Catalysis Communications 41 (2013) 12–16

Contents lists available at SciVerse ScienceDirect

Catalysis Communications

journal homepage: www.elsevier.com/locate/catcom

Short Communication

# A ruthenium-based catalytic system with switchable selectivity between cyclotrimerization and enyne metathesis/Diels–Alder reactions of terminal alkynes ☆

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ARTICLE INFO

*Article history:*
Received 19 March 2013
Received in revised form 14 June 2013
Accepted 14 June 2013
Available online 27 June 2013

*Keywords:*
Enyne metathesis
Diels–Alder reactions
One-pot synthesis
Switchable catalysis

ABSTRACT

In this study, we report a practical catalytic system, $[RuCl_2(p\text{-cymene})]_2$/IPr (IPr: 1,3-bis(2,6 diisopropylphenyl) imidazol-2-ylidene), that can switch between cyclotrimerization and cross enyne metathesis. The cyclotrimerization reaction of phenylacetylene catalyzed by $[RuCl_2(p\text{-cymene})]_2$ can be switched to enyne metathesis by the introduction of a sterically hindered N-heterocyclic carbene. The 1,3-diene formed during this reaction reacts with dienophiles to form the Diels–Alder adduct. A practical one-pot synthesis method, utilizing enyne metathesis/Diels–Alder reactions, was used to construct cyclic compounds in an efficient manner.



## 1. Introduction

Olefin metathesis is a useful synthetic tool for the creation of carbon–carbon bonds [1]. Numerous applications of metathesis have been developed to construct a wide variety of organic materials containing double bonds [2]. Among these applications, enyne metathesis is a unique approach that results in different functionality in the product compared to other metathesis reactions [3,4]. The first enyne metathesis reaction that reorganized an alkene and alkyne to produce 1,3-diene was reported in 1985 [5]. Later, the beneficial effect of ethylene in enyne metathesis was reported by Mori et al. [6,7]. This progress in enyne metathesis has resulted in novel approaches in metathesis chemistry, such as a tandem enyne metathesis/Diels–Alder reaction [8,9]. Using this approach, polycyclic compounds with high molecular complexity were synthesized in an efficient and selective manner [10,11]. Consequently, there is a continuing interest in the production of active metathesis catalysts via practical and simplified routes as exemplified by the *in situ* generation of catalytic ruthenium species [12–14]. In this context, imidazolium salts are employed as the carbene source along with $[RuCl_2(p\text{-cymene})]_2$ to produce an *in situ* ruthenium arene system that is an efficient catalyst for the tandem enyne metathesis/Diels–Alder reactions [15,16]. Recently, Fustero et al. reported a novel method that utilizes ring closing metathesis of 1,7-octadiene as an *in situ* source of ethylene in tandem enyne metathesis/Diels–Alder reactions [17]. A switchable catalytic system based on exchange of the active sites of the Grubbs second generation catalyst was reported to promote two distinct annulation reactions to construct two different tetrasubstituted benzene derivatives via enyne metathesis or oxidative cyclometallation [18].

In the course of our continuing studies on the development of ruthenium-based switchable catalytic systems [19], we discovered that cyclotrimerization of phenylacetylene catalyzed by $[RuCl_2(p\text{-cymene})]_2$ can be switched to enyne metathesis by the introduction of the bulky IPr ligand under an ethylene atmosphere. In this contribution, we report a switchable catalytic system that can switch from cyclotrimerization to enyne metathesis/Diels–Alder reaction of terminal alkynes.

## 2. Experimental

All manipulations were carried out under an atmosphere of nitrogen using Schlenk techniques. 1,3-bis(2,6-diisopropylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene (IPr) were purchased from Sigma–Aldrich and used as received. $[RuCl_2(=CHPh)(IPr)(PCy_3)]$ [20], $[(p\text{-cymene})Ru(Cl)(\mu\text{-}Cl)_2Ru(Cl)(=CHPh)(IPr)]$ [21], and $[RuCl_2(IPr)(p\text{-cymene})]$ [22] were synthesized according to literature procedures.

### 2.1. Instrumentation

$^1H$ NMR spectra were recorded at 25 °C with a Bruker GmbH 400 MHz FT-NMR spectrometer. Tetramethylsilane was used as the reference for $^1H$ and $^{13}C$ NMR. GC-MS analyses were performed with a



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http://dx.doi.org/10.1016/j.catcom.2013.06.023

Shimadzu GC-MS QP5050A using an Optima column, 5–1.0 μm (50 m × 0.32 mm) at a temperature range of 50–320 °C (10 °C/min).

### 2.2. Tandem enyne metathesis/Diels–Alder reactions of arylalkynes

A reactor was charged with $[RuCl_2(p\text{-cymene})]_2$ (0.033 mmol), IPr, (0.066 mmol), and alkyne (0.66 mmol) in 3 ml of toluene and heated to 80 °C under an ethylene atmosphere (1 atm) for 1 h. After complete conversion to the 1,3-diene product was observed, dienophile (0.154 mmol) was added under a nitrogen atmosphere, and the reaction was stirred at 80 °C for 8 h. The reaction mixture was analyzed by GC-MS. The solvents were evaporated under reduced pressure, and the crude product mixture was purified by column chromatography, resulting product was analyzed by $^1H$ and $^{13}C$ NMR analysis.

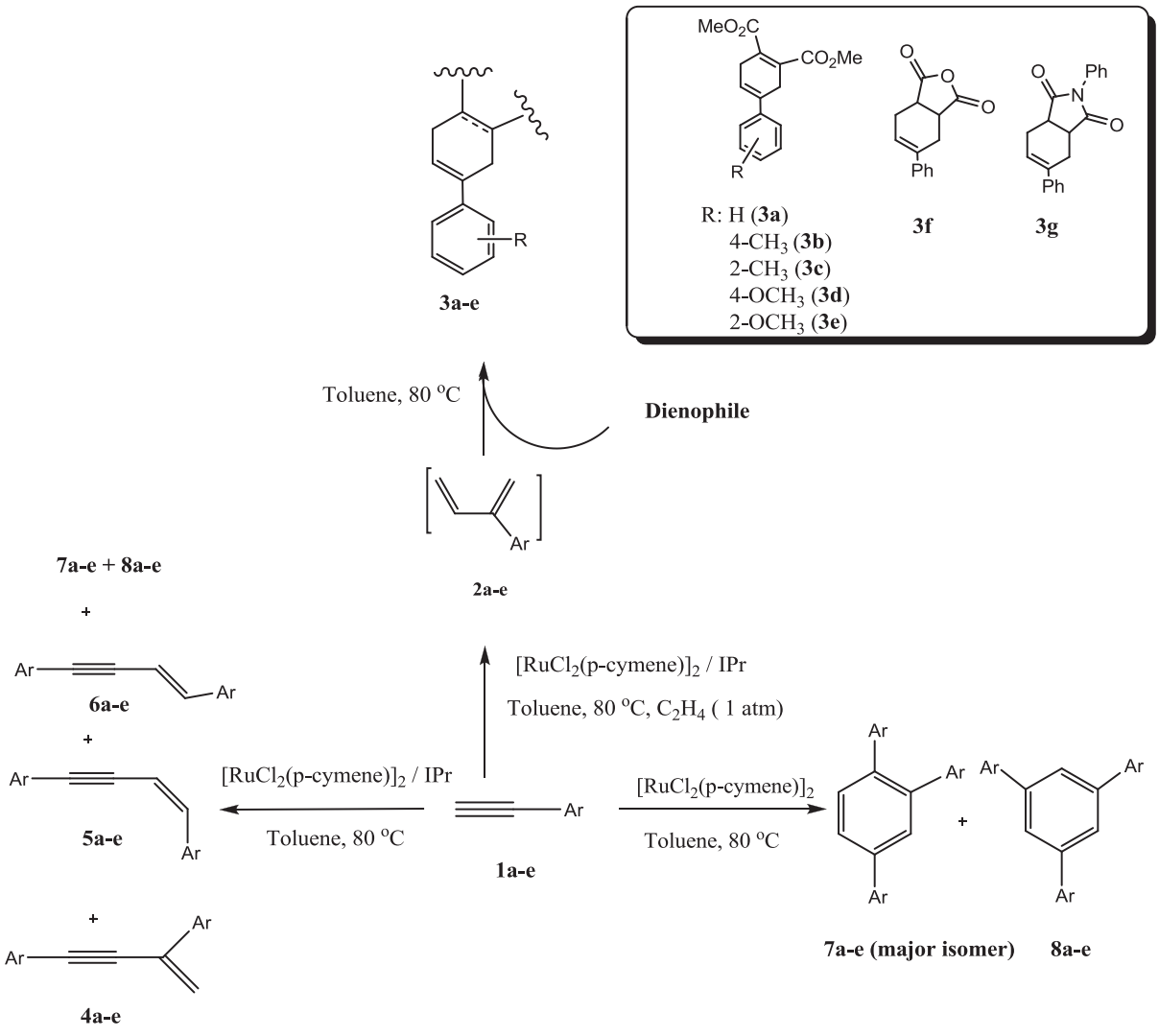
### 2.3. General procedure for the in situ switching between cyclotrimerization and enyne metathesis reactions

A reactor was charged with $[RuCl_2(p\text{-cymene})]_2$ (0.033 mmol, 0.020 g) and phenylacetylene (0.66 mmol, 72 μl) in 3 ml toluene and heated at 80 °C. After 10 min, 2.0 mol equivalent of IPr (0.066 mmol, 0.026 g) was added to the reaction medium and stirred at 80 °C under an ethylene atmosphere (1 atm). Aliquots taken periodically from the reaction mixture were analyzed by GC-MS.

## 3. Results & discussion

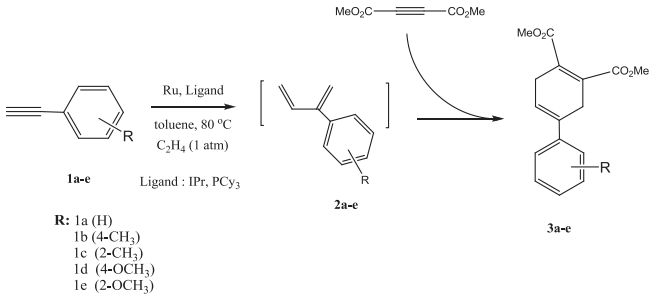
In this study, we evaluate $[RuCl_2(p\text{-cymene})]_2$/IPr as a catalytic system to switch selectivity between cyclotrimerization reactions and enyne metathesis. $[RuCl_2(p\text{-cymene})]_2$ catalyzes the cyclotrimerization reaction of phenylacetylene, which proceeds through the formation of a ruthenocyclopentadiene intermediate. After introduction of N-heterocyclic carbene (NHC) ligands in an ethylene atmosphere, this catalytic intermediate forms a ruthenium methylidene species, which catalyzes the enyne metathesis of phenylacetylene with ethylene to selectively form a 1,3-diene (Scheme 1).

Our first attempts to obtain a switchable catalytic system were based on the introduction of phenylacetylene and $PCy_3$ to a solution of $[RuCl_2(p\text{-cymene})]_2$. We envisioned the formation of a vinylidene intermediate that is converted to a ruthenium methylidene species in the presence of excess ethylene. For this purpose, several catalytic systems were tested in the enyne metathesis/Diels–Alder reaction of phenylacetylene with varying ligand ($PCy_3$ or IPr)/Ru ratios under an atmosphere of ethylene (Table 1).




**Scheme 1.** Ruthenium-catalyzed enyne metathesis/Diels–Alder reactions of aromatic alkynes.

**Table 1**
Enyne metathesis/Diels–Alders reactions of phenylacetyene.

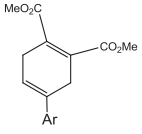
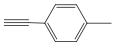
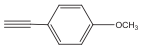
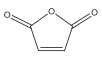
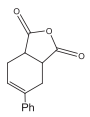
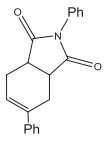



| Run[a] | Alkyne | Ligand | Ligand/Ru | Time (h) | Product[b] % Dimerization (4a-e: 5a-e: 6a-e) | Cyclotrimerization (7a: 8a) | Diene (2a-e) | Diels–Alder adduct[c] (3a-e) |
|---|---|---|---|---|---|---|---|---|
| **1** | 1a | $PCy_3$ | 2 | 24 | 35 (6: 94: 0) | 65(80: 20) | – | – |
| **2** | 1a | $PCy_3$ | 4 | 24 | 43 (7: 90: 3) | 57(79: 19) | – | – |
| **3** | 1a | IPr | 2 | 1 | 2 (17: 83: 0) | 3(80: 20) | 93 | 80 (75) |
| **5** | 1a | IPr | 8 | 1 | 3 (14: 85: 1) | 5(80: 20) | 80 | 70 |
| **6** | 1a | IPr | 10 | 1 | 3 (14: 85: 1) | 5(80: 20) | 76 | 70 |
| **7** | 1b | IPr | 2 | 1 | 5(19: 81: 0) | 5(90: 10) | 90 | 85 (80) |
| **8** | 1c | IPr | 2 | 1 | 0 | 20 (81: 19) | 80 | 75 (72) |
| **9** | 1d | IPr | 2 | 1 | 4 (13: 87: 0) | 4(87: 13) | 90 | 81 (78) |
| **10** | 1e | IPr | 2 | 1 | 0 | 10(84: 16) | 79 | 66 (62) |

a: All reactions were carried out in the presence 4% $[RuCl_2(p\text{-cymene})]_2$ (0.033 mmol) with phenylacetylene (0.66 mmol) and varying IPr-$PCy_3$/Ru (mol/mol) ratios in 3 ml of toluene at 80 °C under an ethylene atmosphere (1 atm).
b: Determined by GC-MS
c: The mixture was reacted for 8 h after the addition of dimethylacetylenedicarboxylate (0.77 mmol) at 80 °C. Isolated yields are in parenthesis.

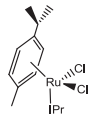
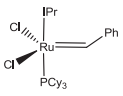
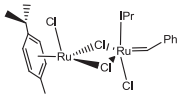
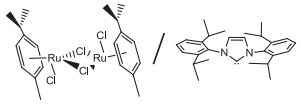
Phenylacetylene was reacted in the presence of 4% $[RuCl_2(p\text{-cymene})]_2$ in toluene at 80 °C under ethylene atmosphere with 4:1 or 2:1 $PCy_3$/Ru ratios. The reactions were monitored by GC-MS analysis. After 24 h, a significant amount of cyclotrimerization products, 65% (**7a**:**8a**; 80:20), and dimerization products, 35% (**4a**:**5a**:**6a**; 6:94:0), were observed with a 2:1 $PCy_3$/Ru ratio. Increasing the $PCy_3$/Ru ratio

Table 2
Enyne metathesis/Diels–Alder reaction of phenylacetylene with various dienophiles.

| Run[a] | | Alkyne | Dienophile | Product[b,c] (%) | |
|---|---|---|---|---|---|
| 1 | 1a |  |  |  3a-e | 3a 80 (75) |
| 2 | 1b |  |  | | 3b 85 (80) |
| 3 | 1c |  |  | | 3c 75 (72) |
| 4 | 1d |  |  | | 3d 81 (78) |
| 5 | 1e |  |  | | 3e 66 (62) |
| 6 | 1f |  |  |  | 3f 83 (79) |
| 7 | 1g |  |  |  | 3g 70 (66) |

a: All reactions were carried out in the presence 4% $[RuCl_2(p\text{-cymene})]_2$ (0.033 mmol) with phenylacetylene (0.66 mmol) and IPr (0.066 mmol) in 3 ml of toluene at 80 °C under an ethylene atmosphere (1 atm).
b: Determined by GC-MS. Isolated yields are in parenthesis.
c: The mixture was reacted for 8 h after the addition of dienophile (0.77 mmol) at 80 °C.

Table 3
Tandem enyne metathesis/Diels–Alder reactions of phenylacetylene with various ruthenium catalysts.

| Run[a] | Catalyst | Diene (2a) %[b] | Diels-Alder Adduct (3a) %[b] |
|---|---|---|---|
| 1 |  Ru-I | 95 | 83 |
| 2 |  Ru-II | 99 | 90 |
| 3 |  Ru-III | 96 | 88 |
| 4 |  Ru-IV | 93 | 80 |

a: All reactions were carried out in the presence of 8% [Ru-I] or [Ru-II] (0.066 mmol) or 4% [Ru-III] or [Ru-IV] (0.033 mmol) with phenylacetylene (0.66 mmol) in 3 ml of toluene at 80 °C under an ethylene atmosphere (1 atm) and reacted for 2 h.
b: GC yield

to 4: 1 didn't have a beneficial effect on the reaction; only cyclotrimerization (57%) and dimerization (43%) product distributions were changed.

These observations indicated the need for ligands that are better σ donors and sterically more hindered then $PCy_3$ to stabilize the 14-electron ruthenium methylidene species. In this context, IPr, a bulky NHC ligand was the best candidate with these characteristics. Upon the addition of 2.0 equivalents of IPr relative to $[RuCl_2(p\text{-cymene})]_2$ and phenylacetylene in toluene at 80 °C, the product distribution dramatically changed to provide a 93% yield of **2a**. Increasing the IPr/Ru ratio to 4:1, 8:1 and 10:1 decreased the amount of **2a** to 89%, 80% and 76%, respectively. Upon the addition of 3 mole equivalents of dimethylacetylenedicarboxylate, the corresponding Diels–Alder adduct **3a** was formed in 80% and 77% yield at the 2:1 and 4:1 IPr:Ru ratios, respectively, after 8 h at 80 °C. Thus, the optimum IPr/Ru ratio was 2:1. Methyl and methoxy substituted aromatic alkynes, **1b–e**, were tested under same reaction conditions and results were listed on Table 1. 4-methyl (**1b**) and 4-methoxy (**1d**) substituted phenylacetylenes show high selectivity towards enyne metathesis reactions and gave corresponding Diels–Alder adducts **3b** (85%) and **3d** (81%). On the other hand, 2-methyl (**1c**) and 2-methoxy (**1e**) substituted phenylacetylenes show relatively poor selectivity towards enyne metathesis reaction and gave Diels–Alder adducts, **3c** (75%) and **3e** (66%) in moderate yields. 4-octyne and 1-octyne were tested under the same reaction conditions. Although the catalytic system worked efficiently for arylacetylenes, all attempts to produce 1,3-dienes from 1-octyne and 4-octyne failed. Only a 2–3% of diene product was observed for 1-octyne and 4-octyne. To expand the scope of the process, different dienophiles were reacted with **2a** and results were given in Table 2. Maleic anhydride and N-phenyl maleimide gave Diels–Alder adducts in 83% (**3f**) and 70% (**3 g**) yields under pre-determined reaction conditions.

To expand the scope of this study, the activity of $[RuCl_2(p\text{-cymene})]_2$/IPr was compared to that of other types of ruthenium catalysts for the enyne metathesis reaction between phenylacetylene and ethylene. For this purpose, several different classes of ruthenium catalysts bearing IPr ligands were synthesized and their activity was tested in tandem enyne metathesis/Diels–Alder reactions of phenylacetylene (Table 3). For this purpose, a reactor was charged with the corresponding ruthenium complexes (8% for **Ru-I** and **II** and 4% for **Ru-III** and **IV**) and phenylacetylene in toluene and reacted under a slow stream of ethylene at 80 °C for 2 h. **Ru-I** catalyzed the enyne metathesis reaction to provide a 95% yield of **2a**. **Ru-II**, a well-known ruthenium alkylidene complex, catalyzed this reaction to give a 99% yield, whereas **Ru-III**, the homobimetallic analog of **Ru-II**, provided a 96% yield. Our catalytic system, **Ru-IV**, displayed comparable activity (93% yield) to the **Ru-I**, **II** and **III** catalytic systems.

After all of the reaction parameters were determined, the switching ability of the catalytic system was investigated in detail. First, phenylacetylene was allowed to react in the presence of 4% $[RuCl_2(p\text{-cymene})]_2$ in toluene at 80 °C under a nitrogen atmosphere to form the cyclotrimerization products **7a** and **8a**; then, IPr ligand was added at different time intervals to switch the reaction to enyne metathesis under an atmosphere of ethylene. The results are listed in Table 3. When phenylacetylene was reacted for 5 min in the presence of only $[RuCl_2(p\text{-cymene})]_2$, the cyclotrimerization product was formed in 3% (**7a**:**8a**; 90:10) yield. The addition of 2.0 mol equivalent of IPr ligand after 5 min shifted the product formation towards **2a** to give a 90% yield after 2 h; the amount of cyclotrimerization product increased to 6% (**7a**:**8a**; 84:16). In addition, trace amounts of the dimerization product (2%) were also observed in the GC-MS analysis. The IPr ligand was introduced into the reaction medium at different time intervals to prove that our catalytic system can be switched *in situ* from the cyclotrimerization

**Table 4**
*In situ* switchable selectivity of the $[RuCl_2(p\text{-cymene})]_2$/IPr catalytic system between cyclotrimerization and enyne metathesis.

| Run[a] | Before addition of IPr | | | | After addition of IPr | | | |
|---|---|---|---|---|---|---|---|---|
| | Time[b] (min.) | Dimer %[c] (4a: 5a: 6a) | Cyclo %[c] (7a: 8a) | Diene %[c] – | Time[d] (h) | Dimer %[c] (4a: 5a: 6a) | (7a: 8a) | Diene %[c] |
| **1** | 5 | | 3 (90: 10) | – | 2 | 2 | 6 (84:16) | 90 |
| **2** | 10 | | 6 (91: 9) | – | 2 | 2 | 10 (83: 17) | 88 |
| **3** | 15 | | 10 (89:11) | – | 2 | 3 | 12 (88:12) | 85 |
| **4** | 20 | | 14 (90:10) | – | 2 | 3 | 17 (90: 10) | 80 |
| **5** | 60 | 1 | 65 (90:10) | – | 2 | 4 | 69 (90:10) | 27 |

a: All reactions were carried out in the presence 4% $[RuCl_2(p\text{-cymene})]_2$ (0.033 mmol) with phenylacetylene (72 μl, 0.66 mmol) in 3 ml of toluene at 80 °C under a nitrogen atmosphere. IPr (0.026 g, 0.066 mmol) was added indicated times under an ethylene atmosphere (1 atm) to switch the reaction to enyne metathesis.
b: Represents the addition time of IPr
c: Determined by GC-MS
d: Represents the time when maximum conversion values were observed

reaction of phenylacetylene to the enyne metathesis at any time during the cyclotrimerization reaction of phenylacetylene (Table 4). As expected, runs 1–4 are in sharp contrast with each other. When phenylacetylene was reacted for 20 min in the presence of 4% $[RuCl_2(p\text{-cymene})]_2$, the cyclotrimerization product was observed in 14% (**7a**:**8a**; 90:10) yield. On addition of IPr under an ethylene atmosphere, **2a** formed in 88% yield after 2 h. A remarkable change in the isomer distribution of cyclotrimerization products was observed after addition of IPr to the reaction medium. This change can be clearly seen in run 1 and run 4. In run 1, phenylacetylene was reacted for 5 min before the introduction of IPr. At the early stages of the reaction, $[RuCl_2(p\text{-cymene})]_2$ is responsible for the cyclotrimerization reaction via the formation of ruthenocyclopentadiene intermediates. Upon addition of IPr to the reaction medium, $[RuCl_2IPr(p\text{-cymene})]$ forms as an intermediate, and at this stage, two complexes, $[RuCl_2(p\text{-cymene})]_2$ and $[RuCl_2IPr(p\text{-cymene})]$ are responsible for the cyclotrimerization reaction of phenylacetylene. However, the latter complex is less selective for the cyclotrimerization reaction and is responsible for the change in the isomer distribution.

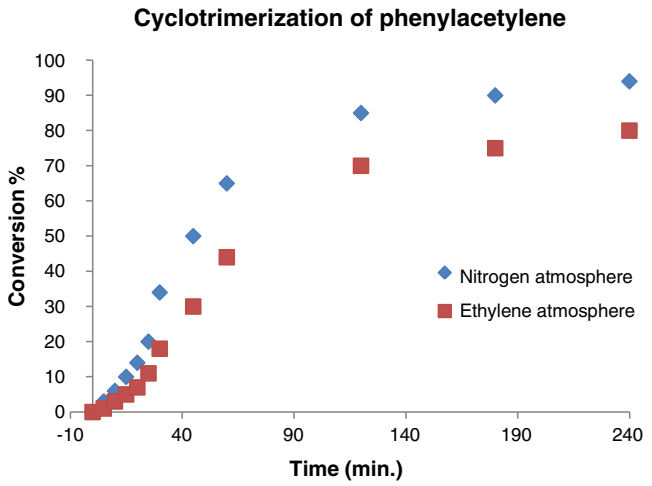
As a final remark, the effect of ethylene on cyclotrimerization reaction rate was investigated in details with 4% $[RuCl_2(p\text{-cymene})]_2$ in toluene at 80 °C (Graphic 1). While cyclotrimerization products formed in 65% yield (**7a** + **8a**) in 1 h under nitrogen atmosphere, this value was decreased to 44% under ethylene atmosphere. It is clear that ethylene slows down the cyclotrimerization reaction and these results were in great coherence with the given data in Table 3.

## 4. Conclusion

In this study, we show that the cyclotrimerization reaction of phenylacetylene catalyzed by $[RuCl_2(p\text{-cymene})]_2$ can be selectively switched to an enyne metathesis reaction by the introduction of bulky NHC ligands (IPr) under an ethylene atmosphere. The 1,3-diene, **2a**, obtained in 93% yield from the cross enyne metathesis reaction of phenylacetylene and ethylene, underwent a Diels–Alder reaction with dimethylacetylenedicarboxylate, to form **3a** in 80% yield. Therefore, by controlling the catalytic intermediates, this catalytic system can be used to catalyze both cyclotrimerization and enyne metathesis/Diels–Alder reactions of arylalkynes in a switchable and selective manner.

## Appendix A. Supplementary data

All experimental details and spectroscopic data can found in supporting information file. Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.catcom.2013.06.023.




**Graphic 1.** Cyclotrimerization reaction of phenylacetylene under nitrogen and ethylene atmosphere.

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