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Additive-Controlled Switchable Selectivity from Cyanobenzenes to 2-Alkynylpyridines: Ruthenium(II) -Catalyzed [2+2+2] Cycloadditions of Diynes and Alkynylnitriles

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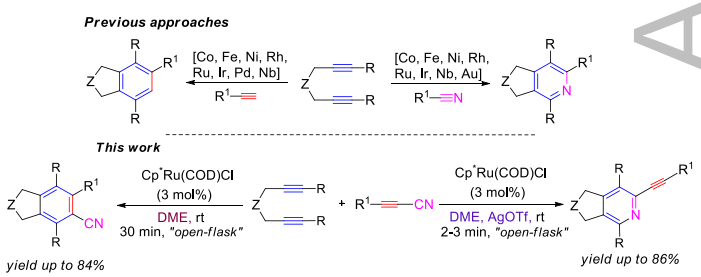
Abstract. A highly efficient additive-dependent chemoselective protocol for the synthesis of fused cyanoarenes and 2-alkynylpyridines has been developed by the reaction of 1,6-diynes with alkynylnitriles using chloro-(pentamethylcyclopentadienyl)(cyclooctadiyne)-ruthenium(II) as catalyst in dimethoxyethane (DME). The course of the reaction can be drastically altered simply by adding a catalytic amount of AgOTf as an additive resulting in a comprehensive shift in product formation from cyanoarenes to 2-alkynylpyridines. Theoretical studies clearly indicate that the neutral Ru-complex is responsible for the formation of cyanobenzenes, whereas the in situ generated cationic Ru-complex plays a crucial role in the 2-alkynylpyridines formation.

Keywords: alkynylnitriles; cyanobenzenes; 2-alkynyl-pyridines; [2+2+2] cycloaddition; ruthenium catalyst

The [2+2+2] cycloaddition reactions between 1,6-diynes and acetylenes/nitriles have already established themselves as elegant, atom-efficient, and group-tolerant processes for the synthesis of fused aromatic carbo- and heterocycles, involving the formation of several C-C and C-heteroatom bonds in a single step. Various transition-metal complexes of cobalt,[1] iron,[2] ruthenium,[3] rhodium,[4] iridium,[5] nickel,[6] palladium,[7] gold,[8] and niobium[9] are presently widely utilized for [2+2+2] cycloaddition reactions of 1,6-diynes and acetylenes/nitriles (used separately) to synthesize different types of fused benzenes and pyridines, respectively (Scheme 1).[10] In continuation of our research in the field of metal-catalyzed [2+2+2] cycloaddition reactions, we devoted our effort to develop a [2+2+2] cycloaddition protocol in which both benzene and pyridine rings could be constructed in a chemoselective manner by simple modification in the reaction conditions such as temperature, additive, etc., keeping the reactants, solvent, and the catalyst unchanged. Therefore, for this purpose, acetylene, and the nitrile moieties should be present in the same compound and, thus, we hypothesized that alkynylnitriles, in this respect, could be the suitable candidates to react with 1,6-diynes in a chemoselective manner to provide either fused cyanobenzenes or 2-alkynylpyridines under appropriate reaction conditions. The challenge was to find out a suitable catalyst and the reaction conditions to make one functional moiety to react chemoselectively in the presence of the other. In this connection, our group has recently demonstrated a protocol for the synthesis of fused cyanoarenes *via* chemoselective iron-catalyzed [2+2+2] cycloaddition reactions of diynes with alkynylnitriles.[11] In addition, Yamamoto *et al.* reported chemoselective synthesis of pyridine rings from the reaction of diynes with conjugated alkynylnitriles.[12] However, none of these reports present chemoselective synthesis of both the cycloadducts (benzenes and pyridines) applying the same

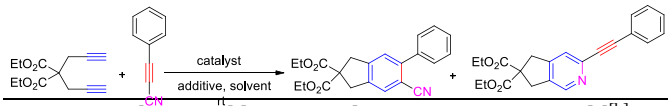


Scheme 1. Transition metal catalyzed [2+2+2] cyclo-addition reactions for the synthesis of fused benzenes and pyridines.

starting materials, solvent, and catalyst. Such a type of selectivity control is highly challenging and rare. In this context, Joyanta *et al.* recently showed a complete switch in the reaction pathway of a rhodium catalyzed C-H functionalization reaction by a simple change in anion and solvent polarity.[13]

Over the last decade, the general synthetic routes to prepare cyanobenzene compounds have mainly encompassed transition-metal-catalyzed cyanation of aryl halides,[14] which involves certain drawbacks such as use of toxic reagents, harsh reaction conditions and formation of undesired byproducts. On the other hand, the synthesis of 2-alkynylpyridines mainly rely on palladium-catalyzed Sonogashira cross-coupling reactions,[15] which are generally accompanied by the formation of Glaser homo-coupling product. In this context, the ruthenium catalyzed [2+2+2] cycloaddition protocol for the synthesis of fused

Table 1. Optimization of reaction conditions[a]



Entry	Catalyst	additive	solvent	time	Yield[b] (%)	
					3aa	**4aa**
1	**[Fe]**	-	DME	20 min	86	-
2	**[Fe]**	AgOTf	DME	0.5 h	70	-
3	**[Fe]**	-	EtOH	0.5 h	81	-
4	**[Fe]**	AgOTf	EtOH	5 h	21	-
5	**[Fe]**	-	THF	2	72	-
6	**[Ru]**	-	DCE	1 h	58	21
7	**[Ru]**	-	THF	1 h	65	-
8	**[Ru]**	-	DMSO	1 h	-	-
9	**[Ru]**	-	DMF	2-3 min	65	10
10	**[Ru]**	-	**DME**	**0.5 h**	**82**	-
11	**[Ru]**	**$BF_3.Et_2O$**	**DME**	**2-3 min**	-	**84**
12	**[Ru]**	**AgOTf**	**DME**	**2-3 min**	-	**86**
13	-	AgOTf/ $BF_3.Et_2O$	DME	24 h	-	-
14	**[Ru]**	Bu_4NBr	DME	1 h	48	-
15	**[Ru]**	Bu_4NCl	DME	1 h	41	-

DME: Dimethoxyethane; DCE: 1,2-Dichloroethane; DMF: N,N-dimethylformamide; **[Fe]**: $FeCl_2.4H_2O$ (5 mol%)/2-(2-6-diisopropylphenyl)-iminomethylpyridine (dipimp) (6 mol%)/Zn (10 mol%); **[Ru]**: Cp*Ru(COD)Cl (3 mol%)

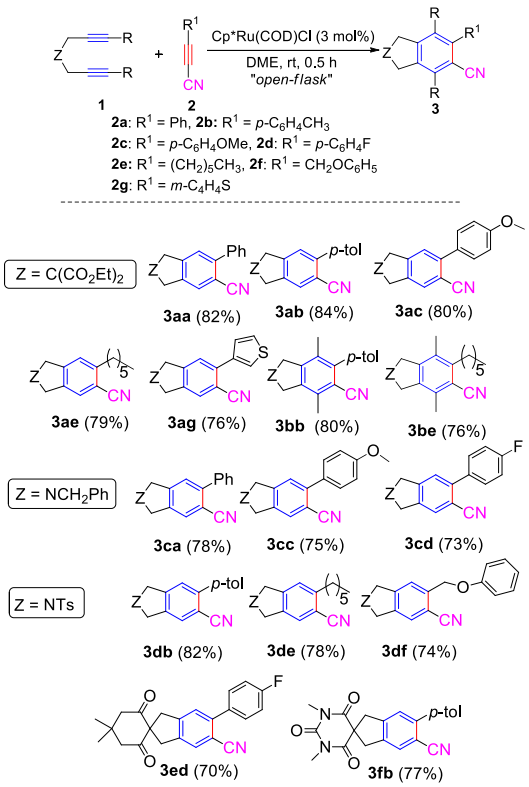
[a] Optimized reaction conditions for **3aa [Method A]**: **1a** (0.5 mmol), **2a** (0.6 mmol), Cp*Ru(COD)Cl (3 mol%), DME (0.5 mL), open flask, room temperature, 30 min. **4aa [Method B]**: **1a** (0.5 mmol), **2a** (0.6 mmol), Cp*Ru(COD)Cl (3 mol%), AgOTf (3 mol%), DME (0.5 mL), open flask, room temperature, 2-3 min.

[b] Isolated yield.

cyanoarenes and 2-alkynylpyridines presented herein is an atom-economical, straight-forward process providing good to high yields within 3-30 min and moreover, to the best of our knowledge, it is the first report to utilize [2+2+2] cycloaddition protocol to prepare arenes and heteroarenes using same reactants, solvent and catalyst (Scheme 1).

To obtain the optimum reaction conditions for the chemoselective [2+2+2] cycloaddition reactions for synthesis of cyanoarenes **3aa** and 2-alkynylpyridines **4aa**, diyne **1a** and 3-phenylpropiolonitrile **2a** were chosen as model substrates for the said purpose.

In the course of our previous survey on several metal complexes $[CpCo(CO)_2]$, $CoCl_2.6H_2O$ /dipimp/Zn, $FeCl_2.4H_2O$/dipimp/Zn, $[Ir(COD)Cl]_2$ /dppe, $(PPh_3)_3RhCl$, $Ni(COD)_2$/xantphos, $Pd_2(dba)_3$ /PPh_3 as suitable catalysts for chemoselective [2+2+2] cycloaddition reactions of alkynylnitriles with diynes, the $FeCl_2.4H_2O$/dipimp/Zn catalytic system in DME was found to be the best choice for the synthesis of fused cyanoarenes **3** in a chemoselective manner (Table 1, entry 1). However, changing several commonly used solvents and adding additive to the said iron catalytic system did not give access to the desired 2-alkynylpyridine **4** (Table 1, entries 2-5). Therefore, we focused our attention on commercially available and relatively inexpensive Cp*Ru(COD)Cl as a catalyst for the said chemoselective cycloaddition

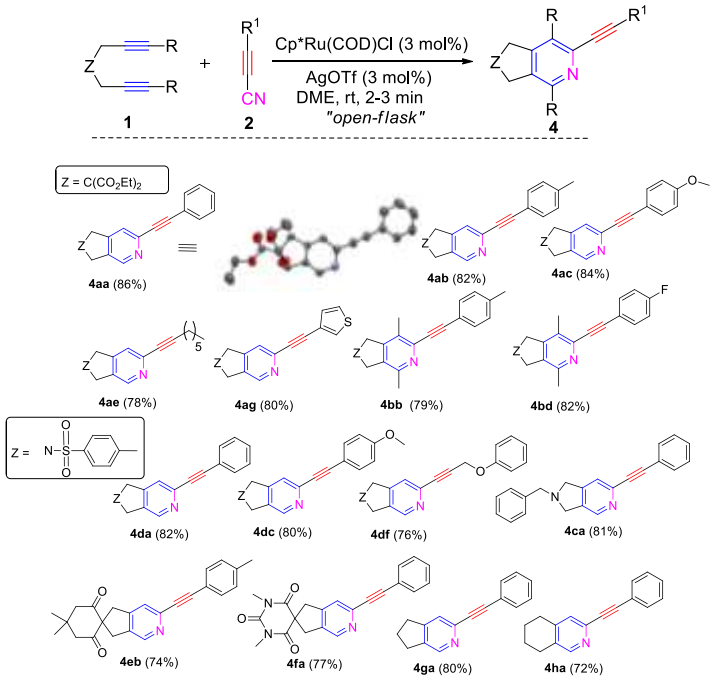


Scheme 2. Chemoselective ruthenium-catalyzed cyclo-additions leading to arylnitriles **3**: **1** (0.5 mmol), **2** (0.6 mmol), Cp*Ru(COD)Cl (3 mol%), DME (0.5 mL), open flask, room temperature, 30 min.

reaction as it is one of the widely used precatalyst for benzene and pyridine rings construction. Among the various solvents tested (Table 1, entries 6-10), DME was found to be best choice for the synthesis of cyanoarene **3aa** in high yield under aerobic conditions (Table 1, entry 10, **method A**).

With a set of optimized conditions in mind for the synthesis of cyanoarene **3aa**, we further devote our attention to accomplish the suitable reaction conditions for the construction of alkynylpyridine **4aa** from the same model substrates **1a** and **2a** using Cp*Ru(COD)Cl as a catalyst in DME. Fortunately, when catalytic amount of $BF_3.Et_2O$ was added as an additive in the said cycloaddition reaction, 2-alkynyl-pyridine **4aa** was obtained as the sole cycloadduct in high yield (Table 1, entry 11). The yield of the pyridine product was further enhanced when AgOTf was added as an additive (Table 1, entry 12, **method B**), while none of the products (**3aa** or **4aa**) was obtained in the absence of Ru catalyst using either AgOTf or $BF_3.Et_2O$ (Table 1, entry 13). However, *n*-Bu_4NX (X = Br, Cl) were able to provide cyanobenzene **3aa** in relatively low yields (Table 1, entry 14-15).

Under the optimized reaction conditions **(method A)**, the scope and generality of this mild protocol was explored. A library of arylnitriles **3** was synthesized from the reaction of terminal and internal diynes with various alkynylnitriles in good to high yields, indicating the remarkable functional group compatibility of this protocol (Scheme 2). In all cases, trace amount of dimer (dimerization of diyne) was obtained, however, no self cyclotrimerization of alkynylnitrile took place.

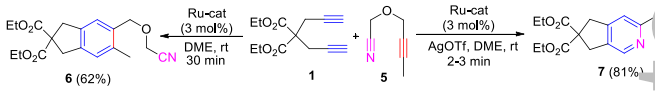


Scheme 3. Synthesis of 2-alkynylpyridines **4** *via* chemoselective ruthenium-catalyzed cycloadditions: **1** (0.5 mmol), **2** (0.6 mmol), Cp*Ru(COD)Cl (3 mol%), AgOTf (3 mol%), DME (0.5 mL), open flask, room temperature, 2-3 min.

We next evaluated the scope for the chemoselective synthesis of 2-alkynylpyridines **4** by ruthenium catalyzed cycloaddition reactions of diynes and alkynylnitriles in presence of AgOTf as an additive **(method B)** and the results are summarized in Scheme 3. It is noteworthy to mention that all the cycloadditions were successfully carried out using various alkyl- and aryl-substituted alkynylnitriles as well as carbon, oxygen, nitrogen tethered diynes, indicating the efficiency and novelty of this protocol. In addition, formation of compounds **4bb** and **4bd** illustrated that the reaction was not limited to terminal diynes but also worked well with internal diynes. Compound **4aa** was isolated as a pure single crystal and the structure was unequivocally confirmed by single-crystal X-ray[16] analysis.

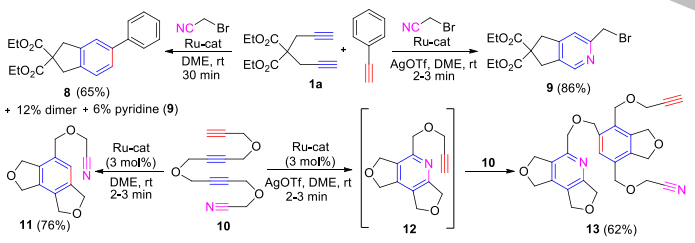
To the best of our knowledge, these results demonstrate the first example of the chemoselective construction of 2-alkynylpyridines (heteroaromatic Sonogashira products) *via* transition metal catalyzed [2+2+2] cycloaddition reactions.

After having the optimized conditions for both the cycloadducts in chemoselective manner, we expanded this cycloaddition reaction to non-conjugated alkynylnitrile to check the general applicability of the protocol. To our delight, our newly developed chemoselective protocol gave access to the compounds **6** and **7** in reasonable to good yields (Scheme 4).



Scheme 4. Synthesis of **6** and **7** *via* chemoselective ruthenium-catalyzed [2+2+2] cycloaddition of 1,6-diyne and non-conjugated alkynylnitrile **5**.

Inspired by these results, we further explored the chemoselectivity of the ruthenium-catalyzed cycloaddition reactions of diyne **1a** with bromoacetonitrile in the presence of phenylacetylene (Scheme 5). Much to our surprise, the desired cycloadducts **8** and **9** were



Scheme 5. Synthesis of compounds **8**, **9**, **11** and **13** by chemoselective ruthenium-catalyzed cycloadditions**.**

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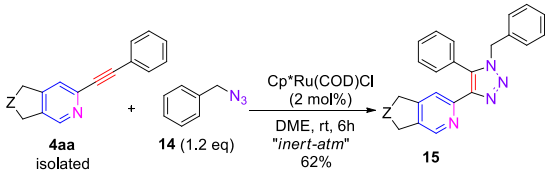
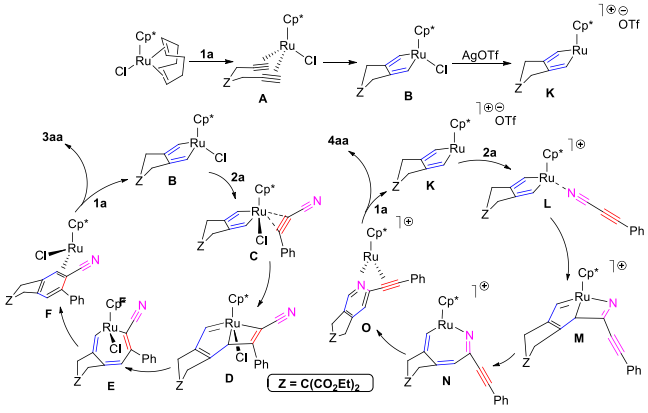
obtained in chemoselective manner depending on the presence or absence of additive. In the similar way, intramolecular cycloaddition of compound **10** was carried out and interestingly, the compound **11** was obtained within 2-3 min as the sole product in the absence of additive. In presence of additive, the reaction did not stop at the stage of compound **12**, double [2+2+2] cycloaddition led to compound **13** as the main product (Scheme 5). These results clearly indicate that the developed protocol could be easily implemented as a late stage methodology for various natural products synthesis.

To our delight, we have also found that the present ruthenium catalyzed cycloaddition protocol can be applied for the preparation of 2-triazole substituted pyridine **15** by a sequential reaction of diyne **1a** with alkynylnitrile **2a** to prepare **4aa** under optimized reaction conditions **(method B)**, followed by the addition of benzyl azide **14** in presence of Cp*Ru(COD)Cl as a catalyst (Scheme 6).



Scheme 6. Synthesis of 2-triazole substituted pyridine **15**.

In the course of understanding the mechanism, it was found from the literature that most of the transition metal complexes coordinate with the triple bond of the acetylene moieties of cyanoacetylenes in η^2-fashion (side-on mode).[17] On the other hand, only cationic ruthenium complexes prefer to co-ordinate with alkynylnitrile through the lone pair of nitrogen in η^1(N)-fashion (end-on mode).[18] Based on this above said information and from energy profile diagram (shown in Figure 1), possible reaction mechanisms for the chemoselective formation of cyanobenzene **3aa** and 2-alkynylpyridine **4aa** are depicted in Scheme 7 (detail of the energy profile diagram is shown in SI).



Scheme 7. Possible catalytic cycles for the chemoselective synthesis of cyanobenzene **3aa** and 2-alkynylpyridine **4aa**.

It is clear from the catalytic cycles that intermediate **B** is responsible for the formation of cyanobenzenes, whereas, ruthenacycle **K** is responsible for the formation of 2-alkynylpyridines. It is anticipated that relatively electron rich neutral Ru-complex **B** (natural charge on Ru metal 0.692) readily reacts with electron poor triple bond of the alkyne moiety of alkynylnitrile to obtain cyanobenzene as the sole cycloadduct (Figure 2). This phenomenon was further supported experimentally when the said cycloaddition was carried out in the presence of *n*-Bu_4NX (Table 1, entries 13-14) to obtain cyanobenzene as the sole product. On the other hand, relatively electron poor cationic Ru-complex **K** (natural charge on Ru metal 0.627) interacts easily with electron rich nitrile moiety of the alkynylnitrile to give 2-alkynylpyridine as the only cycloadduct (Figure 2). Furthermore, it is found that the rate of the reaction is very fast for 2-alkynylpyridine formation compared to cyanobenzene. This observation can be explained on the basis of higher degree of stabilization of intermediate **K** compared to **B**. From the geometrical parameters, it is evident that the positive charge on Ru complex **K** undergoes ring resonance stabilization (as shown in Figure 2), which is not occurring in **B**.

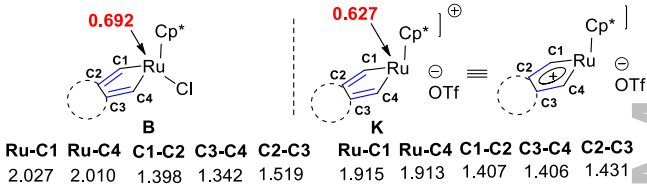
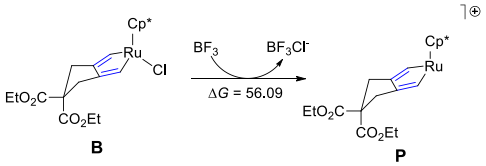


Figure 2. Selected bond lengths (A°) and natural charges (shown in color red) for ruthenacycles **B** and **K**.

DFT calculations to elucidate the role of $BF_3.Et_2O$ were also performed (Table 1, entry 11). It was clear from the calculations that $BF_3.Et_2O$ does not generate cationic Ru species since the free energy of formation for this reaction was positive (ΔG = 56.09 kcal/mol) which makes it highly unsuitable for the reaction to follow the cationic pathway (Scheme 8).



Scheme 8. ΔG value in kcal/mol for the formation of **P.**

Again, calculations were also performed for a neutral pathway where $BF_3.Et_2O$ might coordinate to the nitrogen of alkynylnitrile (Scheme 9). However, the overall energy released in this process was observed to be ΔG = - 90.9 kcal/mol, which was not sufficiently negative (ΔG for the formation of benzene is -120 kcal/mol) to confirm the chemoselectivity of pyridines over benzenes. So at

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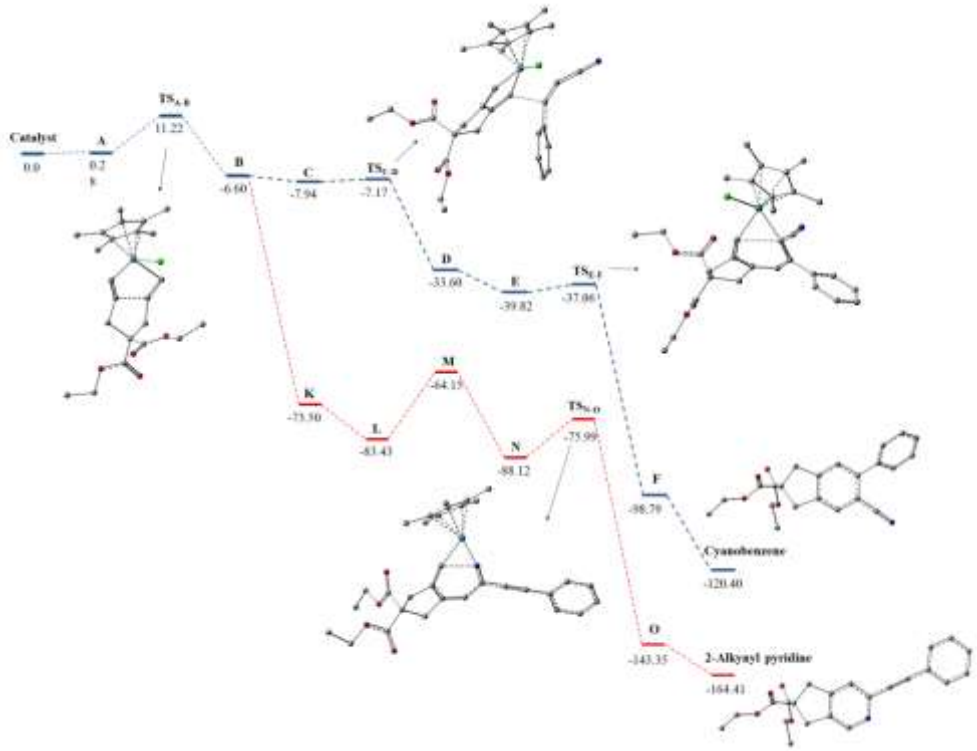
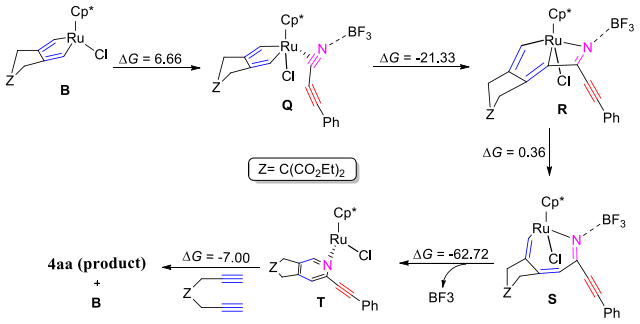


Figure 1. Potential energy surface (based on ΔG values in kcal/mol) for the formation of **3aa** (shown in color blue) and **4aa** (shown in color red) using chemoselective cycloadditions.

this moment, it is difficult to comment on the role of $BF_3.Et_2O$ for the said reaction.



Scheme 9. Formation of **4aa** using $BF_3.Et_2O$ as an additive.

In conclusion, we have developed an additive dependent Cp*Ru(COD)Cl catalyzed cycloaddition protocol for the chemoselective construction of functionalized cyanoarenes and 2-alkynylpyridines in DME with good to very high yields. Due to impressive functional group compatibility of this protocol, a wide range of cyanobenzenes and 2-alkynylpyridines were achieved. The chemoselective cycloaddition reactions were further extended to non conjugated alkynylnitrile to exhibit the general applicability of the protocol. It is important to mention that we have achieved, for the first time, a Ru-based catalytic system which can allow us to construct aromatic and heteroaromatic rings in a chemoselective manner and introduce functional groups (cyanides and alkynyls) on the rings in a single operation.

Experimental Section

General procedure for ruthenium(II) catalyzed chemoselective [2+2+2] cycloaddition reactions leading to the formation of arylnitriles 3: To a round bottom flask, a solution of alkynylnitrile (0.6 mmol) in DME (0.5 mL) was added. Cp*Ru(COD)Cl (5.7 mg, 3 mol%) and diyne (0.5 mmol) were added and the reaction mixture was stirred at room temperature under open flask. After completion of reaction checked by TLC, the crude reaction mixture was filtered and purified through column chromatography over silica gel using hexane/ethyl acetate as eluents to obtain the desired product.

General procedure for ruthenium(II) catalyzed chemoselective [2+2+2] cycloaddition reactions leading to the formation of 2-alkynylpyridines 4: To a round bottom flask, diyne (0.5 mmol), alkynylnitrile (0.6 mmol) and AgOTf (3.8 mg, 3 mol%) were added and dissolved in DME (0.5 mL) followed by the addition of Cp*Ru(COD)Cl (5.7 mg, 3 mol%). The reaction mixture was stirred at room temperature under open flask. After completion of reaction checked by TLC, the crude reaction mixture was purified through column chromatography over silica gel using hexane/ethyl acetate as eluents to obtain the desired product.

Acknowledgements

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UPDATE

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