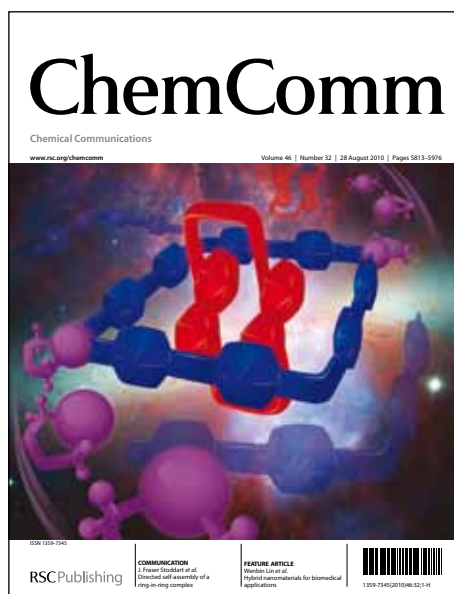


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ARTICLE TYPE

The Iron-Catalyzed Construction of 2-Aminopyrimidines from Alkynenitriles and Cyanamides

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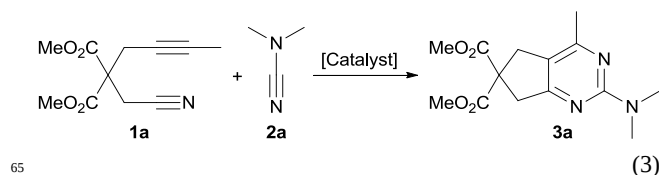
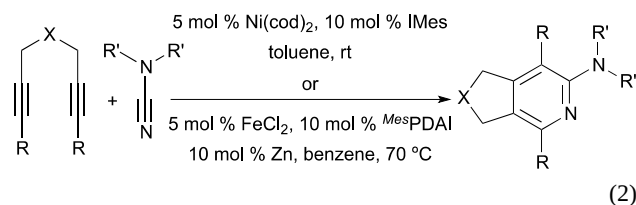
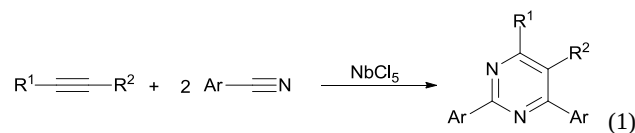
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Several cycloaddition catalysts and reagents were surveyed for their effectiveness toward cyclizing alkynenitriles with cyanamides. Catalytic amounts of FeI_2 , $i\text{PrPDAI}$ and Zn were found to effectively catalyze the [2+2+2] cycloaddition of a variety of cyanamides and alkynenitriles to afford bicyclic 2-aminopyrimidines.

Since the 1948 report by Reppe of acetylene cyclotrimerization in the presence of a transition metal, the field of [2+2+2] cycloaddition has grown immensely.¹ Today, a myriad of carbocycles can be created from various combinations of unsaturated hydrocarbons.² The next development in this field was the incorporation of heteroatoms into cyclic products. Heterocycles (such as pyridones,³ piperidines,⁴ pyridines⁵ etc) of great complexity can now be synthesized from numerous coupling partners.⁶ These systems supply a highly efficient method to form multiple bonds in a single step and are of paramount importance in organic synthesis.

The domain of [2+2+2] cycloaddition is poised to enter a new step in its evolution. Cyclic compounds with multiple heteroatoms constitute another vast collection of compounds attracting considerable interest. Such motifs are abundant in pharmaceuticals, natural products, and other biologically active compounds as well as in polymers and supramolecules.⁷ Despite such importance, the use of [2+2+2] cycloaddition for the construction of these compounds has received little attention. Such a reaction requires the incorporation of two heteroatom coupling partners to one hydrocarbon coupling partner. However, the latter substrates are typically more reactive in cycloaddition and lead to products that exclude the less reactive heteroatom coupling partner.⁸ For example, the combination of alkynes and excess nitriles in the presence of a variety of [2+2+2] cycloaddition catalysts affords either pyridines or substituted benzenes, or a mixture of thereof.⁹ Even when employing nitrile as a solvent, incorporation of multiple nitrogen atoms is typically not observed.¹⁰ Despite this significant obstacle, limited examples demonstrate that strategies to access cyclic compounds with multiple heteroatoms are possible. The first example by Hoberg involved the cycloaddition of an alkyne and two isocyanates in the presence of stoichiometric $\text{Ni}(0)$ producing a pyrimidine dione.¹¹ Our lab revisited this reactivity and successfully developed the first catalytic [2+2+2] route to pyrimidine diones.¹² This work was later followed up by Kondo and co-workers.¹³ A more recent example by Obora utilizes a

niobium Lewis acid to afford pyrimidines from an alkyne and two nitriles (equation 1).¹⁴ While this method is regioselective, it requires an excess of NbCl_5 that must be added in six portions over the course of the reaction. Additionally, yields are moderate and this system is limited to aromatic nitriles. Nevertheless, based on the reactivity of Nb complexes, pyrimidine formation likely involves a nucleophilic attack of the nitrile nitrogen onto a Nb coordinated alkyne complex rather than a Nb catalyzed cycloaddition reaction. Such a scarcity of examples in this area led us to seek a new metal-catalyzed [2+2+2] cycloaddition method for the creation of cyclic compounds with two heteroatoms.



Our group demonstrated that cyanamides perform exceptionally well in Ni- and Fe-catalyzed cycloadditions with diynes (equation 2).^{15,16} Additionally, we showed that utilizing alkynenitriles aid in the incorporation of nitrogen into cycloaddition products when using an iron catalyst.¹⁷ We report herein a novel Fe-catalyzed cycloaddition reaction between alkynenitriles and cyanamides to provide 2-aminopyrimidines (equation 3). The abundant biological activity of 2-aminopyrimidines make such a reaction desirable because complex substitution patterns can be obtained from simple starting materials.^{18,19}

We began by surveying the field of [2+2+2] transition metal

catalysts under their previously developed conditions (Table 1).²⁰

Table 1 Catalyst/Reagent Screening

Entry	Substrates (equiv)	Conditions ^a	% yield 3a ^b
1	1a (1), 2a (2)	5 mol % Rh(cod) ₂ BF ₄ /BINAP	n.d. ^c
2	1a (1), 2a (5)	15 mol % CoCp(CO) ₂	n.d.
3	1a (1), 2a (3)	10 mol % CoCl ₂ , 10 mol % dppe 20 mol % Zn	n.d.
4	1a (1), 2a (1.5)	10 mol % Ni(cod) ₂ , 20 mol % SIPr	n.d.
5	1a (1), 2a (1.5)	10 mol % Ni(cod) ₂ , 20 mol % IMes	n.d.
6	1a (1), 2a (1.5)	10 mol % Ni(cod) ₂ , 10 mol % Xantphos	n.d.
7	1a (1), 2a (1.5)	2 mol % Cp*RuCl(cod)	n.d.
8	1a (1), 2a (3)	2 mol % [Ir(cod)Cl] ₂ , 4 mol % DPPF	trace
9	1a (1), 2a (3)	1.2 equiv NbCl ₅	n.d.
10	1a (1), 2a (3)	5 mol % Ph ₃ PAuOPOF ₂	n.d.
11	1a (1), 2a (3)	5 mol % AuCl ₃ , 1.1 equiv MsOH	n.d.
12	1a (1), 2a (3)	5 mol % AuPEt ₃ Cl, 5 mol % AgSbF ₆	n.d.
13	1a (1), 2a (3)	10 mol % AgOTf, 10 mol % CuBr	n.d.
14	1a (1), 2a (3)	10 mol % FeI ₂ , 20 mol % dppp 20 mol % Zn	n.d.
15	1a (1), 2a (3)	10 mol % FeI ₂ , 20 mol % dppp 20 mol % Zn, 20 mol % ZnI ₂	n.d.
16	1a (1), 2a (2)	20 mol % Fe(OAc) ₂ , 40 mol % Zn, 26 mol % <i>p</i> -OMe, <i>i</i> PrPDAI ^m	trace
17	1a (1), 2a (2)	10 mol % FeCl ₂ , 20 mol % <i>Mes</i> PDAI 20 mol % Zn	16 ^d

^a Detailed conditions available in SI or ref. 20. ^b Detected by GC/MS. ^c n.d. = not detected. ^d NMR yield.

Rhodium, cobalt, nickel, and ruthenium catalysts (entries 1-7) were ineffective while iridium (entry 8) only afforded a trace of **3a** as detected by GCMS. Additionally, niobium, gold, silver and Cu reagents provided no products (entries 9-13). FeI₂/dppp was ineffective (entries 14-15). However, our previous Fe(OAc)₂/*p*-OMe, *i*PrPDAI system^{17,21} provided a trace of 2-aminopyrimidine (entry 16). Curiously, our FeCl₂/*Mes*PDAI catalyst (entry 17), under the conditions used to produce 2-aminopyridines,¹⁶ afforded 2-aminopyrimidine **3a** (Figure 1) in 16 % NMR yield. This result was auspicious considering the low cost, high terrestrial abundance and relatively low toxicity of iron as compared to other metal catalysts.

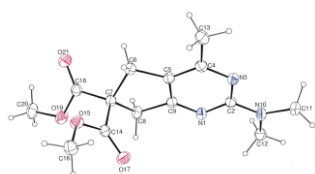


Fig. 1 Ortep of **3a**

Expensive and highly toxic benzene was replaced with toluene at the outset of optimization.²² We initially identified Fe(OAc)₂ as the optimum iron source; however, subsequent optimization with Fe(OAc)₂ was unproductive. We then turned to FeI₂, which allowed for significant improvements. Decreasing concentration, increasing cyanamide loading to 3 equiv and ensuing ligand optimization led to sound improvements in yields. Phosphine, amine, carbene and bisimine ligands were ineffective while PDI ligands could only afford traces of product.²³ Reducing temperature to 40 °C and increasing Zn dust loading to 30 mol % allowed for catalyst loading to be reduced to 5 mol %. At lower concentrations, the reduction of iron pre-catalyst by Zn is perhaps more difficult leading to the necessity for higher loading. Our final conditions utilize a 1:3 ratio of alkynenitrile with 5 mol %

FeI₂, 10 mol % *i*PrPDAI, 30 mol % Zn dust in toluene at 40 °C (Equation 4).

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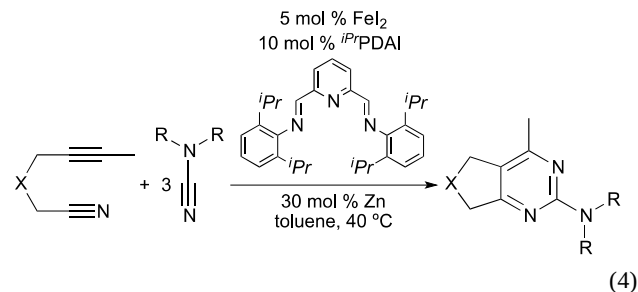


Table 2 Substrate Scope

Entry	Alkynenitrile	Cyanamide	time ^b	Product (% yield)
1	1a	2a	12 h	3a (90)
2	1a	2b	48 h	3b (40)
3	1a	2c	36 h	3c (82)
4	1a	2d	72 h	3d (35)
5	1a	2e	72 h	3e (40)
6 ^c	1b	2a	48 h	3f (27)
7	1c	2a	24 h	3g (n.d.) ^d

^a Conditions: 5 mol % FeI₂, 10 mol % *i*PrPDAI, 30 mol % Zn dust, toluene, 40 °C. ^b Reaction progress monitored by GC. ^c Conditions: 5 mol % FeI₂, 10 mol % *i*PrPDAI, 30 mol % Zn dust, 30 mol % ZnI₂, toluene, 40 °C. ^d n.d. = not detected.

Our final optimized conditions were applied to various combinations of substrates (Table 2). The model substrates **1a** and **2a** afforded **3a** in 90 % yield in 12 hours (entry 1); however, other substrates required extended reaction times. Cyclic cyanamides were incorporated providing **3b**, **3c**, and **3d** in 40, 82, and 35 % yields, respectively (entry 2-4). Me/Ph-cyanamide **2e** provided **3e** in 40 % yield over 3 days (entry 5). Under our

standard conditions, **1b** was unreactive. However, in the presence of 30 mol % ZnI_2 , **3f** was obtained in 27 % yield (entry 6). While ZnI_2 is known to aid in cobalt catalysis by stabilizing Co(I) species,²⁴ its effect in iron-catalyzed reactions remains unclear.^{8,25} Applying ZnI_2 to all reactions involving **1a** resulted in increased reaction times and decreased yields. This conflicting result has been observed in a previous study.²⁵ Finally, the challenging terminal alkynenitrile **1c** failed to react under these conditions (entry 7). Efforts to replace the cyanamide substrate with an unactivated nitrile such as PhCN were ineffective as were 3-component cyclizations of $4\text{-CH}_3\text{PhCCH}$ with either 2 equivalents of free nitriles (i.e., PhCN) or cyanamides (i.e., **2a**). Although yields are modest in many cases, this work demonstrates that bicyclic 2-aminopyrimidines with complex substitution patterns can be prepared through Fe-catalyzed cycloaddition chemistry. In some cases however, yields are high indicating that this system could be synthetically useful if optimization is done on a case-by-case basis.

Conclusions

We have disclosed the first catalytic [2+2+2] cycloaddition to produce aromatic diazaheterocycles. What is especially remarkable is that iron, which has traditionally been an inefficient cycloaddition catalyst for nitrile incorporation, can now incorporate multiple nitriles into aromatic products. Furthermore, traditionally more efficient catalysts were ineffective toward this strategy of 2-aminopyrimidine synthesis. We are actively studying the properties of iron/PDAI catalysts in the hope that a better understanding of these systems will lead to improved yields and expanded substrate scopes.

Notes and references

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