

HETEROCYCLES, Vol. 97, No. 2, 2018, pp. 696 - 701. © 2018 The Japan Institute of Heterocyclic Chemistry  
Received, 13th February, 2018, Accepted, 22nd March, 2018, Published online, 3rd April, 2018  
DOI: 10.3987/COM-18-S(T)46

## RUTHENIUM-CATALYZED [2 + 2] CYCLIZATION OF 1,7-ALLENYNES IN IONIC LIQUID AND CATALYST RECYCLING

Nozomi Saito,<sup>1\*</sup> Momoko Koyama,<sup>2</sup> and Yoshihiro Sato<sup>2</sup>

<sup>1</sup>Meiji Pharmaceutical University, Kiyose, Tokyo 204-8588, Japan, <sup>2</sup>Faculty of  
Pharmaceutical Sciences, Hokkaido University, Sapporo 060-0812, Japan

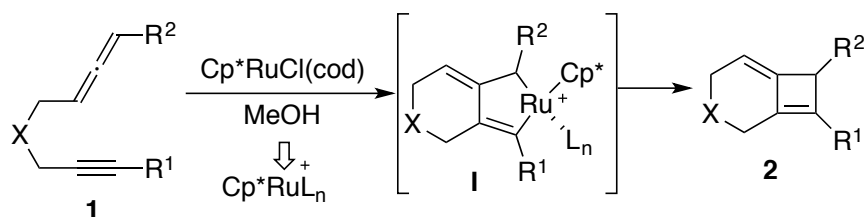
E-mail: nozomi-s@my-pharm.ac.jp

**Abstract** – Ruthenium-catalyzed [2 + 2] cyclization of 1,7-allenynes in ionic liquid ([BDMI]PF<sub>6</sub>) as a reaction medium proceeded to give the corresponding bicyclo[4.2.0]octa-1(8),5-diene derivative in high yield. Furthermore, the recovered catalyst immobilized in the ionic liquid could be recycled up to 10 times.

This paper is dedicated to Professor Kiyoshi Tomioka on the occasion of his 70th birthday.

Ionic liquids (ILs) have attracted much attention as useful reaction media in recent synthetic organic chemistry due to their favorable properties such as high polarity, non-volatility, thermal stability, and high dissolution activity.<sup>1</sup> Furthermore, it is well known that ILs can dissolve and immobilize various transition metal complexes, especially a cationic metal complex. Due to these unique characteristics of ILs, separation of the product and the catalyst in an IL can be easily conducted by simple phase separation after the end of the chemical reaction, and the catalyst immobilized in the IL can be re-used for another reaction. Therefore, many examples of transition metal catalysis in an IL and re-use of the catalyst immobilized in the IL have been reported,<sup>2</sup> and we previously demonstrated rhodium(I)-catalyzed intramolecular hydroacylation of 4-alkenals and cycloisomerization of ene-diene in an IL and recycling of the rhodium catalyst immobilized in the IL.<sup>3</sup>

On the other hand, we have reported ruthenium-catalyzed [2 + 2] cyclization of 1,7-allenynes (Scheme 1).<sup>4,5</sup> Reaction of the allenyne **1** in the presence of Cp\*<sub>2</sub>RuCl(cod) in methanol proceeded to give bicyclo[4.2.0]octa-1(8),5-diene derivative **2** via ruthenacyclopentene intermediate **I**. We also demonstrated that the real active species in the [2 + 2] cyclization was a cationic ruthenium complex generated from Cp\*<sub>2</sub>RuCl(cod) and methanol *in situ*.<sup>4</sup>



**Scheme 1.** Ruthenium-catalyzed [2 + 2] cyclization of 1,7-allenynes in methanol

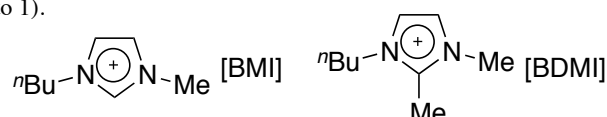
With this as a background, we planned ruthenium-catalyzed [2 + 2] cyclization of 1,7-allenynes in an IL and recycling of the ruthenium catalyst immobilized in the IL.<sup>6</sup> First of all, [2 + 2] cyclization of allenyne **1a** with 5 mol% of  $[\text{Cp}^*\text{Ru}(\text{MeCN})_3]\text{PF}_6$ <sup>7</sup> in THF was carried out as a control experiment (Table 1, run 1). The reaction proceeded smoothly at room temperature to give bicyclic compound **2a** in 96% yield. Cyclization of **1a** in various imidazolium cation-based ILs (BMI = 1-butyl-3-methylimidazolium, BDMI = 1-butyl-2,3-dimethylimidazolium) were examined (runs 2-7), and  $[\text{BDMI}][\text{PF}_6]$  was found to be a potential reaction medium (run 7). Next, the effects of co-solvents were investigated using  $[\text{BDMI}][\text{PF}_6]$  (runs 8-11). When toluene was used as a co-solvent, cyclized product **2a** was obtained in only 11% yield (run 8). On the other hand, the use of polar solvents gave good results, and the reaction of **1a** in a mixed solvent of  $[\text{BDMI}][\text{PF}_6]$  and acetonitrile proceeded to afford **2a** in quantitative yield (run 11).

**Table 1.** Investigation of Ru(II)-catalyzed [2 + 2] cyclization of **1a** in various ILs

| run             | solvent                       | co-solvent                          | temp (°C) | yield (%) <sup>a</sup> |
|-----------------|-------------------------------|-------------------------------------|-----------|------------------------|
| 1               | THF                           | -                                   | rt        | 96                     |
| 2               | $[\text{BMI}][\text{NTf}_2]$  | -                                   | 50        | - (91)                 |
| 3               | $[\text{BMI}][\text{BF}_4]$   | -                                   | 50        | 11 (75)                |
| 4               | $[\text{BMI}][\text{PF}_6]$   | -                                   | 50        | - (79)                 |
| 5               | $[\text{BDMI}][\text{NTf}_2]$ | -                                   | 50        | 5 (84)                 |
| 6               | $[\text{BDMI}][\text{BF}_4]$  | -                                   | 50        | 5 (87)                 |
| 7               | $[\text{BDMI}][\text{PF}_6]$  | -                                   | 50        | 18 (80)                |
| 8 <sup>b</sup>  | $[\text{BDMI}][\text{PF}_6]$  | toluene                             | rt        | 11 (75)                |
| 9 <sup>b</sup>  | $[\text{BDMI}][\text{PF}_6]$  | THF                                 | rt        | 95                     |
| 10 <sup>b</sup> | $[\text{BDMI}][\text{PF}_6]$  | $\text{ClCH}_2\text{CH}_2\text{Cl}$ | rt        | 93                     |
| 11 <sup>b</sup> | $[\text{BDMI}][\text{PF}_6]$  | MeCN                                | rt        | quant                  |

<sup>a</sup>The values in parentheses are the yields of recovered allenyne **1a**.

<sup>b</sup>The reaction was carried out in a mixed solvent of  $[\text{BDMI}][\text{PF}_6]$  and co-solvent (ratio of 1 to 1).



Encouraged by these results, the recyclability of the ruthenium catalyst remaining in the IL after the reaction was evaluated for [2 + 2] cyclization of **1a** in mixed solvents of the IL and polar co-solvents (Table 2). When THF was used as a co-solvent, the second cycle showed a drop in the yield of **2a** (run 1). On the other hand, three consecutive cycles were realized in reactions using 1,2-dichloroethane and acetonitrile as a co-solvent, though a small amount of starting allenyne was recovered in the third run (runs 2 and 3). Since the yield of **2a** obtained by the reaction using acetonitrile as a co-solvent was better than that obtained by the reaction in [BDMI][PF<sub>6</sub>]/1,2-dichloroethane, we next investigated the effect of temperature using a [BDMI][PF<sub>6</sub>]/acetonitrile mixed solvent system. When the reaction was carried out at 50 °C in the presence of 5 mol% of the ruthenium complex, cyclized product **2a** was obtained in high yield for each of five consecutive cycles (run 4). Finally, the use of 10 mol% of the ruthenium catalyst enabled recycling of the catalyst 10 times without loss of yield of **2a** (run 5).<sup>8</sup>

**Table 2.** Effects of co-solvent, temperature and catalyst loading on recyclability of the catalyst<sup>a</sup>

| run | co-solvent                           | temp    | cycle | time (h) | yield (%) <sup>b</sup> |
|-----|--------------------------------------|---------|-------|----------|------------------------|
| 1   | THF                                  | rt      | 1     | 0.5      | 95                     |
|     |                                      |         | 2     | 21       | 31 (68)                |
| 2   | ClCH <sub>2</sub> CH <sub>2</sub> Cl | rt      | 1     | 0.5      | 93                     |
|     |                                      |         | 2     | 1        | 87                     |
|     |                                      |         | 3     | 14       | 86 (14)                |
| 3   | MeCN                                 | rt      | 1     | 2        | quant                  |
|     |                                      |         | 2     | 4        | 97                     |
|     |                                      |         | 3     | 42       | 92 (8)                 |
| 4   | MeCN                                 | 50 °C   | 1     | 0.5      | quant                  |
|     |                                      |         | 2     | 0.5      | quant                  |
|     |                                      |         | 3     | 0.5      | quant                  |
|     |                                      |         | 4     | 14       | quant                  |
|     |                                      |         | 5     | 47       | 93                     |
| 5   | MeCN                                 | 50 °C   | 6     | 50       | 75 (25)                |
|     |                                      |         | 1     | 0.5      | quant                  |
|     |                                      |         | 2     | 0.5      | quant                  |
|     |                                      |         | 3     | 0.5      | quant                  |
|     |                                      |         | 4     | 0.5      | quant                  |
|     |                                      |         | 5     | 0.5      | 95                     |
|     |                                      |         | 6     | 1        | quant                  |
|     |                                      |         | 7     | 4        | quant                  |
|     |                                      |         | 8     | 4        | quant                  |
|     |                                      |         | 9     | 19       | quant                  |
| 10  | 48                                   | 78 (17) |       |          |                        |

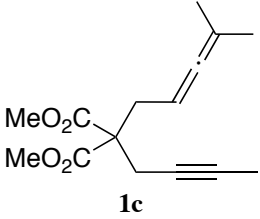
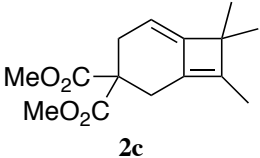
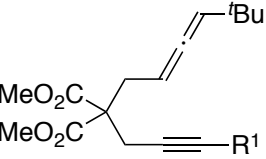
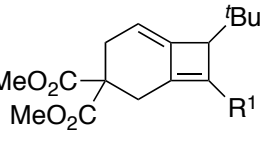
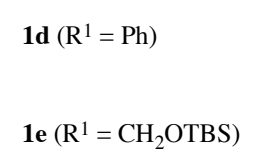
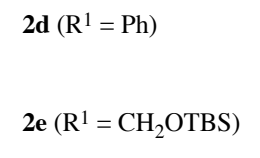
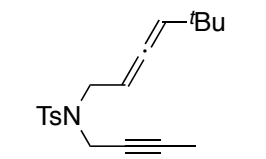
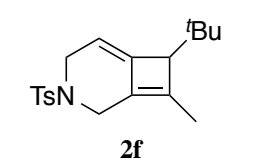
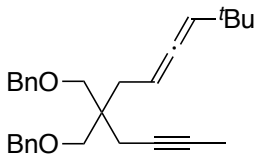
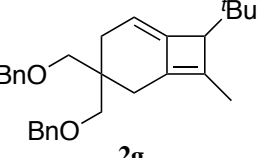
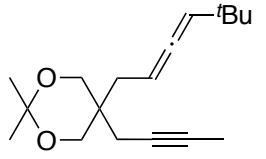
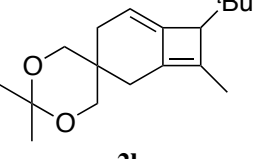
<sup>a</sup> Reaction conditions: [Cp\*Ru(MeCN)<sub>3</sub>][PF<sub>6</sub>] (5 mol%: runs 1-4, 10 mol%: run 5), [BDMI][PF<sub>6</sub>]/co-solvent = 1/1.

<sup>b</sup>The values in parentheses are the yields of recovered allenyne **1a**.

With the optimal conditions in hand, we investigated [2 + 2] cyclization of various allenynes in the combined solvent of [BDMI][PF<sub>6</sub>] and acetonitrile and catalyst recycling (Table 3). It was found that

the yield of the product and recyclability of the ruthenium catalyst were affected by the structure of the substrate. When the reaction of **1h** was carried out, the corresponding cyclized product **2h** was obtained in high yield (run 6). Moreover, the ruthenium catalyst immobilized in the IL could be re-used at least 9 times without significant loss of yield of **2h** (run 6).

**Table 3.** [2+2] Cyclization of various allenyne in IL and catalyst recycling<sup>a</sup>

| run            | allenyne   | product  | cycle | time (h) | yield (%)       |
|----------------|--|--|-------|----------|-----------------|
| 1 <sup>b</sup> | <br><b>1c</b>   | <br><b>2c</b>   | 1     | 0.5      | 89              |
|                |  |  | 2     | 1        | 91              |
|                |  |  | 3     | 22       | 92              |
|                |  |  | 4     | 50       | 17 (55)         |
| 2              | <br><b>1d</b> (R <sup>1</sup> = Ph)                    | <br><b>2d</b> (R <sup>1</sup> = Ph)                    | 1     | 0.5      | 55              |
|                |  |  | 2     | 2        | 77              |
|                |  |  | 3     | 18       | 34 (33)         |
| 3              | <br><b>1e</b> (R <sup>1</sup> = CH <sub>2</sub> OTBS) | <br><b>2e</b> (R <sup>1</sup> = CH <sub>2</sub> OTBS) | 1     | 2        | 95              |
|                |  |  | 2     | 21       | 47 (5)          |
| 4              | <br><b>1f</b>   | <br><b>2f</b>   | 1     | 0.5      | 71              |
|                |  |  | 2     | 21       | 74              |
|                |  |  | 3     | 54       | complex mixture |
| 5 <sup>c</sup> | <br><b>1g</b>   | <br><b>2g</b>   | 1     | 0.5      | 82              |
|                |  |  | 2     | 22       | 31 (57)         |
| 6              | <br><b>1h</b>   | <br><b>2h</b>   | 1     | 0.5      | quant           |
|                |  |  | 2     | 0.5      | quant           |
|                |  |  | 3     | 0.5      | quant           |
|                |  |  | 4     | 0.5      | 91              |
|                |  |  | 5     | 0.5      | 97              |
|                |  |  | 6     | 0.5      | 92              |
|                |  |  | 7     | 0.5      | 93              |
|                |  |  | 8     | 0.5      | 93              |
|                |  |  | 9     | 1        | quant           |
|                |  |  | 10    | 2        | quant           |

<sup>a</sup>Reaction conditions : 10 mol% [Cp\**Ru*(MeCN)<sub>3</sub>]PF<sub>6</sub>, [BDMI][PF<sub>6</sub>]:MeCN = 1;1, 50 °C. <sup>b</sup> The reaction was carried out in the mixed solvent of [BDMI][PF<sub>6</sub>] and ClCH<sub>2</sub>CH<sub>2</sub>Cl (1:1). <sup>c</sup> The reaction was carried out in the mixed solvent of BDMI[PF<sub>6</sub>] and MeCN (1:2).

In summary, we demonstrated that cationic ruthenium-catalyzed [2 + 2] cycloaddition of 1,7-allenyne in [BDMI]PF<sub>6</sub>/co-solvent proceeded to give the corresponding bicyclo[4.2.0]octa-1(8),5-diene derivatives in high yield. We also revealed that the ruthenium catalyst immobilized in the IL could be recycled up to ten times without loss of catalytic activity. Further studies along this line are in progress.

## ACKNOWLEDGEMENTS

This work was supported by a Grant-in-Aid for Scientific Research (C) (No. 26460002) from JSPS.

## REFERENCES AND NOTES

1. a) 'Ionic Liquids in Synthesis', ed. by P. Wasserscheid and T. Welton, WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim 2003; b) 'Metal Catalysed Reactions in Ionic Liquid', ed. by P. Dyson and G. Tilmann, Springer, Dordrecht, The Netherlands 2005.
2. For reviews, see: a) T. Welton, *Chem. Rev.*, 1999, **99**, 2071; b) P. Wasserscheid and W. Keim, *Angew. Chem. Int. Ed.*, 2000, **39**, 3772; c) N. Jain, A. Kumar, S. Chauhan, and S. M. S. Chauhan, *Tetrahedron*, 2005, **61**, 1015; d) V. I. Pârvulescu and C. Hardacre, *Chem. Rev.*, 2007, **107**, 2615; e) R. Skouta, *Green Chem. Lett. Rev.*, 2009, **2**, 121; f) J. P. Hallett and T. Welton, *Chem. Rev.*, 2011, **111**, 3508.
3. a) Y. Oonishi, J. Ogura, and Y. Sato, *Tetrahedron Lett.*, 2007, **48**, 7505; b) Y. Oonishi, A. Saito, and Y. Sato, *Green Chem.*, 2009, **11**, 330.
4. N. Saito, Y. Tanaka, and Y. Sato, *Org. Lett.*, 2009, **11**, 4124.
5. For related reports on the ruthenium-catalyzed cyclization of allenyne, see: a) N. Saito, Y. Tanaka, and Y. Sato, *Organometallics*, 2009, **28**, 669; b) N. Saito, Y. Kohyama, Y. Tanaka, and Y. Sato, *Chem. Commun.*, 2012, **48**, 3754; c) N. Saito, T. Ichimaru, and Y. Sato, *Chem. Asian J.*, 2012, **7**, 1521.
6. For examples of thermal [2 + 2] cyclization of 1,7-allenyne in an ionic liquid, see: a) K. M. Brummond and D. Chen, *Org. Lett.*, 2005, **7**, 3473; b) M. R. Siebert, J. M. Osbourn, K. M. Brummond, and D. J. Tantillo, *J. Am. Chem. Soc.*, 2010, **132**, 11952.
7. a) J. L. Schrenk, A. M. McNair, F. B. McCormick, and K. R. Mann, *Inorg. Chem.*, 1986, **25**, 3501; b) B. Steinmetz and W. A. Schenk, *Organometallics*, 1999, **18**, 943.
8. Typical procedure for recycling of the ruthenium catalyst in [BDMI]PF<sub>6</sub>/MeCN (Table 2, run 5). 1-Butyl-2,3-dimethylimidazolium hexafluorophosphate ([BDMI]PF<sub>6</sub>, 1.0 mL) was put into a test tube, and [BDMI]PF<sub>6</sub> was dried at 70 °C under vacuum over 0.5 h. A solution of **1a** (57.5g, 0.19 mmol) in MeCN (1 mL) and [Cp\**Ru*(MeCN)<sub>3</sub>]PF<sub>6</sub> (10.2 mg, 0.020 mmol) were added to the test tube, and the mixture was stirred at 50 °C for 0.5 h under an argon atmosphere. The ionic liquid layer was extracted with Et<sub>2</sub>O (5 mL, 3 times) via a cannula under an argon atmosphere, and the

combined Et<sub>2</sub>O solution was concentrated. The crude product was purified by flash column chromatography on silica gel (hexane/AcOEt = 15/1) to give **2a** (57.5 mg, quant) as a colorless oil. The remaining [BDMI]PF<sub>6</sub> layer was dried under vacuum at room temperature for 0.5 h and reused for the next cycle.