Selective Enyne Ring-Closing Metathesis with Main Group Metal Catalysts

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Abstract: Ring-closing metathesis (RCM) represents an ideal and atom-economical way to construct cyclic compounds. The precedented reaction systems for *endo*-selective enyne RCM mainly rely on precious transition metal carbene complexes or activated substrates. Here we report the utility of group 13 metal halides, such as $InBr_3$ and InI_3, as simple and efficient catalysts for *endo*-selective RCM of nitrogen-tethered 1,6-enynes under mild conditions. Conventionally, these substrates underwent cycloisomerization to generate 6,3-fused bicycles under transition metal catalysis. The reaction mechanism and nature of the catalytic species have been revealed by kinetic experiments and density functional theory calculations.

Ring-closing metathesis (RCM) is a powerful method for the generation of cyclic compounds and has had a great impact on chemistry, with applications spanning natural product synthesis and drug development (*1*, *2*). In the past decades, a branch of RCM, the enyne RCM, has attracted extensive attention due to its synthetic potential in the preparation of cyclic dienes from readily available acyclic enynes (Figure 1A) (*3*, *4*). However, there is a long-standing challenge in the catalytic enyne RCM: the regiochemical control toward the *endo* selectivity. For instance, the reaction of 1,6-enynes

with ruthenium carbene catalysts commonly leads to the five-membered cyclic dienes (*exo* products) preferentially or gives both products non-discriminately (*3*, *5*). The main challenge originates from the fact that the metal carbene complex may react either with the alkyne or with the alkene moiety to initiate the enyne RCM reaction (*3*). To solve this problem, Hoveyda and Schrock found that when sterically demanding Mo and W catalysts were used, *endo* products can be generated exclusively (Figure 1B) (*6*–*8*). Recently, Choi reported the utility of Grubbs *Z*-selective catalyst for *endo*-selective enyne RCM of carbon-tethered 1,6-enynes (*9*). However, considering the high cost of these transition metal carbene complexes, discovering simple, inexpensive, and readily available catalysts is highly desirable.

Catalytic enyne cycloisomerizations offered an alternative approach for the enyne RCM (*10*, *11*). While catalytic systems for the synthesis of *exo* RCM products are well established in the literature, enyne cycloisomerizations leading to *endo* RCM products are underdeveloped (Figure 1C). Echavarren found that 1,6-enynes containg a terminal alkyne moiety can lead to the *endo* products under gold catalysis albeit with limited scope (*12*). Faller reported a similar ruthenium-catalyzed cycloisomerization of carbon-tethered 1,6-enyne substrates, but only two substrates can form the *endo* RCM products (*13*). Chatani found that the *endo* RCM products were obtained in the indium-catalyzed transformation of carbon-tethered 1,6-enynes as the minor products (*14*, *15*). We noticed that, in all these reports, terminal alkynes were used as the substrates. For internal alkyne substrates, activating groups such as boronates (*16*) and carbonyls (*17*) are generally required. Up to date, for unactivated nitrogen-tethered 1,6-enynes containing internal alkyne units, the only access to the *endo* product is the transition-metal-carbene-catalyzed enyne RCM. Under the catalysis of transition metals, including Au, Pt, Rh, Ir, and Pd, these substrates all led to 6,3-fused

bicyclic products rather than dienes (Figure 1C) (*10*). Mechanistically, these reactions start with an intramolecular cyclopropanation, generating a bicyclic metal carbene intermediate. Then, the subsequent facile [1,2]-hydride shift occurs to furnish the cycloisomerization product.

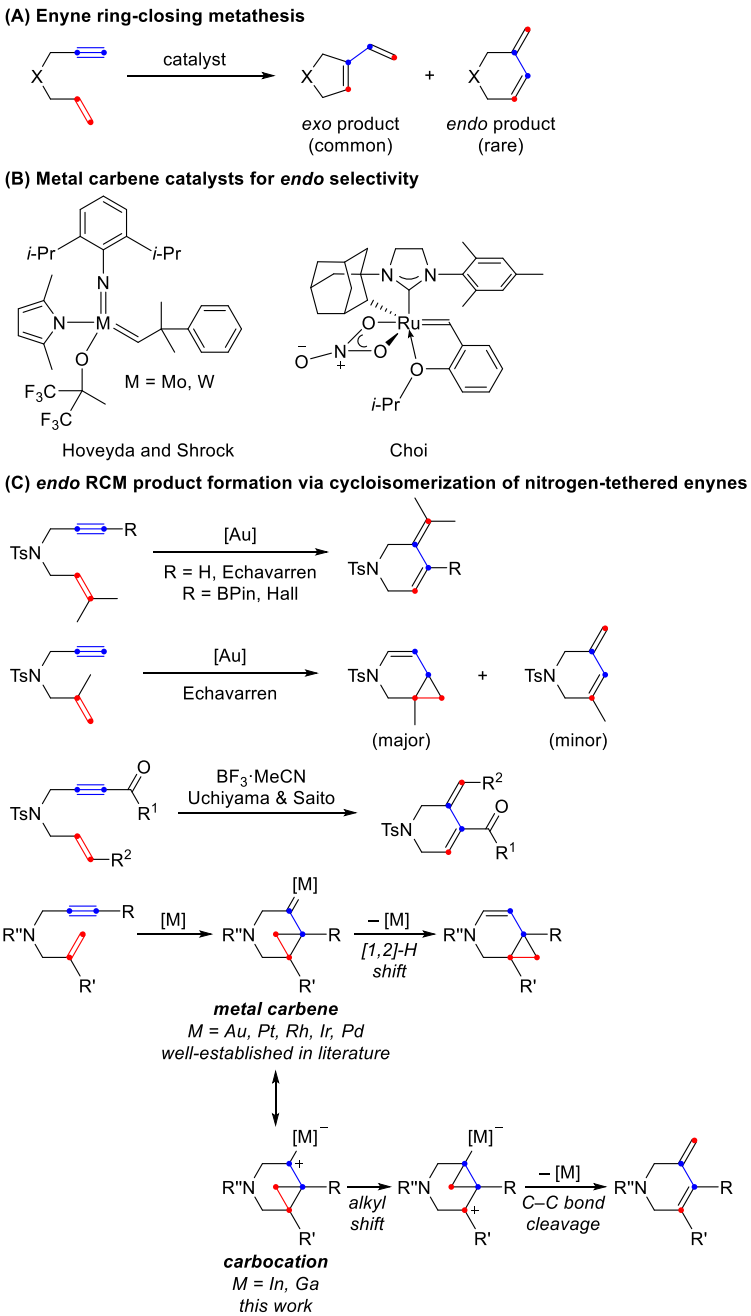


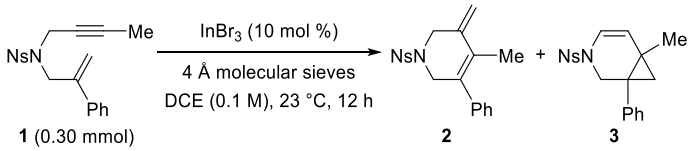
Figure 1. Enyne RCM and cycloisomerization. (A) Enyne RCM and regioselectivity. (B) Metal carbene catalysts for *endo*-selective enyne RCM. (C) Cycloisomerization of nitrogen-tethered enynes leading to *endo* products.

Inspired by Chatani's work on $InCl_3$-catalyzed cycloisomerization of carbon-tethered 1,6-enynes (*14*, *15*), we wondered that if a group 13 metal salt, in which the participation of metal d orbitals are insignificant for bonding (*18*), is used as the catalyst, a different reaction pathway may take place. In this case, carbocation-induced alkyl shift of the cyclopropanation intermediate (*19*) may compete with the hydride shift and lead to the *endo* RCM product selectively (Figure 1C). By utilizing this strategy, conjugated dienes with functionalized piperidine ring structures that are widely found in biologically active natural products and pharmaceuticals, may be generated (*20*).

Based on this hypothesis, we commenced our investigation using enyne substrate **1**. Table 1 provides the optimal reaction conditions and the results for the variation of different reaction parameters. After stirring a suspension of substrate **1**, 10 mol % $InBr_3$, and 4 Å molecular sieves in 1,2-dichloroethane (DCE) at 23 °C for 12 h, diene **2** was isolated in an excellent yield (96%) with excellent chemo- (**2**/**3** > 95:5) and regioselectivities (*endo*/*exo* > 95:5) (entry 1). The structure of **2** has been unambiguously confirmed by x-ray crystallographic analysis. Use of InF_3 as the indium(III) source did not lead to the desired product (entry 2). $InCl_3$ was able to promote the reaction but with lower efficiency (entry 3). Under the catalysis of InI_3, **2** was isolated in a comparable yield (entry 4). Similar counteranion effect was previously observed in the indium-catalyzed intramolecular hydroarylation (*21*) and hydroalkoxylation of alkynes (*22*). Then, we tested two other group 13 metal tribromides. Changing the catalyst to $AlBr_3$ gave no desired product (entry 5) while $GaBr_3$ led to lower yield and chemoselectivity (entry 6). The choice of solvent is critical (*14*). Lower yield was observed when toluene was used as the solvent (entry 7), whereas replacement of DCE by tetrahydrofuran (THF) led to the complete loss of reactivity (entry 8). The addition of 4 Å molecular sieves was also important for this transformation, as evidenced by the loss in reaction yield without

4 Å molecular sieves (entry 9). In addition, control experiments indicated that no reaction occurred in the absence of $InBr_3$ (entry 10).

Table 1. Reaction Development



1 (0.30 mmol) **2** **3**

entry	deviation from above	yield of **2** (%)	**2**/**3**	*endo*/*exo*
1	none	96	>95:5	>95:5
2	InF_3	NR		
3	$InCl_3$	17	>95:5	>95:5
4	InI_3	93	>95:5	>95:5
5	$AlBr_3$	NR		
6	$GaBr_3$	74	93:7	>95:5
7	toluene as solvent	42	>95:5	>95:5
8	THF as solvent	NR		
9	without 4 Å molecular sieves	70	>95:5	>95:5
10	without $InBr_3$	NR		

Reported yields refer to product isolated by silica gel flash chromatography. Ratios were determined by ^{1}H NMR analysis of unpurified mixtures. Ns = 4-nitrobenzenesulfonyl. DCE = 1,2-dichloroethane. THF = tetrahydrofuran. NR = No reaction.

With the optimal reaction conditions in hand, we first investigated the generality of this reaction with respect to the alkene part (Figure 2A). A variety of substrates bearing aryl substituents with different electronic effects, substitution patterns, and functional groups were well tolerated, affording the desired products in good to excellent yields (**4**−**16**). To complete the reaction of substrates with electron-deficient aryl groups, an elevated temperature (40 °C) was required (**9**−**14**). 2-Naphthyl substrate was also suitable for the RCM reaction, giving the desired product **16** in 98% yield. Substrates with alkyl (isopropyl, benzyl, and *p*-methoxybenzyl) substituents also worked well (**17**−**19**). Then, we investigated the scope of the alkyne part. Replacement of the terminal methyl

group in substrate **1** by *n*-butyl and *i*-amyl groups did not affect the reaction significantly (**20** and **21**) and alkyl chloride was tolerated under indium catalysis (**22**). However, terminal alkyne and phenyl-terminated alkyne substrates both gave complex mixtures under the standard conditions, suggesting that the electronic property of the alkyne moiety is crucial for this reaction. Finally, to demonstrate the practicability of this reaction, we carried out a gram-scale reaction of **1** (Figure 2B), which offered a comparable yield with respect to the 0.30 mmol scale reaction.

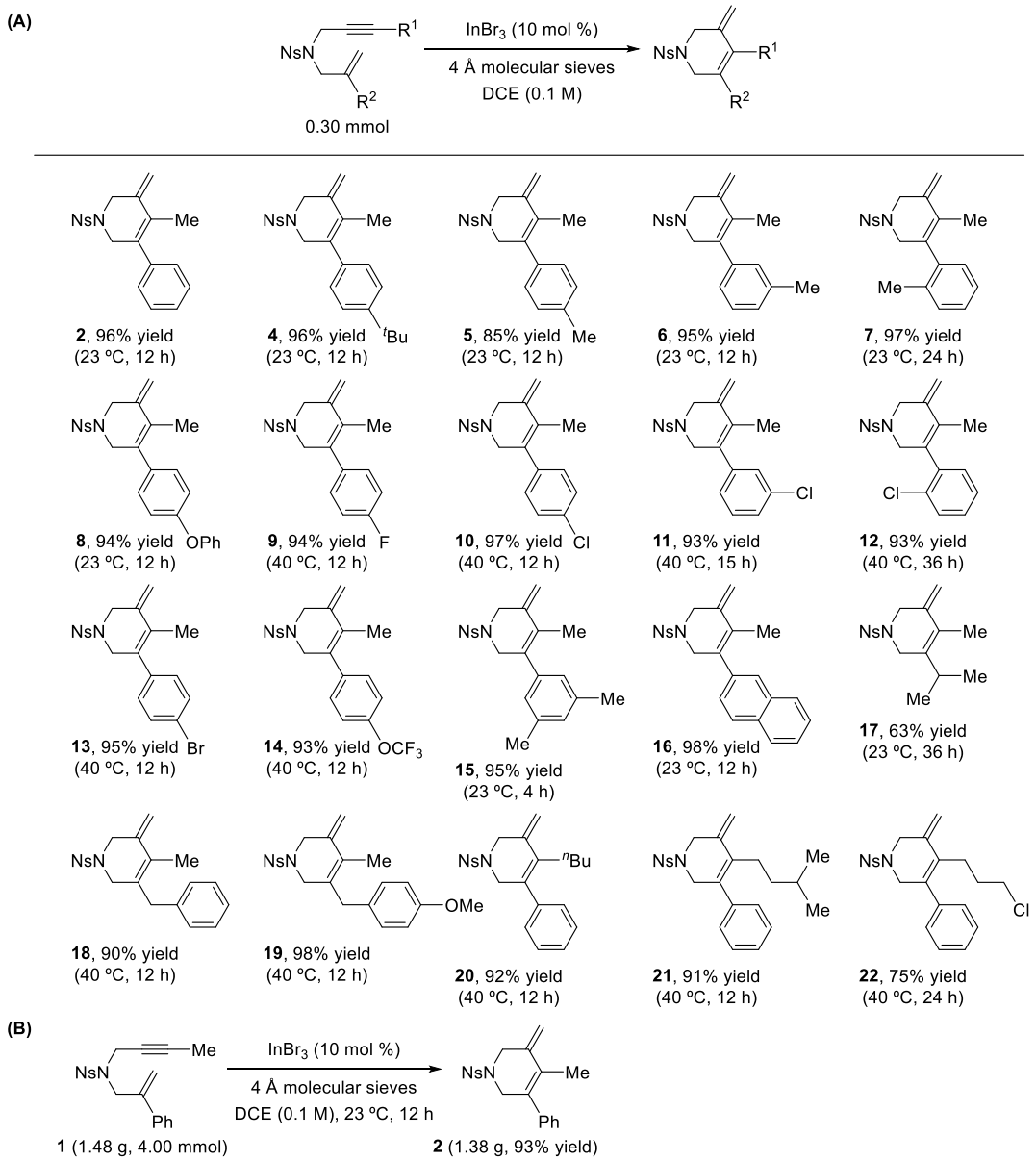


Figure 2. Scope and gram-scale synthesis. (A) Scope. (B) Scale-up experiment.

Subsequently, we investigated the reaction mechanism. First, we treated side product **3** under the standard conditions, finding that the RCM product **2** was not generated. Therefore, our reaction could not take place with the intermediacy of bicycle **3** (Figure 3A). We applied the normalized time scale method to determine the reaction order in the catalyst (*23*). Due to the fact that $InBr_3$ is almost insoluble in $CDCl_3$, we used soluble InI_3 for the kinetic studies. By plotting the concentration of substrate **23** against $t[\text{catalyst}]_T^2$ (t is the reaction time and $[\text{catalyst}]_T$ is the total concentration of catalyst added), the curves of 6, 8, and 10 mol % InI_3 overlaid, suggesting that the reaction order in the catalyst is 2 (Figure 3B). According to these results and the literature (*22*), we proposed that the real catalytic species is the InI_3 homo-dimer, which is further supported by density functional theory (M06-2X) calculations (*24*) (Figure 4). DFT calculations indicated that the resting state (**RS**) of the catalyst is an off-cycle monomeric indium-sulfonamide complex whereas the catalytic species is dimeric. The catalytic cycle starts with the turnover-limiting cyclopropanation step, generating cyclopropylcarbinyl cation **INT1**. The subsequent alkyl shift via transition state **TS2** results in the formation of another cyclopropylcarbinyl cation **INT2** (*19*). Then, the ligand-assisted cyclopropane opening takes place through intramolecular nucleophilic substitution, generating catalyst-product σ complex **INT3**. Finally, the dissociation of the dimeric catalyst occurs via **TS4**, furnishing the RCM product **2**.

Our findings show that simple main group metal halides can be used as efficient catalysts for the *endo*-selective enyne RCM. From a broader perspective, we envision that such a main group strategy will prove a widely applicable solution for the synthesis of valuable cyclic compounds.

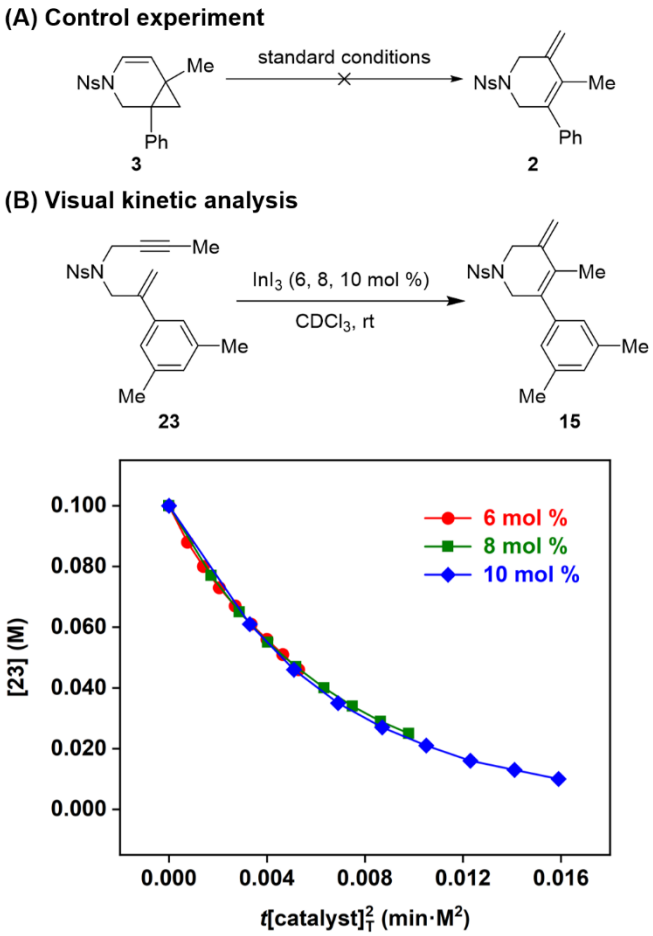


Figure 3. Mechanistic experiments. (A) Control experiment. (B) Visual kinetic analysis.

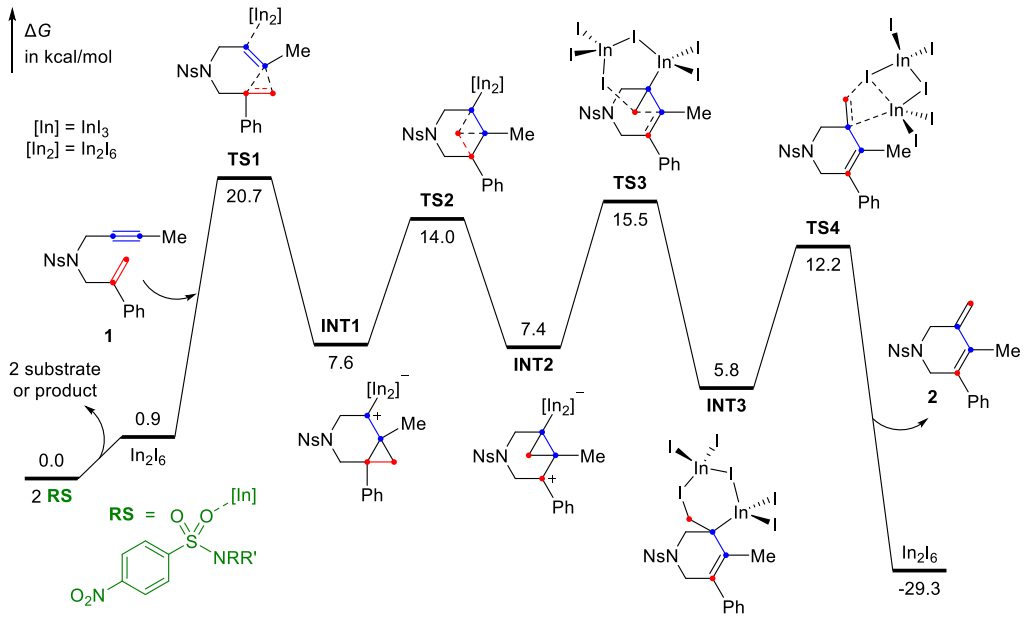


Figure 4. Gibbs energy profile. Computed at the SMD($CHCl_3$)/M06-2X/def2-TZVPP//M06-2X/def2-SVP level. **RS** = resting state.

Acknowledgments

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Notes

The authors declare no competing financial interests.

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