# Catalytic *Z*-selective Olefin Cross-metathesis for Natural Product Synthesis

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## 1. Introduction

### 1.1 Synthesis of *Z*-disubstituted alkenes

• Energy: *E* alkenes < *Z* alkenes → Z-selective alkene synthesis is difficult.

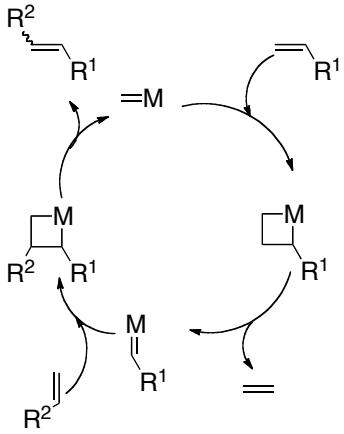
• Typical synthetic methods for *Z*-1,2-disubstituted alkenes

(i) Wittig-type reaction – "Unstable ylides" only, non-catalytic, a lot of waste compounds.

(ii) Catalytic alkyne hydrogenation – Toxic metal catalyst, Alkanes (byproduct) are difficult to separate.

(iii) Cross-coupling reaction – Stereochemistry must be determined through the synthesis of substrates.

→ Alternative synthetic method is required.




### 1.2 Previous Work

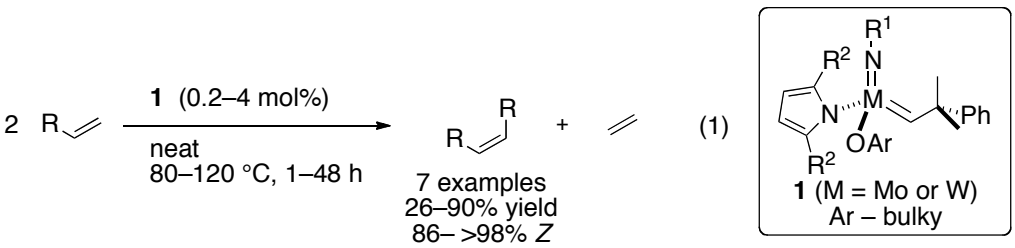
• Olefin metathesis reaction[1] – One of the fundamental C–C double bond formation reaction, by using alkenes as the starting materials, which won Nobel Prize in 2005.

• *Z*-Selective olefin metathesis is a possible alternative.

However, almost all of the reported 1,2-disubstituted alkene syntheses via olefin metathesis were *E*-selective because all of the elementary processes are reversible.

→ Kinetic control is necessary for the achievement of *Z*-selectivity.

• Highly *Z*-selective homo-coupling of terminal alkenes has been already achieved (Eq 1).[2]




– Bulky Ar group of **1** destablized the transition state for *E*-products by the steric factor (Figure 1). → Kinetically controlled *Z*-alkene formation.

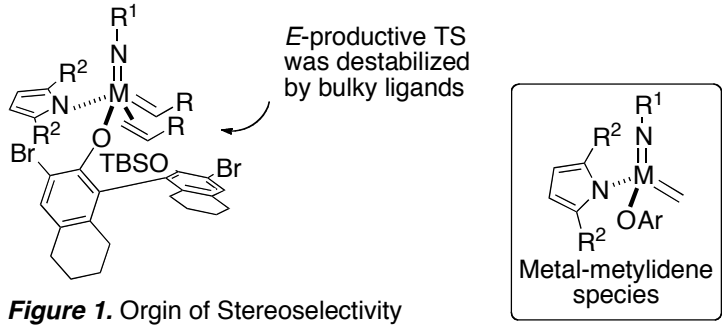


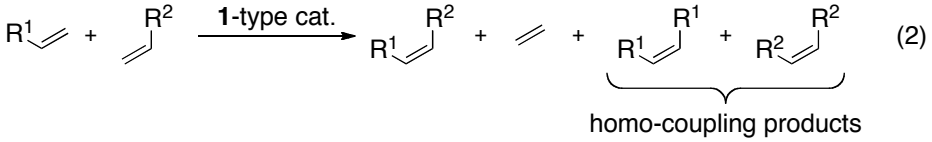

***Figure 1.*** Orgin of Stereoselectivity

– Stereoelectronic effects induced by the electron donor pyrrolide and acceptor monoaryloxide achevied the high activity in spite of the steric bulk.

– Formation of metal-methylidene species from ethylene promotes the back reaction, and the isomerization of the products → Low yield and stereoselectivity for some substrates

### 1.3 This Work

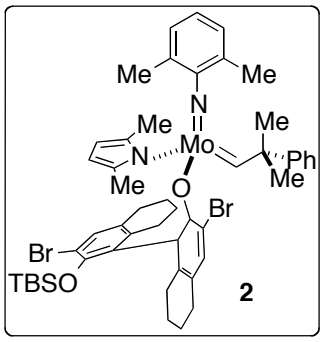
• Development of a highly *Z*-selective cross-metathesis (CM) of terminal alkenes (Eq 2) – practical reaction for organic synthesis




(2)

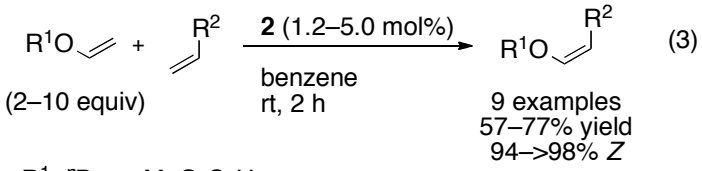
– *Z*-selectivity is expected to be accomplishable by the use of **1**-like catalyst.

– Challenges (i) Suppress homo-coupling reaction (ii) Suppress back reaction




## 2. Results and Discussion

### 2.1 *Z*-Selective CM of enol ethers (Eq 3)




(3)

$R^1$: $^n$Bu, *p*-MeO-$C_6H_4$
$R^2$: Alkyl, Cy, Bn, Ester/halogen/silyl ether/amide containg alkyl groups

• Use enol ethers as the starting materials → (i) Stabilizing enol ether derived alkylidenes thermodynamically (ii) Homo-coupling of enol ether is electronically disfavored.

• Use excess amount of enol ethers → (i) Further promote the formation of enol ether derived alkylidene. (ii) Suppress the reaction of the coupling product with Mo-methylidene.

→ Highly selective and efficient synthesis of (*Z*)-alkenes from enol ether was achieved.

• This reaction was applied to the synthesis of C18 (plasm) – 16:0 (PC) (**8**), an anti-oxidant plasmalogen phospholipid, which was previously synthesized by using catalytic alkyne hydrogenation, and whose (*E*)-isomer is less active[3] (Scheme 1, **5** + **6** → **7**).

– Enol ether **5**, synthesized from commercially available **3**, is valuable than aliphatic alkene **6**. → For a large-scale synthesis, use of excess amount of **5** (Table 1, entry 1) was not practical. → Reduction of the loading of **5** is required.

-> Use of 1.0 equivalent **5** (entry 2) → Homo-coupling from **6** and ethylene formation became problematic (lowered the yield and stereoselectivity).

-> Perform reaction at reduced pressure (entry 3) achieved high yield and selectivity. → successful removal of ethylene from the system, and suppression of the formation of Mo-methylidene species.

-> Use excess amount of inexpensive alkene **6** (Table 1, entry 4) → Yield was improved because the homo-coupling was not taken into account under these conditions.

***Scheme 1.*** Synthesis of C18 (plasm) – 16:0 (PC) by Using CM Reaction

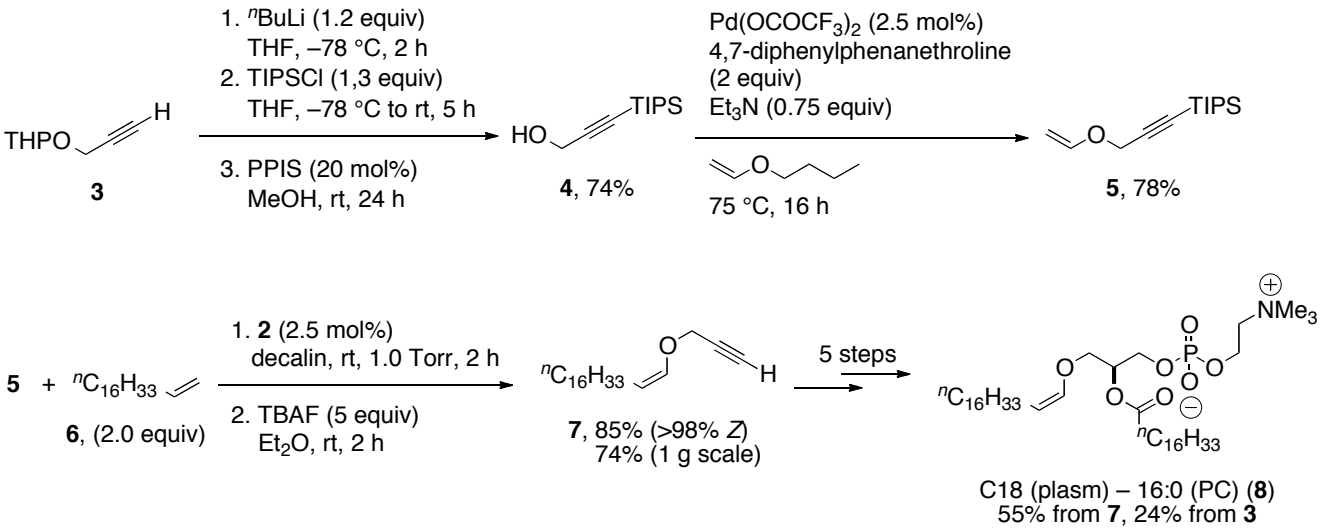
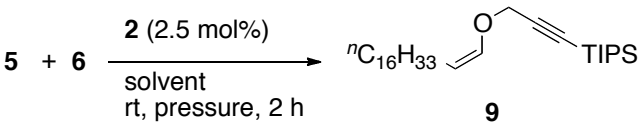



***Table 1.*** Effect of Reduced Pressure on Efficiency and *Z*-selectivity

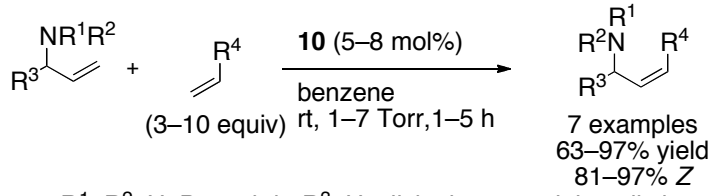



| entry | **5**:**6** | solvent | pressure | yield (%) **9** | *Z*:*E* |
|---|---|---|---|---|---|
| 1 | 5:1 | benzene | 1 atm | 85 | >98:2 |
| 2 | 1:1 | benzene | 1 atm | 47 | 91.5:8.5 |
| 3 | 1:1 | benzene | 1 Torr | 78 | 97:3 |
| 4 | 1:2 | decalin | 1 Torr | 88 | 97:3 |

**2.2 Z-Selective CM of allylic amides (Eq 4)**

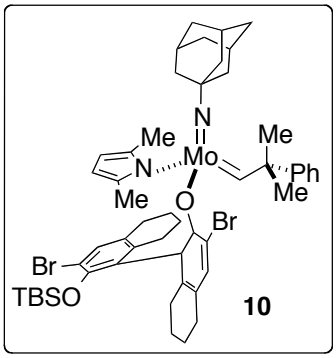
• Use allylic amides as the starting materials would be useful because a lot of biologically active molecules bear C–N bonds, and allylic C–N bond can be functionalized in a variety of ways.

• Homo-coupling of allylic amides can undergo. → To suppress the homo-coupling, excess amount of aliphatic alkenes were employed, and the reaction was performed under vacuum (the same strategy as the large-scale synthesis of compound **7**




(4)

$R^1$, $R^2$: H, Boc, phth, $R^3$: H, silyl ether containing alkyl groups
$R^4$: Alkyl, Cy, Ester/halogen/ether containing alkyl groups



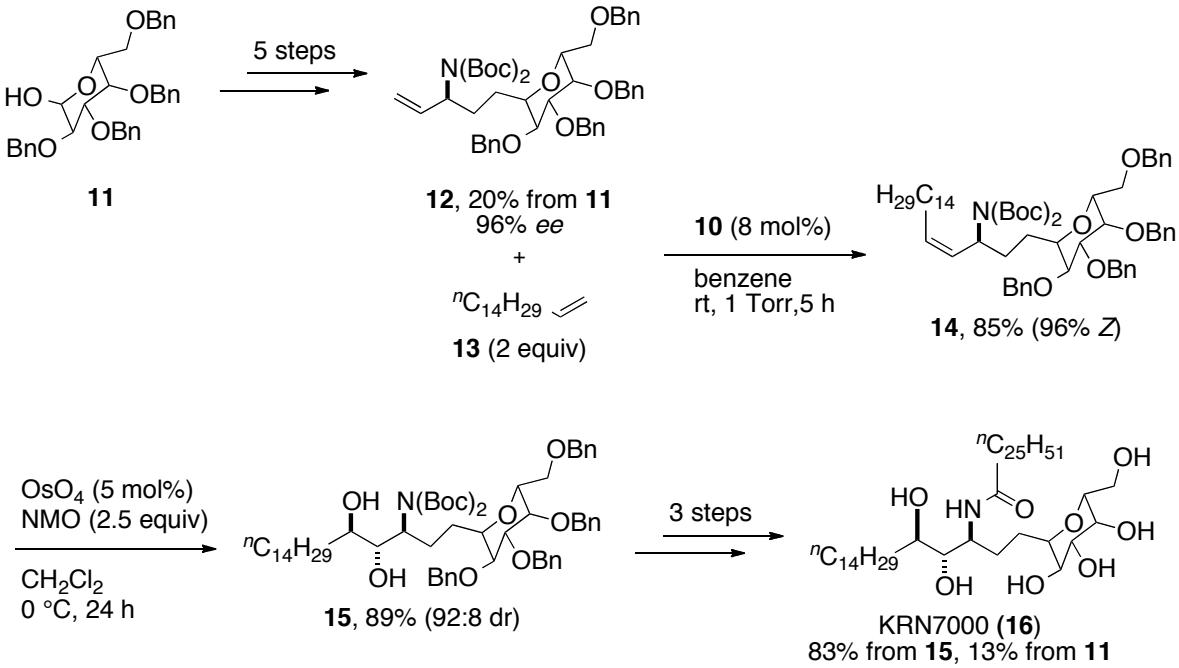
• Adamantylimido complex **10** was the most active catalyst for this conversion. Catalyst **2** also showed good stereoselectivity, but did not show good efficiency (35% yield). → Less hindered **10** seemed to readily promote the conversion from relatively hindered allylic amides.

• The use of excess amount of aliphatic alkenes, and the performing the reaction under vacuum conditions, good reactivity and stereoselectivity was achieved.

• Even from less hindered allylic amides ($R^3$ = H), which are more prone to homo-coupling, the desired products were obtained in relatively good yield (75–87%), although the stereoselectivity became lower.

• This reaction from allylic amide was also applied to the synthesis of a natural product, KRN7000 (**16**, an anti-tumor agent). Diastereoselectivity was derived from the *Z*-alkene **14**.

***Scheme 2.*** Synthesis of KRN7000 (**16**) by Using CM Reaction




## 3. Conclusions

• Highly *Z*-selective CM from enol ethers and allylic amides was developed.

• These reactions could be applied to the key step for the natural product syntheses.

• Use of adequate equivalent of starting materials and/or reaction in vacuum conditions suppressed the undesirable homo-coupling reaction and the formation of Mo-methylidene species, and achieved high yield.

## 4. References

(1) *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, **2003**.

(2) Jiang, A. J.; Zhao, Y.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 16630–16631.

(3) Qin, D.; Byun, H.-S.; Bittman, R. *J. Am. Chem. Soc.* **1999**, *121*, 662–668.