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ARTICLE TYPE

Ruthenium-catalyzed ring-closing metathesis accelerated by long-range steric effect

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Ruthenium-based metathesis catalysts with a *N*-heterocyclic carbene ligand bearing 2,3,4,5-tetraphenylphenyl moieties (1-TPPh and 1-TPPh*) are developed. The highly active catalyst system has been realized in THF by the combination of 1-TPPh* and CuCl as a phosphine scavenger.

Ring-closing metathesis (RCM) is one of the most important synthetic reaction for formation of cyclic compounds containing carbon-carbon double bonds.¹ In the reaction, the Grubbs second-generation catalyst (**1-Me** in Fig. 1)^{2a,b} is widely used and shows much higher catalytic activity than the earlier Grubbs first-generation catalyst (**2**: (PCy₃)₂Cl₂Ru=CHPh).^{2b-d} Mechanistic investigations³ indicate that dissociation^{3c} of the tricyclohexylphosphine (PCy₃) to the four-coordinate 14-electron species (LCl₂Ru=CHPh)^{3b} is crucial. However, surprisingly, **1-Me** only dissociates PCy₃ less efficiently than **2**.^{3c,d} Therefore, in effort to enhance the catalytic activity of **1-Me**, phosphine-free catalysts were prepared by replacing PCy₃ with 3-bromopyridine ligand^{4a} or with intramolecular coordination of an isopropoxy substituent of the alkylidene ligand (Hoveyda catalyst: **1-O-Me** in Fig. 1).^{4c} However, the 3-bromopyridine catalyst decomposes faster^{4b} and **1-O-Me** might be reluctant to dissociate the intramolecular coordination. Furthermore, these alterations and other alkylidene modifications^{4d-f} only provide, in principle, the same active catalytic species as from **1-Me** after a single turnover with olefinic substrates. In contrast, variation of the *N*-heterocyclic carbene (NHC) moiety⁵ must be capable, since it can directly amend the nature of the 14-electron species to enhance catalytic activity or even realize asymmetric reactions with chiral NHCs.

We recently developed highly active catalyst systems utilizing steric effect at long range (long-range steric effect).⁶⁻⁸ To exploit such effect, ligands bearing steric bulk apart (> 1 nm) from a coordination site are requisite. We have already developed very efficient ligands of this nature, i.e., bowl-shaped phosphines⁶ and phosphines bearing peripherally arranged oligo(ethylene glycol) chains.⁷ Besides them, particularly efficient is 2,3,4,5-tetraphenylphenyl (TPPh) moiety which has rigid and widely spread structure.⁸ TPPh moieties provoke steric effect at long range and realize extremely active catalytic activity in Pd-catalyzed air oxidation of alcohol^{8a} and kinetic resolution of racemic vinyl ethers.^{8b} In the Ru-catalyzed RCM reaction, we anticipate that NHC ligands having TPPh at long range facilitate the phosphine dissociation and shield the resulting 14-electron

catalyst species against decompositions⁹ such as dimerization (Fig. 2). In this communication, we report synthesis and catalytic activity of Ru catalysts bearing NHC ligands with TPPh and methylated TPPh (TPPh*) substituents (**1-TPPh** and **1-TPPh*** in Fig. 1) in RCM. **1-TPPh** shows much higher catalytic activity than the conventional catalysts such as **1-Me**. Moreover, **1-TPPh*** maintains high catalytic activity even when PCy₃ is scavenged by added CuCl.

1-TPPh was synthesized from 2-bromo-5-iodo-*m*-xylene (See ESI†).¹⁰ Unfortunately, X-ray analysis of **1-TPPh** was not successful. But, the corresponding Hoveyda-type complex (**1-O-TPPh**) derived from **1-TPPh** and 2-isopropoxystryrene^{4b} afforded good crystals. The molecular structure of **1-O-TPPh** determined by X-ray structural analysis (Fig. 3) clearly shows that the TPPh moiety on the NHC ligand spatially spreads out and shields the Ru coordination sphere at long-range.† The Ru-C (NHC) bond length of **1-O-TPPh** (1.973(5) Å) is quite similar to

Fig. 1 Structures of catalysts.

Fig. 2 Ru metathesis catalyst activated by the long-range steric effect

Fig. 3 Molecular structure of **1-O-TPPh** with thermal ellipsoids at 50% probability levels.

Table 1 Ring-closing metathesis of various diolefins.^a

Entry	Diolefin	Product	Catalyst	Time (h)	Yield (%) ^b
1			1-TPPh	17	91 (84) ^c
2			1-Me		60
3			1-Ph		57
4			1-O-TPPh		48
5			1-TPPh	8	99 (99) ^c
6			1-Me		54
7			1-Ph		51
8			1-TPPh	6	99 (72) ^c
9			1-Me		38
10			1-Ph		29
11 ^d			1-TPPh	5	74
12 ^d			1-Me		10
13 ^d			1-Ph		5
14 ^d			1-TPPh	5	88
15 ^d			1-Me		51
16 ^d			1-Ph		46

^a Diolefin (0.25 mmol), catalyst (2.5 μ mol, 1.0 mol%), in toluene (5.0 mL), at 0 °C. ^b Yield of **4** based on the GC internal standard technique.

^c Isolated yield. ^d In CH₂Cl₂ (5.0 mL) as the solvent.

that of **1-O-Me** (1.981(5) Å),^{4b} implying the TPPh moieties do not obstruct the metal center. **1-Ph** was also prepared similarly.¹⁰

The RCM of diolefins (**3**) was carried out in toluene or CH₂Cl₂ at 0 °C with the catalyst (1.0 mol%) listed in Fig. 1 (Table 1).

Diethyl 2,2-diallylmalonate (**3a**) afforded the corresponding cyclic olefin (**4a**) in 91% yield with **1-TPPh** as catalyst (entry 1). However, the Grubbs second-generation catalyst (**1-Me**) and **1-Ph**, having simple Ph substituent in place of TPPh, provided **4a** in considerably lower yields, 60% and 57%, respectively (entries 2 and 3). The phosphine-free catalyst **1-O-TPPh** was not so effective as **1-TPPh** possibly due to low lability of intramolecular coordination of the isopropoxy unit at such lower temperature (entry 4).¹¹ The efficacy of **1-TPPh** as compared with **1-Me** and **1-Ph** was also confirmed using various diolefins. In the reaction of malonate esters (**3b** and **3c**) affording six- (**4b**) and seven- (**4c**) membered rings, **1-TPPh** provided the products in much higher yields (entries 5 and 8) than **1-Me** (entries 6 and 9) and **1-Ph** (entries 7 and 10). Furthermore, with **1-TPPh** as the catalyst, diallyl ether (**3d**) and 1,7-octadiene (**3e**) afforded the products (**4d** and **4e**) in 74% and 88% yields (entries 11 and 14), respectively, while **1-Me** (entries 12 and 15) and **1-Ph** (entries 13 and 16) were less efficient. In Table 1, selectivities of the products (**4**) were high, and cross metathesis dimerization/oligomerization did not

Table 2 Effect of added PCy₃ on the ring-closing metathesis of **3a**^a

Entry	Added PCy ₃ (mol%)	Catalyst	Yield of 4a (%) ^b
1	0.10	1-TPPh	94
2	0.10	1-Me	38
3	0.20	1-TPPh	39
4	0.20	1-Me	31

^a **3a** (0.25 mmol), catalyst (2.5 μ mol, 1.0 mol%), added PCy₃ (0.25 μ mol: 0.10 mol% or 0.50 μ mol, 0.20 mol%), in toluene (5.0 mL), at 0 °C for 17 h. ^b Yield of the product based on the GC internal standard technique.

substantially occur.

When 0.10 mol% of PCy₃ was added to entry 1 in Table 1 (where 1.0 mol% of **1-TPPh** was employed as catalyst), the catalyst was still active to provide **4a** in 94% yield (entry 1, Table 2). In sharp contrast, the addition of the same amount (0.10 mol%) of PCy₃ to entry 2 in Table 1 (employing 1.0 mol% of **1-Me**), the catalytic activity significantly decreased and **4a** was afforded in 38% yield (entry 2, Table 2). The TPPh moiety on the NHC ligand might suppress re-coordination of PCy₃ more efficiently than **1-Me** and secure the good catalytic activity under these conditions. On the other hand, the addition of the double amount (0.20 mol %) of PCy₃ to the **1-TPPh** catalyst systems resulted in considerable catalyst deactivation providing **4a** in 39% (entry 3) as observed in entry 4. With the larger amount of the added PCy₃, even **1-TPPh** lowered its catalytic activity.

Hence, we tried to remove PCy₃ from the catalyst systems by adding CuCl as a phosphine scavenger¹² (generating ill-characterized CuCl-PCy₃ complex),^{12b} although it is known that these catalysts tend to decompose more rapidly in the presence of CuCl. The reaction of **3a** was carried out with **1-TPPh** as catalyst (1.0 mol%) in the presence of CuCl (4.0 mol%) in THF at 0 °C under otherwise the same reaction conditions as entry 1 in Table 1 (entry 1 in Table 3). Even initial reaction rate in the reaction became much higher, the yield (57% yield after 4 h) did not increase at all during next 24 h, indicating catalyst decomposition. Thus, even **1-TPPh** decomposed fairly fast when the PCy₃ was scavenged by CuCl. **1-Me** decomposed much faster under the same reaction conditions and **4a** was obtained only in 10% yield (entry 2).

Therefore, **1-TPPh*** (Fig. 1) having eight methyl substituents on **1-TPPh** was devised and synthesized by the similar method.¹⁰ Unfortunately, good single crystals of **1-TPPh*** could not be obtained. However, DFT optimized structure (by B3LYP/LANL2DZ) clearly indicated the introduced methyl moieties enhance the shielding effect for the Ru coordination sphere (Fig. S4).¹⁰ In the reaction of **3a** as a substrate, **1-TPPh*** (entry 3) was more efficient catalyst than **1-TPPh** (entry 4) to afford **4a** in 91% yield¹³ in 15 min at 10 °C in the presence of CuCl (4.0 mol %) in THF. When the catalyst loading was lowered to 0.04 mol%, the turnover number (TON) reached 12,000 (entry 5). With more sterically congested **3f**, **1-TPPh*** was a superior catalyst and provided **4f** in 90% yield in 15 min (entry 6), while **1-TPPh** and **1-Me** were not effective giving **4f** in 30% and 29% yields, respectively (entries 7 and 8). These yields in entries 6 and 7 did not increase at all even after 4 h, indicating both the catalysts decomposed within a few minutes under these reaction conditions (Fig. S4).¹⁰ **1-TPPh*** was also better catalyst for **3b** and **3c** as the substrates (entries 9 and 12) as compared

Table 3 The ring-closing metathesis of various diolefins in the presence of CuCl in THF^a

Entry	Diolefin	Product	Catalyst	Temp ^b (°C)	Time (min)	Yield (%) ^c
1 ^d	3a	4a	1-TPPh	0	240	57
2 ^d			1-Me	0	240	10
3			1-TPPh*	10	15	91 (84) ^e
4			1-TPPh	10	15	63
5 ^f			1-TPPh*	RT	60	49
6			1-TPPh*	RT	15	90 (80) ^e
7			1-TPPh			30
8	3f	4f	1-Me			29
9	3b	4b	1-TPPh*	0	10	(95) ^e
10			1-TPPh			75
11			1-Me			33
12	3c	4c	1-TPPh*	0	10	94 (88) ^e
13			1-TPPh			87
14			1-Me			30
15			1-TPPh*	RT	2	99 (77) ^e
16	3g	4g	1-TPPh			94
17			1-Me			33
18			1-TPPh*	0	10	83 (81) ^e
19	3h	4h	1-TPPh			79
20			1-Me			42

^a Diolefin (0.25 mmol), catalyst (2.5 μmol, 1.0 mol%), CuCl (0.010 mmol: 4.0 mol%), THF (2.0 mL). ^b RT = room temperature. ^c Yield of the product based on the GC internal standard technique. ^d THF (5.0 mL) was used. ^e Isolated yield. ^f **3a** (2.5 mmol), **1-TPPh*** (0.10 μmol, 0.040 mol%), CuCl (1.0 μmol, 0.40 mol%) in THF (0.4 mL) at RT for 60 min.

with **1-TPPh** (entries 10 and 13) and **1-Me** (entries 11 and 14). In the reaction of an allyl ether (**3g**) and a sulfonamide (**3h**), both **1-TPPh*** (entries 15 and 18) and **1-TPPh** (entries 16 and 19) showed higher catalytic activity than **1-Me** (entries 17 and 20). It is noteworthy that in the presence of CuCl, THF plays an important role. When the reaction of entry 3 in Table 3 was carried out in toluene under otherwise identical reaction conditions, yield of **4a** was reduced significantly to 44%.¹⁰ Upon addition of a small amount of THF (0.2 mL) to toluene (1.8 mL) as solvent, the yield of **4a** was recovered to 69%. Coordination of THF to stabilize the catalyst center must be important. THF to stabilize the catalyst center must be important.

In conclusion, ruthenium-based metathesis catalysts with a NHC ligand bearing TPPh and TPPh* moieties (**1-TPPh** and **1-TPPh***) were synthesized. A combination of **1-TPPh*** and CuCl as a phosphine scavenger in THF provides much higher catalytic activity. Further studies on application of the present catalytic system are currently under investigation.

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Notes and references

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[†] Electronic Supplementary Information (ESI) available: See DOI: 10.1039/b000000x/

³⁰ [‡] Crystallographic data of **1-O-TTPPh**: C₉₂H₈₀Cl₈N₂O₈Ru, *M* = 1614.35, triclinic, space group *P1* (No. 2), *a* = 12.7107(2), *b* = 14.1983(1), *c* = 24.5773(13) Å, *α* = 86.648(8), *β* = 89.389(8), *γ* = 63.635(6)°, *V* = 3471.3(3) Å³, *Z* = 2, 16946 independent reflections (*R*_{int} = 0.065), *R*₁ (*I* > 2σ(*I*)) = 0.0857, *wR*₂ (all data) = 0.1643. GOF = 1.321. CCDC 825559.

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⁹⁰ ¹³ When **1-TTPPh*** was used as a catalyst in entry 1 in Table 1 under otherwise identical conditions, **4a** was obtained in 91% yield after 24 h.