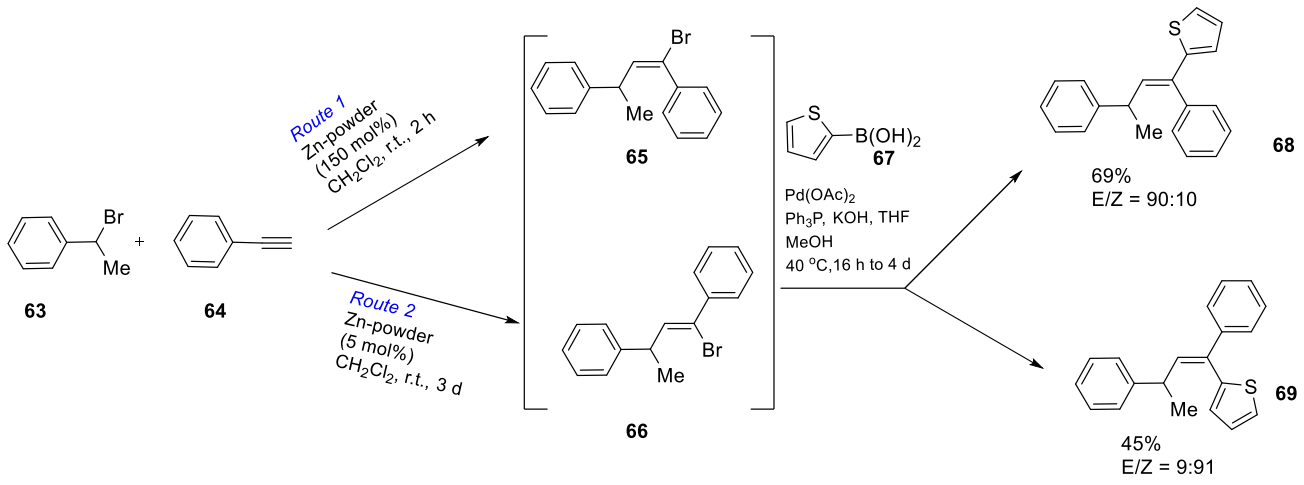


Scheme 24. The construction of C-C bond via Pd-catalysed Zn-promoted Suzuki–Miyaura coupling reaction of organohalides with organoboron compounds. Condition 1 (for aryl bromides): $PdCl_2(amphos)_2$, $((tmeda)Zn(OH)(OTf))_3$, THF, 80 °C; Condition 2 (for aryl chlorides): $(cod)Pd(CH_2TMS)_2$, 2-dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl (XPhos), $((tmeda)Zn(OH)(OTf))_3$, CPME, 120 °C.



Scheme 25. The Zn-mediated Suzuki-Miyaura coupling reaction of aryl borates with benzyl bromides. [a] Reaction time 72 h.

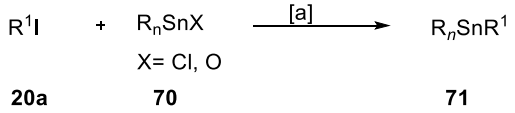
Vinyl bromide derivatives were synthesised via the stereoselective Zn-promoted reaction of terminal alkynes with benzyl bromide (Scheme 26).[42] In this protocol, the amount of zinc used determines the geometry of the carbon-carbon double bond of the desired products. *E*-configured vinyl bromide derivatives were obtained when a high amount of zinc powder (150 mol%) was used, whereas a low amount of zinc was needed for the preparation of its *Z*-configured derivatives (5 mol%). In a one-pot, three-component reaction, a good yield of trisubstituted olefin derivatives was obtained through the Pd-catalysed Suzuki coupling reaction of aryl boronic acids with *in-situ* produced vinyl bromides.



Scheme 26. Vinyl bromides were synthesized via stereodiverse zinc promoted reaction and their Pd-catalysed Suzuki cross coupling reactions.

3. C-Sn Coupling Reactions

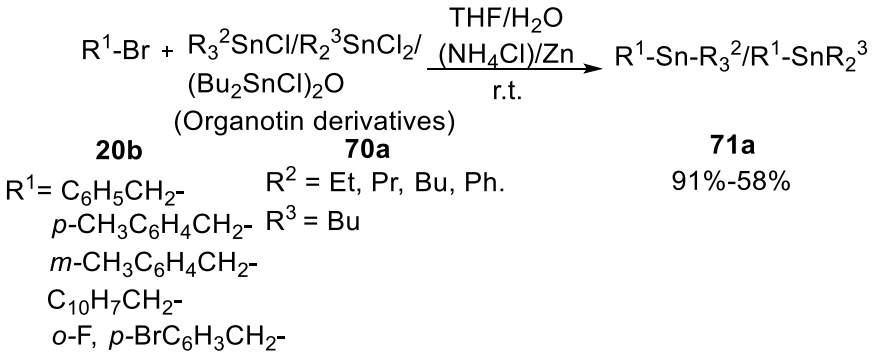
Under the Zn-mediated coupling reaction, hexaalkylstannanes and mixed alkylstannanes were easily synthesised in a one-pot synthetic method.[1] The coupling reaction between organotin halides **70** and 1° alkyl iodides **20a** in the presence of cosolvent, aqueous solution of ammonium chloride promoted by Zn-dust, gave the corresponding mixed alkyltin derivatives **71** (Scheme 27). $(Bu_3Sn)_2O$ also gave the corresponding coupled product, while the 2° alkyl iodides did not give this reaction. The other alkyl halides, such as alkyl bromides and chlorides did not give unsymmetrical tetra-alkyl stannanes, but instead gave ditin compounds. The substrate scope exploration of iodides and organotin derivatives revealed that the yields were decreased when the bulkiness of the substituent increased.



Alkyl iodide	Organotin	Product	Yield
n-BuI	Et_3SnCl	Et_3Sn(n-Bu)	85%
n-PrI	*n*-Pr_3SnCl	*n*-Pr_3Sn(n-Pr)	79%
MeI	*n*-Bu_3SnCl	*n*-Bu_3SnMe	84%
EtI	*n*-Bu_3SnCl	*n*-Bu_3SnEt	79%
MeI	$(n\text{-}Bu_3Sn)_2O$	*n*-Bu_3SnMe	88%
EtI	*n*-Bu_2SnCl_2	*n*-Bu_2SnEt_2	55%

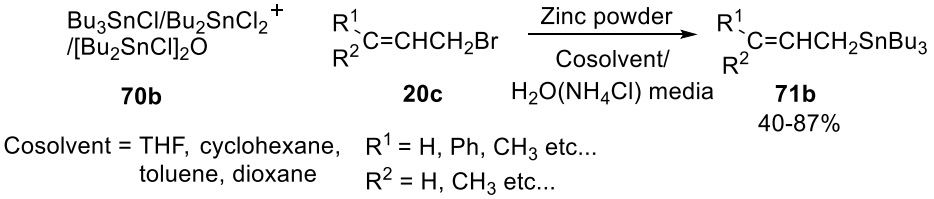
Scheme 27. The preparation of alkyltin compounds via Zn-mediated coupling reaction.

The Zn-promoted one-pot synthesis of benzyl triphenylstannanes and benzyl trialkyl stannanes by the coupling of organotin derivatives and benzyl bromides in THF-aq. NH_4Cl was disclosed by Marton *et al.* in 1996.[44] Also, the synthesis of dibenzyl dibutylstannanes and (2-naphthylmethyl) tributylstannanes were successfully achieved using the developed protocol (Scheme 28).



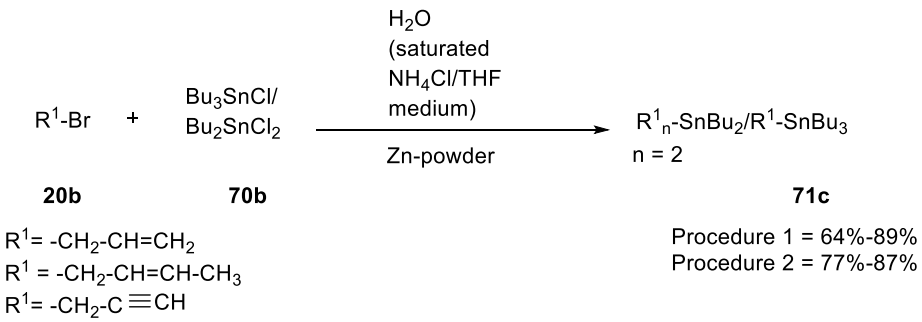
Scheme 28. Synthesis of benzyl triphenyl and benzyl trialkyl stannanes via Zn-promoted coupling reaction.

The zinc-mediated Wurtz-type coupling reaction was carried out between haloorganotin compounds **70b** and various allyl bromides **20c** in saturated aqueous NH_4Cl media that provided the corresponding allylstannanes **71b** and it was devised by Tagliavini *et al.* (Scheme 29).[45] R_3SnSnR_3 was also synthesized when triaryltin chlorides were used in the coupling reaction.



Scheme 29. The Zn-mediated Wurtz-type coupling reaction of haloorganotin compounds with allyl bromides.

Allenyl and allyl stannanes **71c** were synthesised through a novel Zn-mediated coupling reaction of organotin compounds such as Bu_3SnCl or Bu_2SnCl_2 **70b** with allyl/propargylic bromides **20b** in the presence of H_2O (NH_4Cl)/THF medium (Scheme 30).[46] The reaction of excess allyl bromide and butyltin chloride suspended in an aqueous saturated solution of NH_4Cl/THF followed by the addition of Zn-powder with stirring over time is described in procedure 1. While, the procedure 2 describes the dropwise addition of allyl bromide to an aqueous saturated solution of NH_4Cl/THF containing butyltin chloride and excess Zn-powder.

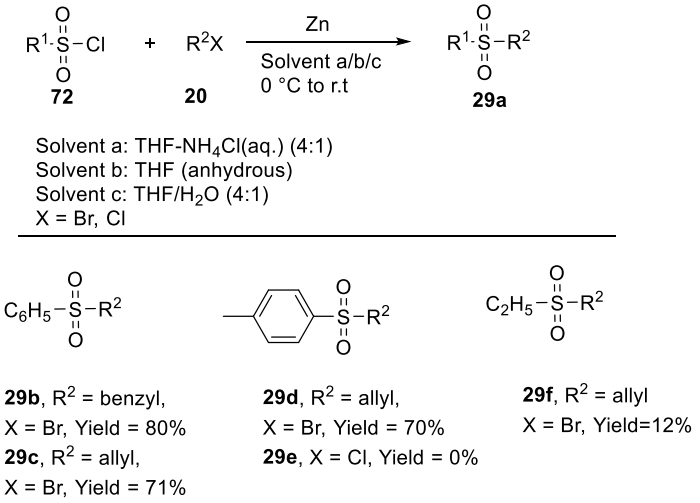


Scheme 30. Allenyl and allyl stannanes were prepared by novel Zn-promoted coupling reaction.

4. C-S Coupling Reactions

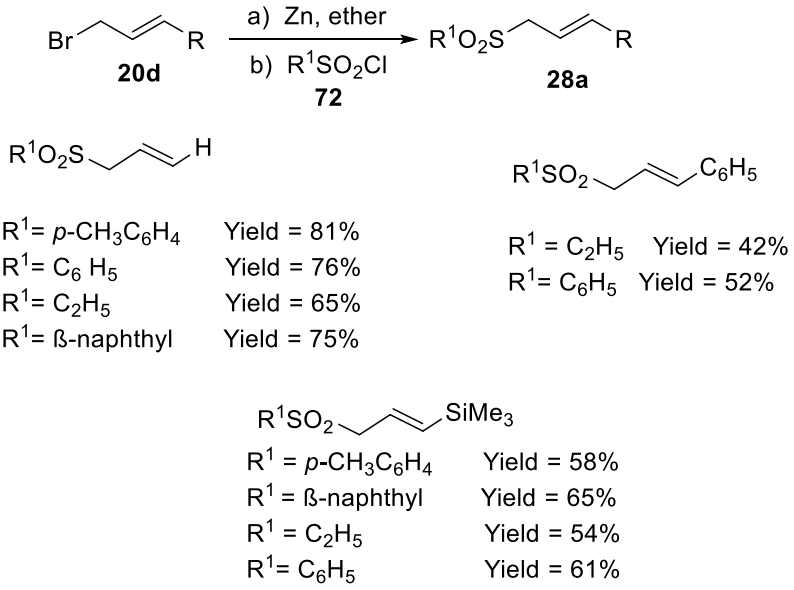
The synthesis of sulphones via zinc-mediated coupling reaction was reported by Zhang *et al.*[47] The reaction was performed using alkyl halides **20** and organic sulphonyl chloride **72** in the presence of Zn dust in aqueous medium at 0 °C to ambient temperature which yielded the corresponding sulphones in 12%-82% (Scheme 31). The benefits of this synthetic strategy include shorter reaction times and milder conditions that consume zinc dust without activation and result in higher yields. The authors conducted a detailed study on the zinc-mediated coupling reaction of several alkyl halides including cinnamyl bromide, benzyl bromide, 2-bromoacetophenone, allyl bromide etc., with organic sulphonyl chlorides provided a reasonable yield of the coupled products. The aliphatic group bearing organic sulphonyl chloride **29f** also underwent the coupling reaction and afforded a lower yield (12%) of the desired product, which may be due to the formation of sulphonic acid from the aliphatic sulphonyl chloride and which is easier to hydrolyse. When compared to

anhydrous solvent, the aqueous medium requires much less time for the reaction to complete. Additionally, the alkyl fluorides and chlorides did not produce the coupled product.



Scheme 31. Synthesis of Sulphones via zinc-mediated coupling.

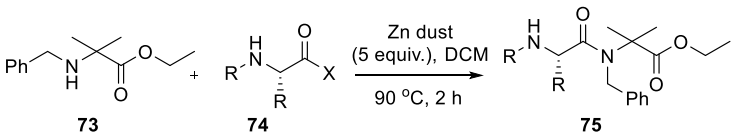
Zhang *et al.* developed a novel synthetic method for β,ϒ-unsaturated sulphones **28a** under zinc-promoted coupling reaction (Scheme 32).[48] In this reaction, allyl bromide **20d** was reacted with a suspension of Zn dust in ether at ambient temperature for 0.5-1 h. The detailed studies on the preparation of unsaturated sulphones showed that, both aryl and alkylsulphonyl chlorides were effective for this reaction. The configuration of the products depends on the configuration of starting allyl bromides.



Scheme 32. The preparation of β,ϒ-unsaturated sulphones through Zn-mediated coupling reaction.

5. C-N Coupling Reactions

Harvey *et al*. reported the synthesis of sterically hindered dipeptides using Zn dust under microwave irradiation.[49] This methodology is applicable towards the synthesis of other hindered *N*-alkyl or α, α-disubstituted amino acids. Here, the compound **73** was coupled with **74** in the presence of 5 equiv. Zn-dust in DCM at 90 °C for 2 h that provided the desired products **75** in 40%-80% yields (Scheme 33). Herein, the authors revealed that, although it is still unknown whether zinc plays any other role in these reactions, it is possible that it acts solely as a neutral acid scavenger.



73 **74** **75**

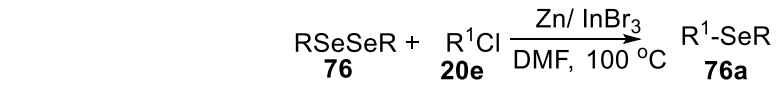
Entry No.	Compound	Yield (%)
1	Fmoc-Phe-*N*Bn-Aib-OEt	61%
2	Fmoc-Val-*N*Bn-Aib-OEt	54%
3	Fmoc-Ile-*N*Bn-Aib-OEt	40%
4	Fmoc-Phe-*N*Me-Aib-OEt	80%
5	Fmoc-Pro-*N*Me-Aib-OEt	46%

Scheme 33. Synthesis of sterically hindered dipeptides via Zn-mediated reaction.

6. C-Se Coupling Reactions

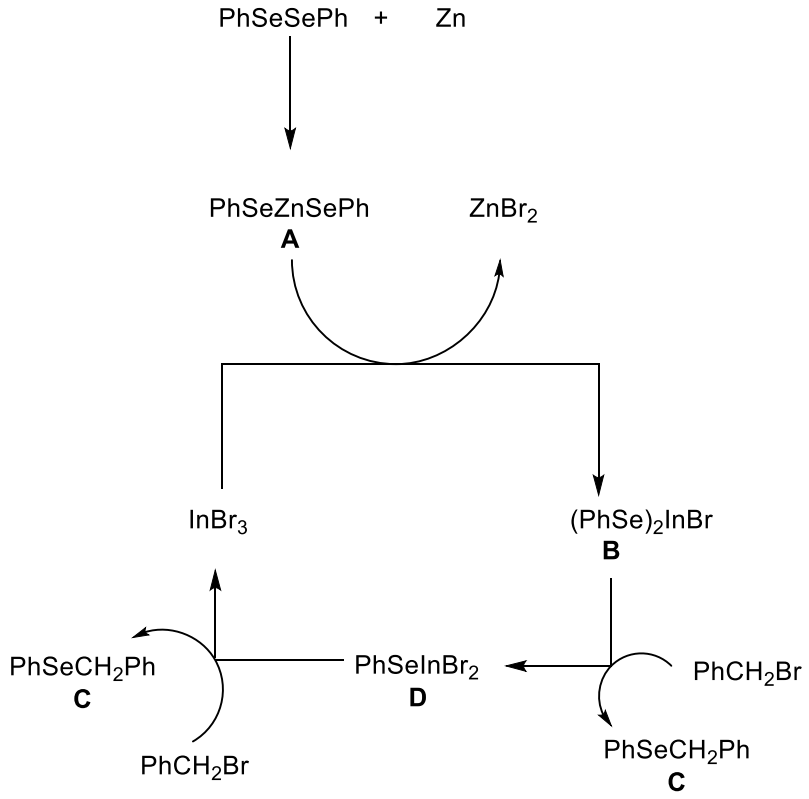
A Zn powder-mediated synthesis of unsymmetrical diorganyl selenides via a one-pot In(III)-catalysed protocol was devised by Braga *et al.*[50] Various aryl or alkyl diselenides **76** as well as organic halides like non-reactive chlorides **20e** underwent the coupling reaction effectively in the presence of Zn-powder and $InBr_3$ in DMF at 100 °C (Scheme 34). The substrate scope studies indicated that, excellent yield of selenides was obtained from benzyl and allyl bromides. Additionally, the reaction carried out between dibutyl diselenide and organo bromides gave the desired products in acceptable yields. The increase in catalyst loading from 2.5 to 10 mol% increased the yield to 98% in a shorter reaction period.

The proposed mechanism began with the generation of di(organylselenyl) zinc **A** by the insertion of zinc into Se-Se bond (Scheme 35). The compound **A** was reacted with In(III) catalyst provided In(III)active species **B**, which on reaction with organo halides (R'X) gave the desired diorganyl selenides **C** and other product **D.** Finally, the coupling of organo halide with compound **D** generated diorganyl selenide **C**, regenerating InX_3.



R	Halide	Time (h)	$InBr_3$ (mol%)	Yield (%)
Bu	$CH_3(CH_2)_{10}CH_2Br$	48	2.5	67
Bu	$CH_3(CH_2)_{10}CH_2Br$	22	10	94
Ph	CH_2=$CHCH_2Br$	1	2.5	82
Ph	$PhCH_2Br$	1	2.5	93
$PhCH_2$	$CH_3(CH_2)_{10}CH_2Br$	22	10	57
Bu	$PhCH_2Br$	48	2.5	58
Ph	$CH_3CH_2CH_2CH_2Cl$	1	2.5	83
Ph	$CH_3CH_2CH_2CH_2I$	1	2.5	90
$PhCH_2$	$PhCH_2Br$	48	10	58

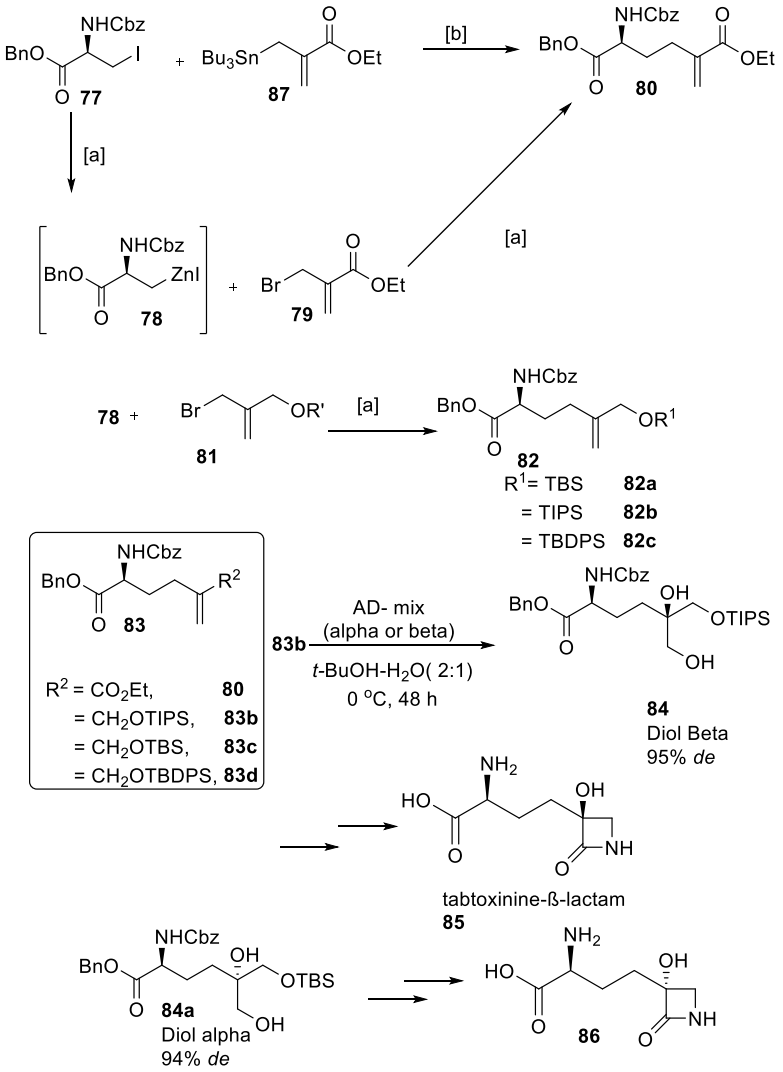
Scheme 34. The substrate scope studies of unsymmetrical diorganyl selenides.



Scheme 35. The proposed reaction mechanism.

7. Natural Product Synthesis

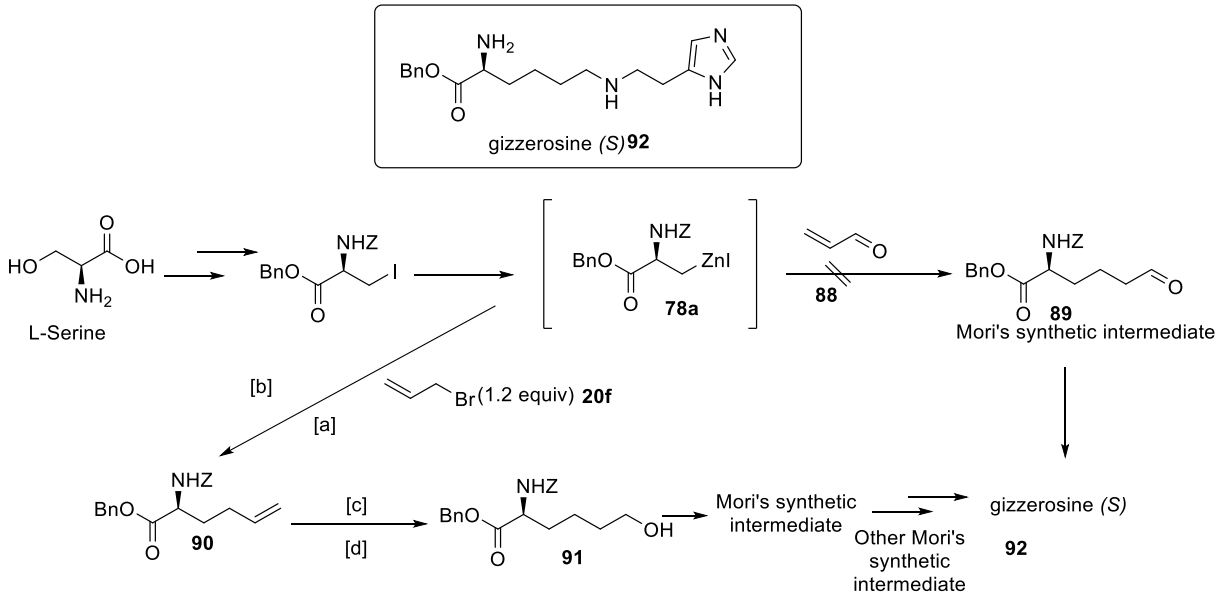
Kiyota *et al.* stereoselectively synthesised (–)-Tabtoxinine β-lactam **85**, a well-known phytotoxin that causes tobacco wildfire disease[51-56] via a Zn-mediated coupling reaction (Scheme 36).[57] In this synthetic strategy, **77** was reacted with zinc to yield the intermediate **78**, which on reaction with **79** under the same reaction condition gave **80** in 98% yield. The compound **80** was obtained in 61% yield by reacting **77** with **87** in the presence of AIBN in toluene at 70 °C. A similar synthetic methodology was utilized for the synthesis of **82a**, **82b** and **82c** by reacting silyl ethers **81** with **78**. Then, **83b** on asymmetric dihydroxylation provided intermediate **84**, which was converted to **85** through a sequence of several chemical reactions. The compound **86**, an isomer of **85**, was synthesized using the same pathway as used for the preparation of compound **85**.



Scheme 36. Synthesis of (–)-Tabtoxinine β-lactam Reaction conditions: [a] i) Zn, DMF, r.t., 20 min; ii) bromide (56 or 58), CuCN·2LiCl, DMF. [b] AlBN, toluene, 70 °C, 61%.

Kiyota et al. used a palladium-catalyzed and zinc-mediated coupling reaction to synthesize gizzerosine **92**, an effective activator of gizzard erosion in chickens (Scheme 37).[58] The initial attempt to synthesize the Mori's intermediate through the zinc-mediated 1,4-conjugate addition of the iodine compound

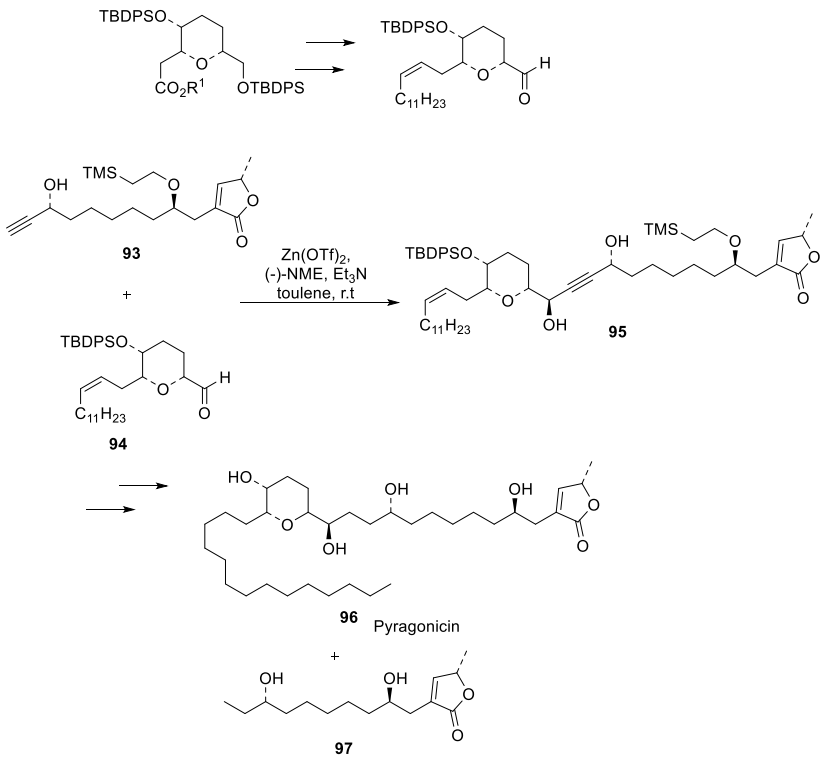
78a with acrolein resulted in the synthesis of an alanine derivative instead of the Mori's intermediate. The efforts to synthesize the Mori's other intermediate, the alcohol **91**, commenced with the zinc-mediated coupling reaction of allyl bromide with the organo zinc compound **78a** in the presence of dibromoethane and TMSCl in DMF by heating at 60 °C for 50 min. The synthesized alcohol was further transformed into Mori's synthetic intermediate by hydroboration reaction, which lead to the formation of gizzerosine (S) **92** by means of well-defined steps.



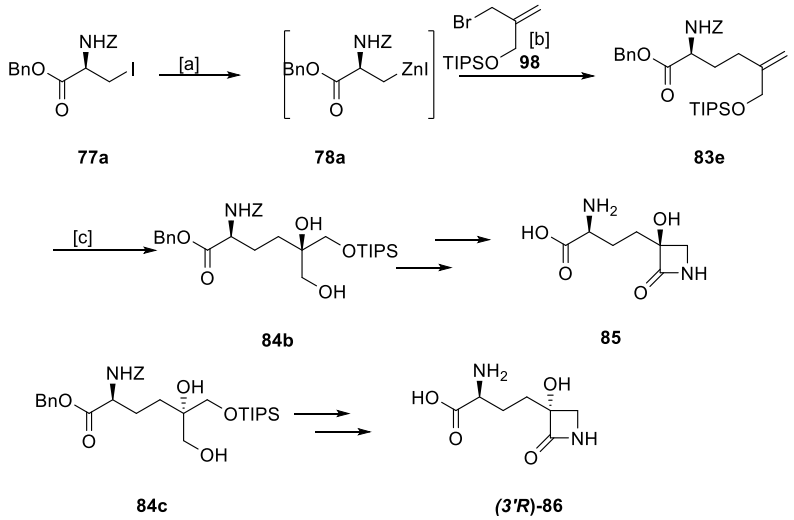
Scheme 37. The synthesis of gizzerosine *(S) via* zinc-mediated coupling reaction. Reaction condition: [a] **20f** (1.2 equiv.), Zn (6.0 equiv.), $(CH_2Br)_2$ (0.3 equiv.), TMSCl (0.06 equiv.), DMF, 60 °C, 50 min; [b] CuCN (1 equiv.), LiCl (2 equiv.), -78 °C, 2 h (98%); [c] $BH_3.SMe_2$ (0.5 equiv.), THF, 0 °C, 12 h; [d] H_2O_2 (30%, 3.3 equiv.), NaOAc (2.5 equiv.) (68%).

Rein *et al.* synthesised pyragonicin **96** via a convergent stereo-controlled process.[59] The pyragonicin's core structure was subsequently produced by linking the highly functionalized two intermediates **93** and **94** via a controlled stereoselective coupling reaction promoted by zinc forming **95**, which was converted into the target product **96** via a series of chemical transformations (Scheme 38).

Kiyota and colleagues stereoselectively synthesized Tabtoxinine β-lactam **65** and its isomer *(3'R)-**86*** via a Zn-mediated coupling reaction (Scheme 39).[60] Here, **77a** was converted into the key intermediate **78a** by using zinc powder in DMF at room temperature by stirring for 20 min. Then, it was coupled with compound **98** in the presence of CuCN.2LiCl in DMF to provide the resultant product **83e**, which underwent a series of chemical reactions including asymmetric hydroxylation and β-lactam formation of hydroxamate etc., as significant steps, yielding the target product **85**. *(3'R)*-**86** is the isomer of **85** and is prepared by using the same synthetic route used for the synthesis of Tabtoxinineβ-lactam **85**.

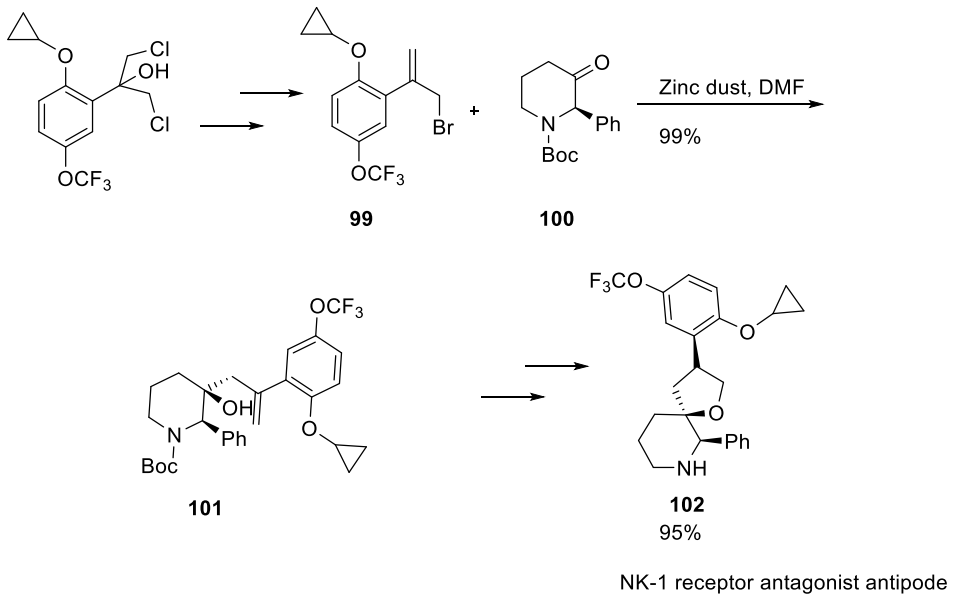


Scheme 38. The synthesis of pyragonicin via zinc-promoted coupling reaction.



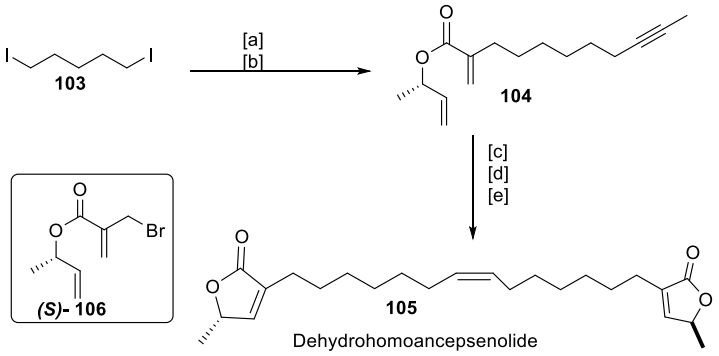
Scheme 39. Tabtoxinine-β-lactam and its isomer were synthesised by using Zn-mediated coupling reaction. Reaction conditions: [a] Zinc, DMF, r.t., 20 min, [b] CuCN.2LiCl, DMF, [c] AD-mix (β), *t*-BuOH/H_2O (2:1), 0 ^oC, 48 h.

The NK-1 receptor antagonist **102** antipode**,** a well-known spirobicylic compound was synthesised through a diastereoselective Zn-mediated coupling reaction of *(R)*-piperidone **100** with allylic bromide **99** (Scheme 40).[61] The resultant compound **101** was converted into the desired product **102** with 95% yield via a sequence of chemical transformations.



Scheme 40. Synthesis of NK-1 receptor antagonist antipode.

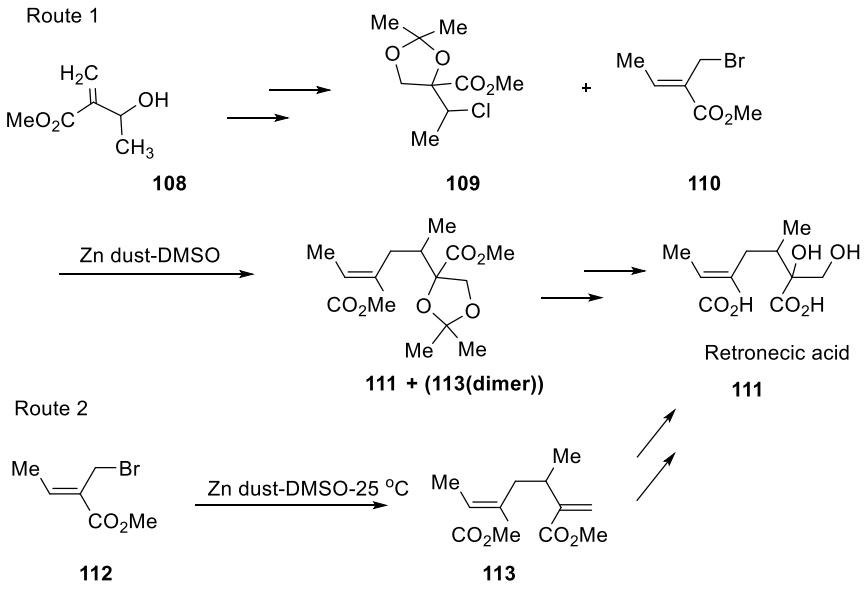
Furstner *et al.* reported the total synthesis of dehydrohomoancepsenolide **105** via a Zn-promoted three-component coupling reaction.[62] A 1,5-heterobimetallic intermediate was produced by inserting zinc into both of the carbon-iodine bonds of **103** and then adding copper(I) cyanide (CuCN) and LiCl to the resulting bis organozinc complex (Scheme 41). The compound **104** was formed in 70% yield by reacting this key bimetallic intermediate with **107** (-35 °C for 15 h) followed by reaction with (***S)*-106** at -78 °C for 1 h. The resultant compound **104** underwent ring closing metathesis using Grubb's catalyst, $(PCy_3)_2Cl_2Ru$=CHPh followed by alkyne metathesis with $(t\text{-}BuO)_3W{\equiv}CCMe_3$ led to the dimerization that was transformed to the target product **105** in 96% yield via a Lindlar reduction.



Scheme 41. The total synthesis of dehydrohomoancepsenolide via Zn-mediated coupling reaction. Reaction conditions: [a] Zn, THF, 40 °C, 24 h, [b] (i) CuCN, LiCl, THF, 0 °C, 15 min, (ii) 1-iodo-1-propyne (0.7 equiv.) **107**, hexane, -60 to -35 °C,15 h, (iii) ***(S)*-106**(1.5 equiv.), 1 h, -78 °C to r.t. [c] $(PCy_3)_2Cl_2Ru$=CHPh 10 (16 mol %), CH_2Cl_2, reflux, 24 h, 70%, [d] $(tBuO)_3W{\equiv}CCMe_3$ 12 (10 mol %), toluene, 100 °C, 10 h, 75%, [e] Lindlar catalyst, quinoline cat., hexane/EtOH (1/1), H2 (1 atm), rt, 30 min, 96%.

Hoole *et al.* devised two synthetic methodologies (route 1 and route 2) for the synthesis of Retronecic acid through Zn-mediated coupling reaction of halogeno esters.[63] In the case of route 1, **109** was coupled with

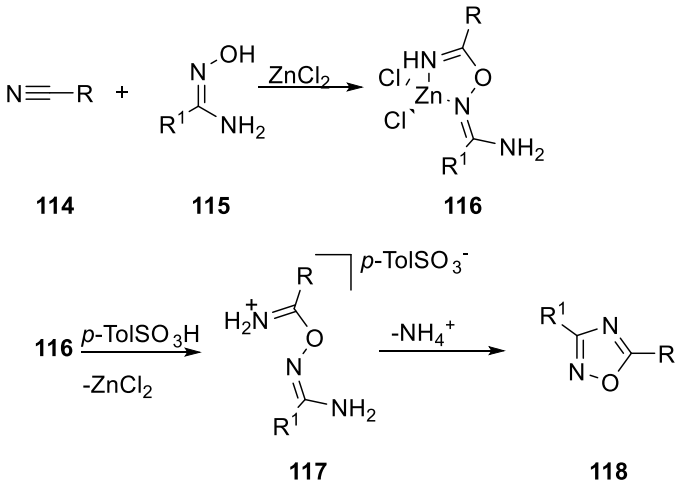
110 in the presence of Zn dust using DMSO as the solvent to afford the desired coupled products, that was then subjected to further chemical reactions for the formation of retronecic acid **111** along with its isomers. In route 2, the compound **112** in DMSO was slowly added to the zinc dust slurry in DMSO. The synthesized diene **113** was converted into only target compound **111** via a sequence of well-defined chemical reactions such as epoxide formation, hydroxylation, acetylation, epoxide ring opening, deprotection of acetyl groups and then ester hydrolysis. (Scheme 42). In comparison to route 2, route 1 was more complex in terms of purification and yields.



Scheme 42. The synthesis of retronecic acid via Zn-mediated coupling reaction.

Miscellaneous Reactions

Kukushkin *et al.* devised a methodology for achieving 1,2,4-oxadiazoles via a Zn/H^+-promoted nitrile-amidoxime coupling reaction.[64] Initially, a zinc-promoted coupling reaction between amidoximes **115** and either conventional nitrile or cyanamides (RCNs) **114** was performed, yielding the corresponding zinc chelated product **116** (Scheme 43). Due to the liberation of chelated ligands **117**, the resulting complex rapidly gave iminium salt in strong acidic conditions (*p*-$TolSO_3H$). Furthermore, at 20-65 °C, this iminium salt was spontaneously converted into the desired product **118**. In a side reaction, substituted urea was formed when cyanamide derived compounds underwent the Tiemann rearrangement



114 **115** **116** **117** **118**

Scheme 43. The synthesis of 1,2,4-oxadiazoles via Zn/H^+-promoted nitrile-amidoxime coupling reaction.

Conclusions

The Zn-promoted coupling reactions are the most versatile reactions that can be used for the fabrication of C-C and C-heteroatom bonds. The metallic zinc possesses a lot of characteristics such as being environment friendly, harmless, low cost, etc. The mild reaction environments and the fact that reactions usually occur at room temperature are the advantages of the coupling reaction. These reactions are eco-friendly and also involve water-mediated coupling reactions with good yields. Also, this system is highly effective and inexpensive as compared to other metal-mediated coupling reactions, like the Sm-mediated system. In some cases, certain additives, such as formamide, were added to this reaction system to enhance product yield. It will be more attractive if the reaction proceeds without any additives. In some cases, the reaction time was found to be too long. This draw back needs to be addressed in future studies. In addition, this zinc-mediated reaction should be extended to different π-component systems.

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References

1. Peterson, D. J. *J. Org. Chem*. **1968**, *33,* 780-784. https://doi.org/10.1021/jo01266a061
2. Wittig, G.; Giessler, G. *Just Liebigs Ann. Chem*. **1953,** *580,* 44-57. https://doi.org/10.1002/jlac.19535800107
3. Horner, L.; Hoffmann, H.; Wippel, H. G. *Ber.* **1958**, *91*, 61-63. https://doi.org/10.1002/cber.19580910113
4. Julia, M.; Paris, J. M. *Tetrahedron Lett.* **1973**, *14*, 4833-4836. https://doi.org/10.1016/S0040-4039(01)87348-2

5. King, A. O.; Okukado, N.; Negishi, E. *J. Chem. Soc., Chem. Commun.* **1977**, *19*, 683-684. https://doi.org/10.1039/c39770000683
6. Haas, D.; Hammann, J. M.; Greiner, R.; Knochel, P. *ACS Catal.* **2016**, *6*, 1540−1552. https://doi.org/10.1021/acscatal.5b02718
7. Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, *20*, 3437-3440. https://doi.org/10.1016/S0040-4039(01)95429-2
8. Heck, R. F.; Nolley, J. P. *J. Org. Chem.* **1972**, *37*, 2320-2322. https://doi.org/10.1021/jo00979a024
9. Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975***, 16***,** 4467-4470. https://doi.org/10.1016/S0040-4039(00)91094-3
10. Milstein, D.; Stille, J. K. *J. Am. Chem. Soc*. **1978**, *100,* 3636-3638. https://doi.org/10.1021/ja00479a077
11. Tamao, K.*;* Sumitani, K.; Kumada, M. *J. Am. Chem. Soc*. **1972**, 94**,** 4374–4376. https://doi.org/10.1021/ja00767a075
12. Corriu, R. J. P.; Masse*,* J. P. *J. Chem. Soc., Chem. Commun.* **1972**, 144a-144a. https://doi.org/10.1039/c3972000144a
13. Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1988***, 53*, 918-920. https://doi.org/10.1021/jo00239a056
14. Chodkiewicz,W. *Ann. Chim. Paris* **1957**, *2*, 819–69. https://doi.org/10.1136/bmj.2.5048.819
15. Guram, A. S.; Buchwald*,* S. L. *J. Am. Chem. Soc*. **1994**, *116*, 7901-7902. https://doi.org/10.1021/ja00096a059
16. Okuyama, H.; Yokoshima, S.; Yamashita, T.; Fukuyama, T. *Tetrahedron Lett.* **1998**, *39,* 3189-3192. https://doi.org/10.1016/S0040-4039(98)00456-0
17. Yamamoto, Y.; Nakano, S.; Maekawa, H.; Nishiguchi, I. *Org. Lett.* **2004***, 6*, 799-802. https://doi.org/10.1021/ol036506e
18. Yamada, T.; Alpers, D. H.; Owyang, C.; Powell, D. W.; Silverstein, F. E. *Textbook of gastroenterology*, 5th Ed. Chichester: Blackwell, 2009; pp 495, 498, 499, 1274, 2526.
19. Sun, X.; Wang, L.; Zhang, Y. *Synth. Commun.* **1998**, *28*, 1785-1791. https://doi.org/10.1080/00397919808007009
20. McGinnis, T. M.; Thane, T. A.; Jarvo, E. R. *Org. Lett.* **2022**, *24*, 5619−5623. https://doi.org/10.1021/acs.orglett.2c02362
21. Jing, T.; Liu, N.; Xu, C.; Bu, Q. *Eur. J. Org. Chem.* **2022**, *2022,* e202200178-e202200182. https://doi.org/10.1002/ejoc.202200178
22. Pei, G.; Xu, W.; Li, J. *Org. Chem. Front.* **2021,** *8,* 3372-3380. https://doi.org/10.1039/D1QO00386K
23. Yeh, C-H.; Korivi, R. P.; Cheng, C-H. *Adv. Synth. Catal.***2013**, *355*, 1338 – 1344. https://doi.org/10.1002/adsc.201300073
24. Krasovskiy, A.; Thomé, I.; Graff, J.; Krasovskaya, V.; Konopelski, P.; Duplais, C.; Lipshutz, B. H. *Tetrahedron Lett.* **2011**, *52,* 2203–2205. https://doi.org/10.1016/j.tetlet.2010.11.160
25. Shu, C.; Sidhu, K.; Zhang, L.; Wang, X.- j.; Krishnamurthy, D.; Senanayake, C. H. *J. Org. Chem.* ***2010*****,** *75*, 6677–6680.

https://doi.org/10.1021/jo100983c
26. Krasovskiy, A.; Duplais, C.; Lipshutz, B. H. *J. Am. Chem. Soc.* **2009**, *131,* 15592–15593. https://doi.org/10.1021/ja906803t
27. M. Lombardo, E. Mosconi, F. Pasi, M. Petrini, C. Trombini, *J. Org. Chem.* **2007**, *72*, 1834-1837. https://doi.org/10.1021/jo062265n
28. Zhao, M. M.; Qu, C.; Lynch, J. E. *J. Org. Chem.* **2005**, *70*, 6944-6947. https://doi.org/10.1021/jo050500g
29. Alcaide, B.; Almendros, P.; Rodrı´guez-Acebes, R. *J. Org. Chem.* **2005**, *70*, 3198-3204. https://doi.org/10.1021/jo050130w
30. Chen, Y. K.; Walsh, P. J. *J. Am. Chem. Soc.* **2004**, *126,* 3702-3703. https://doi.org/10.1021/ja0396145
31. Yamamoto, Y.; Nakano, S.; Maekawa, H.; Nishiguchi, I. *Org. Lett.* **2004**, *6,* 799-802. https://doi.org/10.1021/ol036506e
32. Sekiguchi, T.; Sato, K.; Ishihara, T.; Konno, T.; Yamanaka, H. *Chem. Lett.* **2004**, *33*, 666-667. https://doi.org/10.1246/cl.2004.666
33. P. Wipf, C. Kendall, C. R. J. Stephenson*, J. Am. Chem. Soc.* **2003**, *125*, 761-768. https://doi.org/10.1021/ja028092a
34. Venkatraman, S.; Li, C.-J. *Tetrahedron Lett.***2000**, *41*, 4831-4834. https://doi.org/10.1016/S0040-4039(00)00658-4
35. Morgan, A. B.; Tour, J. M. *Macromolecules* **1998**, *31*, 2857-2865. https://doi.org/10.1021/ma9715482
36. Hazarika, B.K.; Dutta*,* D. K. *Synth. Commun.* **2011**, *41*, 1088–1093. https://doi.org/10.1080/00397911003797833
37. Yang, Y.-S.; Shen, Z.-L.; Loh, T.-P. *Org. Lett.* **2009**, *11*, 2213-2215. https://doi.org/10.1021/ol900619d
38. Yang, J-H.; Li, J-T.; Zhao, J-L.; Li, T-S. *Synth. Commun.* **2004**, *34*, 993-1000. https://doi.org/10.1081/SCC-120028629
39. Wang, L. ; Sun, X.; Zhang, Y. *J. Chem. Res. (S).* **1998**, 336-337. https://doi.org/10.1039/A800478A
40. Niwa, T.; Uetake, Y.; Isoda, M.; Takimoto, T.; Nakaoka, M.; Hashizume, D.; Sakurai, H.; Hosoya, T. *Nat. Catal.* **2021**, *4*, 1080–1088. https://doi.org/10.1038/s41929-021-00719-6
41. Procter, R. J.; Dunsford, J. J.; Rushworth, P. J.; Hulcoop, D. G.; Layfield, R. A.; Ingleson, M. J. *Chem. Eur. J.* **2017**, *23*, 15889-15893. https://doi.org/10.1002/chem.201704170
42. Miersch, A.; Kohlmeyer, C.; Hilt, G. *Synthesis* **2013**, *45*, 3228–3232. https://doi.org/10. 1055/s-0033-1339616
43. Marton, D.; Tari, M. *J. Organomet. Chem.***2000**, *612*, 78–84. http://dx.doi.org/10.1016/S0022-328X(00)00388-0
44. Marton, D.; Russo, U.; Stivanello, D.; Tagliavini, G. *Organometallics* **1996**, *15*, 1645-1650. https://doi.org/10.1021/om9507742
45. von Gyldenfeldt, F.; Marton, D.; Tagliavini, G. *Organometallics,* **1994**, *13*, 906-913. https://doi.org/10.1021/om00015a025

46. Carofiglio, T.; Marton, D.; Tagliavini, G. *Organometallics,* **1992,** *11*, **2**963-2965. https://doi.org/10.1021/om00045a003
47. Sun, X.; Wang, L.; Zhang, Y. *Synth. Commun.* **1998***, 28,* 1785-1791. https://doi.org/10.1080/00397919808007009
48. Sun, P.; Wang, L.; Zhang, Y. *Tetrahedron Lett.* **1997**, *38,* 5549-5550. https://doi.org/10.1016/S0040-4039(97)01240-9
49. Cianci, J.; Baell, J. B.; Harvey, A. J. *Tetrahedron Lett.* **2007**, *48*, 5973–5975. https://doi.org/10.1016/j.tetlet.2007.06.109
50. Braga, A. L.; Schneider, P. H.; Paixao, M. W.; Deobald, A. M. *Tetrahedron Lett*. **2006**, *47*, 7195-7198. https://doi.org/10.1016/j.tetlet.2006.07.148
51. Wolf, F. A.; Foster, A. C. *Science* **1917**, *46,* 361-362, https://doi.org/10.1126/science.46.1189.361
52. Woolley, D. W.; Pringle, R. B.; Braun, A. C. *J. Biol. Chem.* **1952**, *197,* 409-417, https://doi.org/10.1016/S0021-9258(18)55690-8
53. Woolley, D. W.; Schaffner, G.; Braun, A. C. *J. Biol. Chem.***1952**, *198*, 807-813, https://doi.org/10.1016/S0021-9258(18)55538-1
54. Woolley, D. W.; Shaffner, G.; Braun, A. C. *J. Biol. Chem.* **1955**, *215*, 485-493, https://doi.org/10.1016/S0021-9258(18)65970-8
55. Stewart, W. W. *Nature.***1971**, *229,* 174-178. https://doi.org/10.1038/229174a0
56. Durbin, R. D.; Uchytil, T. F. ; Steele, J. A. ; de Ribeiro, R. L. D. *Phytochemistry* **1978,** *17,* 147-147. https://doi.org/10.1016/S0031-9422(00)89699-5
57. Kiyota, H.; Takai, T.; Shimasaki, Y.; Saitoh, M.; Nakayama, O.; Takada, T.; Kuwahara, S. *Synthesis* **2007**, 2471–2480. https://doi.org/10.1055/s-2007-983785
58. Shimasaki, Y.; Kiyota, H.; Sato, M.; Kuwahara, S. *Synthesis* **2005**, 3191-3192. https://doi.org/10.1055/s-2005-918447
59. Strand, D.; Rein, T. *Org. Lett.* **2005**, 7, 2779-2781. https://doi.org/10.1021/ol050997g
60. Kiyota, H.; Takai, T.; Saitoh, M.; Nakayama, O.; Oritani, T.; Kuwahara, S. *Tetrahedron Lett.* **2004***, 45*, 8191-8194. https://doi.org/10.1016/j.tetlet.2004.09.033
61. Maligres, P. E.; Waters, M. M.; Lee, J.; Reamer, R. A.; Askin, D.; Ashwood, M. S.; Cameron, M. *J. Org. Chem.* **2002**, *67,* 1093-1101. https://doi.org/10.1021/jo0157472
62. Furstner, A.; Dierkes*,* T. *Org. Lett.* **2000**, *2,* 2463-2465. https://doi.org/10.1021/ol006122d
63. Ameer, F.; Drewes, S. E.; Hoole, R.; Kaye, P. T.; Pitchford*,* A. T. *J. Chem. Soc. Perkin Trans.* **1985**, *1,* 2713-2717. https://doi.org/10.1039/P19850002713
64. Bolotin, D. S.; Kulish, K. I.; Bokach, N. A.; Starova, G. L.; Gurzhiy, V. V.; Kukushkin, V. Y. *Inorg. Chem.* **2014**, *53*, 10312−10324. https://doi.org/10.1021/ic501333s

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