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# Iridium-Catalyzed Cycloisomerization of Alkynoic Acids: Synthesis of Unsaturated Lactones

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**Abstract.** The iridium-catalyzed cycloisomerization of various alkynoic acids was successfully developed, and a series of five-, six-, and especially seven-membered unsaturated lactones were constructed with moderate yields and excellent regioselectivities (up to 68% yield, >99:1 rr). In addition, the indole compound can be easily prepared with 75% yield through this efficient synthetic methodology. Moreover, a plausible mechanism for this Ir-catalyzed cycloisomerization of alkynoic acids was proposed.

**Keywords:** cycloisomerization, alkynoic acids, unsaturated lactones, regioselectivity, indole.

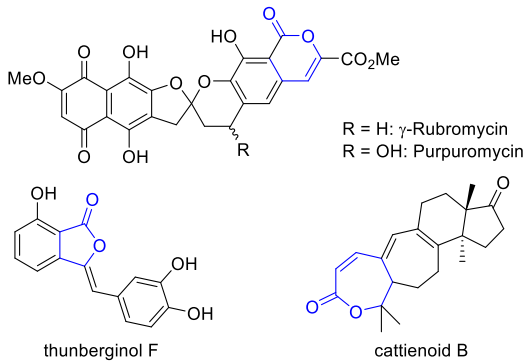
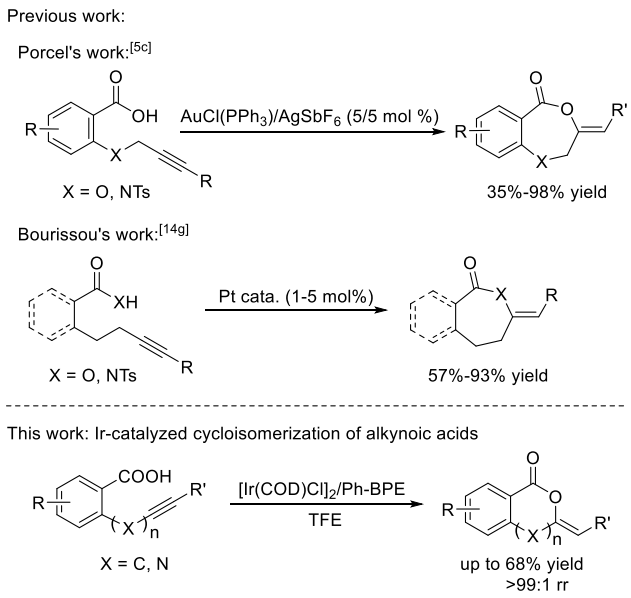



**Figure 1.** Examples of natural products and biologically active molecules containing lactone motifs.

The lactones and their derivatives have been identified as an important kind of heterocyclic motifs, which are widely distributed in many natural products and biologically active molecules.[1] For example, γ-Rubromycin shows the activity against the reverse transcriptase of human immunodeficiency virus-1 and telomerase, which is overproduced in cancer cells (Figure 1).[1d-e] Purpuromycin is a potential topical agent for the treatment of vaginal infections.[1f] The natural product thunberginol F and its derivatives exhibit anti-allergic and anti-microbial effects.[1g-h] The steroid cattienoid B displays cytotoxicity against KB (a human epidermal carcinoma) cells, which is isolated from fruiting bodies of Tomophagus cattienensis.[1i] In addition, these special skeletons are useful and versatile building blocks, and key intermediates in the field of organic synthesis.[2]

Owing to the great importance of these intriguing structures, much attention was paid to exploring synthetic methods, and tremendous progress have been achieved over the last decades. Many synthetic methodologies were well established to prepare lactones,[3-14] such as oxidative cyclization reaction of alkynylbenzaldehydes catalyzed by NHC (N-heterocyclic carbenes),[3f] bromolactonization of long-chain olefinic acids promoted by sulfur-based zwitterionic organocatalyst,[8] intermolecular [6+2] cyclization of amphoteric molecules with siloxy alkynes,[9] oxtene ring-opening reaction,[10] borylated lactones from esters with electrophilic oxyboration,[11] and intramolecular addition of carboxylic acids or esters to alkynes or alkenes promoted by transition metal, organic acids or bases.[3a-e, 3g, 4, 5, 6a, 12-14] Among these synthetic routes to lactones, the cycloisomerization of alkynoic acids is a straightforward and attractive synthetic method to access lactones with great atom economy.[14] These cycloisomerization reactions have been extensively investigated by Pd,[3b, 3e, 4a, 5a, 14a-f, 14h-k] Rh,[3a, 5b] Ru,[4b] Pt[14g] and Au[3d, 3g-i, 4c, 5c] catalytic systems. And they were mainly focused on the preparation of five- and six-membered lactones, the synthesis of seven-membered lactones is very challenging and less studied, which were always listed as one to three examples with poor to moderate yields. Among these research work, only Porcel's group[5c] and Bourissou's group[14g] concentrated on the construction of seven-membered lactones through the cycloisomerization of alkynoic acids promoted by Au and Pt catalytic system with moderate to high yields

(Scheme 1). To the best of our knowledge, there was rare exploration about Ir-catalyzed cycloisomerization of alkynoic acids to construct lactones, only one example was involved with 4-pentynoic acid as the substrate catalyzed by Ir/NCN pincer ligand complexes with moderate conversions.[15] It was until now that there is nearly no investigation about Ir-catalyzed cycloisomerization of alkynoic acids to prepare seven-membered lactones. Based on our interest in this cycloisomerization, great efforts were made to realize Ir-catalyzed cycloisomerization of alkynoic acids for the synthesis of a series of five-, six-, and especially seven-membered unsaturated lactones with moderate yields and excellent regioselectivities (Scheme 1, see also Supporting Information).

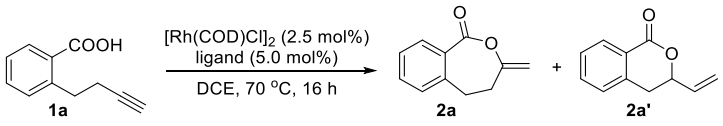



**Scheme 1.** The construction of seven-membered unsaturated lactones and derivatives through cycloisomerization of alkynoic acids and derivatives.

The initial research for the cycloisomerization of alkynoic acids was started with 2-(but-3-yn-1-yl)benzoic acid **1a** as model substrate to investigate phosphine ligands (Figure 2) in the presence of $[Rh(COD)Cl]_2$ at 70 ºC in DCE for 16 h. As shown in Table 1, a series of phosphine ligands were applied in this transformation. Poor reactivities and regioselectivities were obtained with Bisbi, Tribi and Tetrabi as the ligands (7%-15% conversions, 2%-3% yields, 50:50-17:83 rr, Table 1, entries 1-3). The electron-deficient ligands bisphosphoramidite **L1**, triphosphoramidite **L2** and tetraphosphoramidite **L3** did not work in this reaction, and no conversion was observed (Table 1, entries 4-6). Although the highly electron-rich ligand Ph-BPE provided poor reactivity, good regioselectivity was obtained (31% conversion, 24% yield, 85:15 rr, Table 1, entry 7). The reaction solvents always have great influence on the reactivity and selectivity. This $[Rh(COD)Cl]_2$/Ph-BPE-catalyzed cycloisomerization was then carried out in different solvents. Poor results obtained in DCM and toluene (17%-28% conversions, 11%-22% yields, 63:37-79:21 rr, Table 1, entries 8-9). No reaction was detected in THF, 1,4-dioxane and $CHCl_3$ (Table 1, entries 10-12). To our delight, excellent regioselectivity was observed in MeCN, albeit with low yield and moderate conversion (52% conversion, 19% yield, >99:1 rr, Table 1, entry 13). The reactivity was improved greatly with $[Ir(COD)Cl]_2$ as metal precursor, and the regioselectivity was not affected (96% conversion, 42% yield, >99:1 rr, Table 1, entry 14).

In order to achieve full conversion and higher yield, the $[Ir(COD)Cl]_2$/Ph-BPE catalytic system was continued to be investigated in various solvents. Good to excellent conversions, poor to moderate yields and excellent regioselectivities were provided in MeCN, MeOH and TFE (85%->99% conversions, 30%-50% yields, >99:1 rr, Table 2, entries 1-2, 7). Poor conversions were obtained in EtOH, $^{i}$PrOH, THF and toluene (Table 2, entries 3-6). It is possible that the polymerization of substrate **1a**, intermolecular addition, polymerization of vinyl lactone product **2a**, which may lead to the undesirable yield of this reaction. When the reaction temperature was decreased to 65 °C, it may be helpful to this cycloisomerization, and moderate yield can be obtained (54% yield, Table 2, entry 8). In addition, we found that this transformation can be finished within 18 h (Table 2, entry 10). Furthermore, 61% isolated yield can be afforded when the reaction was carried out with 0.3 mmol scale (Table 2, entry 11).

**Table 1**. Screening ligands and solvents for Rh-catalyzed cycloisomerization of 2-(but-3-yn-1-yl)benzoic acid (**1a**). [a]




| entry | ligand | solvent | conv. (%) [b] | rr (**2a**:**2a'**) [b] | yield (%) [c] |
|---|---|---|---|---|---|
| 1 | Bisbi | DCE | 13 | 30:70 | 2 |
| 2 | Tribi | DCE | 15 | 17:83 | 3 |
| 3 | Tetrabi | DCE | 7 | 50:50 | 2 |
| 4 | **L1** | DCE | NR | NA | NA |

| | | | | | |
|---|---|---|---|---|---|
| 5 | **L2** | DCE | NR | NA | NA |
| 6 | **L3** | DCE | NR | NA | NA |
| 7 | Ph-BPE | DCE | 31 | 85:15 | 24 |
| 8 | Ph-BPE | DCM | 28 | 79:21 | 22 |
| 9 | Ph-BPE | toluene | 17 | 63:37 | 11 |
| 10 | Ph-BPE | THF | NR | NA | NA |
| 11 | Ph-BPE | 1,4-dioxane | NR | NA | NA |
| 12 | Ph-BPE | $CHCl_3$ | NR | NA | NA |
| 13 | Ph-BPE | MeCN | 52 | >99:1 | 19 |
| 14 [d] | Ph-BPE | MeCN | 96 | >99:1 | 42 |

[a] Unless otherwise mentioned, all reactions were carried out with the ratio of $[Rh(COD)Cl]_2$/ligand/**1a** (0.2 mmol) of 2.5/5.0/100 in 2.0 mL DCE at 70 °C for 16 h. DCE is 1, 2-dichloroethane, THF is tetrahydrofuran. NR is no reaction, NA is not available.
[b] The conversion and regioselectivity were determined by $^1$H NMR analysis.
[c] The yield is $^1$H NMR yield with $CH_2Br_2$ as internal standard.
[d] $[Ir(COD)Cl]_2$ was used as metal precursor, 24 h.

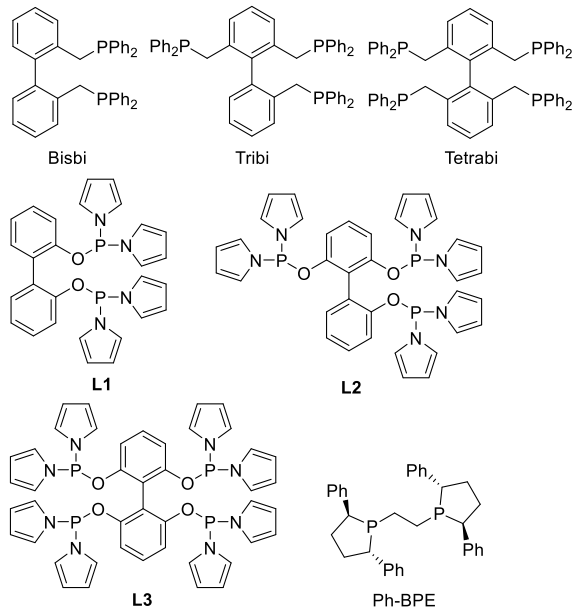
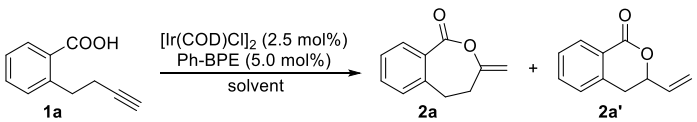



**Figure 2.** The structure of phosphine ligands.

With the optimized reaction conditions in hand, we then focused on the investigation of the substrate scope study for this cycloisomerization. As shown in Table 3, a variety of alkynoic acids could participate in this reaction smoothly, and the corresponding desired products seven-membered vinyl lactones were formed with moderate yields and excellent regioselectivities. The substrates (**1b-1d**) with electron-withdrawing group or electron-donating group on the phenyl ring were tolerated well, affording the products (**2b-2d**) with 48%-68% yields and >99:1 regioselectivity. The naphthyl substituted substrate **1e** also worked well to prepare product **2e** with moderate yield and excellent regioselectivity (52% yield, >99:1 rr). To our surprise, the substrate with dialkynoic acid **1f** can be proceeded to provide the corresponding desired product **2f** with 29% yield. The seven-membered nitrogen-containing heterocyclic vinyl

**Table 2.** Screening solvents for the Ir-catalyzed cycloisomerization of 2-(but-3-yn-1-yl)benzoic acid (**1a**).[a]



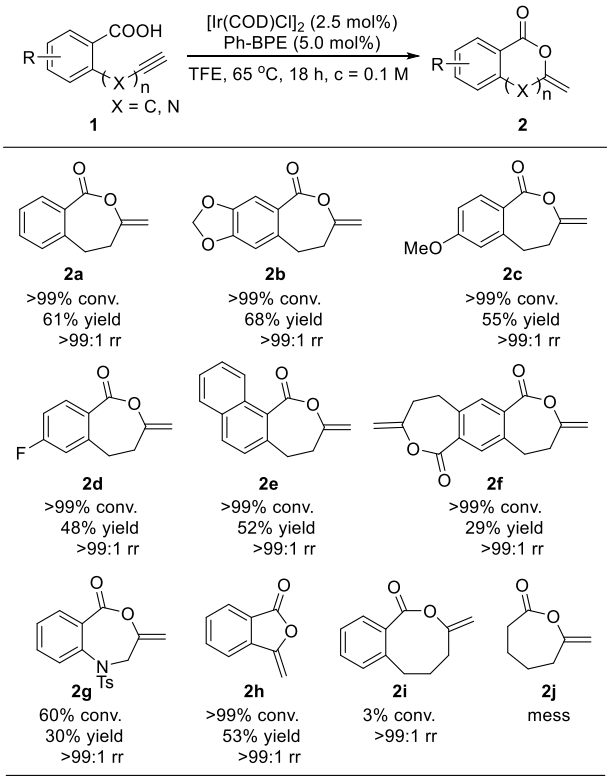

| entry | solvent | T (°C) | Time (h) | conv. (%) [b] | rr (**2a**:**2a'**) [b] | yield (%) [c] |
|---|---|---|---|---|---|---|
| 1 | MeCN | 70 | 24 | 96 | >99:1 | 42 |
| 2 | MeOH | 70 | 24 | 85 | >99:1 | 30 |
| 3 | EtOH | 70 | 24 | 57 | >99:1 | 13 |
| 4 | $^i$PrOH | 70 | 24 | 5 | >99:1 | 1 |
| 5 | THF | 70 | 24 | 10 | 98:2 | 3 |
| 6 | toluene | 70 | 24 | 18 | >99:1 | 5 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 7 | TFE | 70 | 24 | >99 | >99:1 | 50 |
| 8 | TFE | 65 | 24 | >99 | >99:1 | 54 |
| 9 | TFE | 60 | 24 | >99 | >99:1 | 40 |
| 10 | TFE | 65 | 18 | >99 | >99:1 | 54 |
| 11 [d] | TFE | 65 | 18 | >99 | >99:1 | 61 |

[a] Unless otherwise mentioned, all reactions were carried out with ratio of $[Ir(COD)Cl]_2$/(*S*,*S*)-Ph-BPE/**1a** (0.2 mmol) of 2.5/5.0/100 in 2.0 mL solvent at 70 °C for 24 h.
[b] The conversion and regioselectivity were determined by $^1H$ NMR analysis.
[c] The yield is $^1H$ NMR yield with $CH_2Br_2$ as internal standard.
[d] 0.3 mmol substrate **1a**, 5 mol% catalyst, 3.0 mL TFE, isolated yield.

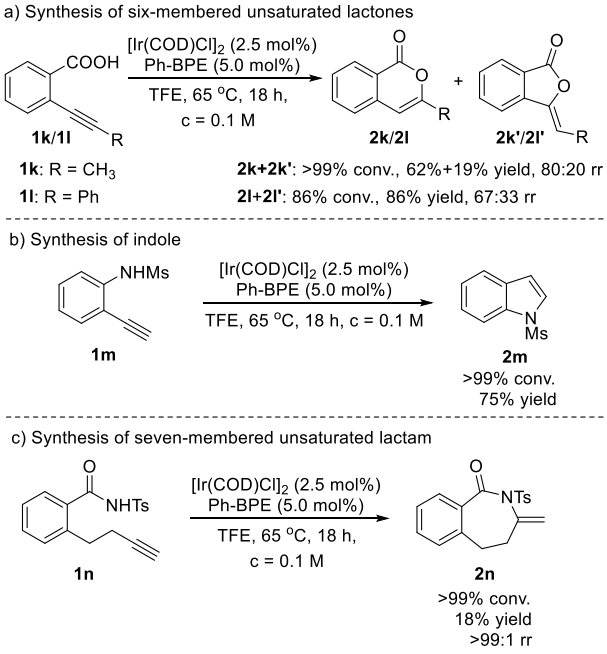
lactone **2g** can be prepared through this cycloisomerization with moderate conversion. And the five-membered vinyl lactone **2h** was afforded with 53% yield and >99:1 regioselectivity. However, it is difficult and challenging to access eight-membered vinyl lactone **2i** through this reaction, very poor conversion was provided. In addition, more flexible substrate hept-6-ynoic acid **1j** was applied into this cycloisomerization, but mess reaction system was observed.

**Table 3.** Substrate scope study for Ir-catalyzed cycloisomerization of alkynoic acids. [a]




[a] Unless otherwise mentioned, all reactions were carried out with the ratio of $[Ir(COD)Cl]_2$/(*S*,*S*)-Ph-BPE/substrate **1** (0.3 mmol) of 2.5/5.0/100 in 3.0 mL TFE at 65 °C for 18 h. The conversion and regioselectivity were determined by $^1H$ NMR analysis. The yield is isolated yield.

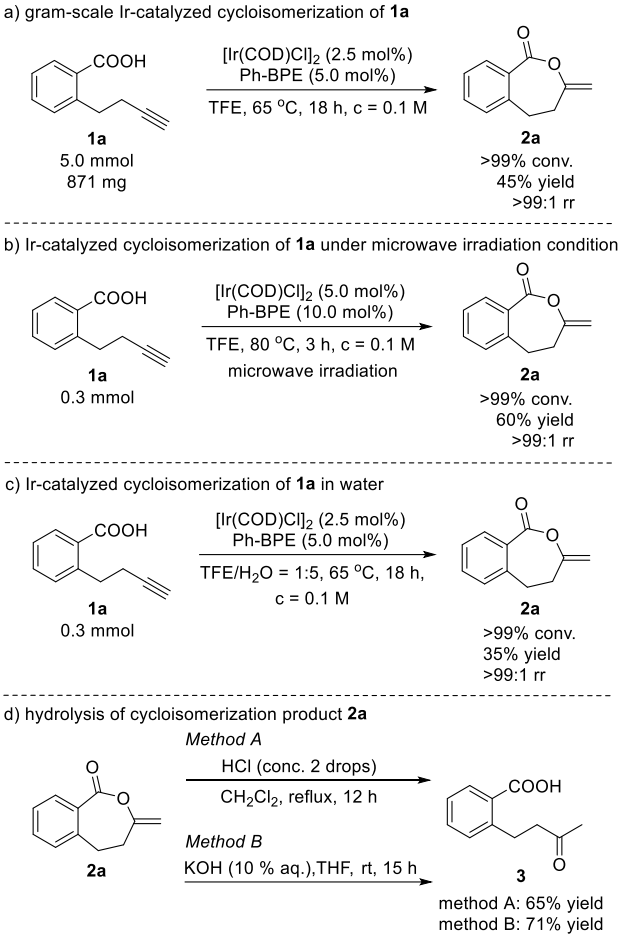
As shown in Scheme 2a, the disubstituted alkynoic acids substrates were further investigated in this catalytic system, the six-membered unsaturated lactones **2k** and **2l** were obtained with moderate results. Moreover, the indole compound **2m** was easily constructed through this cycloisomerization with 75% yield, which provided an efficient synthetic method to prepare indole (Scheme 2b). In addition, it is very challenging to produce seven or eight-membered lactams through the metal-catalyzed cycloisomerization of alkynyl amides.[16] The alkynyl amide substrate 2-(but-3-yn-1-yl)-N-tosylbenzamide **1n** was then examined in this Ir-catalyzed cycloisomerization, the desired product seven-membered unsaturated lactam **2n** could be obtained but with 18% yield (Scheme 2c).




**Scheme 2.** Synthesis of unsaturated lactones, indole and lactam.

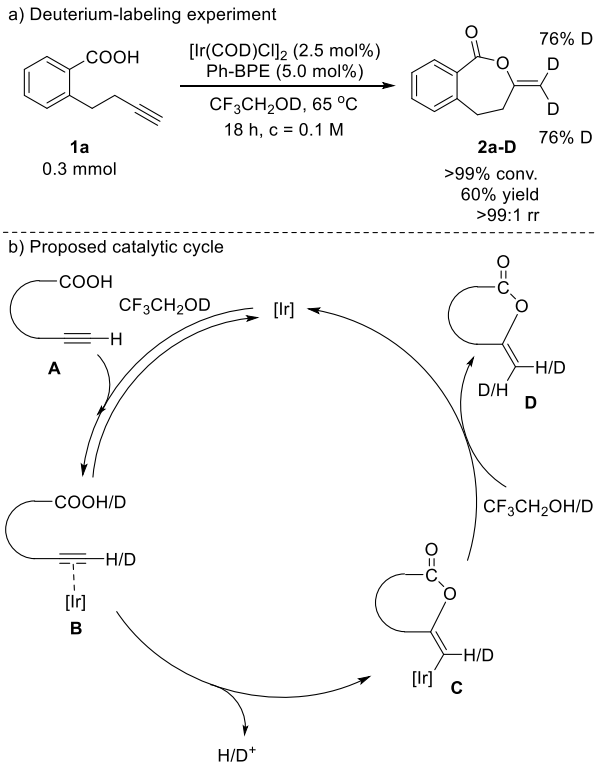
The synthetic application potentiality of this Ir-catalyzed cycloisomerization methodology was demonstrated by the gram-scale transformation. The Ir-catalyzed cycloisomerization of model substrate 2-(but-3-yn-1-yl)benzoic acid **1a** with gram scale was proceeded smoothly to provide the desired product **2a** with >99% conversion, 45% yield and >99:1 regioselectivity (Scheme 3a). In addition, Ir-catalyzed cycloisomerization of **1a** can be performed efficiently under microwave irradiation condition, and 60% yield and >99:1 regioselectivity were obtained (Scheme 3b). This cycloisomerization of 2-(but-3-yn-

1-yl)benzoic acid **1a** also can be proceeded in the presence of water (Scheme 3c). Moreover, the cycloisomerization product **2a** was easily hydrolyzed in acid or alkalinous reaction condition, which generated 2-(3-oxobutyl)benzoic acid **3** with moderate yields (Scheme 3d).




**Scheme 3.** Ir-catalyzed cycloisomerization of **1a** and hydrolysis of product **2a**.

In order to get insight into a reasonable reaction mechanism, the deuterium-labeling experiment was conducted. As shown in Scheme 4a, the model substrate 2-(but-3-yn-1-yl)benzoic acid **1a** went through Ir-catalyzed cycloisomerization in $CF_3CH_2OD$, and the deuterium product **2a-D** was obtained containing partial deuteration on the hydrogen atoms of the vinyl group with full conversion, >99:1 rr and 60% yield. Based on the experimental observation and literature results,[4c, 14h, 14k, 17] a plausible reaction mechanism is proposed in Scheme 4b. Initially, the substrate alkynoic acid **A** could be went through partial deuterium exchange in the presence of $CF_3CH_2OD$ and iridium catalyst, which indicated that this deuteration process may be reversible. And then it was coordinated with Ir-catalyst species to activate the triple bond, which went through cyclization and delivered intermediate **C**. The intermediate **C** was protonated by $CF_3CH_2OH/CF_3CH_2OD$ to deliver the final desired product **D**, and to regenerate the Ir-catalyst species, which was involved in the next catalytic cycle.




**Scheme 4.** Deuterium-labeling experiment and proposed catalytic cycle.

In summary, we successfully developed Ir-catalyzed cycloisomerization of various alkynoic acids to prepare a series of five-, six-, and especially seven-membered unsaturated lactones with moderate yields and excellent regioselectivities (up to 68% yield, >99:1 rr). Moreover, the indole compound can be easily available through this efficient synthetic methodology. In addition, a plausible mechanism for this Ir-catalyzed cycloisomerization methodology were proposed according to the reaction results.

## Experimental Section

**General procedure for Ir-catalyzed cycloisomerization of alkynoic acids:** In an argon-filled glove-box, a solution of $[Ir(COD)Cl]_2$ (5.0 mg, 2.5 mol%) and (*S*,*S*)-Ph-BPE (7.6 mg, 5 mol%) in 3 mL anhydrous TFE (trifluoroethanol) was stirred at rt for 2.0 h and then transferred into the sealed tube which was charged with 0.3 mmol substrate alkynoic acids **1**. The vials were taken out of glove-box and placed in the preheated 65 °C oil bath and stirred at this temperature for 18 h. The reaction mixture was subjected to a short celite column on silica gel to remove the metal complex. The product was analyzed by $^1H$ NMR spectra for conversion-determination with $CH_2Br_2$ as internal standard and subsequent purification by flash column chromatography using PE/EA (20: 1) to provide the desired product.

## Acknowledgements

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# Iridium-Catalyzed Cycloisomerization of Alkynoic Acids: Synthesis of Unsaturated Lactones

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