


# Highly exo selective, photochemically promoted cyclization of iodoallene derivatives

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## Abstract

A photochemically promoted intramolecular cyclization of aryl-, vinyl-, and alkylido allenes has been developed. The optimal conditions employed [Ir(ppy)<sub>2</sub>(dtbbpy)]PF<sub>6</sub> (1 mol%) as catalyst affording products with high exo selectivity in moderate to good yields. Chiral substrates showed diastereoselectivity of up to 95/5 favoring *trans* product.

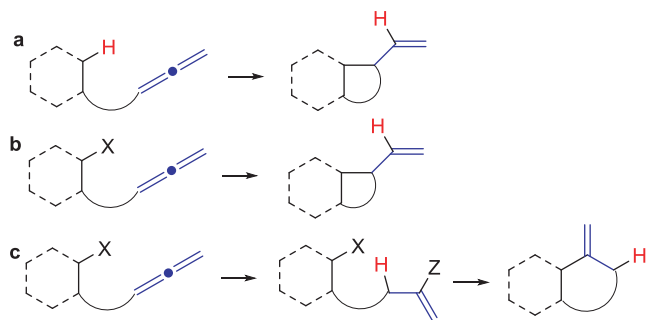
## 1 | INTRODUCTION

Although known for more than a century allenes have been intensively studied only in recent several decades [1]. Their unique structural properties and chemical reactivity created wide interest for this class of compounds and many synthetic methodologies based around these molecules have been developed [2]. The C-3 allenic synths are particularly useful in metal-catalyzed cascade processes [3]. These transformations are usually initiated by activation of either of the double bonds by metal followed by reaction with nucleophiles. The alternative pathway involves carbometalation of the allene moiety and further transformation of the generated vinyl or allyl-metal species.

Cyclative hydroarylation/alkylation reactions of allenes promoted by metals are a variant of these transformations in which formally C–H bond can be added across allenic functionality affording carbo- or

heterocyclic products. Literature survey suggests that this can be achieved in several ways: by a metal activation of C–H bond and subsequent addition of generated intermediate across the allene functionality (Scheme 1, method a), by exploiting reactivity of other functionalities in place of C–H bond while achieving formal hydroarylation/alkylation (Scheme 1, method b) and by initial functionalization of allene followed by the coupling reaction (Scheme 1, method c).

Transformations related to method **a** employ various metals as efficient promoters from perhaps less common Bi(III) or Hg(II) to typically used Au(I), Rh(II), Pt(II), or Pd(0) [4]. Some of these reactions do not proceed via initial activation of C–H bond but rather via activation of the allene functionality making it susceptible to the nucleophilic attack by various activated aromatic rings formally producing hydroarylated products. Intramolecular variants of this process have also been developed [3b,5]. The pathway **b** outlined in Scheme 1 is



**SCHEME 1** Cyclative hydroarylation/alkylation of allenes

usually based on generation of a radical intermediate via homolytic dissociation of the C–X bond or via alternative related methods and subsequent reaction with the allene moiety [6]. This methodology found wide application in the synthesis of many natural products [6a]. Finally, pathway **c** (Scheme 1) would proceed via initial regioselective functionalization of allene followed by the cross-coupling to afford the hydroarylated product. This variant, up to date, has been reported only as an intermolecular transformation but it might be amendable to intramolecular processes [7]. Generally, it shows high regioselectivity of the initial hydroarylation step and high efficiency in the following Pd-promoted intramolecular cross-coupling.

Various options, of methodologies based on the approach **b**, were reported in the literature but they often utilize the stoichiometric amount of sensitive or harmful agents such as  $\text{SmI}_2$  or  $\text{R}_3\text{SnH}$  to promote the participation of C–X bond in the reaction [6a]. We felt that this approach can be further upgraded by using alternative processes to activate C–X bond. In recent years, photochemical methods employing various promoters, notably Ir- or Ru-complexes, proved to be very useful in these processes [8]. Although these reactions are usually very efficient, incorporating allenes in reaction sequence is not without potential glitches. Namely, depending on the cyclization mode, allenes might afford various ring size products [9]. In addition, allenes themselves can participate in a single electron transfer [10]. Obviously, full control over both processes was necessary in order to develop a valuable synthetic methodology.

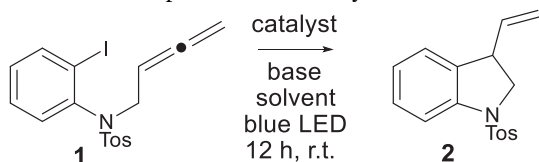
As C–I bond can be activated photochemically in the presence of several Ru- or Ir-complexes they were our choice for the initial study of the cyclative processes of iodoallenes (Table 1) [8b–e]. The first metal complex used for these purposes was  $\text{Ru}(\text{bpy})_3(\text{PF}_6)_2$  whose redox potential ( $\text{Ru}^{\text{II}}/\text{Ru}^{\text{I}} -1.33 \text{ V}$ ) was expected to be sufficient to reduce C–I bond ( $E_{\text{s/s}^-}^0 -1.16 \text{ V}$ ).

The reaction was performed in acetonitrile with allene **1** as starting material and in the presence of an

excess of diisopropylethyl amine. Irradiation of this mixture with blue LED light at room temperature for 12 h, to our delight, afforded exclusively compound **2** albeit in only 28% yield (Table 1, entry a). Replacing acetonitrile as a solvent with DMSO or DMF (Table 1, entries b and c) resulted in the same product but even lower yields. Although we had full regiochemical control with substrate **1** it was necessary to further improve the reaction yield so we explored other photochemical catalysts. Switching to different Ru-complex,  $[\text{Ru}(\text{Phen})_3]\text{Cl}_2$ , under otherwise the same conditions (Table 1, entry d) did not have any beneficial effect on the reaction yield. Next,  $[\text{Ir}(\text{ppy})_2(\text{dtbbpy})]\text{PF}_6$  was used as a catalyst. It has more negative redox potential ( $\text{Ir}^{\text{III}}/\text{Ir}^{\text{II}} -1.51 \text{ V}$ ) compared to those of the initially studied Ru-complexes. The reaction with this catalyst (Table 1, entry e) was performed in acetonitrile with excess base as in previous cases and under the same photochemical conditions affording **2** in 65% yield. Further variations of the conditions such as solvent replacement (Table 1, entries f and g) or the increase of catalyst amount (Table 1, entry k) had an adverse effect on the reaction yields. Similar results were obtained by decreasing the amount of base (Table 1, entries h and i). Performing the reaction with no base (Table 1, entry l) did not afford the product at all, demonstrating its essential role in the reaction process. An additional experiment was carried out using  $[\text{Ir}(\text{dF}(\text{CF}_3)_3\text{ppy})_2(\text{dtbpy})]\text{PF}_6$  under the described conditions resulting in the expected product but in slightly lower yield (Table 1, entry m vs. entry e).

Upon selection of optimal reaction conditions, we further explored the reaction scope (Table 2). Various arylidoallenes were synthesized and used for the cyclization processes. The majority of them afforded expected products in moderate to good yields. The presence of O-linkage or NAc-linkage between the arylido and allenic moieties in place of NToS used in our initial experiments did not affect the reaction significantly and the products **4a–c**, **4h** were isolated in yields ranging from 52% to 67%. Additional halide functionality on the aromatic ring, such as fluorine or bromine (**4f**, **4g**), was also tolerated by the reaction conditions yielding **4f** and **4g** in acceptable 51% yields. Interestingly, lower yields of the products were obtained from starting material possessing methyl substituents directly attached to the aromatic ring. Two products, **4d** and **4e**, were isolated in only 25% and 23% yields, respectively. This is likely to be an outcome of the side processes caused by the transformation of the benzylic C–H bond as suggested by inspection of  $^1\text{H}$  NMR of the crude reaction mixture, although isolation of the products of this origin was hampered by the complexity of the reaction mixture. Replacing benzene ring with pyridine afforded product **4c** with slightly lower but

TABLE 1 Optimization of the cyclization of iodoallenes under photochemical conditions



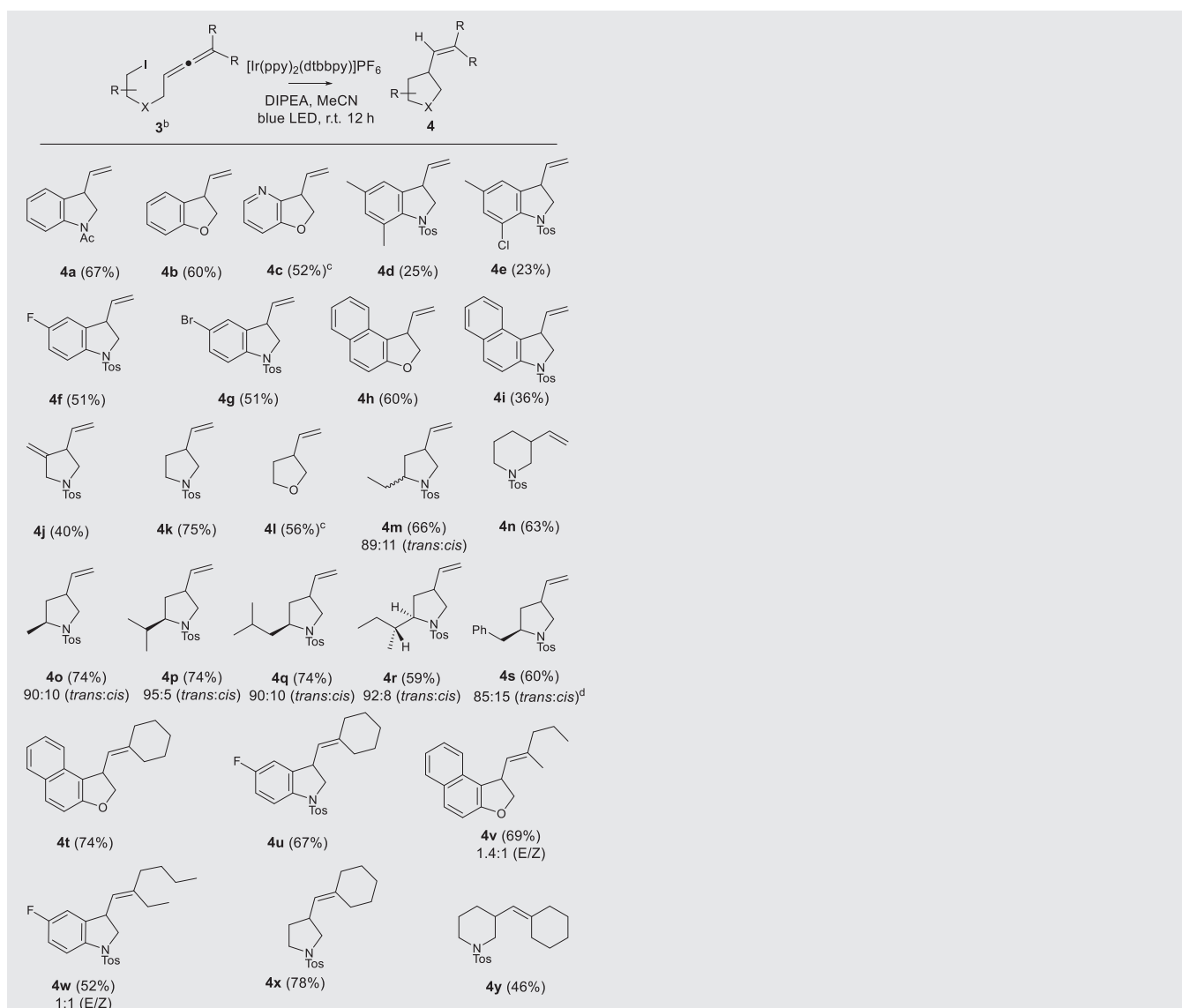
Entry	Catalyst	Base	Solvent	Yield (%) <sup>a</sup>
a	1 mol% Ru(bpy) <sub>3</sub> (PF <sub>6</sub> ) <sub>2</sub>	10 eq. DIPEA	MeCN	28.0
b	1 mol% Ru(bpy) <sub>3</sub> (PF <sub>6</sub> ) <sub>2</sub>	10 eq. DIPEA	DMSO	19.4
c	1 mol% Ru(bpy) <sub>3</sub> (PF <sub>6</sub> ) <sub>2</sub>	10 eq. DIPEA	DMF	8.3
d	1 mol% [Ru(Phen) <sub>3</sub> ]Cl <sub>2</sub>	10 eq. DIPEA	MeCN	9.1
e	1 mol% [Ir(ppy) <sub>2</sub> (dtbbpy)]PF <sub>6</sub>	10 eq. DIPEA	MeCN	65.0
f	1 mol% [Ir(ppy) <sub>2</sub> (dtbbpy)]PF <sub>6</sub>	10 eq. DIPEA	DMSO	41.5
g	1 mol% [Ir(ppy) <sub>2</sub> (dtbbpy)]PF <sub>6</sub>	10 eq. DIPEA	DMF	50.6
h	1 mol% [Ir(ppy) <sub>2</sub> (dtbbpy)]PF <sub>6</sub>	5 eq. DIPEA	MeCN	51.3
i	1 mol% [Ir(ppy) <sub>2</sub> (dtbbpy)]PF <sub>6</sub>	1 eq. DIPEA	MeCN	34.6
j	1 mol% [Ir(ppy) <sub>2</sub> (dtbbpy)]PF <sub>6</sub>	10 eq. Et <sub>3</sub> N	MeCN	54.6
k	5 mol% [Ir(ppy) <sub>2</sub> (dtbbpy)]PF <sub>6</sub>	10 eq. DIPEA	MeCN	46.8
l	1 mol% [Ir(ppy) <sub>2</sub> (dtbbpy)]PF <sub>6</sub>	—	MeCN	—
m	1 mol% [Ir(dF(CF <sub>3</sub> )ppy) <sub>2</sub> (dtbbpy)]PF <sub>6</sub>	10 eq. DIPEA	MeCN	52.6

<sup>a</sup>Established by <sup>1</sup>H NMR.

comparable yield. Finally, participation of the larger substituent in the reaction pathway such as the naphthyl ring was validated, though products **4h** and **4i** were isolated in variable yields, 60% and 36%, respectively. Vinyliodo allene proved also to be suitable starting material yielding **4j** in a moderate 40% yield. Alkylido allenes with Csp<sup>3</sup>–I bond, cyclized under the above-described conditions producing saturated heterocycles with better efficiency than the aryl equivalents possessing Csp<sup>2</sup>–I bond. All products, **4k–s**, were isolated in yields ranging from 59% to 75%. Apart from pyrrolidine formation, the synthesis of **4n** demonstrated the potential of this methodology in synthesis of piperidine derivatives as well. Interesting results were obtained when allenes having a remote chiral carbon, derived from appropriate amino acids, were used as the cyclization precursors. All products, **4m, o–s**, were isolated in good yields (59%–74%) with diastereoselectivity ranging from 85:15 to 95:5 in favor of *trans* isomer. We further briefly studied allenes with substituents at the terminal carbon. Generally, the cyclization processes leading to 5-membered rings were as efficient as with nonsubstituted allenes with comparable yields (products **4t–x**), while the formation of the 6-membered ring was slightly less effective (**4y** vs. **4n**).

Based on the literature reports the proposed mechanism for the above-described transformation is outlined in Scheme 2. The reaction is initiated with the formation of Ir<sup>2+</sup> from Ir<sup>3+</sup> via several steps involving N,N-

Diisopropylethylamine (DIPEA). Upon reduction of C–I bond via single electron transfer from Ir<sup>2+</sup> and creation of radical intermediate **3'** the cyclization takes place to afford intermediate **4'** and final product cyclopentane derivative **4**. The observed products were created via 5-*exo* mode of radical cyclization which is a kinetically favored process [9,11]. Analysis of transition state for the cyclization of hepta-5,6-dien-1-yl radical by Guo et al revealed that activation free energy for the formation of cyclopentylvinyl radical via 5-*exo* process is 0.9 kcal/mol lower than the activation free energy for the formation of 6-membered ring via 6-*exo* cyclization despite the fact that it leads to intermediate allyl radical **4'''** [9]. The energy difference between the observed pathway and the pathway leading to 7-membered vinyl radical **4''** which would involve 7-*endo* transformation is even higher and was calculated to be 2.5 kcal/mol [9]. Although differences in the activation free energy for three competitive processes suggest a possibility of formation of 6-membered product, careful examination of <sup>1</sup>H NMR spectra of the crude reaction mixtures did not indicate the presence of either of them. In addition, we did not observe any product related to fragmentation of radical **3'** (where it was possible) which would be imaginable due to a formation of more stable radical species. All these observations imply that the 5-*exo* radical cyclization is kinetically favored over other possible courses of the reaction.

TABLE 2 Scope of the cyclization reaction<sup>a</sup>

<sup>a</sup>Reaction conditions: Iodoallene (1 equiv.), [Ir(ppy)<sub>2</sub>(dtbbpy)]PF<sub>6</sub> (0.01 equiv.), DIPEA (10 equiv.) in acetonitrile (ACN) irradiated with blue LED (12 V DC, 4.8 W) for 12 h.

<sup>b</sup>See Supporting Information for the synthesis of starting materials.

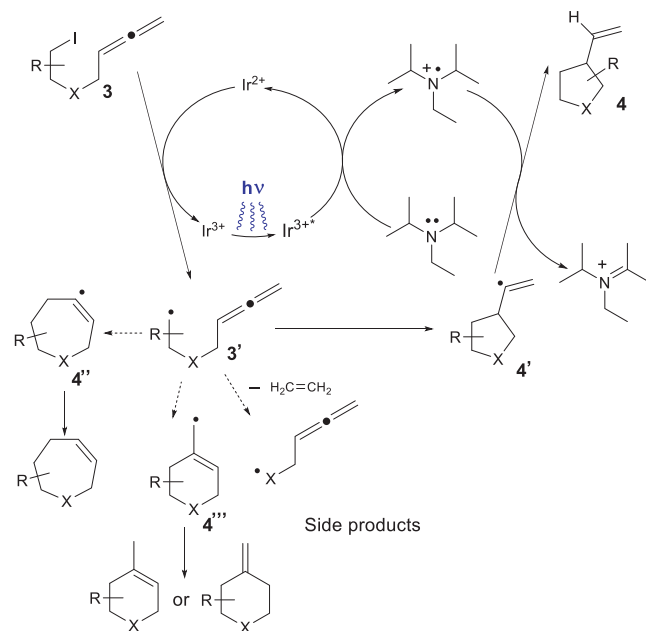
<sup>c</sup>Isolated yields. For products **4c** and **4l** yields were established by <sup>1</sup>H NMR due to volatility.

<sup>d</sup>2D spectra available in Supporting Information.

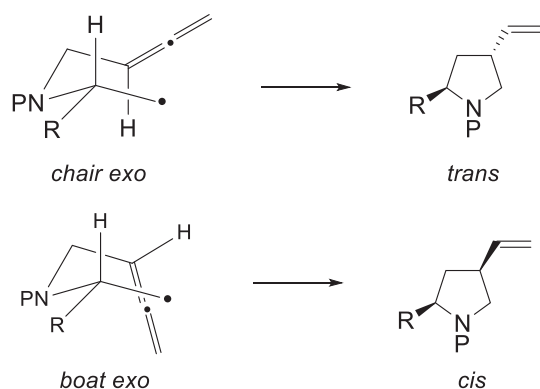
Utilizing this mechanistic rationalization it would also be possible to address observed diastereoselectivity (Table 2, **4m, o–s**). Namely, upon reduction of C–I bond generated radical can adopt either *chair exo* or *boat exo* transition state, Scheme 3. *Trans* product was obtained via more favored *chair exo* transition state as predicted by the Beckwith–Houk model [11a–c]. The results also suggest that branching at the α-position to the chiral atom increases the diastereomeric ratio.

Finally, in order to demonstrate the synthetic utility of the product created by the described methodology several transformations were carried out, Scheme 4.

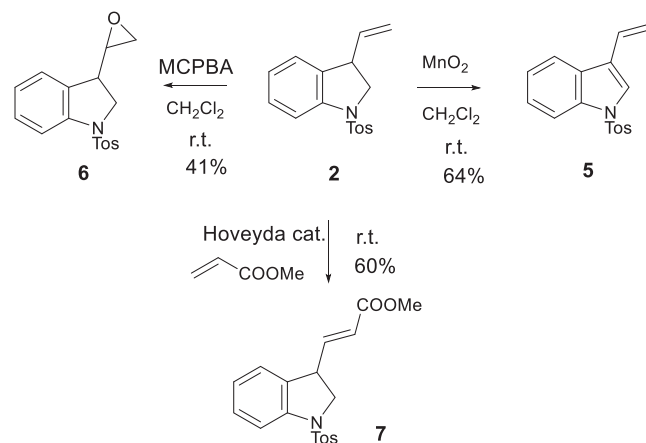
Routine, unoptimized oxidation of **2** with MnO<sub>2</sub> afforded very useful vinyl indole **5** in 64% yield [12]. This compound found wide synthetic applicability, particularly in preparation of other heterocycles, as it can be used as either [2π] or [4π] component in the cycloaddition reactions [13]. Two further modifications of the terminal double bond, namely oxidation [14] to afford epoxide **6** and cross-metathesis [15] to produce derivative **7** with a conjugated double bond, illustrated some additional valuable transformations of the product accessed via described methodology (see Supporting Information).



SCHEME 2 Mechanistic rationalization



SCHEME 3 Rationalization of the observed diastereoselectivity



SCHEME 4 Chemical transformations of the cyclization product

In conclusion, we developed highly exo selective, photochemically promoted cyclative transformations of allenyl iodide. Aryl, vinyl, and alkyl iodides afforded products in good yields and excellent regioselectivity under mild conditions. Described process is a useful alternative to current related transformations with a potential to find wider application in synthetic organic chemistry.

## 2 | EXPERIMENTAL SECTION

### 2.1 | General procedure for photocatalytic cyclization of allenyl iodides

Iodoallene (1 equiv.) and  $[\text{Ir}(\text{ppy})_2(\text{dtbbpy})]\text{PF}_6$  (0.01 equiv.) were dissolved with ACN in a vial. The vial was degassed and DIPEA (10 equiv.) was added toward the end of the degassing process. The vial was sealed and placed in the irradiation apparatus. The irradiation apparatus was assembled using a 3 L beaker wrapped with blue light-emitting diode strip 10 m (12 V DC, 4.8 W). The reaction mixture was stirred 12 h at room temperature. The reaction mixture was then filtered and concentrated under reduced pressure. Flash chromatography afforded the products **2** and **4a–y**.

### DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the Supporting Information of this article.

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