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Multicomponent syntheses of 5- and 6-membered aromatic heterocycles using group 4–8 transition metal catalysts

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In this *Perspective*, we discuss recent syntheses of 5- and 6-membered aromatic heterocycles via multicomponent reactions (MCRs) that are catalyzed by group 4–8 transition metals. These MCRs can be categorized based on the substrate components used to generate the cyclized product, as well as on common mechanistic features between the catalyst systems. These particular groupings are intended to highlight mechanistic and strategic similarities between otherwise disparate transition metals and to encourage future work exploring related systems with otherwise-overlooked elements. Importantly, in many cases these early- to mid-transition metal catalysts have been shown to be as effective for heterocycle syntheses as the later (and more commonly implemented) group 9–11 metals.

1. Introduction

Atom- and step-economy are increasingly important measures in the development of new synthetic processes.¹ One strategy that can rapidly increase synthetic efficiency is the use of multicomponent reactions (MCRs). These reactions incorporate three or more separate or tethered functional groups to form multiple bonds in a single chemical process to generate a new product.² MCRs can dramatically increase chemical complexity in a single step and often benefit from readily accessible, simple, and modular starting materials. Importantly, key classes of heterocycles (in particular 5- and 6-membered monocyclic aromatic heterocycles) can be synthesized by MCRs. The imperative to develop efficient routes to 5- and 6-membered heterocycles results from their ubiquitous application in pharmaceuticals,^{3–14} electronic materials,^{15–18} polymer science,^{5,13,19} pesticides,^{14,20} and dyes.^{5,13,14,21}

In this *Perspective*, we will discuss recent (10–15 years) group 4–8 catalyzed MCRs of 5- and 6-membered aromatic heterocycles. Many such catalytic MCRs have been demonstrated by group 9–11 metals.^{13,22–25} In recent years, the earlier group 4–8 metals have increasingly emerged as useful catalysts for 5- and 6-membered heterocycle syntheses, and often have advantages with respect to cost and earth abundance.^{26,27} Although groups 4–8 are often considered quite disparate in their properties, there is strikingly significant overlap in multicomponent synthetic strategies using these elements, in particular in the synthesis of pyrroles and pyridines (Fig. 1). While Ru catalysts have perhaps been most heavily investigated (owing to historically significant early reactions), earth-abundant^{26,27} Fe and Ti are also well-represented.

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This *Perspective* is organized by retrosynthetic strategies for each 5- and 6-membered heterocycle. There is a preponderance of examples of pyrrole and pyridine syntheses, which is likely

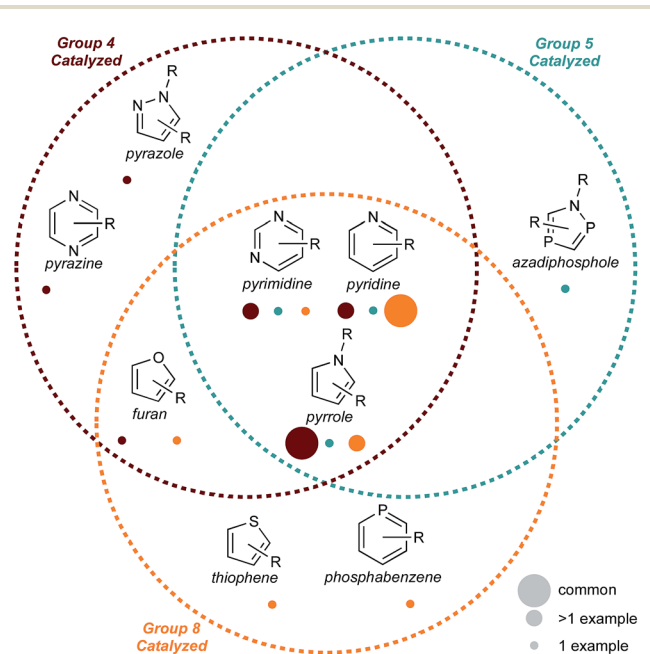


Fig. 1 Summary of recent group 4–8 catalyzed multicomponent reactions for aromatic heterocycle synthesis discussed in this *Perspective*. Circle color is correlated to methods of synthesis from a particular catalyst group (4, 5, or 8), while size is correlated to the prevalence of methods (common, multiple examples, or 1 example). There are no examples of group 6 catalysts and only 1 example of group 7.



a function of the importance of these heterocycles in bioactive molecules.^{20,28} Importantly, although pyridine synthesis is dominated by group 8 and pyrrole synthesis by group 4, there are similar mechanistic or retrosynthetic demonstrations with the other elements. These early hints into new and complementary reactivity demonstrate that there remains a substantial opportunity to explore the catalytic syntheses of other 5- and 6-membered heterocycles using group 4–8 transition metals. We hope that in highlighting these examples, common mechanistic threads will ultimately lead to new methods development across the early- and mid-transition metal series.

2. 5-Membered rings

2.1 Pyrroles, furans, and thiophenes

Monocyclic aromatic heterocycles such as pyrroles, furans, and thiophenes are typically prepared through condensation reactions like the Paal–Knorr cyclization of a 1,4-diketone with the appropriate heteroatomic nucleophile. However, the scope and efficacy of these condensation reactions are often limited by the need for specific substitution patterns or complex carbon skeleton preconstruction. As a result, there has been considerable effort in developing multicomponent approaches for the convenient construction of these heterocycles, some of which have been summarized previously.^{29,30} Because of their similar structures, approaches to the synthesis of the monocyclic aromatic heterocycles are often similar. In fact, several of the MCR strategies catalyzed by groups 4–8 can be applied across all three heterocycles, although the majority of demonstrated examples have been aimed toward the synthesis of pyrroles. Most methods involve combinations of on-metal cycloadditive or insertion reactions, combined with final heterocycle formation through electrocyclization (either on-metal or off-metal).

2.1.1 Formal [2 + 2 + 1] strategies: coupling of alkynes with E₁ units (E = N, S, O). The most common strategy for pyrrole construction *via* MCRs with groups 4–8 is the formal [2 + 2 + 1] cyclization of two alkynes with a nitrogen source. The scope of nitrogen sources for these reactions includes amines (*via* hydroamination and subsequent condensation) or nitrenes (*via* group transfer from azides, diazenes, or sulfoximines). Catalytic MCRs facilitated by group 4–8 transition metals of monocyclic furans and thiophenes mirror those seen with pyrroles: for example, *via* [2 + 2 + 1] cyclizations using diynes and O-atom transfer reagents (nitrones, DMSO) or S-atom transfer reagents (thiocarbonyls).

When amines are used as the nitrogen source, pyrrole formation can be achieved from a cascading sequence of alkyne hydroamination followed by electrocyclization. For example, Ti-catalyzed hydroamination of 1,4-diynes (**1**) or 1,5-diynes (**4**)³¹ *via* azatitanacyclobutene intermediates^{32,33} results initially in the formation of monoiminated 4-iminoalkyne (**2**) and 5-iminoalkyne (**5**) products, respectively (Fig. 2). These iminoalkyne intermediates can then undergo 5-*endo-dig* (4-iminoalkyne) or 5-*exo-dig* (5-iminoalkyne) cyclization to ultimately form 2,5-disubstituted pyrrole products. Either Ti(NMe₂)₂(dpma) (**CAT1**) or Ti(NMe₂)₂(dmpm) (dpma = di(pyrrolyl- α -methyl)methylamine; dmpm = 5,5-dimethyldipyrrolylmethane) (**CAT2**) can be

used as the hydroamination catalyst to form the 4- or 5-iminoalkyne. In both reactions, the Ti catalyst is only responsible for the formation of the iminoalkyne product that subsequently cyclizes to form the pyrrole product. These reactions are compatible with both terminal and internal diynes featuring phenyl and alkyl (Me, ⁿBu) groups. **CAT1** was used exclusively for terminal diynes, while **CAT2** was used exclusively for internal diynes. Unsubstituted 1,4-pentadiyne resulted in a double hydroamination product rather than pyrrole. However, substituted 1,4-diynes slowed the rate of the second hydroamination, allowing for pyrrole formation. Terminal substituted diynes (R¹ = H) resulted in formation of the Markovnikov amination product in all cases. Similarly, high regioselectivity is obtained in reactions with unsymmetrical 1,4-diynes with aryl and alkyl substituents, due to selective amination β to the phenyl moiety. With some substrates such as 1-phenyl-1,4-pentadiyne, oligomerization of the diyne fragment prevented productive catalysis.

Nitrene group transfer reactions catalyzed by Ti, V, and Ru have also been broadly used in the [2 + 2 + 1] synthesis of pyrroles. The first example of a nitrene group transfer strategy was reported in 2016,³⁴ in the [2 + 2 + 1] multicomponent cycloaddition of alkynes and aryl diazenes catalyzed by simple Ti imido halides (Fig. 3), such as **CAT3**. The proposed catalytic cycle for this process, determined through combined experimental and computational studies,^{35–38} is highlighted in Fig. 3. First, a Ti \equiv NR imido (**IM1**) undergoes [2 + 2] cycloaddition with an alkyne to form azatitanacyclobutene **IM2**, identical to the first step of Ti-catalyzed hydroamination.³² Next, a second alkyne equivalent undergoes alkyne insertion into the reactive Ti–C bond of **IM2** to form an azatitanacyclohexadiene (**IM3**),³⁹ which then undergoes C–N reductive elimination to afford pyrrole and Ti^{II}. The Ti imido is then regenerated through disproportionation of the diazene oxidant. This reaction can be

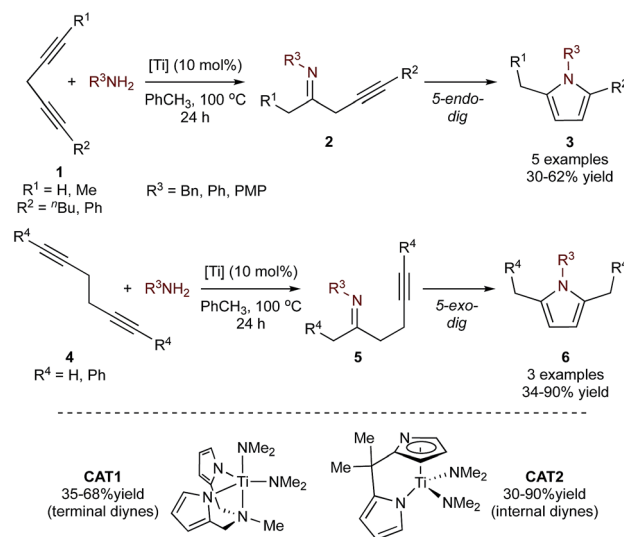


Fig. 2 Ti-catalyzed [2 + 2 + 1] synthesis of pyrroles from diynes and amines through monohydroamination and subsequent 5-*endo-dig* or 5-*exo-dig* cyclization.



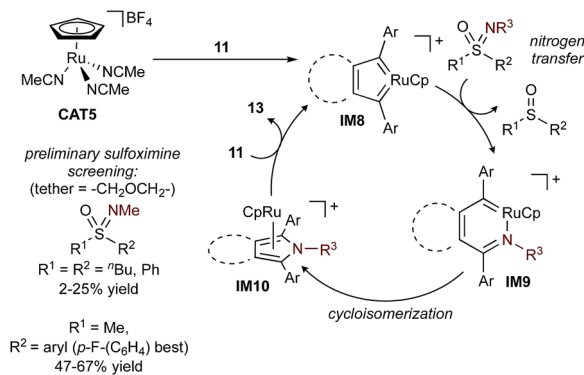
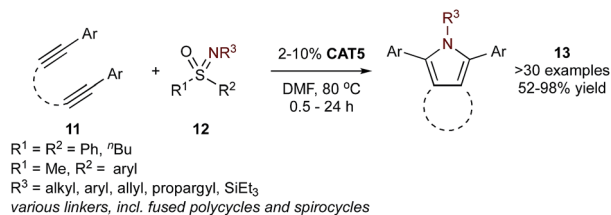


Fig. 6 Top: Ru-catalyzed [2 + 2 + 1] synthesis of bicyclic *N*-alkyl pyrroles from diynes and sulfoximines. Bottom: mechanism for the Ru-catalyzed [2 + 2 + 1] synthesis of pyrroles from diynes and sulfoximines.

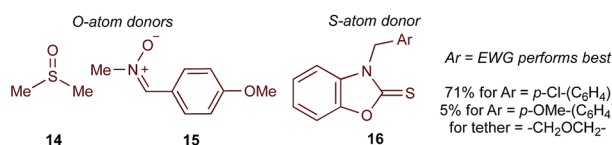
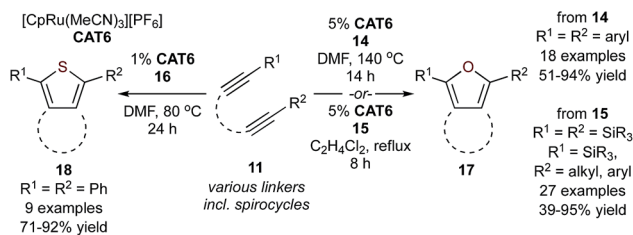


Fig. 7 Ru-catalyzed [2 + 2 + 1] synthesis of furans and thiophenes from O- and S-atom donors.

deficient aryl diynes underwent shorter reaction times. These reactions were also found to tolerate ester, ketone, nitrile, and sulfone functional groups. Reactions using the nitron group transfer reagent **15** expanded functional group tolerance on the diyne fragment to include bulky silyl groups. This increased tolerance was attributed to the milder reaction conditions (refluxing 1,2- $\text{Cl}_2\text{C}_2\text{H}_4$, approx. 84°C).

In the catalytic syntheses of thiophenes (**18**) using thiocarbonyl group transfer reagents (**16**), it was found that electron-deficient thiocarbonyls ($\text{Ar} = \text{p-Cl-C}_6\text{H}_4$, 71%) generated thiophenes in higher yields than electron-rich thiocarbonyls ($\text{Ar} = \text{p-OMe-C}_6\text{H}_4$, 5%). Like the furan [2 + 2 + 1] reactions, both electron-rich and -deficient aryl diynes generated thiophenes in excellent yields ranging from 71–92%. Alkyl diynes also generated thiophenes, however at more moderate yields (50–62%). These reactions

demonstrated similar functional group tolerance to the furan and pyrrole reactions, although TMS-substituted (TMS = trimethylsilyl) diynes were desilylated upon thiophene formation. Diynes containing the bulkier TBS (TBS = *tert*-butyldimethylsilyl) group generated a mixture of desilylated and silylated thiophene in 36% and 49% yield, respectively.

2.1.2 Other formal [2 + 2 + 1] strategies. Another potential strategy for catalytic multicomponent heterocycle syntheses is to generate metallacycles *in situ* and transmetallate them prior to ring closure. Stoichiometric transmetalations of group 4 metallacycles to main group elements are common, and Fagan–Nugent-like heterocycle synthesis is well-precedented.⁵⁰ A recent catalytic example that cleverly extends this manifold further is the titanocene-catalyzed multicomponent synthesis of 2,3,5-substituted 1*H*-pyrroles (**20**) incorporating two equivalents of nitrile and a terminal alkyne (Fig. 8, top).⁵¹ This reaction is initiated by reduction of $\text{Cp}_2\text{-TiCl}_2$ (**CAT7**) to “ $\text{Cp}_2\text{Ti}^{\text{II}}$ ” using Mg. An equivalent of alkyne reacts with “ $\text{Cp}_2\text{Ti}^{\text{II}}$ ” to form a titanacyclopriene intermediate (**IM11**), which is then proposed to undergo insertion of two nitriles to form a diazatitanacycloheptatriene intermediate (**IM12**). This then undergoes transmetalation with stoichiometric EtAlCl_2 to form Cp_2TiCl_2 and a proposed diazaaluminumacycloheptatriene (**19**), which undergoes ring-closing pyrrole formation upon hydrolysis. The cycle is closed by another reduction of Cp_2TiCl_2 by Mg. This reaction was compatible with both alkyl and aryl nitriles in combination with alkyl and aryl terminal alkynes.

This reaction can be further used for the synthesis of furans (**22**) from alkynes and esters (Fig. 8, bottom).^{52,53} Here, the metallacyclopriene ($\text{M} = \text{Ti, Zr}$) intermediate undergoes insertion with two equivalents of ester forming a dioxametallacycloheptene, which is then converted to **21** following

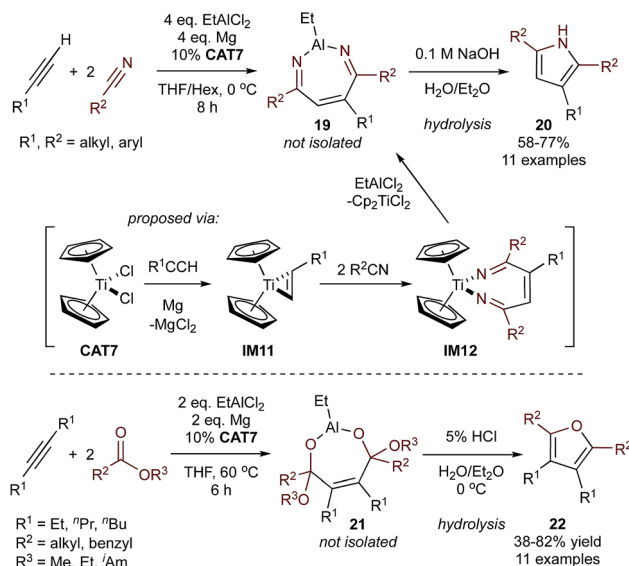


Fig. 8 Top: Cp_2TiCl_2 -catalyzed [2 + 2 + 1] synthesis of multi-substituted 1*H*-pyrroles from terminal alkynes and nitriles. Bottom: Cp_2TiCl_2 -catalyzed [2 + 2 + 1] synthesis of multi-substituted furans from alkynes and carboxylic esters.

transmetallation with EtAlCl₂. The proposed mechanism of cyclization upon transmetallation to Al/aqueous workup is different than that of the pyrrole reaction: here, Al is directly involved in elimination of the alkoxide substituents from **21** prior to cyclization. Catalysis with Cp₂ZrCl₂ was also successful, but compared to smaller Cp₂TiCl₂ (**CAT7**) the use of the larger Zr resulted in formation of side products from the dimerization or trimerization of the alkyne. Unlike in the synthesis of 1*H*-pyrroles, symmetrical internal alkynes with various alkyl substituents were shown to be applicable for furan synthesis. A number of esters were examined and it was found that conjugated substituents will not react under the examined conditions, but the reaction does proceed with alkyl, aryl, and heteroaryl rings that are separated from the carbonyl by a methylene unit (not conjugated).

1,2,3,5-Tetrasubstituted pyrroles (**25**) can be synthesized through FeCl₃ (Lewis acid)-catalyzed domino Michael addition/cyclization of amines, dialkyl acetylenedicarboxylates (**23**), and phenacyl bromides (**24**) (Fig. 9, top).⁵⁴ This reaction is proposed to occur through initial hydroamination of the alkyne (Michael addition) to an enamine (**IM13**), followed by FeCl₃-promoted nucleophilic addition to phenacyl bromide to form an enaminone (**IM14**). Spontaneous cyclization then produces the pyrrole product. This protocol was later extended to include β-nitrostyrenes (**26**) in place of phenacyl bromide (Fig. 9, bottom) through a similar mechanism.⁵⁵ These protocols provide complementary regioselectivity, with phenacyl bromides yielding 1,2,3,5-substituted pyrroles (**25**) and β-nitrostyrene derivatives yielding 1,2,3,4-substituted pyrroles (**27**).

2.1.3 Other cyclization strategies. [2 + 2] cycloadducts of Ti≡NR imidos and alkynes can also be intercepted in other ways to generate pyrroles *via* “interrupted hydroamination” reactions. For example, reaction of alkynes, isonitriles, and arylamines catalyzed by a Ti indolyl catalyst (**CAT8**) yields 2,3-

diaminopyrroles (**28**) *via* a [2 + 1 + 1 + 1] iminoamination reaction (Fig. 10).⁵⁶ Here, the key reaction step is sequential 1,1-insertions of an isonitrile into the azatitanacyclobutene intermediate (**IM16**) to form first **IM17** then **IM18**. Subsequent protolytic cleavage by an amine releases an enamine formimine (**IM19**) that undergoes cyclization and tautomerization to the final product. This method is suitable for both terminal and internal alkynes (symmetrical and unsymmetrical), however, internal alkynes require harsher conditions. A number of aniline derivatives were successfully implemented in this reaction, but *ortho*-substituted anilines resulted in the formation of formamidine or iminoamination products from competing side reactions.

Although it only involves two components (and is thus not formally an MCR), an interesting example of Ru-catalyzed synthesis of multi-substituted 1*H*-pyrroles (**31**) is the formal [3 + 2]-cycloaddition between 2*H*-azirines (**30**) and activated alkynes (**29**) (Fig. 11).⁵⁷ This reaction was proposed to occur through the initial ring-opening of 2*H*-azirines by a Ru catalyst (**CAT9**) to form an azaruthenacyclobutene intermediate (**IM21**). This intermediate (and its subsequent reactivity) is similar to the intermediates of Ti≡NR and alkyne [2 + 2] cycloaddition (**IM2**, Fig. 3). A follow-up computational study⁵⁸ revealed that **IM21** has significant nitrene character and undergoes Ru=N + alkyne [2 + 2] cycloaddition to **IM22** rather than Ru-C alkyne insertion (Ti-C insertion occurs in **IM2** to **IM3**). Subsequent C-N reductive elimination and isomerization affords the pyrrole product. This method is limited to activated alkynes (**29**) with electron-drawing substituents such as esters and ketones.

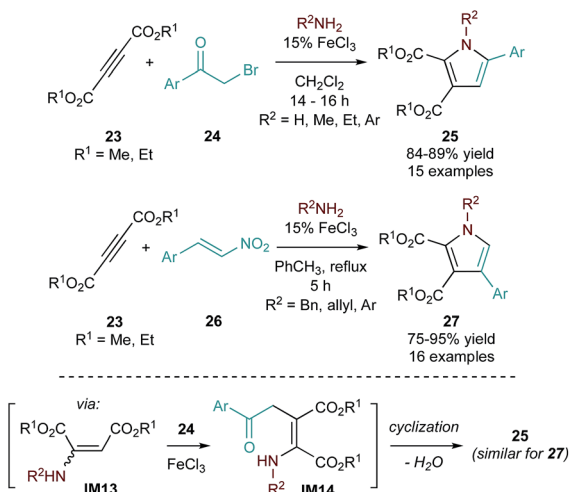


Fig. 9 [2 + 2 + 1] synthesis of tetra-substituted pyrroles catalyzed by FeCl₃ using highly activated alkynes and amines with either phenacyl bromides (top) or β-nitrostyrenes (middle), along with a proposed mechanism (bottom).

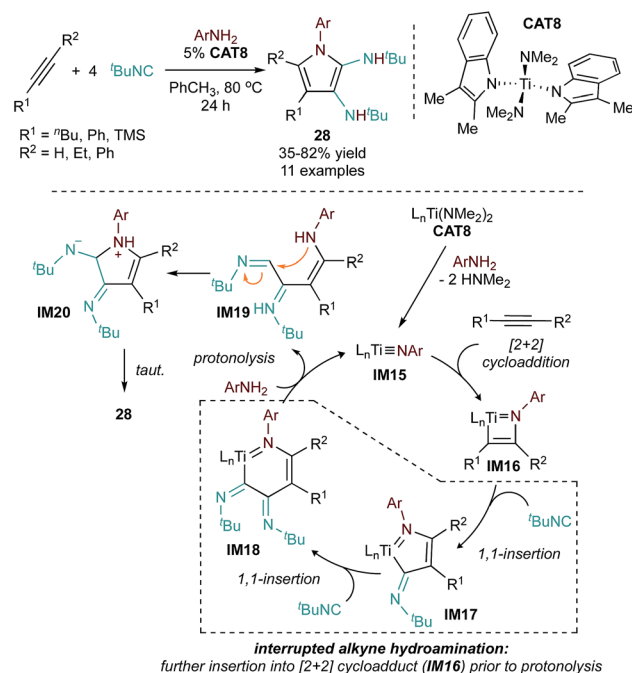


Fig. 10 Top: Ti-catalyzed [2 + 1 + 1 + 1] synthesis of *N*-aryl 2,3-diaminopyrroles from isonitriles, arylamines, and unactivated alkynes. Bottom: mechanism for Ti-catalyzed synthesis of 2,3-diaminopyrroles *via* an iminoamination reaction that occurs through “interrupted alkyne hydroamination”.



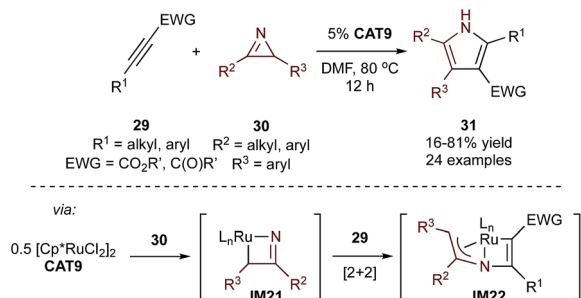


Fig. 11 Top: Ru-catalyzed [3 + 2] synthesis of multi-substituted 1H-pyrroles from activated alkynes and 2H-azirines. Bottom: DFT-proposed mechanism proceeds through C–N oxidative addition followed by Ru–N + alkyne [2 + 2] cycloaddition.

The use of activated alkynes ensures insertion is selective, resulting in a single regioisomer. The reaction is sensitive to the sterics of both the carbonyl substituents and alkyne substituent when R^1 = aryl, where *ortho* substitution was observed to greatly hinder reactivity. In contrast, a wide range of 2H-azirines was found to be compatible, with minimal impact from electronics or sterics of the substituents.

2.2 Pyrazoles

Knorr condensation of hydrazines with 1,3-diketones or 1,3-dipolar cycloaddition of hydrazones with alkynes are the most commonly used synthetic routes to multi-substituted pyrazoles.⁷ Multicomponent strategies toward pyrazoles have mirrored these methods, and include several strategies for generating C_3 frameworks *in situ* that can undergo ring closure *via* hydrazine condensation. Unlike pyrroles, there are only a few examples of MCRs with group 4–8 catalysts.

An early example of a MCR for pyrazoles synthesis includes a 3-component reaction using alkynes that proceeds through a 1-pot, 2-step Ti-catalyzed iminoamination/hydrazine condensation sequence (Fig. 12, top).⁵⁹ In the first step, alkynes undergo iminoamination to 1,3-diimine tautomers (**IM23**) *via* an interrupted alkyne hydroamination sequence (*vide supra*), where the [2 + 2] cycloaddition intermediate is intercepted by 1 equiv. of isonitrile prior to protonolysis. **IM23** can then undergo Knorr-like cyclization through condensation with hydrazine in a second step. Both terminal and internal alkynes are tolerated, however, the method is complicated by the potential for mixtures of regioisomers to be formed during hydrazine condensation when using terminal or unsymmetrical internal alkynes. Typically, the reactions were generally found to favor 1,4-disubstituted pyrazoles with terminal alkynes (**28**, where R^1 = alkyl or aryl, R^2 = H).⁶⁰ Similarly, for internal alkynes such as 1-phenylpropyne, there is preferential formation of the regioisomer with the aryl group in the 4-position (**28**, R^2 = aryl). The formation of 1,3-disubstituted pyrazoles is not generally favored due to preferential attack onto the aldimine carbon by the hydrazine NH_2 during the condensation step. However, a 3-substituted pyrazole was favored (6 : 1) over the

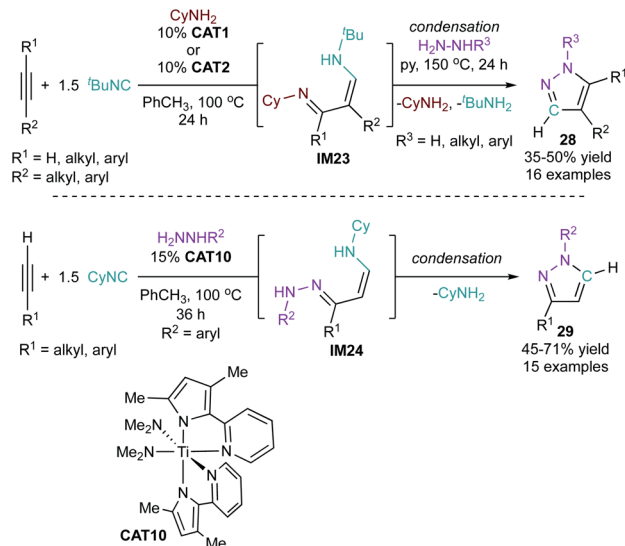


Fig. 12 Formal [2 + 2 + 1] syntheses of pyrazoles from alkynes, isonitriles, and hydrazines. Top: 2-step Ti-catalyzed iminoamination/condensation sequence. Bottom: improved 1-step Ti-catalyzed iminoamination/cyclization strategy.

4-substituted product with **CAT1** if H_2NNH_2 and 1-hexyne are used.

This 2-step sequence was later improved to a multicomponent synthesis of pyrazoles starting from terminal alkynes, isonitriles, and hydrazines (Fig. 12, bottom).⁶¹ The key advance of this reaction was using hydrazine (rather than cyclohexylamine) to perform an interrupted alkyne hydrohydrazination, wherein the resultant 1,3 imine-hydrazone (**IM24**) can undergo direct cyclization with loss of H_2NR to form the pyrazole product. Unlike the 2-step process, this single-step reaction is limited to terminal alkynes featuring small alkyl and aryl groups. A single 1,3-disubstituted regioisomer (**29**) was able to be obtained in all cases due to the selectivity of the [2 + 2]-cycloaddition in which the substituent of the terminal alkyne is always opposite to the metal center.

2.3 Imidazoles

Simple imidazoles can be synthesized by condensation of glyoxal, formaldehyde, and ammonia. Syntheses of more complex imidazoles from MCRs vary widely,⁶² although there are no formal MCRs catalyzed by group 4–8 metals. However, catalytic [3 + 2] annulations with Ti provide insights into potential strategies that could be extended to MCRs. For example, highly regioselective formation of multisubstituted imidazoles (**31**) from propargylamines (**30**) and nitriles can be accomplished using a titanacarborane amide catalyst (**CAT11**) (Fig. 13).⁶³ This reaction is proposed to proceed through an initial amine-exchange reaction between the amide catalyst and the propargylamine substrate to afford a titanacarborane amide (**IM25**). Coordination of a nitrile (**IM26**) and subsequent migratory insertion (**IM27**) is followed by intramolecular insertion of the alkyne into the Ti–N



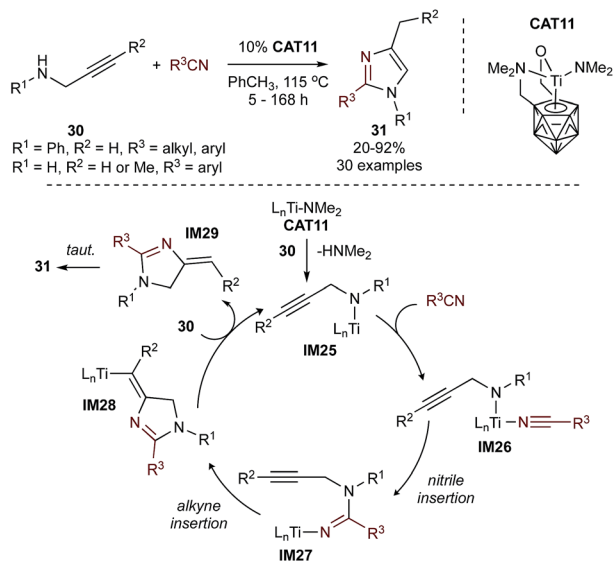


Fig. 13 Ti-catalyzed [3 + 2] annulation of propargylamines with nitriles yields imidazoles.

bond to form **IM28**. This then undergoes protonolysis to regenerate the initial Ti-amido species and liberate the imidazole product upon isomerization of **IM29**. This reaction is notable in that it does not proceed through a Ti≡NR imido, unlike most of the other Ti-catalyzed N-heterocycle syntheses herein. An extensive scope revealed that alkyl-, aryl- and heteroaryl-nitriles are all tolerated. Arylnitriles were observed to be more reactive than alkylnitriles, especially when featuring donor *ortho*-substituents. Terminal and internal propargylamines, as well as *N*-functionalized propargylamines, are also tolerated. This reaction was further extended for the synthesis of 2-aminoimidazoles by replacing the nitrile fragment with carbodiimines.⁶⁴

2.4 Azadiphospholes

Azadiphospholes are 5-membered aromatic heterocycles containing 2 P atoms and 1 N atom. The general metal-mediated synthesis of these heterocycles was, until recently, limited to only a handful of stoichiometric couplings of phosphalkynes with simple V and Ti imido complexes,^{65,66} yielding 1,2,4-azadiphosphole.⁶⁷ Building off of this stoichiometric example, a V-catalyzed [2 + 2 + 1] synthesis of multisubstituted azadiphospholes (**33**) from phosphalkynes (**32**) and azobenzene was recently reported (Fig. 14).⁶⁸ Similarly to Ti- and V-catalyzed [2 + 2 + 1] pyrrole syntheses (Fig. 3 and 5), the mechanism of this reaction is proposed to go through initial [2 + 2] cycloaddition of the phosphalkyne with a V=NR imido, followed by further phosphalkyne insertion before reductive elimination. Phosphalkynes are highly reactive functional groups, and as such, the scope was limited to bulky tertiary phosphalkynes such as adamantyl or dimethylbenzyl phosphalkyne. A variety of substituted azobenzenes were examined with adamantyl phosphalkyne giving yields of 47–66%.

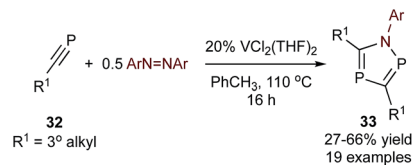


Fig. 14 [2 + 2 + 1] V-catalyzed synthesis of azadiphospholes from phosphalkyne and diazene substrates.

3. 6-Membered heterocycles

3.1 Pyridines

The multicomponent synthesis of pyridines has been extensively studied, in particular strategies involving the formal [2 + 2 + 2] cycloaddition of alkynes and nitriles.^{11,13,22,69–74} This topic has been the subject of numerous recent reviews, so this perspective will focus primarily on comparing and contrasting mechanistic and scope aspects of the group 4–8 catalysts. In the context of group 4–8 metal-catalyzed [2 + 2 + 2] syntheses, methods are primarily dominated by Ru and Fe, although there are several emergent examples with group 4 and 5 that suggest they may have unrealized potential for pyridine synthesis as well. These formal [2 + 2 + 2] reactions can be categorized into 2 classes: (1) partially intramolecular tethered substrates such as diynes or alkynynitriles that avoid inherent problems of chemo- and regioselectivity; and (2) fully intermolecular 3-component reactions. The reactions typically occur through either a metallacyclopentadiene-like intermediate (**IM30**, alkyne + alkyne first) or an azametallacyclopentadiene-like intermediate (**IM31**, alkyne + nitrile first) (Fig. 15). Depending on the metal, **IM30** can be considered a true metallacyclopentadiene (wherein the metal has undergone 2-electron oxidative coupling—typically invoked for groups 4 or 5) or a biscarbenoid metallacycle (typically invoked for Ru). These pathways are also believed to be operative in the analogous [2 + 2 + 2] reactions catalyzed by late transition metals such as Co,⁷⁵ Ir⁷⁶ (alkyne + alkyne) and Ni^{77,78} (alkyne + nitrile) respectively.^{12,79}

3.1.1 Formal [2 + 2 + 2]: partially intramolecular tethered examples. Ru-based catalysts have attracted significant interest over the last two decades as a cycloaddition catalyst for the syntheses of pyridines, both in the coupling of tethered diynes with nitriles and in the coupling of tethered alkynynitriles with alkynes.

Ru-catalyzed [2 + 2 + 2] diyne + nitrile methods are typified by the Cp***RuCl(COD)** (**CAT12**)-catalyzed reaction shown in Fig. 16. In initial work from 2001,⁸⁰ unsymmetric 1,6-diyne were

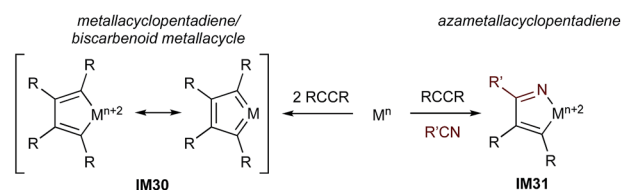


Fig. 15 Comparison of potential first steps in pyridine synthesis via [2 + 2 + 2] cycloaddition of alkynes and nitriles.



reacted with several nitriles to yield pyridine products, **35** and **35'**. The regiochemistry can be influenced by reacting **34** with electron-deficient nitriles to favor **35**. Alternatively, **35'** can be isolated if both the diyne and nitrile contain an electron-withdrawing group (EWG). Compared to other transition metals, Ru-based catalysts provide complementary access to pyridines with electron-deficient nitriles,^{80–82} which are often challenging substrates for later transition metals like Co.⁸³ In contrast, cycloaddition using simple nitriles such as MeCN and PhCN is challenging with Ru due to often endothermic nitrile insertion,⁸¹ although examples of partially or fully intermolecular $[2 + 2 + 2]$ cycloaddition with nitriles containing coordinating groups have been reported.^{81,84,85}

Detailed experimental and computational studies (both of $[2 + 2 + 2]$ alkyne cyclotrimerization and pyridine formation)^{22,86} have revealed that Cp^{*}RuCl(COD)-catalyzed reactions of α,ω -diynes likely proceed first through initial oxidative cyclization of the diyne to form ruthenacyclic biscarbenoid **IM32**. This intermediate, which related complexes have been structurally characterized *via* X-ray crystallography and NMR in several instances,⁸⁷ is shared between $[2 + 2 + 2]$ pyridine formation, alkyne cyclotrimerization, and $[2 + 2 + 1]$ pyrrole/furan/thiophene synthesis (*vide supra*). Nitrile then coordinates to the ruthenacycle to form a η^1 - or η^2 -nitrile complex (see Fig. 17, **IM36B'** or **IM36B**), with the η^2 -nitrile being the productive intermediate despite being less thermodynamically stable. Insertion of nitrile leads to the Ru-bridged intermediate azaruthenabicyclo[3.2.0]heptatriene **IM33**, followed by Ru–C bond cleavage to afford an azaruthenacycloheptatriene **IM34**. Finally, reductive elimination yields pyridine and regenerates the Ru

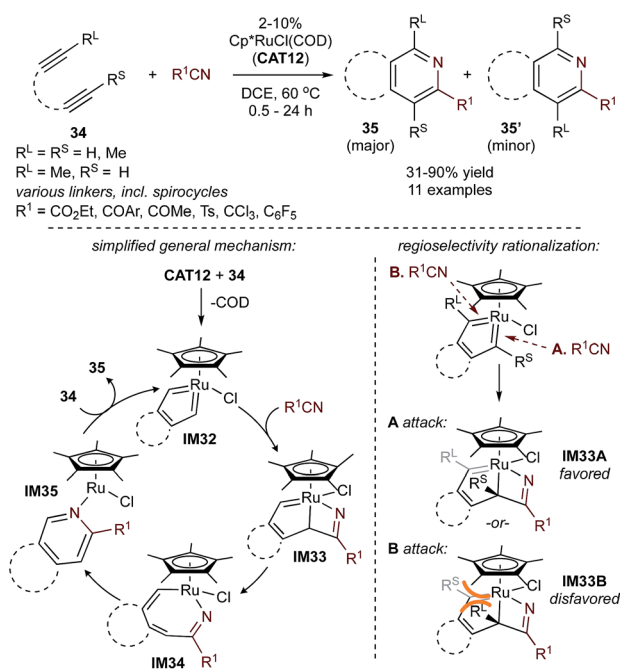


Fig. 16 CAT12-catalyzed $[2 + 2 + 2]$ pyridine synthesis from tethered diynes and nitriles. Bottom: initial mechanistic proposal (left, R^L and R^S omitted for clarity) and regioselectivity rationalization (right).⁸⁰

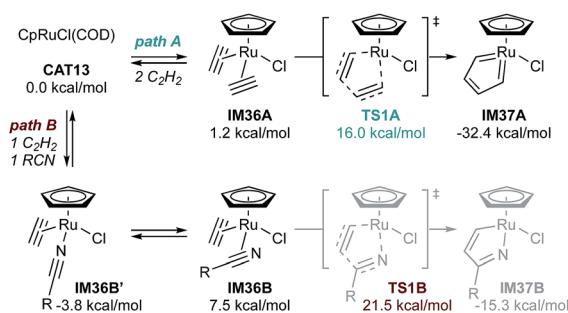


Fig. 17 Computed free energies of potential alkyne + alkyne coupling (path A) and alkyne + nitrile coupling (path B) in Ru-catalyzed $[2 + 2 + 2]$ pyridine synthesis, demonstrating kinetically and thermodynamically favored formation of **IM36A**. B3LYP; single point free energies calculated with SDD (Ru) and 6-311++G(d,p) for all other elements. $R = CF_3$.

catalyst. Calculations on the coupling of acetylene with trifluoroacetonitrile by CpRuCl(COD) (CAT13) agree with this general mechanistic picture (Fig. 17). In this case, the biscarbenoid ruthenacycle route (path A) is both thermodynamically and kinetically favorable with $\Delta\Delta G^\ddagger = -5.5$ kcal mol⁻¹ between **TS1A** and **TS1B** and $\Delta\Delta G = -17.1$ kcal mol⁻¹ between **IM37A** and **IM37B**. Later computational analysis further corroborates the predominance of the “biscarbenoid ruthenacycle” path A over path B.^{22,86}

Although mechanistic investigations point primarily to the “biscarbenoid ruthenacycle” mechanism for these Ru-catalyzed partially intramolecular couplings, the regiochemical outcome of the intermolecular $[2 + 2 + 2]$ of ethyl cyanoformate with 2 equiv. of ethyl propiolate indicates that the “azametallacyclopentadiene” route may still play a role (Fig. 18). In this instance, only 2 of the 4 possible regioisomers of **36** are produced, which are hypothesized to arise solely from **IM38**. Here, selective formation of **IM38** is proposed to arise from the polarization of the propiolate. Indeed, given the relatively small $\Delta\Delta G^\ddagger = 5.5$ kcal mol⁻¹ calculated for acetylene (Fig. 17), it is reasonable to expect that either pathway may play a role depending on stereoelectronic modifications to the substrates or the catalyst structure.

Further studies have revealed subtle catalyst structure effects on reaction selectivity and mechanism. In a demonstration of switchable selectivity, it was found that CAT12-catalyzed $[2 + 2 + 2]$

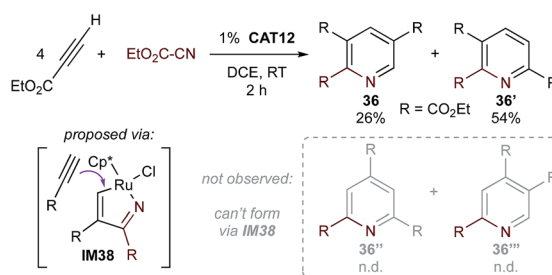


Fig. 18 Regiochemical outcome of CAT12-catalyzed $[2 + 2 + 2]$ cycloaddition of ethyl propiolate supports an “alkyne + nitrile” mechanism through **IM38**.⁸¹



2] reactions of tethered diynes (**37**) with conjugated alkynyl nitriles (**38**) could yield either cyano-substituted benzenes (**39**) or alkynylpyridines (**40**), in either the absence or presence of AgOTf, respectively (Fig. 19).⁸⁸ In this example, DFT calculations indicated that the more electron-rich neutral Cp*Ru(metallacycle) (**IM39**) preferred coordination of the π -acid alkyne of the alkynyl nitrile, leading to formation of cyanobenzene, while the electron-deficient cationic Cp*Ru(metallacycle) (**IM40**), generated by halide abstraction by Ag⁺, preferred coordination of the nitrile, leading to pyridine formation.

In recent years, there has been an increased interest in generating 2-heteroatom-substituted pyridines using heteroatom-substituted nitriles. For example, [Cp*Ru(MeCN)₃]PF₆ (**CAT14**) is an efficient catalyst in the synthesis of 2-aminopyridines (**42-NR₂**) by [2 + 2 + 2] cycloaddition of tethered diynes and cyanamides (Fig. 20).^{89,90} Heterocumulene-like cyanamides are highly reactive partners in [2 + 2 + 2] cycloaddition reactions. The system could be further modified to use simple solvent-free conditions by using a RuCl₃·nH₂O catalyst.⁹¹ Applications were sought in the synthesis of related fluorescent azafluorenones with promising results.⁹² Further studies have extended 2-heteroatom-substituted pyridine synthesis across a diverse array of heteroatoms, leading to efficient syntheses of 1-(2-pyridyl)indoles (**42-Ind**),⁹³ 2-aryloxy pyridines (**42-OR**),⁹⁴ including 3-(2-thiopyridyl)indoles (**42-SR**),⁹⁵ and 2-selenopyridines (**42-SeR**),^{96,97} variously demonstrated with either **CAT12** or **CAT14** (Fig. 20). Mono- and dihalodiyne can also be transformed to halopyridines *via* reaction with nitriles, providing a platform for further functionalization through cross-coupling reactions.⁹⁸

Cationic **CAT14** was also found to be a selective catalyst for the coupling of alkynyl triazenes (**44**) and alkynyl nitriles (**43**) (Fig. 21, top)⁹⁹ yielding 5,6-tethered 3-triazenylpyridines (**45**) with excellent regioselectivity. Conveniently, synthesis of the other isomer, 5,6-tethered 3-triazenylpyridines (**47**) could be achieved *via* reaction of triazenyl diyne **46** with nitriles catalyzed by **CAT15** (Fig. 21, bottom), albeit with slightly lower

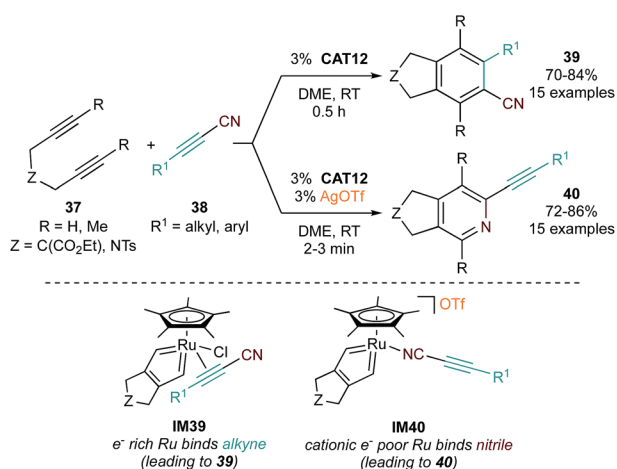


Fig. 19 Top: example of AgOTf-induced switchable chemoselectivity in Ru-catalyzed [2 + 2 + 2] cycloaddition of diynes and alkynyl nitriles. Bottom: potential mechanistic rationale for selectivity change with AgOTf.

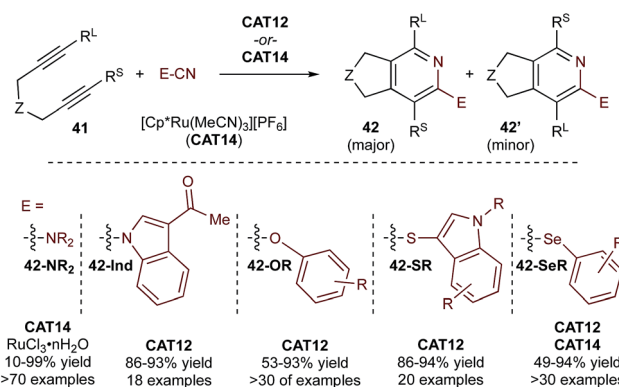


Fig. 20 Examples of Ru-catalyzed [2 + 2 + 2] cycloaddition of tethered diynes with various heteroatom-substituted nitriles.

regioselectivities resulting from misinsertion of the nitrile. Here, the synthetic versatility of the triazene group could be put to use, resulting in facile subsequent access to a variety of functionalized pyridines.

Given the success found with Ru, there has been increased attention on Fe-catalyzed [2 + 2 + 2] pyridine synthesis as well. Fe-catalyzed [2 + 2 + 2] methods go back decades, including a notable report on the [2 + 2 + 2] synthesis of 1,2,4-triazenes from adiponitriles with nitriles.¹⁰⁰ Following up on early [2 + 2 + 2] pyridine syntheses from the 1990s,^{101,102} several advanced Fe-based systems with good chemoselectivity have been developed in the past decade. For example, reduced *bis*(phosphine)Fe complexes can be made *in situ* through reduction of Fe halide salts by Zn. These complexes are competent for the formal [2 + 2 + 2] coupling of internal tethered diynes (**48**) with a variety of nitriles with yields ranging from 43–98% (Fig. 22).¹⁰³ Regioselective cycloadditions of unsymmetrical alkynes, in combination with competition experiments of phenylacetylene with nitrile, suggest that azaferracyclopentadienes (**IM41**), rather than the two-alkyne coupled ferracyclopentadiene, are likely the key intermediate prior to the formation of pyridine. Both *bis*(diphenylphosphino)ethane (dppe) and 1,3-

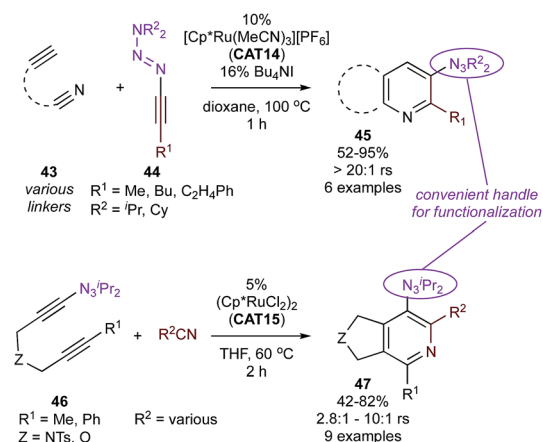


Fig. 21 Ru-catalyzed [2 + 2 + 2] cycloaddition reactions with alkynyl triazene components. rs = regioselectivity over other regioisomers.



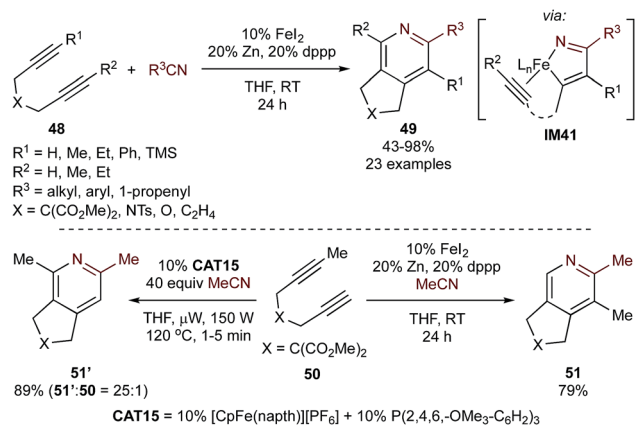


Fig. 22 Top: Fe-catalyzed [2 + 2 + 2] synthesis of pyridine using diynes and nitriles in the presence of Zn and 1,3-bis(diphenylphosphino)propane (dppp). Bottom: comparison of the regioselectivity between CAT15 microwave pyridine synthesis (left) and reduced Fe/dppp-catalyzed pyridine synthesis (right).

bis(diphenylphosphino)propane (dppp) ligands yielded pyridine formation, however, reactions with dppp could be conducted at lower catalyst loadings (5% FeI₂, 10% dppp) without erosion of the yield.

Interestingly, the regiochemistry of the [2 + 2 + 2] reaction could be inverted by employing a system catalyzed by CpFe(naph)PF₆/P(2,4,6-OMe₃C₆H₂)₃ (CAT15) under microwave irradiation (Fig. 22, bottom left).¹⁰⁴ Although a specific rationale for the inversion of the regioselectivity was not provided, it was noted that the yields of reactions catalyzed by the Cp-derived system are very sensitive to sterics, which may also play a role in the alkyne chemoselectivity of the initial alkyne/nitrile oxidative coupling to form IM41.

Louie and co-workers also reported a Fe-catalyzed synthesis of pyridine using sterically encumbered pyridyl *bis*(aldimine) (PDAI) ligands in the presence of tethered alkynyl nitriles and both symmetric or unsymmetric alkynes (Fig. 23).¹⁰⁵ Several pyridyl *bis*(ketimine) and *bis*(aldimine) ligands were screened, and it was found that pyridyl *bis*(aldimine) ligands gave higher conversion than pyridyl *bis*(ketimine) ligands, with PDAI-1 giving the best yield.

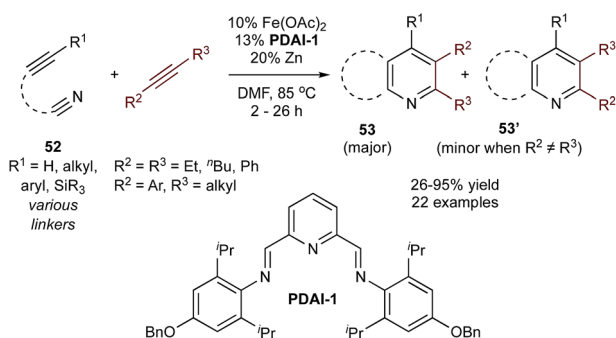


Fig. 23 (PDAI-1)-Fe catalyzed [2 + 2 + 2] coupling of alkynyl nitriles with alkynes.

This PDAI-based ligand system was then extended to the coupling of diynes (54) with highly reactive cyanamides using modified PDAI-2, leading to the regioselective synthesis of 2-aminopyridines (55) (Fig. 24).^{106,107} In this instance, the mechanism of the reaction was proposed to proceed through initial diyne coupling (IM42) on the basis of the regiochemistry, which mirrors that of related Co-catalyzed pyridine syntheses.^{108,109} Interestingly, reactions of diynes with cyanamides catalyzed by an *in situ*-generated (dppp)Fe catalyst resulted in the opposite regioisomer 55'.¹¹⁰ In these cases, the catalyst-controlled regioselectivity is proposed to be a function of a change in mechanism (IM42 for PDAI-2, IM43 for (dppp)Fe), although detailed comparative mechanistic studies are not available. Nonetheless, the development of initial examples of catalyst-controlled selectivity is an important step toward broader method development.

3.1.2 Formal [2 + 2 + 2]: fully intermolecular examples.

There are few examples of fully intermolecular 3-component [2 + 2 + 2] pyridine syntheses, owing to the challenge and complexity of selective reactivity. Nonetheless, there are several key selective demonstrations of this strategy. Extending upon the cyanamide strategy above, fully intermolecular couplings of alkynes and cyanamides have been reported using PDAI-2, resulting in the selective formation of 2,4,6-trisubstituted aminopyridines (56) (Fig. 25).¹⁰⁷ Mirroring the selectivity trends in the tethered diyne examples, reaction of *p*-F-phenylacetylene with *N,N*-dimethylcyanamide and *in situ* formed “(dppp)Fe” results in the opposite (2,3,6) regioselectivity (56'), although only a single intermolecular example has been reported for this system.¹¹⁰

Additionally, *in situ* formed low-valent Nb complexes catalyze the [2 + 2 + 2] cycloaddition of *tert*-butylacetylene with aryl nitriles, yielding 2,3,6-trisubstituted pyridines (57) (Fig. 26).^{111,112} This example is an extension of earlier work where low valent Nb complexes (made *in situ* from reduction with LiAlH₄, Zn, or other reductants) were used to catalyze alkyne cyclo-trimerization.^{112,113} In this case, it was found that alkoxy silane

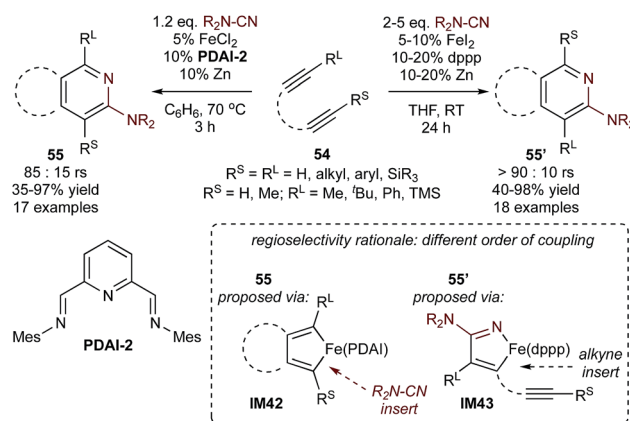


Fig. 24 Comparison of regiochemical outcomes of cyanamide and diyne [2 + 2 + 2] cycloaddition catalyzed by pyridyl *bis*(aldimine) or *bis*(phosphine)-based Fe catalysts. rs = regioselectivity for the major product (55 or 55') relative to the minor product (55' or 55).



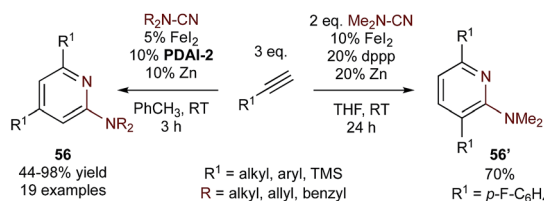


Fig. 25 Intermolecular Fe-catalyzed [2 + 2 + 2] cyclization of cyanamides and alkynes.

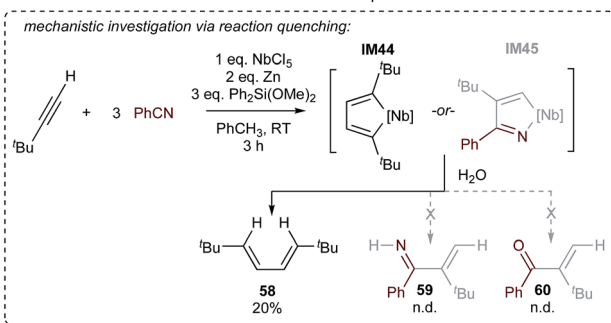
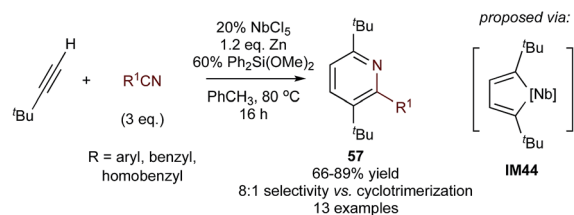


Fig. 26 Nb-catalyzed [2 + 2 + 2] synthesis of tri-substituted pyridines with a minor formation of cyclotrimerization product.

additives such as $\text{Ph}_2\text{Si}(\text{OMe})_2$ can dramatically improve the chemoselectivity against benzene formation. Mechanistic studies suggest that niobacyclopentadiene **IM44**, formed from oxidative coupling of alkynes on Nb^{III} , is a key intermediate. **IM44** can then undergo nitrile insertion followed by reductive elimination. The intermediacy of **IM44** was identified *via* reaction of $t\text{BuCCH}$ and benzonitrile with the *in situ* reduced Nb complex under ambient conditions, which led solely to the formation of diene **58** rather than aminated (**59**) or oxygenated (**60**) products that would result from azaniobacyclopentadiene intermediate **IM45**. Interestingly, the regiochemistry of these Nb-catalyzed [2 + 2 + 2] reactions is the same as in the (dppp)Fe-catalyzed intermolecular example (**56'**, Fig. 25) although *via* a different proposed intermediate.

Although there are no catalytic reports of [2 + 2 + 2] cycloaddition, group 4 metals can also produce pyridines *via* coupling of metallacyclopentadienes with nitriles,^{114–116} somewhat analogous to the mechanisms seen with Ru, Fe, and Nb (Fig. 27). For example, there are several well-established protocols^{117,118} for the stepwise addition of alkynes to “Ti^{III}” synthons, resulting in selective formation of titanacyclopentadienes (**IM46**). Treatment of *in situ* generated **IM46** with $\text{ToI}\text{SO}_2\text{CN}$ results in **IM48**, either from **IM47** or **IM47'**. Elimination of $-\text{SO}_2\text{ToI}$ forms titanated pyridine **IM49**, which can then be trapped with

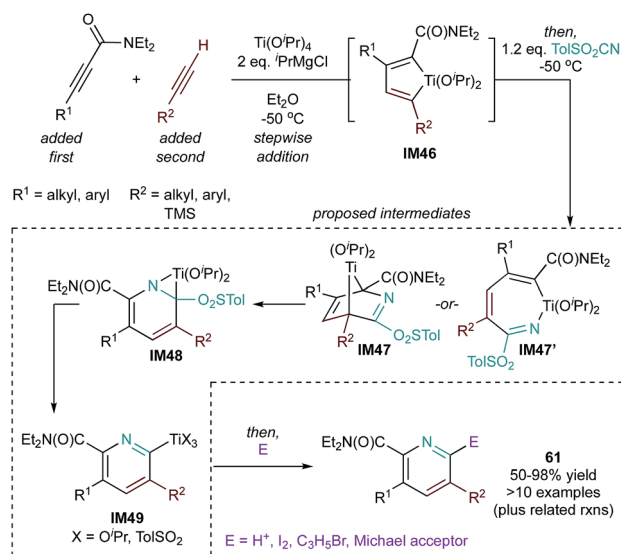


Fig. 27 Stoichiometric stepwise coupling of alkynes with “Ti^{III}” and subsequent cascading reactivity with nitriles.

several electrophiles, resulting in tetrasubstituted pyridines (**61**) in good yield.¹¹⁹ An analogous zirconacyclopentadiene intermediate was also recently isolated and shown to yield pyridines upon reaction with nitrile (*vide infra*).¹²⁰

3.1.3 Formal [3 + 2 + 1] strategies. While the majority of pyridine syntheses rely on variations of formal [2 + 2 + 2] cycloadditions, there are several Ti-catalyzed formal [3 + 2 + 1] methods that capitalize on multistep, one-pot hydroamination/functionalization sequences, similar to those seen in the various hydroamination-derived routes to 5-membered heterocycles. For example, **CAT1** or **CAT2**-catalyzed iminoamination of alkynes^{31,33,121} (*cf.* Fig. 12) generates 1,3-diimine tautomers **IM23**, which can then undergo reaction with malononitrile to yield highly functionalized 2-amino-3-cyanopyridines (**62**) (Fig. 28, top).¹²² Additionally, **CAT16**-catalyzed hydroamination of alkynes with silylamines regioselectively forms reactive *N*-

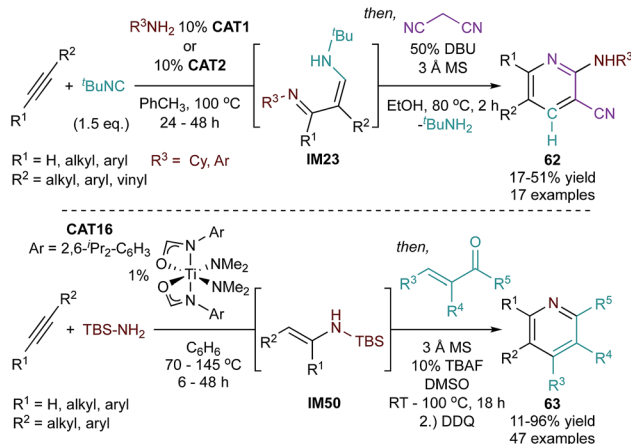


Fig. 28 Formal [3 + 2 + 1] syntheses of pyridines *via* multistep, one-pot hydroamination/functionalization sequences.



silylenamines (**IM50**), which can undergo subsequent reaction with α,β -unsaturated carbonyls to yield tri-, tetra-, or pentasubstituted pyridines (**63**) upon oxidation (Fig. 28, bottom).¹²³ Based on the regiochemical outcome, reaction of the silylamine **IM50** with the α,β -unsaturated carbonyl was proposed to occur *via* either condensation or a Stork enamine reaction.

3.2 Pyrimidines

Pyrimidines are core structures in a wide variety of pharmaceuticals and materials.^{14,16,17,28} Much like pyridines, formal [2 + 2 + 2] cycloaddition is a common strategy to form pyrimidines, in this case from the head-to-tail coupling of two nitriles with an alkyne. The strategies for [2 + 2 + 2] pyrimidine synthesis mainly focus on Lewis acid-promoted cyclization and low valent metal-catalyzed cycloaddition, catalyzed primarily by the harder early transition metals and first row metals like Fe. Beyond these strategies, condensation strategies featuring formal [3 + 2 + 1] coupling schemes with amidines as the 3-atom component have been variously reported with alcohols, alkynes, and isonitriles.

3.2.1 Formal [2 + 2 + 2]: alkynes and nitriles. Synthesis of tetrasubstituted pyrimidines from alkynes and nitriles can be accomplished *via* FeCl₃-assisted, NbCl₅ Lewis acid-catalyzed cycloaddition (Fig. 29).¹²⁴ Previous studies showed that NbCl₅ solely can mediate stoichiometric cycloadditive pyrimidine synthesis.¹²⁵ In both instances, the proposed mechanism begins with nitrile activation by the NbCl₅ Lewis acid to generate **IM51**, which then undergoes a nucleophilic attack by a second nitrile to generate **IM52**. [4 + 2] cycloaddition of alkyne across **IM52** generates the NbCl₅-coordinated pyrimidine **IM53**. In the catalytic variant, FeCl₃ serves as a stoichiometric sacrificial Lewis acid, forming **64-FeCl₃** and preventing the pyrimidine product from coordinating to Nb and inhibiting catalysis. Despite that Nb was found to be effective in activating nitriles,¹²⁵ sequential nitrile addition was still rather challenging, as illustrated by the modest yields of the reaction and the need for solvent quantities

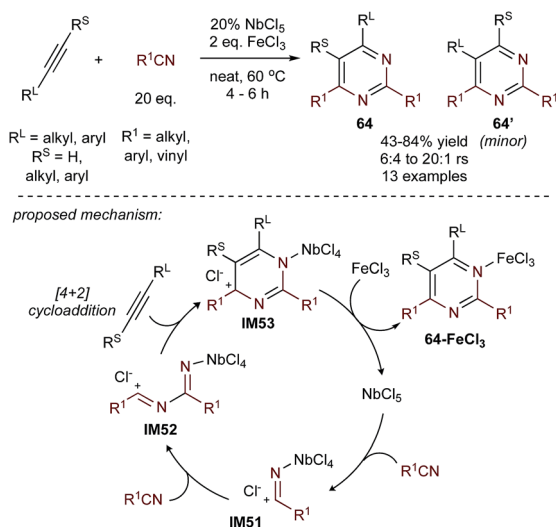


Fig. 29 Fe-assisted, Nb (Lewis acid)-catalyzed [2 + 2 + 2] pyrimidine synthesis. rs = regioselectivity of **64** relative to **64'**.

of nitrile. Another underlying challenge is the regioselectivity of the cycloaddition of alkyne when an unsymmetric alkyne is used. High regioselectivity can be obtained with terminal alkynes, while unsymmetrical internal alkynes had diminished preference in [4 + 2] cycloaddition.

Masked low valent early transition metals were also found to be efficient catalysts for cycloadditive pyrimidine synthesis. The cumulene-masked “Zr^{II}” zirconocene species **CAT17** can serve as the catalyst for the synthesis of tetrasubstituted 4-silylethynyl-3-silylpyrimidine **66** *via* the coupling of diyne **65** with benzonitrile (Fig. 30).¹²⁶ Under elevated temperature the precatalyst can be activated to **IM54** by releasing one equivalent of diyne. The resulting zirconacyclopentene can undergo twofold nitrile insertion to **IM56**, followed by reductive elimination of **66** and regeneration of the low-valent zirconocene. Excellent chemoselectivity of up to 50 : 1 against the formation of pyridine has been observed in this reaction. Stoichiometric studies revealed that the formation of azazirconacyclopentadiene from the cycloaddition of an alkyne and a nitrile was the key intermediate to the selectivity, while the other possible intermediate, zirconacyclopentadiene from two alkynes, was minor.

Similarly, the anthracene-masked zirconium(II) complex **CAT18** was found to be an efficient catalyst for the synthesis of tri- and tetrasubstituted pyrimidines (**67**) from terminal or internal alkynes with benzonitrile derivatives (Fig. 31).¹²⁰ When terminal alkynes were used as substrates, the major product was the 2,4,6-trisubstituted pyrimidine, similar to the selectivity observed in NbCl₅-catalyzed reactions (Fig. 29).^{124,125} **IM58** could be as isolated as the major product by reacting 2 equiv. of TolCN and 1 equiv. of PhCCH with the 2-electron reduced **IM57**. The pyrimidine product **67** could then be isolated from reaction of **IM58** with an equivalent of PhCN. Alternatively, when **IM57** is treated with only 2 equivalents of PhCCH, the zirconacyclopentadiene **IM59** forms. Treatment of **IM59** with PhCN results in the formation of pyridine **68**. Based on this reactivity, facile pre-coordination of nitrile to Zr appears to be key for selective pyrimidine (**67**) formation during catalysis. Interestingly, neither **IM58** nor **IM59** react with an equivalent of PhCCH to generate trisubstituted pyridine (**68**) or benzene (**69**), respectively.

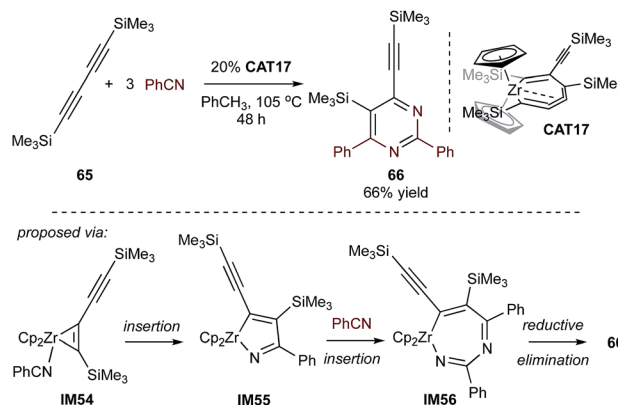


Fig. 30 [2 + 2 + 2] pyrimidine synthesis from 1,4-bis(trimethylsilyl)-1,3-diyne and nitrile catalyzed by zirconocene-based complex.



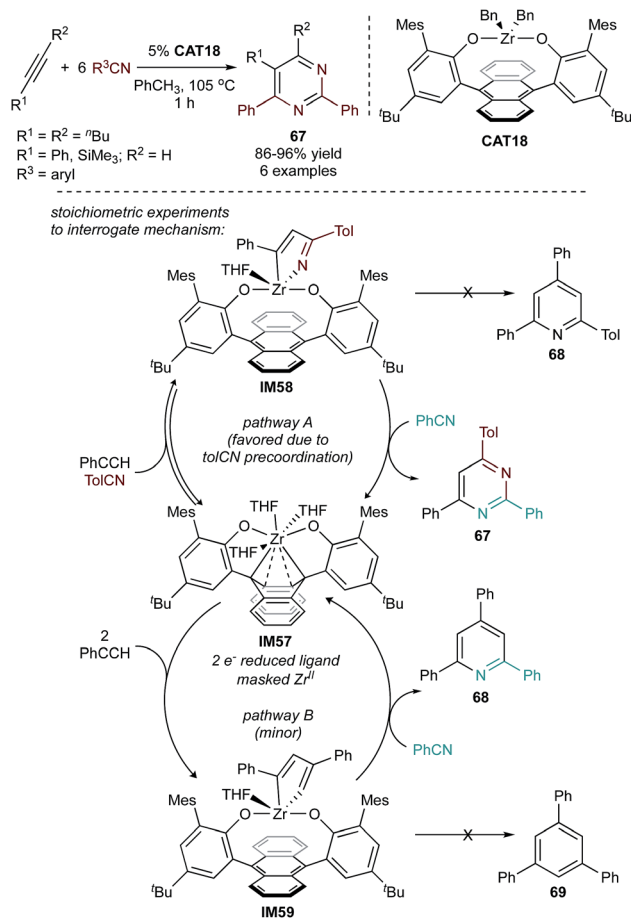


Fig. 31 [2 + 2 + 2] pyrimidine synthesis from alkynes and nitriles catalyzed by anthracene-masked Zr(II) complex.

In addition to the early transition metal-catalyzed reactions above, low-valent (PDAI-3)Fe complexes are also competent for the synthesis of bicyclic 2-aminopyrimidines (71) through formal [2 + 2 + 2] cycloaddition from tethered alkynynitriles (70) and cyanamides (Fig. 32).¹²⁷ The system is a modification from previous work on Fe-catalyzed 2-aminopyridine synthesis from tethered diynes and cyanamides (Fig. 24).¹⁰⁶ Interestingly, catalysis with Fe(OAc)₂ was unproductive compared to FeI₂, leading to speculation on the potential role of ZnI₂ as a Lewis acid in catalysis.

3.2.2 Formal [3 + 2 + 1]: condensation of amidine components. Amidines can serve as 3-atom components in intermolecular [3 + 2 + 1] pyrimidine syntheses *via* condensation reactions. For example, trisubstituted pyrimidines (73) can be synthesized *via* a CAT19-catalyzed alcohol dehydrogenation/multicomponent condensation strategy (Fig. 33).¹²⁸ This reaction is part of a larger class of acceptorless dehydrogenation strategies used for heterocycle synthesis.¹²⁹ In this case, dehydrogenation of primary and secondary alcohols together generates a ketone and aldehyde which can undergo aldol condensation, followed by further condensation with the amidine component 72 to yield 73. This chemistry has been further extended into a four-component reaction using three alcohols to generate tetrasubstituted pyrimidines.¹³⁰

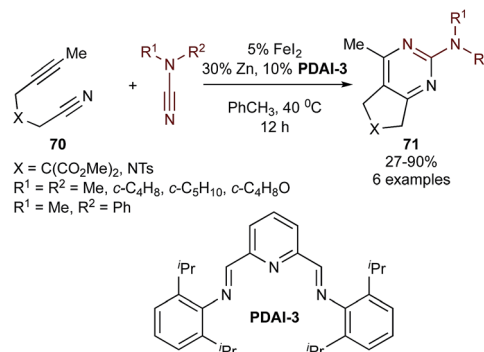


Fig. 32 Fe-catalyzed [2 + 2 + 2] synthesis of bicyclic 2-aminopyrimidines from tethered alkynynitriles and cyanamides.

Additionally, interrupted alkyne iminoamination (*cf.* Fig. 12) can be used to generate 1,3-diimines (IM23) that can then similarly undergo condensation with amidines to generate pyrimidines (74) (Fig. 34).¹³¹ In these examples, two different Ti-catalysts (CAT1 (ref. 132) or CAT2 (ref. 133)) were found to be most effective for the 2-step iminoamination/condensation sequence.

3.3 Pyrazine

Despite the wide utility of pyrazines,^{134,135} there are few examples of catalytic MCRs for their synthesis. Hypothetically, pyrazine could be divided into one alkyne and two nitriles in [2 + 2 + 2] cycloaddition just like pyrimidines. However, because of the polarized nature of the nitrile, “head-to-tail” coupling (resulting in pyrimidines) is more common than “tail-to-tail” coupling (resulting in pyrazines).

However, a recent report has capitalized on the tail-to-tail coupling of nitriles on “Cp₂Ti^{II}”,^{136,137} resulting in a formal [2 + 2 + 1 + 1] coupling of nitriles to tetrasubstituted pyrazines (Fig. 35) *via* Ti-to-Al transmetalation (*cf.* Fig. 8).¹³⁸ In this case, a single nitrile serves as both the 2-atom component and the 1-atom component. This reaction is proposed to occur first through oxidative cyclization of 2 nitriles to yield a 2,5-diazatitanacyclopentadiene (IM60). Two subsequent nitrile insertions lead to the formation of a ring-expanded 1,3,6,8-tetraazatitanacyclononatetraene (IM61), which then undergoes transmetalation with EtAlCl₂ to form IM62 (or linear oligomers thereof). Hydrolysis likely results in subsequent cyclization to 75. This interesting 4-component cyclization results in good yields of the resulting pyrazine, although it is currently limited to aryl and benzyl nitriles and symmetric products.

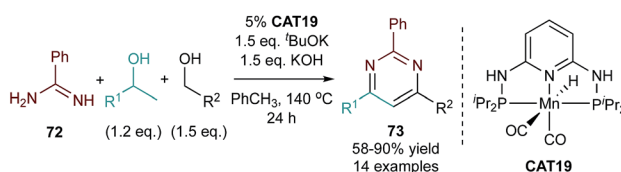


Fig. 33 Mn-catalyzed [3 + 2 + 1] synthesis of pyrimidine from alcohols and benzamidine.



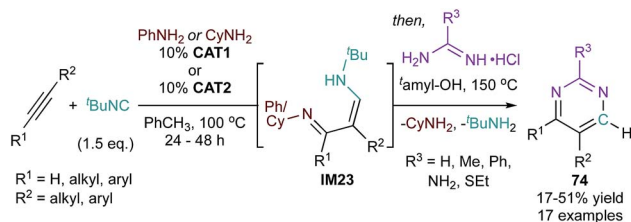


Fig. 34 Ti-catalyzed [3 + 2 + 1] synthesis of pyrimidine from alkynes, *tert*-butylisocyanide, amidines, and amines.

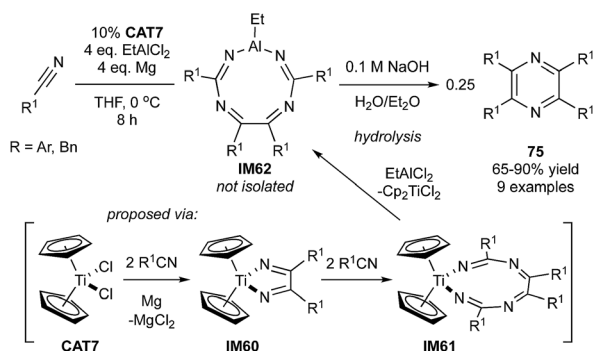


Fig. 35 Ti-catalyzed [2 + 2 + 1 + 1] synthesis of pyrazine.

3.4 Phosphabenzene

Extending [2 + 2 + 2] heterocycle synthesis to the heavier congeners, the first catalytic cycloadditive [2 + 2 + 2] syntheses of phosphabenzenes were recently reported using FeI_2 as a catalyst (Fig. 36).¹³⁹ Tri- and tetrasubstituted phosphabenzenes **77** can be synthesized from tethered diynes **76** and phosphalkynes with either tertiary alkyl or bulky siloxide (TBDPS) substituents—the latter of which could be deprotected to 2-phosphaphenols.¹⁴⁰ Notably, group 9 metal catalysts also exhibited catalytic activity, however in much lower yields and with poorer chemoselectivity against trimerization of alkyne. The intermediacy of the two alkyne-coupled intermediate **IM63** was proposed, although alkyne/phosphaalkyne coupled intermediates analogous to **IM43** (Fig. 24) could not be ruled out. Interestingly, computational analysis (B3LYP/6-311G**) of the Gibbs free energy change for the [2 + 2 + 2] cycloaddition processes were similar for benzenes ($-119.4 \text{ kcal mol}^{-1}$), pyridines ($-83.6 \text{ kcal mol}^{-1}$), and phosphabenzenes ($-101.2 \text{ kcal mol}^{-1}$), despite the fact that phosphalkynes are significantly less thermodynamically stable than alkynes and nitriles.

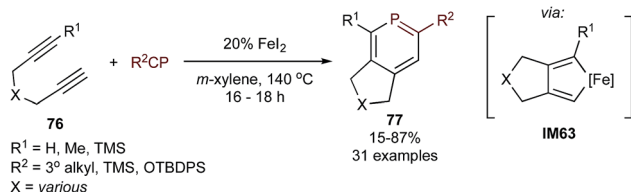


Fig. 36 Fe-catalyzed [2 + 2 + 2] synthesis of phosphabenzenes from diynes and phosphalkynes or siloxyphosphaethynes.

4. Conclusions and future outlook

The above examples illustrate the limited instances of group 4–8 metal catalyzed syntheses of 5- and 6-membered aromatic heterocycles. Of the examples summarized in this *Perspective*, catalysis is dominated by group 4 (5-membered rings) and group 8 (6-membered rings), and can be broadly classified as “on-metal” cycloadditive processes (e.g. formal [2 + 2 + 2] cycloaddition) or “off-metal” cycloadditive processes that take place after catalysis (e.g. interrupted hydroamination/cyclization). Although partially intramolecular tethered syntheses have now been demonstrated with exquisite selectivity, there remains a significant challenge in controlling the selectivity of fully intermolecular reactions for nearly all heterocycle classes.

Within the 5-membered ring MCRs, it is interesting to note overlapping [2 + 2 + 1] strategies between Ti/V and Ru: each metal can couple alkynes and nitrene equivalents to pyrrole, albeit through a different order of addition. The extension of Ru catalysis into [2 + 2 + 1] thiophene and furan syntheses raises the question of potential compatibility of the earlier (and more oxophilic) transition metals for similar reactions, which are ubiquitous in pyrrole synthesis.

For [2 + 2 + 2] cycloaddition reactions, early examples have been dominated by Ru, and method development with Ru catalysts remains an active area of research. However, significant advances with Fe have brought potentially earth-abundant alternatives to the fore, along with the potential for different mechanisms (order of component addition, for example) and subsequent potential for control of regio- and chemoselectivity in intermolecular examples. Nascent similar transformations have now also been reported for the early transition metals as well, where the harder, more electropositive metals appear well-poised for incorporating additional electronegative moieties (e.g. 2 nitriles in pyrimidine synthesis) into MCRs.

Notably absent in recent examples are catalytic variants with groups 6 and 7. However, stoichiometric syntheses with both Mo¹⁴¹ and W exist,^{142,143} and given the complementary reactivity between groups 4/5 and group 8, there is compelling evidence to explore these elements for catalysis, as well.

Author contributions

C. W. F. contributed to Section 2 and Y. C. and D. T. E. contributed to Section 3. D. N. H. and I. A. T. conceived and contributed to all portions of the manuscript.

Conflicts of interest

There are no conflicts to declare.

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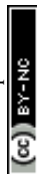
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