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Ruthenium-Catalyzed [2 + 2 + 2] Cycloaddition Reaction Forming 2-Aminopyridine Derivatives from α,ω-Diynes and Cyanamides

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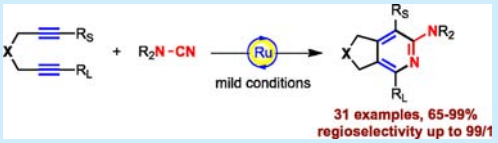
Supporting Information

ABSTRACT: A novel, efficient, and mild synthetic route for the preparation of 2-aminopyridines via ruthenium-mediated [2 + 2 + 2] cycloaddition of α,ω-diynes and cyanamides has been developed. This atom-economical catalytic process demonstrated remarkable regioselectivities to access pyridine derivatives of high synthetic utility.



Because 2-aminopyridines represent a privileged scaffold in organometallic and medicinal chemistry (Figure 1),[1] numerous strategies targeting such heterocycles including Chichibabin aromatic substitution,[2f,g] amination reactions,[2h−o,s,t] hetero-Diels−Alderreactions,[2r] and multicomponent transformations[2p,q] have been developed.[2]

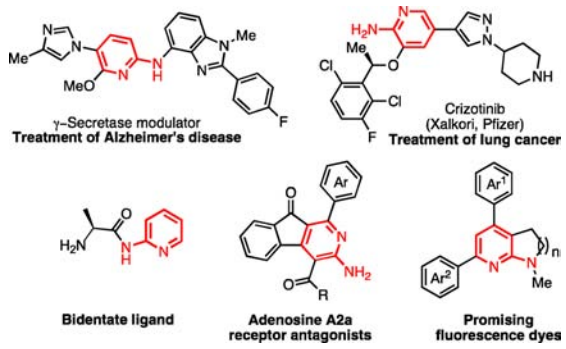
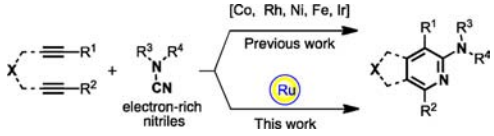


Figure 1. Selected examples with 2-aminopyridine units.

Alternatively, transition-metal-catalyzed [2 + 2 + 2] cycloaddition reactions are powerful methods to prepare heteroaromatic compounds.[3] In particular, [2 + 2 + 2] cycloadditions of alkynes and nitriles have been extensively explored to access pyridine derivatives.[3−5] However, as far as 2-aminopyridines are concerned, only a few examples of [2 + 2 + 2] cycloaddition of α,ω-diynes and cyanamides based on Co, Rh, Ni, Fe, and Ir catalysis have been reported (Scheme 1).

After the pioneering cobalt-mediated [2 + 2 + 2] cycloaddition of acetylene and cyanamide reported by Bönnemann et al. using (η^6-boranato)cobalt at 130 °C under 40 bar,[6a] Heller and co-workers described one example of [CpCo(cod)]-promoted cycloaddition of acetylene and dimethylcyanamide with 46% yield[6b] and a photocatalyzed cycloaddition of acetylene with *N*-cyanopyrrolidine and *N*-cyanopiperidine.[6d,h] A single example was reported by Eaton et al. using a water-soluble cobalt(I) catalysts.[6c] Maryanoff et al. showed the cyclotrimerization of α,ω-diynes and cyanamides in refluxing dioxane for 18−24 h with 15 mol % of $CpCo(CO)_2$ to provide 2-aminopyridines in a range of 19−88% yield.[6e−g] Schmalz et al. synthesized allocolchicine analogues in 27% and 35% yields employing 20 mol % of $CpCo(CO)_2$ under microwave conditions at 150 °C.[6i] Malacria, Aubert, Gandon et al. used 10 mol % of [CpCo(CO) (dmfu)] to provide annulated 2-aminopyridines through [2 + 2 + 2] cycloaddition of yne−ynamides and cyanamides at 110 °C in toluene for 15 h with yields ranging from 20 to 85%.[6j,k] Tanaka et al. disclosed a single example of Rh(I)/BINAP-catalyzed [2 + 2 + 2] cycloaddition of a malonate-tethered diyne and cyanomorpholine in 47% yield.[7] Louie et al. successfully developed the Ni/Xantphos-mediated cycloaddition of 2,7-diynes with *N*-cyanopyrrolidine, *N*-cyanomorpholine, diallylcyanamide, and *N*,*N*-dimethylcyanamide at room temperature to access 6,6-fused cycloadducts in, respectively, 99%, 75%, 76%, and 86% yield with complete regioselectivity. The Ni-catalyzed cycloaddition was also accomplished with alkynes and cyanamides.[8] The same group[9a,c] and Wan's group[9b] respectively achieved the Fe-catalyzed synthesis of 2-aminopyridines using 5 mol % of $FeCl_2$/10 mol % of Zn in C_6H_6 at 70 °C and 5 mol % of FeI_2/10 mol % of dppp/10 mol % of Zn in THF at rt in 40−99% yields. Terminal alkynes were also used as partners.[9] Takeuchi et al. developed the efficient $[Ir(cod)Cl]_2$/BINAP or DPPF [2 + 2 + 2] cycloaddition of various α,ω-diynes and cyanamides in refluxing benzene with 31−97% yield and excellent regioselectivities.[10] To the best of our knowledge, no Ru-catalyzed synthesis of functionalized pyridines with electron-rich nitriles such as cyanamides has been reported so

Scheme 1. Our Strategy To Construct 2-Aminopyridine Derivatives via Ru-Catalyzed [2 + 2 + 2] Cycloadditions



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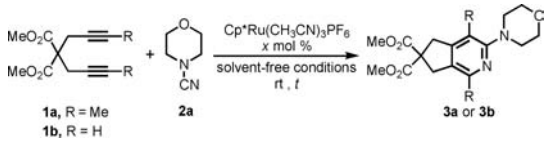
far (Scheme 1).[11] In continuation of our previous work on the construction of fused functionalized arenes,[12] we report herein a novel, highly efficient, and mild [2 + 2 + 2] cycloaddition process to access functionalized substituted 2-aminopyridines based on atom-economical Ru-catalyzed [2 + 2 + 2] cycloadditions of α,ω-diynes and cyanamides (Scheme 1).

Initially, the Ru-catalyzed cycloaddition of dimethyl-substituted internal diyne **1a** with cyanamide **2a** was investigated under solvent-free conditions at room temperature. Several ruthenium complexes were evaluated, but no desired products were obtained when $[Ru(PPh_3)_3Cl_2]$ and $[Ru(p\text{-cymene})Cl_2]_2$ were used as catalyst (Table 1, entries 1 and 2). Fortunately, we

Table 1. Optimization of Reaction Conditions[a]



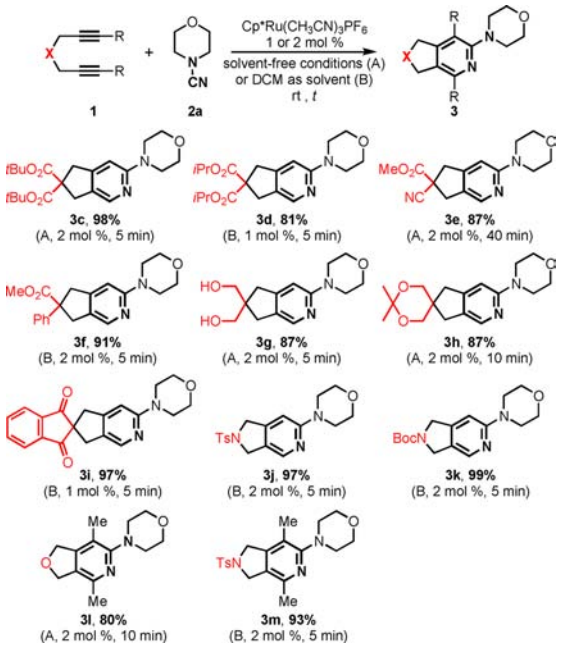
entry	1	conditions: cat. (x), time	conv[b] (%)	yield[c] (%)
1	**1a**	$Ru(PPh_3)_3Cl_2$ (5), 8 h	NR	ND
2	**1a**	$[Ru(p\text{-cymene})Cl_2]_2$ (2.5), 8 h	NR	ND
3	**1a**	Cp*Ru(cod)Cl (2), 5 min	>99	85
4	**1a**	$Cp^*Ru(CH_3CN)_3PF_6$ (5), 5 min	>99	93
5	**1a**	$Cp^*Ru(CH_3CN)_3PF_6$ (2), 5 min	>99	91
6	**1a**	$Cp^*Ru(CH_3CN)_3PF_6$ (1), 60 min	80	ND
7	**1b**	$Cp^*Ru(CH_3CN)_3PF_6$ (2), 3 min	>99	94
8[d]	**1b**	$Cp^*Ru(CH_3CN)_3PF_6$ (1), 2 min	>99	95
9[d]	**1b**	$Cp^*Ru(CH_3CN)_3PF_6$ (0.5), 18 h	90	82

[a]Reaction conditions: Ru complex (0.5–5 mol %), diyne **1** (0.5 mmol), and cyanamide **2a** (1.0 mmol) were stirred in a screw-capped tube under solvent-free conditions and argon atmosphere. [b]Determined by crude ^1H NMR analysis. [c]Isolated yield. [d]With 0.6 mmol of cyanamide **2a** and 0.5 mL of dichloromethane as solvent.

found that both pentamethylcyclopentadienyl (Cp*) complexes [Cp*Ru(cod)Cl] and $[Cp^*Ru(CH_3CN)_3]PF_6$ were effective in giving full conversion of the starting material, providing **3a** in, respectively, 85% and 93% yields (entries 3 and 4). The catalyst loading could be efficiently reduced to 2 mol % (entries 4–6). In addition, we also found that the addition of a small amount of dichloromethane allowed the formation of **3b** in a similar high yield. In this case, the catalyst loading (1 mol %) and consumption of cyanamide (1.2 equiv) were further reduced (entries 7 and 8). However, attempts to reduce the catalyst loading to 0.5 mol % resulted in a decreased yield even when the reaction time was prolonged to 18 h (entry 9).

With a set of optimized conditions in hand, the scope and generality of this mild protocol were explored. The reactions of various symmetrical diynes with cyanamide **2a** are summarized in Scheme 2. The diynes with a quaternary-carbon tether reacted with **2a** to give the corresponding 2-aminopyridines in high yields. Diynes bearing methyl, bulkier *tert*-butyl, and isopropyl ester moieties could smoothly react with **2a** to deliver **3c–f** in high to excellent yields. Notably, a nitrile substituent on the diyne was compatible with the reaction conditions. A diyne bearing a free hydroxyl group was also compatible, furnishing the targeted compound **3g** in 87% yield. The spirocyclic derivatives **3h** and **3i** were also synthesized in 87% and 97% yields, respectively. The reaction was not limited to a quaternary-carbon tethered diyne since both *N*- and *O*-tethered diynes were successfully used, leading to **3j–m** in 80% to 99%

Scheme 2. Scope of Symmetrical Diynes[a]



[a]Reaction conditions: $Cp^*Ru(CH_3CN)_3PF_6$ (1–2 mol %), diyne **1** (0.5 mmol), and cyanamide **2a** (A: 2.0 equiv, B: 1.2 equiv) were stirred in a screw-capped tube under solvent-free (A) or dichloromethane (0.5 mL) (B) conditions and argon atmosphere. Full conversion was obtained unless otherwise mentioned. Isolated yield.

yield. The formation of compounds **3l** and **3m** illustrated that the reaction was not limited to terminal diynes but also worked well with internal diynes. It is noteworthy that the reaction was feasible under both solvent and solvent-free conditions to furnish the desired product in a short reaction time.

We next evaluated the scope and limitations on the cyanamide partners. The results are summarized in Scheme 3. Cyanamides bearing a secondary amine substituent smoothly underwent the cycloaddition reactions to produce the corresponding 2-aminopyridines in high yields. Cyclic cyanamide **2b** successfully reacted with diynes **1a** and **1b** to deliver the corresponding products **4a** and **4b** in 81% and 90% yields. The diethyl-, di-*n*-propyl-, dibenzyl-, and methyl-*n*-butyl-substituted cyanamides were slightly less reactive, and the corresponding products **4c–f** were obtained in 76–86% yields. High yields were obtained for 2-aminopyridines bearing a phenyl (**4g**) group and a monobenzyl group (**4h** and **4i**) in the presence of 1–2 mol % of Ru catalyst.

The transition-metal-catalyzed cycloaddition of diversely substituted unsymmetrical diynes with nitriles for the regioselective synthesis of pyridines has been carefully studied.[3−5] However, little attention has been paid to halogen-substituted diynes.[5n] The first example of halopyridines, prepared from haloalkynes and nitriles, was recently reported by Kotora with a low regioselectivity.[5n] Aware of the synthetic potential of challenging halopyridines, we evaluated the reactivity of monobromodiynes (**5a–d**) and monoiododiyne (**5e**) in the Ru-catalyzed [2 + 2 + 2] cycloadditions (Scheme 4).

To our delight, the desired *o*-halopyridines **6a–e** were obtained in good to high yields as well as high regioselectivities.

In some cases, the catalyst loading was increased to 5 mol % as well as the reaction temperature (50 °C) to reach full

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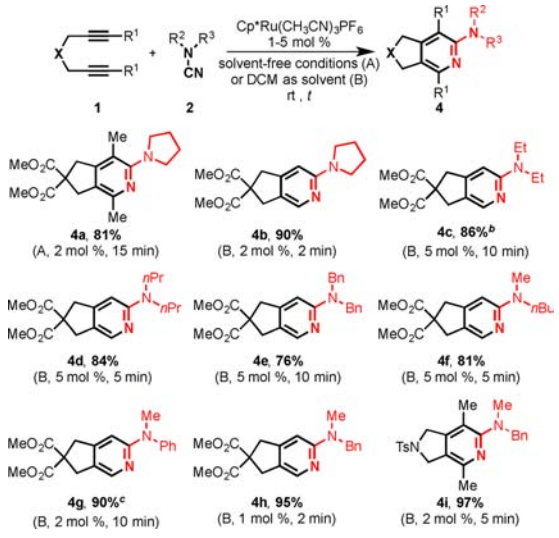
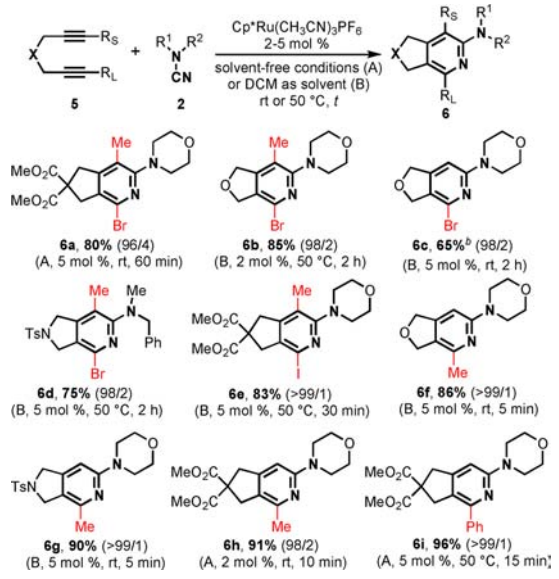
Scheme 3. Scope of Cyanamides[a]



[a]Reaction conditions: $Cp^*Ru(CH_3CN)_3PF_6$ (1−5 mol %), diyne **1** (0.5 mmol) and cyanamide **2** (A: 2.0 equiv, B: 1.2 equiv) were stirred in a screw-capped tube under solvent-free (A) or dichloromethane (0.5 mL) (B) conditions and argon atmosphere. Full conversion was obtained unless mentioned. Isolated yield. [b]Conversion = 93%. [c]Conversion = 92%.

Scheme 4. Regioselective [2 + 2 + 2] Cycloaddition of Unsymmetrical Diynes[a]



[a]Reaction conditions: $Cp^*Ru(CH_3CN)_3PF_6$ (1−5 mol %), diyne **5** (0.5 mmol) and cyanamide **2** (A: 2.0 equiv, B: 1.2 equiv) were stirred in a screw-capped tube under solvent-free (A) or dichloromethane (0.5 mL) (B) conditions and argon atmosphere. Full conversion was obtained unless otherwise mentioned. Isolated yield. [b]Conversion = 74%.

conversion in a short reaction time. Furthermore, both heteroatom-tethered diynes and malonate-derived diynes, possessing a terminal alkyne moiety and a methyl- or phenyl-substituted internal alkyne moiety, were well tolerated to afford the corresponding functionalized 2-aminopyridines **6f−i** in high yields (86−96%) and excellent regioselectivities (>99:1). Notably, it was clearly demonstrated that the regioselectivity was reasonably explained by the favorable formation of less hindered *ortho*-substituted 2-aminopyridines as the major product (structure determined by 2D-NMR analysis; see the Supporting Information).

To conclude, a straightforward approach to access 2-aminopyridines is described. This strategy involves the novel Ru-catalyzed [2 + 2 + 2] cycloaddition reaction of α,ω-diynes and cyanamides, which efficiently and regioselectively allows under mild conditions the construction of an annulated 2-aminopyridine core. Furthermore, this expeditious process requires only the commercially available and easy to handle $Cp^*Ru(CH_3CN)_3PF_6$ complex with neither additional ligands nor additives. Further challenging applications of this method are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00130.

Experimental procedures, analytical data, and NMR spectra for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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