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# Recent Strategies for the Synthesis of Pyridine Derivatives

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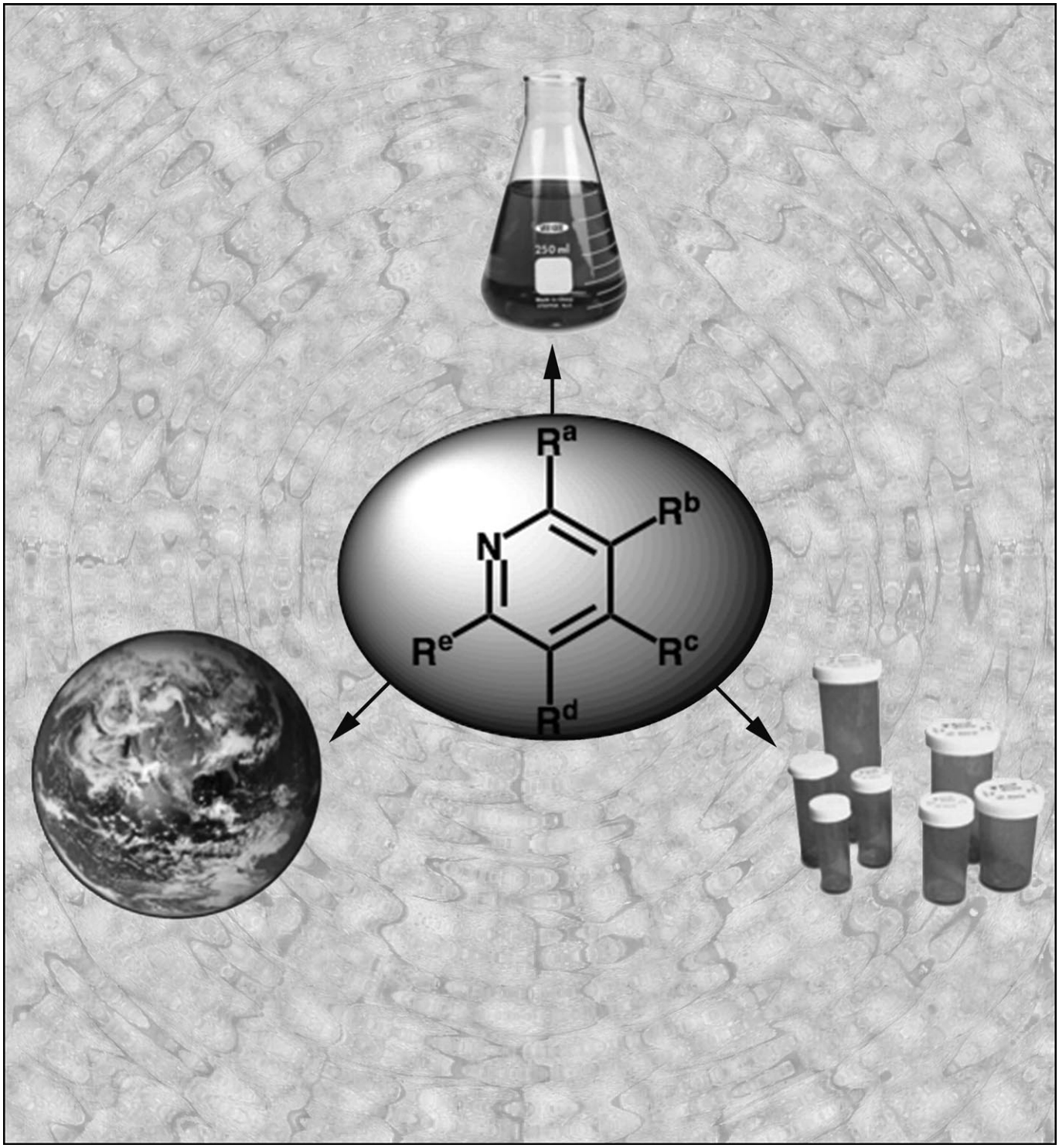


**Abstract:** Recent advances in pyridine synthesis are described. Modification of traditional condensation strategies continues to be a recurrent theme in contemporary literature. Advancements in transition-metal-catalyzed cyclization and cross-coupling procedures offer new routes to functionalized pyridine derivatives. These recently developed methodologies are a valuable addition to azaheterocycle synthesis.

**Keywords:** annulation · condensation · cyclization · heterocycles · pyridine

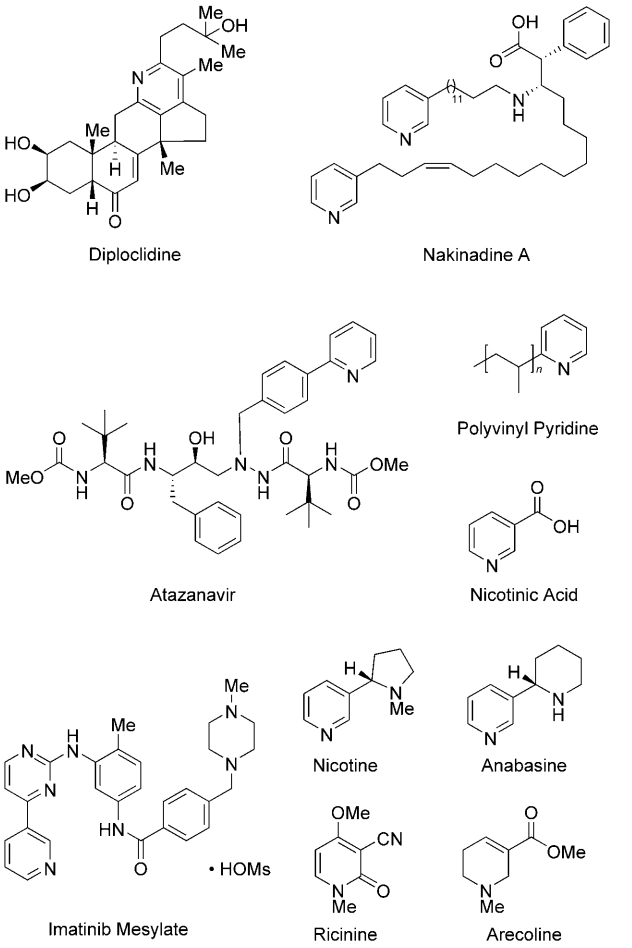
## Introduction

Pyridine derivatives are an important class of azaheterocycle found in many natural products, active pharmaceuticals, and functional materials.[1] Diploclidine[2] and nakinadine A[3] are two examples of recently isolated and structurally diverse natural products containing the pyridine core (Scheme 1). Pyridine-derived pharmaceuticals include atazanavir[4] (Reyataz) and imatinib mesylate[5] (Gleevec) (Scheme 1). These drugs are prescribed for human immunodeficiency virus (HIV) and chronic myelogenous leukemia, respectively. Pyridine derivatives are also incorporated into polymers such as polyvinyl pyridine (PVP, Scheme 1).[6] For well over a century, chemists have developed methodologies for pyridine synthesis and it is unlikely that interest in the field will decrease due to the continued importance of the pyridine core in both biological and chemical fields.

Many pyridine-based alkaloid natural products are derivatives of nicotinic acid (also known as vitamin $B_3$ and niacin, Scheme 1).[7] In nature, this important component of coenzymes nicotinamide adenine dinucleotide ($NAD^+$) and nicotinamide adenine dinucleotide phosphate ($NADP^+$) is synthesized from L-tryptophan by way of the kynurenine pathway in animals, or from glyceraldehyde 3-phosphate and L-aspartic acid in many plants.[7] Both pathways rely on decarboxylation of quinolinic acid as a final step, but are otherwise very different.

Nicotine is formed by the incorporation of a pyrrolidine moiety derived from L-ornithine onto the molecular framework of nicotinic acid (Scheme 1). Like nicotine, similar alkaloids, including anabasine, ricinine, and arecoline, all originate from nicotinic acid (Scheme 1).[7]

While picoline was isolated in 1846,[8] Körner's and Dewar's elucidation of the pyridine structure in 1869 and 1871, respectively, marked the beginning of significant chemical research in the field.[9] Coal tar served as an initial source of pyridine, however, recent commercial methods have been developed for its preparation from crotonaldehyde, formaldehyde, and ammonia in the gas phase.[1b]




Scheme 1. Representative compounds containing a pyridine substructure. Ms = mesyl.

Historically, many pyridine syntheses rely on condensation of amine and carbonyl compounds. These, and other methods for the preparation of the pyridine core, are often characterized by the number of atoms in each fragment contributing to the six-atom azaheteroaromatic ring. Ammonia ($NH_3$) has served as the nitrogen source in countless protocols, including [5+1] condensation with 1,5-dicarbonyls (Scheme 2).[10] Like many condensation methods, autoxidation is necessary for aromatization. Ammonia is also frequently used in the [2+2+1+1] Hantzsch pyridine synthesis (Scheme 3).[11,12] Other pyridine syntheses rely on alkyl or vinyl amines such as the [3+3] example: 1,3-dicarbonyl derivative condensation with a vinylogous amide (Scheme 4).[13]

Methods that do not rely on condensation chemistry have become increasingly important. Boger et al. have developed

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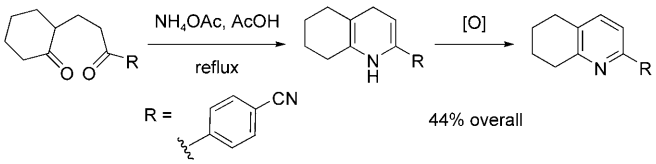
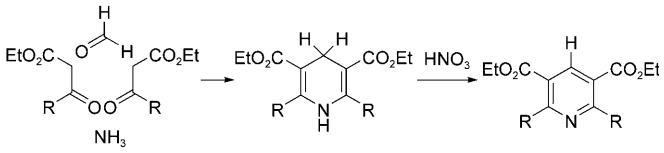
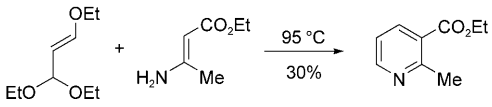



Scheme 2. The [5+1] condensation route to substituted pyridines.[10]

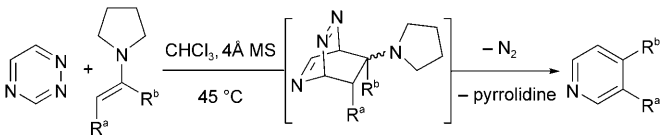



Scheme 3. The [2+2+1+1] Hantzsch pyridine synthesis.[11]

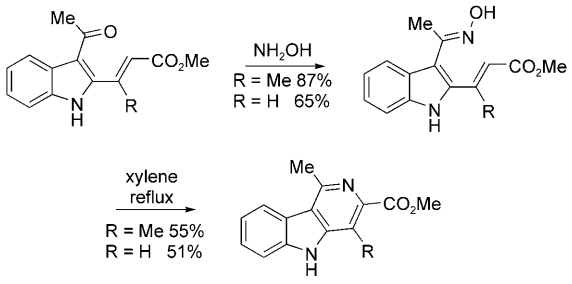



Scheme 4. The [3+3] condensation of a 1,3-dicarbonyl derivative and vinylogous amide.[13]

a [4+2] inverse electron demand aza-Diels–Alder reaction between enamines and 1,2,4-triazine (Scheme 5).[14] 6π-Electrocyclization approaches are also of continuing importance (Scheme 6).[15] A well-developed [2+2+2] approach utilizes two alkyne equivalents and a nitrile species (Scheme 7).[16]

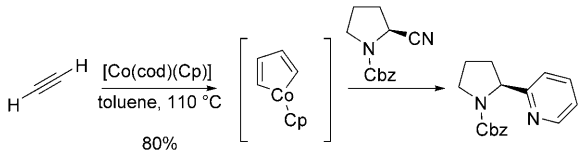



Scheme 5. The [4+2] aza-Diels–Alder approach to pyridine derivatives.[14] MS = molecular sieves.

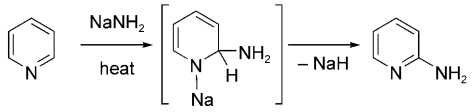



Scheme 6. The [4+2] rhodium-mediated synthesis of pyridines.[15]

Azaheterocycle substituent modification is described in several reviews.[17] Some methods, including the Chichibabin reaction (Scheme 8),[18] rely on the electron-deficient character of the pyridine ring. Recent advancements in cross-coupling chemistry have increased the popularity and practicality of substituent modification reactions. Activated pyridines

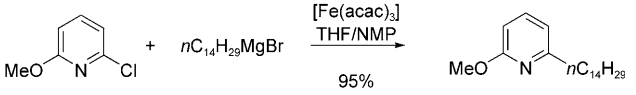



Scheme 7. The [2+2+2] cobalt-mediated synthesis of substituted pyridines.[16] Cbz = carbobenzyloxy, cod = cyclooctadiene.

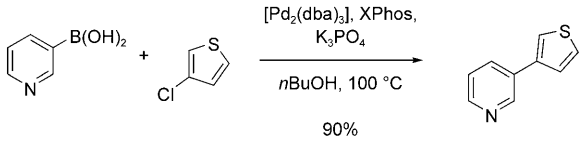



Scheme 8. The Chichibabin reaction.[18]

can be used with numerous transition-metal catalysts to afford a structurally diverse set of pyridine derivatives (Schemes 9 and 10).[17,19,20]




Scheme 9. Iron-catalyzed cross-coupling of activated pyridines.[19] acac = acetylacetate.




Scheme 10. Suzuki–Miyaura cross-coupling of activated pyridines.[20] XPhos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl, dba = dibenzylideneacetone.

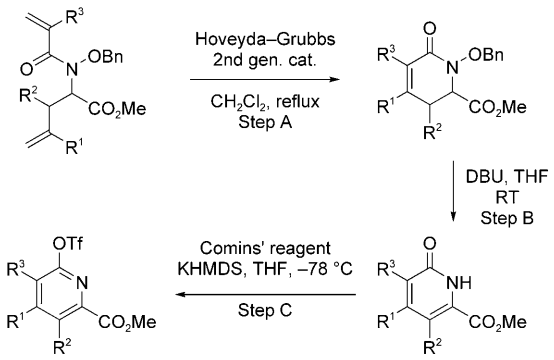
*Dr. Matthew D. Hill earned degrees in biochemistry, molecular biology, and legal communication from Ohio University (OU) in 2003. While at OU, Matthew got his first taste of academic research when he synthesized phorbol analogues under the supervision of Professor Mark McMills. Matthew also spent a summer at Columbia University where he performed research on age-related macular degeneration with Professor Koji Nakanishi. In 2008 he received his Ph.D. in organic chemistry from The Massachusetts Institute of Technology (MIT). Matthew developed several new methodologies for the preparation of azaheterocycles in the lab of Professor Mohammad Movassaghi. After leaving MIT, Matthew started his current position within the neuroscience chemistry division of drug discovery at Bristol-Myers Squibb.*

## Recent Advances in Pyridine Synthesis

Although the literature on pyridine synthesis enjoys a rich history of versatile methodologies,[1] new approaches remain valuable to the contemporary collection of synthetic strategies. Some of these methodologies employ the direct condensation of amine and carbonyl substrates, whereas other reports describe multicomponent reactions to afford substituted pyridine derivatives. Recent synthetic strategies also take advantage of many transition-metal catalysts developed over the past several decades.

Ring-closing metathesis (RCM) has proven to be one of the most utilized chemical breakthroughs of the twentieth century.[21] This technology has been used by Donohoe et al. for the multistep synthesis of 2,6-di- and 2,3,6-trisubstituted pyridines with alkyl, aryl, and alkoxy substituents (Scheme 11).[22] The Hoveyda–Grubbs second generation

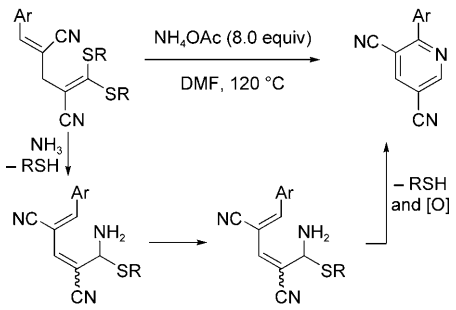



$R^1$, $R^2$ = H, $R^3$ = H, Step A 98%, Step B 94%, Step C 70%
$R^1$, $R^2$ = H, $R^3$ = $CF_3$, Step A 75%, Step B 65%, Step C 67%
$R^1$, $R^2$ = H, $R^3$ = OBn, Step A 85%, Step B 98%, Step C 87%

Scheme 11. RCM strategy for pyridine synthesis.[22] KHMDS = potassium hexamethyldisilazide, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, Bn = benzyl.

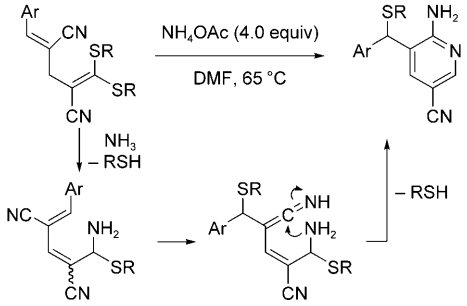
ruthenium catalyst was optimal for the conversion of amide precursors to the corresponding α,β-unsaturated lactams. Subsequent 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)-promoted benzyl alcohol elimination, and lactam trapping with Comins' reagent afforded the pyridine products in moderate to excellent overall yield. Post-RCM chemical manipulation gave access to additional substitution patterns and further increased the utility of this protocol.

A recent report by Hu et al. describes a [5+1] approach to 2,3,5-trisubstituted pyridines.[23] Interestingly, the mode of cyclization was found to be temperature dependent and provided two distinct classes of pyridine derivative (Schemes 12 and 13). This method relies on available 1,1-bisalkylthio-1,4-pentanedienes, prepared in one step from ketene-(*S*, *S*)-acetals, allylic alcohols, and ammonium acetate ($NH_4OAc$) as an ammonia source.[24] Electron-rich arenes with alkyl thio-substitution gave the desired products in moderate to good yield, however electron-neutral and -poor aromatics gave little or none of the corresponding pyridine.




Ar = 4-EtOPh, R = Et, 56%
Ar = 4-MeOPh, R = Bn, 54%
Ar = 4-ClPh, R = Et, 0%

Scheme 12. The [5+1] strategy for 2,3,5-trisubstituted pyridine synthesis.[23]

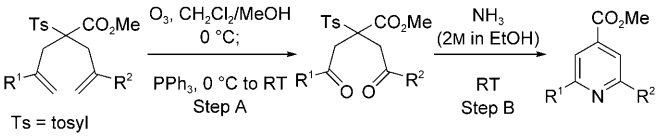



Ar = 4-EtOPh, R = Et, 74%
Ar = 4-MeOPh, R = Bn, 77%
Ar = Ph, R = Et, 36%

Scheme 13. The [5+1] alternative cyclization pathway for 2,3,5-trisubstituted pyridine synthesis.[23]

Craig and Henry reported a new variation of a well-established [5+1] methodology utilizing 1,5-dicarbonyl condensation with ammonia.[25] Both 2,4-di- and 2,4,6-trisubstituted pyridines with alkyl, aryl, and ester substituents were prepared from 1,6-dienes by ozonolysis, subsequent condensation with ammonia, and elimination of sulfinic acid (Scheme 14). This reaction sequence was demonstrated in both two separate steps, and in one step from the 1,6-diene.

[4+2] Strategies for construction of the pyridine ring are prevalent in azaheterocycle literature.[1] Many of these

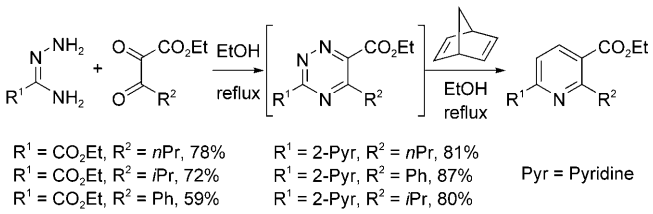



| 1 Step | 2 Steps |
|---|---|
| $R^1$ = H, $R^2$ = Et, 42% | $R^1$ = H, $R^2$ = Ph, Step A 77%, Step B 82% |
| $R^1$ = H, $R^2$ = *n*Oct, 56% | $R^1$ = Me, $R^2$ = Ph, Step A 57%, Step B 80% |
| $R^1$ = Me, $R^2$ = Me, 83% | $R^1$ = Me, $R^2$ = Me, Step A 86%, Step B 83% |

Scheme 14. The [5+1] ozonolysis/condensation route to pyridines.[25] *n*Oct = *n*-octyl.

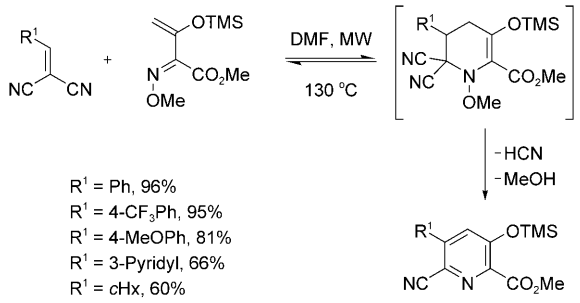
  

methods rely on transition-metal catalysts, whereas others, such as a recent aza-Diels–Alder method reported by Stanforth et al., rely on cycloaddition of 1,2,4-triazines with dienophiles.[26] Established aza-Diels–Alder methods afford 3,4-disubstituted pyridines with both substituents originating from the dienophile.[14] Stanforth et al. have developed a single-step synthesis of alkyl, aryl, heteroatom, and ester 2,3,6-trisubstituted pyridines in moderate to good yield from amidrazones, α,β-diketoesters, and 2,5-norbornadiene (Scheme 15). Interestingly, this aza-Diels–Alder reaction provides access to pyridine derivatives of which all substituents are derived from the parent 1,2,4-triazine.



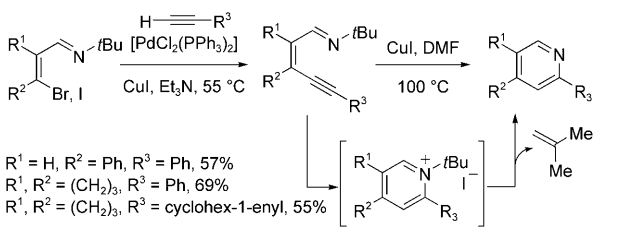

Scheme 15. The [4+2] aza-Diels–Alder approach to 1,2,6-trisubstituted pyridines.[26]

In a recent report, Lu et al. took advantage of the [4+2] cycloaddition between a 1-aza-1,3-butadiene and α,α-dicyanoalkenes (Scheme 16).[27] The readily accessible α,α-dicyanoalkenes acted as alkyne surrogates and provided 2,3,5,6-tetrasubstituted pyridines in a single and regioselective step. The activating substituent located on the nitrogen was critical to the efficiency of cycloaddition, with O-methyl proving optimal over O-silyl substituents. Whereas the reaction proceeded moderately under conventional thermal conditions, microwave irradiation improved isolated yields. Under the optimal reaction conditions, an electronically diverse set of aromatic- and heteroaromatic-substituted α,α-dicyanoalkenes, in addition to a single alkyl example, were converted to the desired cyanohydroxypyridines in moderate to excellent yield.




Scheme 16. The [4+2] regioselective synthesis of pyridine derivatives by cycloaddition.[27] MW = microwave, *c*Hx = cyclohexyl.

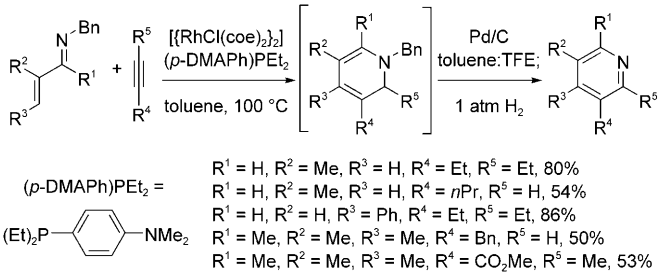
The Larock group has developed a [4+2], two-step, transition-metal-catalyzed route to 2,4-di- and 2,4,5-trisubstituted pyridines (Scheme 17).[28] Palladium-catalyzed coupling




Scheme 17. The [4+2] palladium-/copper-catalyzed route to pyridines.[28]

of vinylic imines with terminal alkynes followed by subsequent copper-catalyzed cyclization gave aryl-, vinyl-, and alkyl-substituted pyridines in moderate yields. Significantly, this method was extended to the synthesis of alkaloid decumbenine B and various other isoquinolines.

Ellman et al. have developed a single-step, transition-metal-catalyzed [4+2] method for the synthesis of di-, tri-, tetra-, and pentasubstituted pyridines from α,β-unsaturated imines and alkynes.[29] This approach takes advantage of rhodium-catalyzed C–H alkenylation followed by 6π-electrocyclization (Scheme 18). The dihydropyridine intermediates can be isolated in some cases or carried on directly to the desired pyridines by subsequent palladium-catalyzed debenzylation/oxidation. This process gives pyridine derivatives in modest to good yields with various substitution patterns, including alkyl, aryl, and ester substituents.

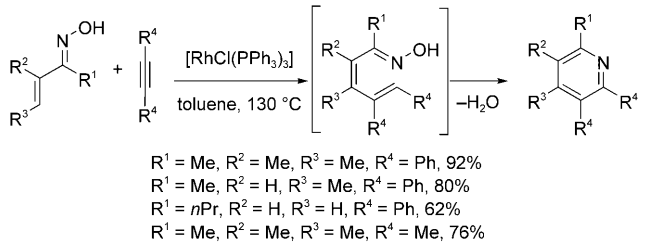



Scheme 18. The [4+2] rhodium- /palladium-catalyzed route to pyridines.[29] coe = cyclooctene.

In a related report, Cheng et al. developed a [4+2] one-pot synthesis of alkyl-, aromatic-, and heteroaromatic-substituted pyridines through a rhodium-catalyzed C–H alkenylation of α,β-unsaturated ketoximes with symmetrical alkyne substrates (Scheme 19).[30] 6π-Electrocyclization of the azatriene intermediate and subsequent loss of water affords the desired tri-, tetra-, and pentasubstituted pyridines in moderate to good yield.

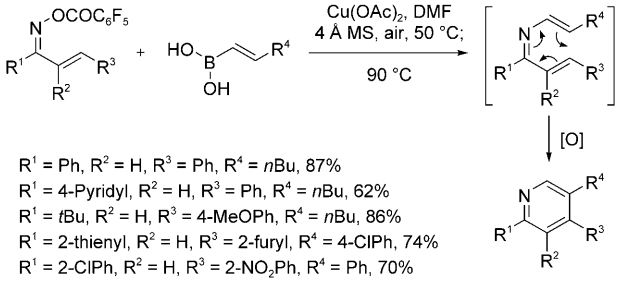
While carbon–carbon cross-coupling/6π-electrocyclization cascade reactions in pyridine synthesis are well known, carbon–nitrogen coupling/electrocyclization cascades are not. Liu and Liebeskind took advantage of recently developed carbon–nitrogen cross-coupling methodology for the N-imination of boronic acids in their recent report on the one-pot synthesis of 2,4,5-tri-, 2,3,4,5-tetra-, and 2,3,4,5,6-




Scheme 19. The [4+2] synthesis of pyridine derivatives through a rhodium-catalyzed C–H alkenylation/6π-electrocyclization reaction sequence.[30]

pentasubstituted pyridines with alkyl, aryl, and heteroaryl substituents (Scheme 20).[31] Copper-catalyzed coupling of α,β-unsaturated ketoxime *O*-pentafluorobenzoates with

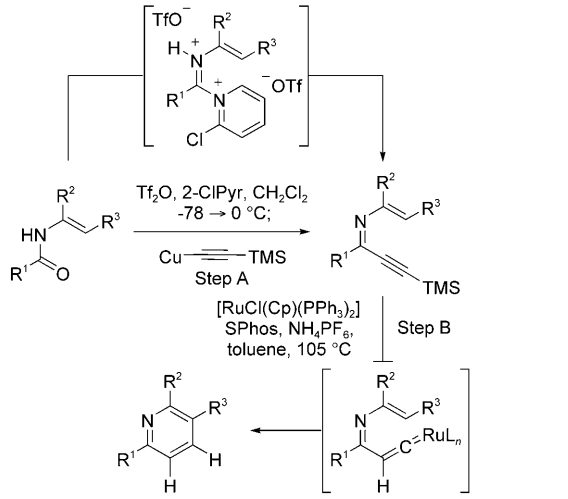



Scheme 20. The [4+2] copper-catalyzed, one-pot synthesis of pyridines.[31]

alkyl- and aryl-substituted alkenyl boronic acids afforded 3-azatriene intermediates that underwent 6π-electrocyclization and autoxidation upon heating. This [4+2] procedure provided the desired pyridines in moderate to good yields and provides a novel approach to azaheterocycles.

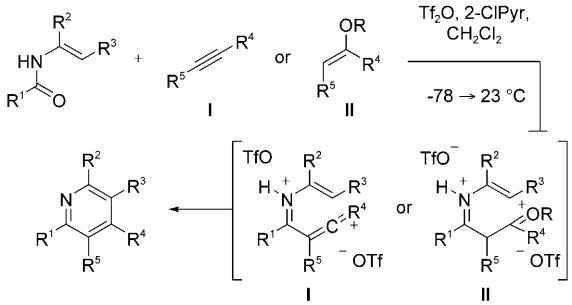
Movassaghi and Hill recently reported a convergent [4+2], two-step pyridine synthesis.[32] This methodology relied on trifluoromethanesulfonic anhydride ($Tf_2O$) and 2-chloropyridine (2-ClPyr) activation of N-vinyl amides to provide 3-azadienyne substrates for ruthenium-catalyzed cycloisomerization and the formation of 2,5-di- and 2,3,6-trisubstituted pyridines. The mild reagent combination of $Tf_2O$/2-ClPyr provided access to pyridines from sensitive amide substrates (Scheme 21). Amide activation and trapping with copper(I) trimethylsilylacetylide gave the silylated 3-azadienynes in moderate to excellent yields. Subsequent treatment of these intermediates with a ruthenium(II) complex led to the formation of a metal vinylidene that readily underwent 6π-electrocyclization and reductive elimination to afford the desired pyridines in moderate to excellent yields. Both steps of this method were tolerant of aryl, heteroaryl, aliphatic, and heteroatom substituents.

The Movassaghi group described a direct synthesis of pyridine derivatives from N-vinyl amides and π-nucleophiles.[33] Both acetylenes and enol ethers were found to add into electrophilic, $Tf_2O$/2-ClPyr-activated intermediates




Scheme 21. The [4+2] two-step pyridine synthesis from N-vinyl amides.[32] TMS = trimethylsilyl.

(Scheme 22). Subsequent annulation afforded a structurally diverse group of 2,3,6-tri-, 2,3,4,6-tetrasubstituted, and fully substituted pyridines in modest to excellent yields. This method is a single step, which is compatible with a variety of functional groups, and provides access to pyridines with aromatic, aliphatic, and heteroatom substituents. Significantly, an optically active amide substrate could be converted to the desired pyridine without loss of enantiomeric excess (*ee*).

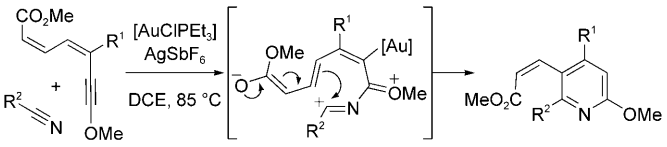



Scheme 22. The [4+2] single-step pyridine synthesis from N-vinyl amides.[33] TIPS = triisopropylsilyl, SPhos = 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl, TPS = triphenylsilyl.

Barluenga et al. recently described a gold-catalyzed dehydro-aza-Diels–Alder reaction of dienynes and nitriles.[34] This [4+2] route provides tetrasubstituted pyridines with

alkyl, aryl, vinyl, heteroatom, and heteroaromatic substitution in moderate to good yields, however, the C-2 Z-vinyl moiety and C-6 methoxy group are invariable (Scheme 23). The authors suggest nitrile addition into gold-activated, electron-rich alkyne intermediates occurs prior to cyclization. Interestingly, the C-3 olefin geometry of the pyridine products is believed to be set by its participation in the ring-closing event (Scheme 23).

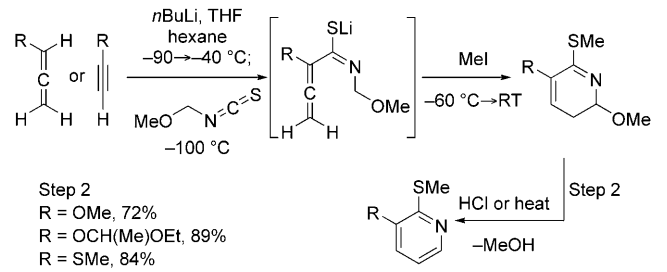



DCE = 1,2-dichloroethane

$R^1$ = Ph, $R^2$ = *n*Pr, 64%
$R^1$ = Ph, $R^2$ = Ph, 67%
$R^1$ = Ph, $R^2$ = 2-furyl, 69%
$R^1$ = Ph, $R^2$ = vinyl, 75%
$R^1$ = *n*Bu, $R^2$ = Me, 71%
$R^1$ = *t*Bu, $R^2$ = Me, 61%

Scheme 23. The [4+2] synthesis of tetrasubstituted pyridines reported by Barluenga et al.[34]

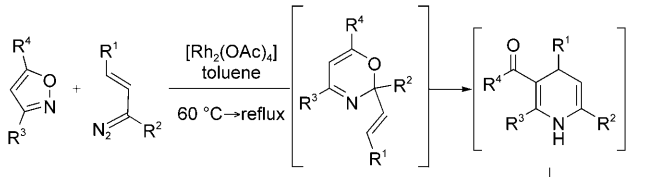
Brandsma et al. developed a new [3+3] two-step route to 5-substituted 6-(alkylthio)-2-methoxy-2,3-dihydropyridines that are easily converted to the corresponding pyridine adducts (Scheme 24).[35] 2-Methoxy-2,3-dihydropyridines were synthesized from lithiated allenes or acetylenes and alkyl isothiocyanates.[36] Loss of methanol with aromatization upon heating gave the desired disubstituted pyridines in good to excellent yields.




Step 2
R = OMe, 72%
R = OCH(Me)OEt, 89%
R = SMe, 84%

Scheme 24. The [3+3] synthesis of pyridines from allenes or acetylenes and alkyl isothiocyanates.[35]

In a recent report, the Davies group described a rhodium carbenoid induced ring expansion of isoxazoles that led to 2,3,4,6-tetrasubstituted pyridines.[37] This [3+3] one-pot procedure utilized readily accessible vinyldiazomethanes and isoxazoles, each providing three atoms of the pyridine core. After N–O insertion, two reaction pathways could lead to 1,4-dihydropyridines: 1) Claisen rearrangement followed by tautomerization or 2) electrocyclic ring opening, 6π-electrocyclization, and then tautomerization (Scheme 25). DDQ-oxidation gave the desired tetrasubstituted pyridines, and one fully substituted pyridine, in low to high yields. The product yields show a slight preference for electron-deficient

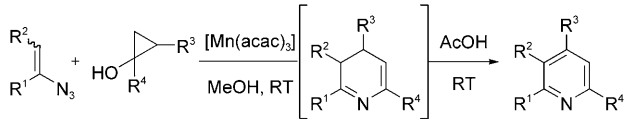



$R^1$ = Ph, $R^2$ = $CO_2$Me, $R^3$ = Me, $R^4$ = Me, 69%
$R^1$ = Ph, $R^2$ = COMe, $R^3$ = Me, $R^4$ = Me, 64%
$R^1$ = Me, $R^2$ = $CO_2$Me, $R^3$ = Me, $R^4$ = Me, 32%
$R^1$ = Ph, $R^2$ = $CO_2$Me, $R^3$ = Ph, $R^4$ = Ph, 69%
$R^1$ = $CO_2$Me, $R^2$ = $CO_2$Me, $R^3$ = Et, $R^4$ = Ph, 66%

Scheme 25. The [3+3] Davies one-pot synthesis of pyridine derivatives.[37] DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

aromatics at the 4-position of the pyridine ring. While some tolerance for nonaromatics was shown at the 4-position, the scope was limited to carbonyl moieties at the 3- and 6-positions.

Chiba and Wang developed an interesting manganese(III)-mediated synthesis of 2,6-di-, and 2,3,6- and 2,4,6-trisubstituted pyridines from cyclopropanols and vinyl azides.[38] This [3+3] approach is believed to occur through one-electron oxidation of a cyclopropanol by manganese(III), which forms a β-keto radical (Scheme 26). Subsequent addition of the radical into a vinyl azide affords an iminyl radical upon elimination of dinitrogen. This species can undergo cyclization, manganese(II) reduction, and elimination of water to afford a 3,4-dihydropyridine intermediate. Whereas catalytic amounts of the manganese(III) complex could be used in conjunction with an oxidant, such as oxygen or DDQ, to give the final products, the optimal conditions call for superstoichiometric manganese(III). This method provides pyridines in low to high yields with alkyl, aryl, vinyl, and carbonyl substituents.

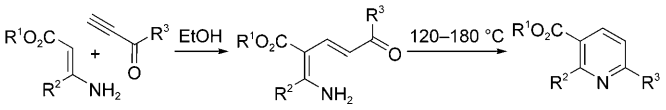



$R^1$ = Ph, $R^2$, $R^3$= H, $R^4$ = Ph, 84%
$R^1$ = 4-$CO_2$MePh, $R^2$, $R^3$= H, $R^4$ = Ph, 70%
$R^1$ = Ph, $R^2$ = Me, $R^3$= H, $R^4$ = Ph, 45%
$R^1$ = $CO_2$Et, $R^2$ = Ph, $R^3$= H, $R^4$ = Ph, 30%
$R^1$ = Ph, $R^2$, $R^3$= H, $R^4$ = $CO_2$Me, 33%

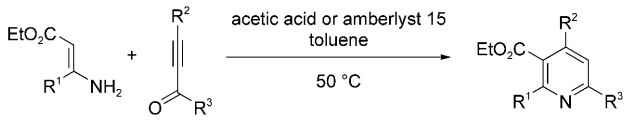
Scheme 26. The [3+3] synthesis of pyridine derivatives through the manganese(III)-mediated reaction of cyclopropanols with vinyl azides.[38]

The Bohlmann–Rahtz synthesis was originally reported over 50 years ago for the preparation of pyridines from β-amino crotonates and ynone precursors (Scheme 27).[39] Recently the Bagley group reported a mild, single-step variant of the reaction that utilizes either acetic acid or amberlyst 15 ion-exchange resin to promote cyclization (Scheme 28).[40] This [3+3] method gives 2,3,6-tri- and 2,3,4,6-tetrasubstitut-




Scheme 27. The original [3+3] Bohlmann–Rahtz pyridine synthesis.[39]

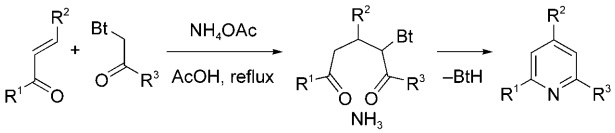



$R^1$ = Me, $R^2$ = $Me_3Si$, $R^3$ = Me, 79%
$R^1$ = Me, $R^2$ = Et, $R^3$ = Me, 85%
$R^1$ = Ph, $R^2$ = Et, $R^3$ = Me, 65%
$R^1$ = Ph, $R^2$ = H, $R^3$ = Me, 73%
$R^1$ = 2-furyl, $R^2$ = $Me_3Si$, $R^3$ = Me, 80%
$R^1$ = Me, $R^2$ = Ph, $R^3$ = Me, 71%

Scheme 28. New single-step Bohlmann–Rahtz variant.[40]

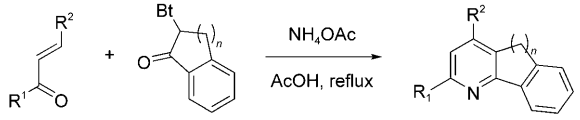
ed pyridines with alkyl, aryl, heteroaromatic, heteroatom, and ester substituents in moderate to excellent yields.

Katritzky et al. reported a [3+2+1] synthesis of 2,4,6-tri- and 2,3,4,6-tetrasubstituted pyridine derivatives in good yield.[41] This method relied on readily available α-benzotriazolyl ketone[42] and α,β-unsaturated ketone substrates. These starting materials gave access to 2,4,6-triaryl pyridines with both electron-rich and -poor arene substituents when heated with ammonium acetate in acetic acid (Scheme 29). Fused 2,3,4,6-tetrasubstituted pyridines were also formed from appropriate fused bicyclic ketone substrates (Scheme 30).




$R^1$ = Ph, $R^2$ = Ph, $R^3$ = Ph, 81%
$R^1$ = Ph, $R^2$ = 4-ClPh, $R^3$ = 4-ClPh, 80%
$R^1$ = 4-BrPh, $R^2$ = 4-MePh, $R^3$ = 4-MeOPh, 85%

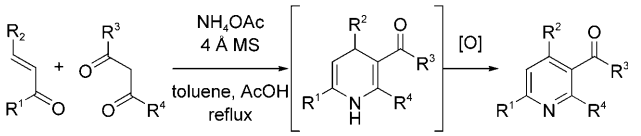
Scheme 29. The [3+2+1] Katritzky synthesis of 2,4,6-triaryl pyridine derivatives.[41]




$R^1$ = Ph, $R^2$ = Ph, $n$ = 1, 77%
$R^1$ = 4-BrPh, $R^2$ = 4-MeOPh, $n$ = 1, 72%
$R^1$ = Ph, $R^2$ = Ph, $n$ = 2, 55%

Scheme 30. The [3+2+1] synthesis of fused pyridine derivatives.[41]

Rodriguez et al. have developed a [3+2+1] regioselective, oxidative multicomponent synthesis of 2,3,4,6-tetrasubstituted pyridine derivatives from 1,3-dicarbonyl compounds, β,γ-unsaturated-α-ketoesters, and ammonium acetate (Scheme 31).[43] Following Michael addition and ring closure, autoxidation provides pyridines with methyl, aryl, carbonyl,

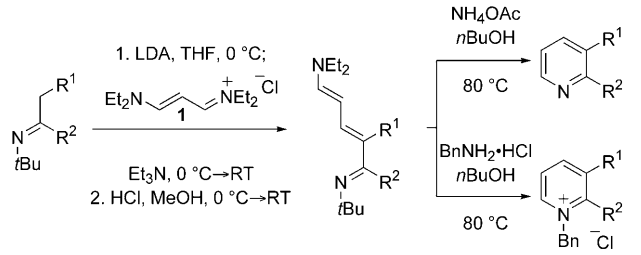



$R^1$ = $CO_2Et$, $R^2$ = Me, $R^3$ = OMe, $R^4$ = Me, 73%
$R^1$ = $CO_2Me$, $R^2$ = Ph, $R^3$ = NHPh, $R^4$ = Me, 91%
$R^1$ = $CONH_2$, $R^2$ = Ph, $R^3$ = OMe, $R^4$ = Me, 73%
$R^1$ = $PO(OEt)_2$, $R^2$ = Me, $R^3$ = OEt, $R^4$ = Ph, 69%

Scheme 31. The [3+2+1] synthesis of tetrasubstituted pyridines.[43]

and phosphonate groups. Significantly, the use of α-ketocarbonyl Michael acceptors prevented reversible addition, and provided access to 4-substituted pyridines.[44]

A recent [3+2+1] three-step synthesis of 3-mono- and 2,3-disubstituted pyridines and pyridinium chlorides was reported by Marazano et al. (Scheme 32).[45] This three-step




| | NH4OAc | BnNH2•HCl |
|---|---|---|
| $R^1$ = *n*Pent, $R^2$ = H | 90% | 89% |
| $R^1$ = Ph, $R^2$ = H | 94% | 96% |
| $R^1$ = Ph, $R^2$ = Ph | 92% | 91% |

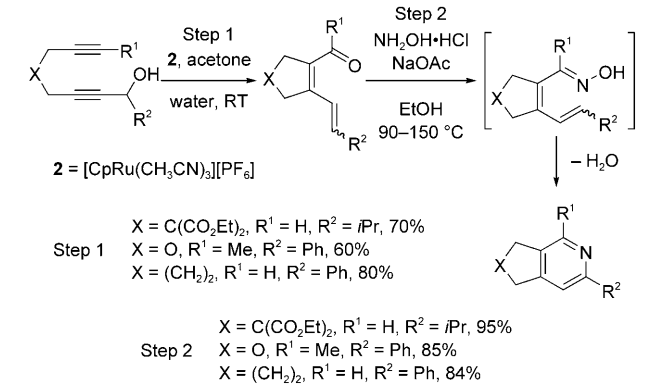
Scheme 32. The [3+2+1] three-step synthesis of pyridine and pyridinium chloride derivatives.[45] LDA = lithium diisopropylamide, *n*Pent = *n*-pentyl.

procedure utilizes aldimine starting materials that upon deprotonation were capable of nucleophilic addition into vinamidinium salt **1**, providing aminopentadieneimine salts in moderate yields. These salts were heated in the presence of ammonium acetate or benzylammonium chloride to provide pyridine and pyridinium derivatives, respectively, with alkyl and phenyl substitution in good to excellent yields.

Trost and Gutierrez recently developed a two-step [3+2+1] synthesis of pyridines that makes use of a ruthenium-catalyzed cycloisomerization and subsequent 6π-electrocyclization.[46] A variety of structurally diverse diynols were useful precursors for the ruthenium-catalyzed synthesis of dienals (Scheme 33). Isolation of the dienal products, followed by heating in the presence of hydroxylamine hydrogen chloride, gave tri- and tetrasubstituted pyridines with alkyl and aryl substituents in moderate to excellent yields.

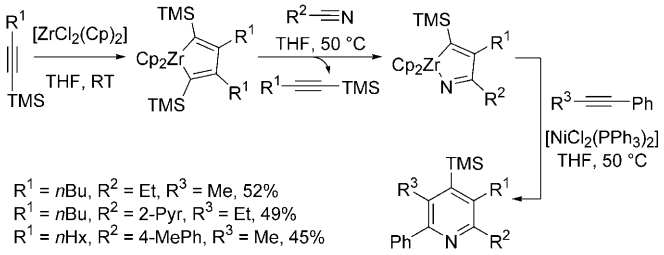
Formation of pyridine derivatives from two alkynes and a nitrile is a well-established [2+2+2] method.[1,16] Takahashi et al. reported a nickel-mediated variant that uses two different unsymmetrical alkynes and an alkyl or aryl nitrile (Scheme 34).[47] This process involves nitrile displacement of



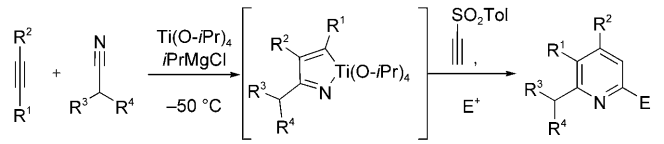

Scheme 33. The [3+2+1] ruthenium-catalyzed cycloisomerization/6π-electrocyclization synthesis of pyridines.[46]

one equivalent of alkyne from a zirconacyclopentadiene intermediate, followed by addition of the second alkyne with nickel to afford pentasubstituted pyridines. While the yields of this transformation are modest, the reactions proceed with complete regiochemical control.




Scheme 34. The [2+2+2] nickel-mediated synthesis of pentasubstituted pyridines.[47] Cp = cyclopentadiene, *n*Hx = *n*-hexyl.

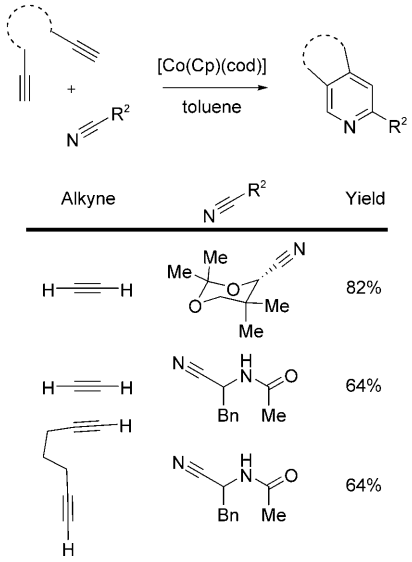
Suzuki et al. have reported a titanium-mediated [2+2+2] pyridine synthesis.[48] This method utilized an azatitanacyclopentadiene intermediate (Scheme 35), generated by the reaction of an alkyne, a nitrile, and *iso*-propyl magnesium chloride with titanium isopropoxide. Symmetrical alkyl-substituted alkynes were required to avoid a mixture of regioisomeric products, but a trimethylsilyl group, when located on an alkyne substrate, was shown to direct regiochemistry




Scheme 35. Suzuki's [2+2+2] titanium-mediated pyridine synthesis.[48] TBS = *tert*-butyldimethylsilyl, Tol = tolyl.

of the titanacycle intermediate. Subsequent addition of ethynyl *p*-tolyl sulfone, followed by reaction quench gave a variety of 2,3,4-tri- and 2,3,4,6-tetrasubstituted pyridines with alkyl, aryl, silyl, and iodo substituents. Significantly, numerous optically active pyridines were formed from chiral α-oxynitriles with complete retention of enantiomeric excess.

Cobalt catalysis is a common theme in pyridine synthesis.[49] Heller et al. developed a new cobalt-catalyzed [2+2+2] synthesis of chiral 2-mono-, 2,4,5-tri-, and 2,3,4,5,6-pentasubstituted pyridines from chiral nitriles and symmetrical alkynes in moderate to good yields (Scheme 36).[50] The sub-



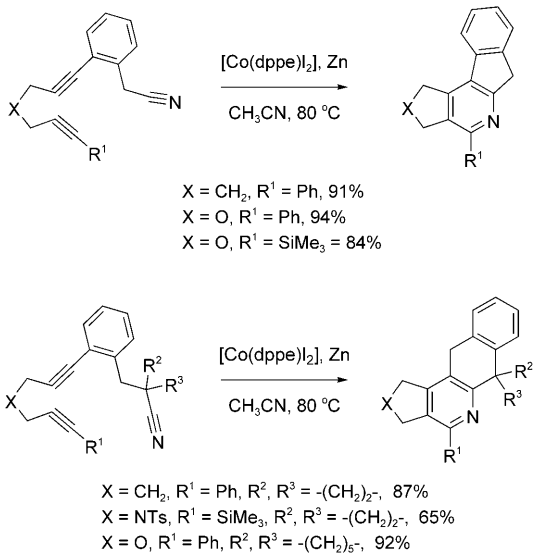

Scheme 36. Cobalt-catalyzed procedure for the synthesis of chiral substituted pyridines.[50]

strate scope included nitrile-containing starting materials with stereogenic centers, both adjacent to and removed from the cyano functionality. The reaction of a nitrile with 1,6-heptadiyne provided a tethered substrate that provided an interesting 5,6-fused bicycle.

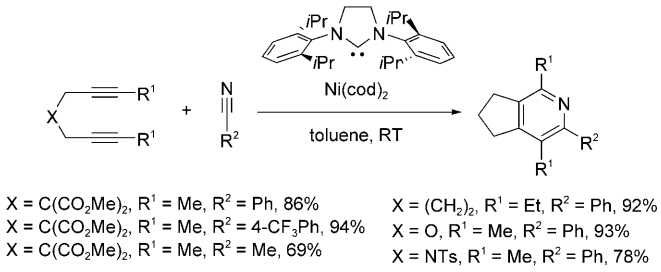
Tethered diynes are commonly seen in [2+2+2] pyridine syntheses (see above), however, nitrilediyne substrates are far less common. Chang et al. have developed both symmetric and asymmetric nitrilediyne substrates that can undergo a cobalt-catalyzed cyclotrimerization reaction to afford fully substituted, fused polycyclic pyridines (Scheme 37).[51] Importantly, a bulky substituent was required at the terminal alkyne carbon for the reaction to proceed in moderate to excellent yields.

Louie et al. have developed another tethered variation of the [2+2+2] approach.[52] In this nickel-catalyzed method, both symmetrical alkynes are tethered and form nickelapyrrole intermediates en route to the desired azaheterocycles (Scheme 38). Pyridines with alkyl, aryl, and heteroaromatic substituents were formed in moderate to excellent yields. Interestingly, this method was extended to one example each of an untethered alkyne and an unsymmetrical alkyne.




Scheme 37. Intramolecular cobalt-catalyzed cyclotrimerization of nitrile-diynes.[51] dppe = 1,2-bis(diphenylphosphino)ethane.




Scheme 38. The [2+2+2] nickel-catalyzed synthesis of pentasubstituted pyridine derivatives.[52]

## Summary and Outlook

Several recent and convergent synthetic approaches to pyridines have been published. Many of these reports offer new modifications to existing methodologies, whereas others describe unprecedented transformations. Condensation chemistry of amine- and carbonyl-containing fragments is still common, but the current trend appears to be toward transition-metal-catalyzed processes, whether it is assembly of the pyridine ring or substituent modification by cross-coupling chemistry. Each of these new methods serves as a valuable addition to a field rich in chemical history.

## Acknowledgements

I thank the Massachusetts Institute of Technology for granting permission to publish the introduction of this review as it appears in the Ph.D. thesis Direct Synthesis of Pyridine and Pyrimidine Derivatives; more details can be found therein.[53] I also thank Professor Mohammad Movassaghi for his critique of the introduction.

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